The role of musculoskeletal ultrasonography (MSUS) in investigating pain in patients with inflammatory arthritis

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DEDICATION

To my beloved father,

It has been four heartbreaking months since you left this world, and not a single day passes without feeling your absence deeply. I was away pursuing this PhD when you took your final breath, missing the precious chance to hold your hand and tell you, one last time, how much you mean to me.

You were the first to believe in me, long before I learned to believe in myself. I will forever cherish the countless moments when you silenced every voice that doubted a woman's worth, including my own. Your unwavering faith in me ignited a light that still burns within my heart, guiding me with strength, courage, and warmth every single day.

Though you are no longer here to witness this moment, I feel your presence all around me, steady, proud, and full of love, urging me onward whenever the road feels long. You remain my greatest source of inspiration and the quiet strength behind every one of my accomplishments.

This achievement, this dream realised, is as much yours as it is mine. I wish I could share this victory with you, to see the pride in your eyes. I miss you endlessly, more than words can express, and I hope, from the depths of my heart, that I am making you proud.

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Abstract

Rheumatoid arthritis (RA) is a prevalent and enduring inflammatory joint disorder characterised by autoimmune responses and persistent joint inflammation. This inflammation results in pain, which is regarded as the hallmark symptom of RA. Numerous patients with RA continue to experience pain despite effectively controlled inflammation. This chronic pain is linked to musculoskeletal conditions that can diminish quality of life. Various mechanisms underlie the clinical pain experienced in RA, including nociceptive and nociplastic pathways. Nociceptive pain in RA has predominantly been associated with inflammatory changes within the joints, whereas nociplastic pain is considered non-inflammatory and related to central sensitisation. A comprehensive understanding of the nature of pain in RA could facilitate the development of improved pain management strategies.

The primary objective of this thesis is to investigate the pain mechanisms in RA through the utilisation of musculoskeletal ultrasonography (MSUS). MSUS is valuable for detecting peripheral inflammation that causes nociceptive pain. Furthermore, when pain persists despite inflammation management, MSUS can be used to confirm the absence of inflammatory changes within the joints.

The data used in this thesis were collected from six clinical studies. The initial phase involved assessing the prevalence of persistent pain in early RA using the SERA dataset. Subsequently, the study examined the relationship between Ultrasound power Doppler (USPD) and pain intensity, as measured by the pain visual analogue scale (VAS), within the TaSER dataset. Given that the TaSER dataset comprises a reduced sample of patients with early RA who underwent ultrasound examinations, the third chapter focused on analysing the correlation between MSUS findings and pain measures using the larger Spanish RA cohort dataset (Naredo), which also includes diverse MSUS metrics and a wider range of joints.

In the following chapter, the validation of the findings from the previous chapter (the correlation between pain and MSUS) within a population afflicted by a different form of inflammatory arthritis, specifically Psoriatic Arthritis (PsA), has been explored, utilising the CENTAUR dataset. This dataset includes subjective pain measures, such as the pain VAS, as well as semi-objective pain assessments, namely Quantitative Sensory Testing (QST).

In the concluding chapter, the relationship between pain and MSUS metrics was analysed, this time utilising objective pain measurement tools, specifically neuroimaging via functional Magnetic Resonance Imaging (fMRI), as objective indicators of pain signal processing. The capability of ultrasound to detect nociceptive pain was evaluated by establishing correlations with the traditional pain pathway, specifically the sensorimotor network (SMN)-Thalamus connectivity. Furthermore, the effectiveness of MSUS in identifying inflammation that contributes to the mixed pain state was assessed by correlating MSUS metrics with the nociplastic pain marker, namely the Default Mode Network (DMN)-Insula.

Within the SERA chapter, it was observed that a portion of patients reported experiencing pain during follow-up. Among those who reported pain, few participants exhibited a negative swollen joint count (SJC), while a notable proportion had normal erythrocyte sedimentation rate (ESR) levels. In the TaSER chapter, no significant correlation was identified between ultrasound power Doppler (USPD) and the pain visual analogue scale (VAS). These findings might be due to the reduced sample size and the limited number of joints included in the TaSER dataset. However, within the Spanish RA cohort, which had a larger sample size, more MSUS metrics, and a broader range of joints included, a notable correlation was established between MSUS metrics, namely USPD, ultrasound synovial hypertrophy (USSH), and ultrasound joint effusion (USJE), and pain VAS at both baseline and follow-up visits.

In the CENTAUR analysis, no substantive correlations emerged between USSH, enthesitis metrics, and pain VAS scores, nor between QST, namely pressure pain threshold algometry (PPT) and MSUS parameters. Furthermore, no significant associations were detected linking MSUS findings with fibromyalgia (FM). FM serves as a prototype for nociplastic pain. In a distinct examination of the CENTAUR dataset, a negative correlation was observed between US enthesitis and SMN-thalamus connectivity. A correlation was not observed between MSUS and DMN-insula connectivity. Notably, significant correlations were established in the SOAR and TEMPO datasets between MSUS parameters, including USPD and ultrasound bone erosion (USBE), and DMN-insula connectivity, albeit no significant association was found between MSUS and SMN-thalamus metrics. This thesis substantiates the reliability of ultrasound as an investigative tool in assessing inflammatory changes within the joints of patients with inflammatory arthritis. It demonstrates that MSUS can effectively evaluate nociceptive pain, evidenced by significant correlations in the extensive Spanish RA cohort. Furthermore, MSUS holds promise as a diagnostic tool to discern the presence or absence of peripheral inflammation

contributing to non-inflammatory pain in this patient population. Finally, the findings indicate that MSUS can identify the contributions of nociceptive pain to the overall mixed pain experience in patients with RA and FM.

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Author's declaration

I, Norah Aldehmi, declare that the work described in this thesis is original and was generated as a result of my own work. No part of this thesis has been submitted for any other degree, either at the University of Glasgow or at any other institution.

Signature:

Printed Name: NORAH ALDEHMI

List of Abbreviations

ACC – Anterior Cingulate Cortex

ACR – American College of Rheumatology

antIC – Anterior Insula Cortex

BASDAI – Bath Ankylosing Spondylitis Disease Activity Index

bDMARDs – Biologic Disease-Modifying Anti-Rheumatic Drugs

BMI – Body Mass Index

BOLD – Blood Oxygenation Level Dependent

CDAI – Clinical Disease Activity Index

CNS – Central Nervous System

CPM – Conditioned Pain Modulation

CRP – C-Reactive Protein

CsDMARDs – conventional synthetic Disease-Modifying Anti-Rheumatic Drugs

CZP – Certolizumab

DAPSA – Disease Activity in Psoriatic Arthritis

DAS – Disease Activity Score

deoxHb – Deoxygenated Haemoglobin

DIP – Distal Interphalangeal Joint

dlPFC – Dorsolateral Prefrontal Cortex

DMARDs – Disease-Modifying Anti-Rheumatic Drugs

DMN – Default Mode Network

ESR – Erythrocyte Sedimentation Rate

EULAR – European Alliance For Associations For Rheumatology

FIQ – Fibromyalgia Impact Questionnaire

FLS – Fibroblast-Like Synoviocytes

FM – Fibromyalgia

FMness – Fibromyalgianess

fMRI – Functional Magnetic Resonance Imaging

HCQ – Hydroxychloroquine

IASP – International Association for The Study Of Pain

IBD – Inflammatory Bowel Disease

IC – Insula Cortex

ICN – Intrinsic Connectivity Networks

IPL – Inferior Parietal Lobule

IQR – Interquartile Range

IV – Intravenous

JAKs – Janus Kinases

JASP – Jeffrey's Amazing Statistics Program

LEI – Leeds Enthesitis Index

MASES – Maastricht Ankylosing Spondylitis Enthesitis Score

midIC – Middle Insula Cortex

MNI – Montreal Neurological Institute

mPFC – Medial Prefrontal Cortex

MRI – Magnetic Resonance Imaging

MSUS – Musculoskeletal ultrasound

NRS – Numeric Rating Scales

NSAIDs – Non-Steroidal Anti-Inflammatory Drugs

OA – Osteoarthritis

OMERACT – Outcome Measures in Rheumatoid Arthritis Clinical Trials

oxHb – Oxygenated Haemoglobin

PCC – Posterior Cingulate Cortex

PDQ – Pain Detect Questionnaire

PFC – Prefrontal Cortex

PGA – Patient Global Assessment

pIC – Posterior Insula Cortex

PPT – Pressure Pain Threshold

PPTol – Pressure Pain Tolerance

PROMIS – Patient-Reported Outcomes Measurement Information System

PROs – Patient-Reported Outcomes

PsA – Psoriatic Arthritis

PsO – Psoriasis

QST – Quantitative Sensory Testing

RA – Rheumatoid Arthritis

RAMRIS – Rheumatoid Arthritis Magnetic Resonance Imaging Scoring System

RF – Rheumatoid Factor

RFP – Radio Frequency Pulse

ROI – Region of Interest

rs-fMRI – Resting State Functional Magnetic Resonance Imaging

SD – Standard Deviation

SI – Primary Somatosensory Cortex

SII – Secondary Somatosensory Cortex

SJC – Swollen Joints Count

SMN – Sensory Motor Network

SpA – Spondyloarthritis

SPM12– Statistical Parametric Mapping 12

SPSS – Statistical Package for the Social Sciences

SSS – Symptoms Severity Score

T – Tesla

T1 – Time Constant 1

T2 – Time Constant 2

T2* – Time Constant 2 Star

TCZ – Tocilizumab

TJC – Tender Joints Count

TNF – Tumour Necrosis Factor-α

TS – Temporal Summation

US – Ultrasound

USBE – Ultrasound Bone Erosion

USJE – Ultrasound Joint Effusion

USPD – Ultrasound Power Doppler

USSH – Ultrasound Synovial Thickening

VAS – Visual Analogue Scales

WPI – Widespread Pain Index

Chapter 1 Background and Rationale

The background chapter aims to provide the necessary foundation for understanding the role of musculoskeletal ultrasound (MSUS) in evaluating pain in rheumatoid arthritis (RA). This chapter provides a comprehensive overview of RA, encompassing its epidemiology, aetiology, pathophysiology, clinical manifestations, diagnostic criteria, and contemporary management strategies. This background information aims to provide a better understanding of the disease within the broader clinical context, fostering deeper insight into its multifaceted nature. Pain is a prevalent and disabling symptom of RA, explored in detail with emphasis on its various mechanisms and classifications to highlight the complexity of pain experiences in this population. Subsequently, an introduction to MSUS is presented, highlighting its effectiveness as a sensitive tool for identifying synovial inflammation and structural changes relevant to pain mechanisms. This structured background aims to provide context for the current research and to clarify the rationale and objectives of the study. It highlights the clinical importance of understanding and accurately assessing pain in RA using advanced imaging techniques, namely MSUS.

1.1 Introduction

RA presents as a prevalent and persistent inflammatory joint condition characterised by autoimmune responses, persistent joint inflammation, and the presence of specific autoantibodies, such as Rheumatoid Factor (RF) and Anti-Citrullinated Peptide Antibodies (ACPA), including Anti-Cyclic Citrullinated Peptides (anti-CCP) (Scott et al., 2010). It exhibits a spectrum of severity, from mild to severe forms, often leading to disability in the long term, with a significant reduction in life expectancy (Lourida et al., 2022). RA predominantly affects small joints and commonly presents with symmetrical symptoms, including stiffness, tenderness, pain, swelling, and joint deformities, which impact daily activities and work productivity (Conforti et al., 2021).

1.1.1 The clinical features of RA

The clinical features of RA include swelling and stiffness, which predominantly affect the smaller joints of the hands and feet. RA commonly impacts the metacarpophalangeal, proximal interphalangeal, and wrist joints (Gulati et al., 2018).

The clinical features of synovitis, inflammation of the synovial membrane, are most noticeable in the morning. A common indicator of RA is morning stiffness in and around the joints that lasts for at least an hour before improving significantly. This is a subjective

symptom, and it is essential to clearly explain to the patient the difference between pain and stiffness. The duration of morning stiffness is associated with disease activity (Gulati et al., 2018).

1.2 Classification of rheumatoid arthritis

1.2.1 2010 ACR-EULAR RA classification criteria

The 2010 ACR/EULAR RA classification criteria were developed collaboratively by the ACR and EULAR with the aim of defining RA at an earlier stage (Table 1.1). These criteria were designed to identify patients with inflammatory arthritis (IA) who have experienced a relatively short symptom duration and would benefit from prompt diagnosis and initiation of Disease-Modifying Anti-Rheumatic Drugs (DMARDs) therapy (Aletaha et al., 2010). To apply these criteria, patients must meet two essential requirements. Firstly, clinical evidence of synovitis, indicated by joint swelling, must be present in at least one joint, with the exception of specific joints typically affected by osteoarthritis. Secondly, synovitis should not be better explained by another diagnosis, such as systemic lupus erythematosus (SLE), psoriatic arthritis, or gout. Definite classification as RA is determined by achieving a total score of 6 or more out of 10 across four domains, including the number and location of involved joints (score range 0–5), serological abnormalities (score range 0–3), elevated acute phase response (score range 0–1), and symptom duration (score range 0–1) (Aletaha et al., 2010).

Table 1.1: 2010 American College of Rheumatology/ European League Against Rheumatism classification criteria for rheumatoid arthritis. Adopted from (Aletaha et al., 2010).

Joint involvement[1]	
1 large[2] joint	0
2–10 large joints[3]	1
1–3 small joints (with or without involvement of large joints)	2
4–10 small joints (with or without involvement of large joints)	3
>10 joints[4] (at least one small joint)	5
Serology (at least one test result is needed for classification)	
Negative RF AND negative ACPA	0
Low positive RF OR low positive ACPA	2
High positive RF OR high positive ACPA	3
Acute phase reactants (at least one test result is needed for classification)	
Normal CRP AND normal ESR	0
Abnormal CRP OR abnormal ESR	1
Duration of symptoms[5]	
<6 weeks	0
≥6 weeks	1

(1) Joint involvement encompasses the presence of any swollen or tender joint upon examination, which may be validated by imaging evidence of synovitis. Categorisation of joint distribution is based on the location and the number of affected joints, with assignment to the highest applicable category determined by the pattern of joint involvement. (2) Large joints comprise the shoulders, elbows, hips, knees, and ankles. (3) Small joints consist of the wrists, metacarpophalangeal (MCP) joints, proximal

interphalangeal (PIP) joints, thumb interphalangeal (IP) joints, and metatarsophalangeal (MTP) joints 2–5. (4) Within this classification, at least one of the affected joints must be a small joint; the remaining joints may include any combination of large and additional small joints, as well as other joints not explicitly enumerated elsewhere (e.g., temporomandibular, acromioclavicular, and sternoclavicular joints). (5) Duration of symptoms refers to the patient's self-reported duration of signs or symptoms of synovitis (e.g., pain, swelling, tenderness) in joints clinically involved at the time of assessment, irrespective of treatment status. ACPA: anti-citrullinated protein/peptide antibodies; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; RF: rheumatoid factor; ULN: upper limit of normal.

1.3 Epidemiology of RA

RA is the predominant type of chronic inflammatory arthritis, showing varying prevalence rates across different regions. Based on data from the Global Burden of Disease (GBD), RA shows higher prevalence and incidence rates in northern and western European nations (approximately 0.40% prevalence and 20–30 new cases per 100,000 patient-years) compared to southern and eastern ones (approximately 0.20% prevalence and 7–15 new cases per 100,000 patient-years) (Finckh et al., 2022). While the GBD estimates indicate a slight increase in RA prevalence and incidence in Europe from 1990 to 2015, conflicting findings suggest a decrease in RA incidence in the UK post-2005 (Abhishek et al., 2017). Variations in prevalence and incidence across regions are attributed to differences in smoking habits. Some studies report higher prevalence rates for specific European countries than those reported by the GBD, possibly due to methodological differences and age adjustments. Female-to-male ratios for RA incidence hover around 2:1, with prevalence ratios varying from 1.4:1 in Poland to 5.7:1 in France (Finckh et al., 2022). In North America, GBD data estimate an age-standardised prevalence of 0.38% and an age-standardised incidence of 22.5 per 100,000 patient-years for RA (Crane et al., 2015). A 2008 study by the US Centres for Disease Control found the prevalence of RA in the USA to be around 0.6%, while recent analysis of healthcare claims suggests a prevalence between 0.54% and 0.63%, with women having a higher prevalence compared to men (0.73% versus 0.29%) (Finckh et al., 2022).

1.4 Aetiology and Pathophysiology of RA

1.4.1 Pathophysiology of RA

Although the precise aetiology of RA remains unknown, it is widely acknowledged that RA is a multifactorial disease, including both genetic and environmental factors, that promote the susceptibility and onset of RA. Over 80% of Patients with RA carry the HLA-DRB1*04 epitope, often referred to as the 'Rheumatoid Epitope' (Holoshitz, 2010). This epitope is believed to significantly influence both the onset of disease and its long-term severity (Symmons et al., 2002).
Genome-wide association studies employing single-nucleotide polymorphisms have identified numerous loci associated with disease susceptibility, with many of these loci implicated in immune mechanisms and some linked to other inflammatory conditions. Foremost among these genetic associations is the HLA system, which predicts disease occurrence and provides information on disease severity, potential complications, and mortality risk (Petrelli et al., 2022). Additionally, several other loci play significant roles in RA pathogenesis through various mechanisms, including cytokine signalling, altered co-stimulatory pathways, innate immune activation, and modulation of lymphocyte receptor activation threshold (Burmester et al., 2014; McInnes et al., 2017). Notable loci in this regard include CD28, CD40, and PTPN22, among others (Petrelli et al., 2022). Distinctive antibodies detected in Patients with RA include autoantibodies against IgG, commonly known as rheumatoid factor, which is present in up to 70% of patients, and autoantibodies against citrullinated peptides (ACPAs), exhibiting higher specificity than rheumatoid factor (Van Delft et al., 2020).

The immune response constitutes the body's inherent defence mechanism against invading pathogens. It triggers an inflammatory response aimed at isolating and eliminating the pathogen from the body. Initially, phagocytes, such as macrophages, engulf pathogens to contain them. These phagocytes release messenger cells called cytokines (e.g., Interleukin and Tumour Necrosis Factor-alpha (TNF-alpha)) to alert other immune cells of the invasion. T-cells and B-cells are the two primary types of lymphocytes involved in the immune-inflammatory response. B-cells confer "humoral immunity" by producing antibodies that bind to specific antigens. At the same time, T-cells provide "cell-mediated immunity," performing various functions such as aiding B-cells and macrophages, suppressing the immune response, and signalling infected cells to undergo apoptosis

(Figure 1.1). However, in autoimmune diseases like RA, prolonged inflammation at joint sites destroys healthy cells (Lin et al., 2020). To integrate the structural joint changes observed in rheumatoid arthritis with the underlying immune-mediated mechanisms, Figure 1.1 provides a schematic comparison between a healthy synovial joint and an RA-affected joint, alongside an overview of the key cellular and molecular processes driving synovial inflammation, angiogenesis, and bone destruction.

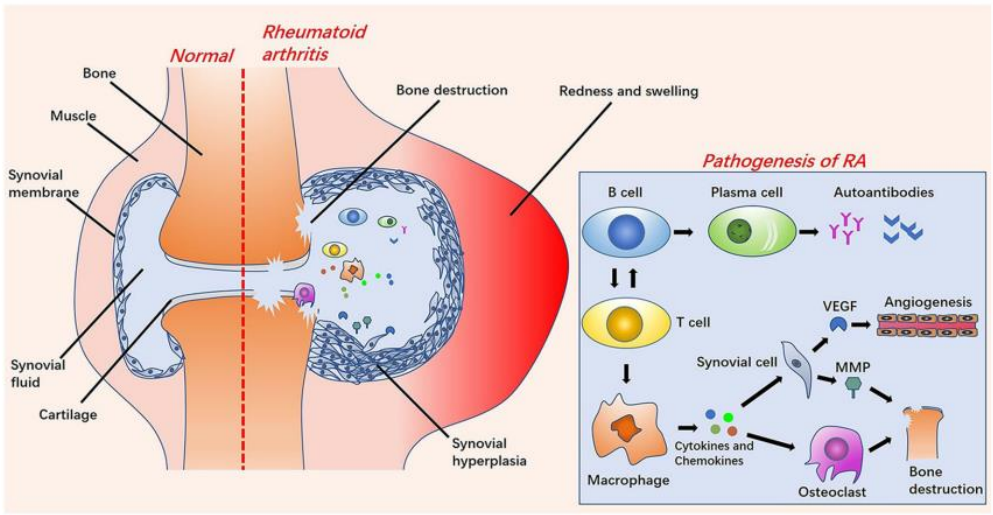

Figure 1.1 : The comparison diagram illustrates the differences between normal joints and those affected by RA. In the healthy synovial joint depicted on the left side of the figure, there is no swelling in the synovial joint capsule, and both cartilage and bone remain intact. In RA-affected joints shown on the right, there is synovial hyperplasia, increased synovial fluid, redness, swelling, and bone destruction. The accompanying overview of the pathological process of RA elucidates how various pathogenic factors activate B cells and T cells, initiating a cascade of interactions. Upon activation, B cells transform into plasma cells, releasing autoantibodies, while T cells differentiate into macrophages, releasing cytokines and chemokines. These factors stimulate the activation of synovial cells and osteoclasts, leading to the production of vascular endothelial growth factors (VEGFs) by synovial cells, promoting angiogenesis. Collaboration between osteoclasts and matrix metalloproteinases (MMPs) results in bone destruction. Source: (Wang et al., 2020).

The precise cause of this activation and the localised response in joint regions remains unknown. Nonetheless, T-cells, B-cells, and pro-inflammatory cytokines play crucial roles in the pathophysiology of RA. In the initial stages of RA, the immune response is triggered by Antigen-Presenting Cells (APCs) in the synovium. These APCs process antigens into peptides that are presented on HLA-DR4 molecules, engaging with specific T cells and activating CD4+ memory cells. This leads to the release of cytokines, such as Interleukin-2 (IL-2), which promotes T-cell expansion and the expression of surface molecules. Subsequently, the production of soluble mediators stimulates macrophages to produce pro-inflammatory cytokines, resulting in osteoclast formation, fibroblast activation, and

synoviocyte proliferation. While the role of T-cells in RA pathogenesis is well-established, the precise role of B-cells remains less characterised. B-cells act as antigen-presenting cells to activate helper T-cells and directly contribute to the production of RF. RF-specific B cells may migrate to the synovium, perpetuating increased B-cell activation and RF production, thereby prolonging inflammation (Petrelli et al., 2022). The role of Anti-citrullinated Peptide Antibodies (ACPA) in the inflammatory response is also of interest, as they are more specific to RA than RF antibodies, potentially representing a distinct subclass of RA. Enhanced understanding of RA pathophysiology has led to the development of more effective medications targeting specific mediators in the immune-inflammatory response, such as anti-TNF biologics.

Assessing the degree to which genetic factors contribute to RA onset has proven challenging due to solid gene-environment interactions, changes in disease prevalence over time, and the specificity of identified gene alleles. Initial studies suggested a low concordance rate of approximately 15% among Monozygotic (MZ) twins, implying a significant role for environmental factors (Holoshitz, 2010). However, subsequent research by MacGregor and colleagues (2000) highlighted the need to consider changes in population prevalence when estimating RA heritability, suggesting a higher heritability rate of approximately 60%. Furthermore, the presence of HLA-DR SE alleles in non-RA diseases and their absence in approximately 20% of Patients with RA has raised questions about their specificity to RA. As a result, it has been proposed that the stronger association between HLA-DR SE and established RA suggests its relevance to more severe and aggressive forms of the disease rather than its role as a precursor to disease onset (Symmons et al., 2002). Numerous environmental factors have been delineated as potential risk factors. Among these, smoking stands out as the most notable, correlating with heightened susceptibility to RA and RF development. In 1996, Silman et al. conducted a twin study to explore the impact of smoking on the susceptibility to RA. Questionnaires were distributed to 79 identical Monozygotic (MZ) twins and 71 same-sex Dizygotic twins (DZ), both with and without RA. The limited number of discordant pairs, where one twin had RA and smoked while the other did not smoke and did not have RA, was attributed to both twins sharing similar environmental exposures. Nonetheless, the analysis revealed a strong association between RA and smoking. Smokers, especially those carrying shared epitope genes, are at an escalated risk of developing ACPA-positive RA (Viatte et al., 2013). The presence of RF or Anti-citrullinated Peptide antibodies (ACPA) has been identified as a significant risk factor for RA development, as well as a predictor of increased erosive damage (Scott et al., 2003; Nishimura et al., 2007). ACPAs, such as anti-citrullinated protein antibodies (anti-CCP), have been found to be more effective in

predicting the risk of RA than RF antibodies (Nishimura et al., 2007). Szodoray and colleagues (2010) indicate that ACPA production in the synovium can occur years before symptom onset, underscoring its role as a biomarker in RA. Moreover, evidence suggests that the presence of the HLA-DRB shared epitope (SE) is associated explicitly with ACPA-positive RA, raising speculation about the role of HLA-DR SE in mediating ACPA production. While direct evidence for this causal relationship is lacking, it emphasises the importance of considering genetic and ACPA information when studying these subsets of Patients with RA (Van Heemst et al., 2014). Furthermore, the relationship between smoking and ACPA-positive RA suggests an interaction involving HLA-DR SE, smoking, and ACPA-positive RA. The exact mechanisms by which these specific genetic and environmental factors contribute to the pathophysiology observed in ACPA-positive RA are not fully understood. Still, Klareskog et al. (2006) indicate that individuals with both HLA-DR SE and a history of smoking have a 21-fold increase in relative risk compared to those lacking the gene and who do not smoke, significantly higher than either factor in isolation. Conversely, the use of oral contraceptives and pregnancy has been linked to a reduced incidence of RA. To illustrate, the prevalence of RA is notably higher in post-menopausal women compared to premenopausal women, sparking speculation about the potential role of hormonal factors in RA onset. Studies have shown that women who take Oral Contraceptive Pills (OCPs) have approximately half the incidence of RA compared to those who have never taken them, along with reduced susceptibility during pregnancy (Raine and Giles, 2022). However, it remains unclear whether there exists a direct causal link between OCP use and RA onset or if OCP use serves as a surrogate marker for other lifestyle choices, such as smoking, among women who opt for OCP. Moreover, Doran and colleagues (2004) have not demonstrated any association between women's use of Hormone Replacement Therapy (HRT) during menopause and RA onset; however, Merlino et al. (2003) note that HRT has been associated with a lower risk of RA.

1.4.2 The pathophysiology of pain

Joint damage stimuli activate the primary sensory neurons, known as high-threshold nociceptors. These mechanisms of nociceptor activation involve temperature-sensitive ion channels such as vanilloid receptors (VR1 and VR2), mechanosensitive channels responsive to joint inflammation, and chemosensitive receptors activated by purines, protons, amines, peptides, and cytokines released during joint inflammation (Woolf et al., 1999). Reducing the activation threshold and increasing responsiveness at the peripheral end of sensory nerve fibres is known as peripheral sensitisation. This process is mediated

by changes in ion channel kinetics and post-translational modifications, which increase membrane excitability and action potential generation (Gangadharan et al., 2013). Furthermore, inducing long-lasting changes in the spinal cord dorsal neurons results in pain hypersensitivity, leading to central sensitisation. This phenomenon occurs due to sustained nociceptor activity, which raises neural excitability. The mechanism involves releasing excitatory neurotransmitters and neuropeptides from C-fibres, triggering intracellular kinase cascades and enhancing NMDA receptor function through activation of ionotropic and metabotropic receptors. Consequently, the pain pathway becomes activated, producing amplified responses to noxious stimuli and allowing stimuli to generate pain signals (allodynia). Central sensitisation is strongly associated with both inflammatory and non-inflammatory pain states, as sensitised peripheral afferents drive this central plasticity and alter ion channel expression. These mechanisms enable non-nociceptive A-fibres to contribute to pain signalling, which can gradually lead to persistent hypersensitivity. Additionally, reduced inhibitory control contributes to central sensitisation, as lower levels of inhibitory neurotransmitters weaken descending inhibitory pathways or lead to the loss of inhibitory interneurons within the dorsal horn (Woolf et al., 1999).

1.5 Assessment Tools of RA

1.5.1 The Disease Activity Score (DAS)

DAS is a clinical measure of RA activity, amalgamating data on swollen and tender joints, acute phase response, and overall well-being. Its inception stemmed from a large-scale prospective trial comparing rheumatologists' decisions to initiate or discontinue DMARDs in patients with high and low disease activity levels, respectively (Van Riel et al., 2016). Various statistical methods, including multiple regression analysis, were employed to pinpoint the clinical and laboratory variables predominantly influencing rheumatologists' clinical management decisions. The original DAS formulation incorporated the Ritchie score, swollen joint count out of 44, erythrocyte sedimentation rate (ESR), and the patient's global assessment, exhibiting a strong correlation with progressive joint damage over time (Van der Heijde et al., 1990). Despite its validation, the DAS's time-consuming nature prompted the development of the DAS28, a modified disease activity score that was developed using 28 joint counts, using the same patient cohort. Notably, reducing joint counts did not compromise discriminant function or validity. Both DAS and DAS28 are integral to the European League Against Rheumatism (EULAR) response criteria,

categorising patients into good, moderate, or non-responders based on individual changes in DAS and the reached DAS value (Fransen and Van Riel, 2005). However, although widely utilised and validated, joint counts have inherent limitations reliant on assessor training and experience, with variable reproducibility. Additionally, joint inflammation can be undetectable on palpation, posing challenges in accurately assessing disease activity. The DAS28, developed by Prevoo et al. (1995), modified the original DAS by employing a 28-joint count for both swollen and tender joints, emphasising the impact of ESR on the overall score. It is critical to distinguish between DAS and DAS28 to avoid biased comparisons, although formulas exist to convert DAS-44 to DAS28 (Van Gestel et al., 1998). Modifications, such as the Simplified Disease Activity Index (SDAI), offer enhanced sensitivity to changes in disease activity and serve as a validated means of quantifying overall disease activity (Aletaha et al., 2005). While the DAS28 categorisation aids in stratifying patients into remission, low, moderate, and high disease activity groups (Van Gestel et al., 1998).

Although the DAS28 is typically viewed as a continuous gauge of disease activity, spanning from 0 to 9.4, it has been widely adopted for categorising patients into remission, low, moderate, and high disease activity brackets. Validated against the American College of Rheumatology (ACR) remission criteria, a DAS28 score below 2.6 has been endorsed as the defining threshold for remission (Fransen and Van Riel, 2005). Moreover, the EULAR recommendations for managing RA suggest biologic DMARDs for patients with high disease activity (DAS28 score exceeding 5.1) (Smolen et al., 2019). Recent inquiries have surfaced regarding the adequacy of this threshold, particularly questioning if patients with moderate DAS28 scores (just below the biologic DMARD threshold) achieve sufficient control with conventional DMARDs alone (Nikiphorou et al., 2016).

DAS28 has many advantages in evaluating pain in RA. Inflammatory pain is commonly assessed in conjunction with a swollen joint count (SJC) and a tender joint count (TJC) to assess disease activity in RA. This assessment is reflected in the DAS28, as both SJC and TJC are key components that contribute to increased disease activity. Consequently, the DAS28 score serves as a valuable tool for monitoring treatment and its effects on pain, particularly in cases where pain arises from peripheral changes associated with RA (Mehta and Taylor, 2020).

Nonetheless, DAS28 may also reflect pain that is not related to inflammation. When patients with RA achieve clinical remission according to the DAS28 criteria, the pain they report may originate from a non-inflammatory cause. Therefore, the DAS28 may be utilised as a supplementary tool for evaluating pain in RA, in conjunction with established

pain assessment methodologies (Motyl et al., 2024). However, DAS28 may be influenced by non-RA factors such as age, sex, and adiposity. Additionally, it may overestimate disease activity in cases of chronic pain syndromes (e.g., fibromyalgia) (Johnson et al., 2020). A further limitation of the DAS28 is that it excludes assessment of the feet and ankles, despite foot involvement being common in RA and frequently representing an early or hallmark feature of the disease. Inflammation of the metatarsophalangeal (MTP) joints is highly prevalent in RA and may persist even when the 28-joint count suggests low disease activity or remission. Consequently, reliance solely on DAS28 may underestimate peripheral inflammatory burden, particularly in patients with predominant forefoot involvement (van der Heijde et al., 1992; Hensor et al., 2011). This limitation is clinically relevant, as subclinical or unassessed foot inflammation may contribute to ongoing pain, functional impairment, and structural progression despite apparently controlled DAS28 scores.

1.5.2 The ACR remission criteria

The ACR remission criteria strongly consider clinical signs and symptoms of inflammation, with all six items belonging to the domain of clinical symptoms and signs of inflammation: fatigue, joint pain, morning stiffness, joint tenderness, joint swelling, and ESR (Ranganath et al., 2006).

To meet the ACR remission, at least five of the following criteria must be present over two consecutive months: Morning stiffness lasting 15 minutes or less, absence of fatigue, no joint pain, no tenderness or pain upon joint motion, no soft tissue swelling in joints or tendon sheaths, and an ESR of 30 mm/h or less for females or 20 mm/h or less for males.

The ACR/EULAR criteria for remission is achieved using two definitions: First, using a Boolean-based definition: At any given time, a patient must fulfil all of the following criteria: Tender Joint Count (TJC) ≤ 1, Swollen Joint Count (SJC) ≤ 1, C-reactive Protein (CRP) ≤ 1 mg/dL, and Patient Global Assessment (PGA) ≤ 1 (on a scale from 0 to 10). Alternatively, remission according to ACR/EULAR is achieved when a patient has an SDAI score of ≤ 3.3 at any given time (Studenic et al., 2022).

1.5.3 RA Clinical Biomarkers

Biomarkers are quantifiable characteristics that can indicate normal biological processes, pathological processes, or responses to treatment. RA exhibits heterogeneity in disease progression and outcome. This recognition has spurred research into various disease susceptibility, severity, progression, and treatment response biomarkers. Different types of biomarkers are used to evaluate various aspects of RA, including markers of the inflammatory process and disease-associated autoantibodies.

Inflammatory biomarkers reflect the levels of inflammation in the body, often associated with pain conditions such as arthritis or fibromyalgia. Erythrocyte Sedimentation Rate (ESR) and C-reactive protein (CRP) are the most commonly used laboratory markers of disease activity in clinical practice (Van den Broek, 2008). CRP measures proteins that are altered in pain states or following pain treatment (Mackey et al., 2025).

Both are integrated into widely used disease activity scoring systems. ESR reflects disease activity over recent weeks, while CRP reflects more short-term changes. These biomarkers monitor the extent of inflammation and its relation to pain states, aiding in diagnosing and monitoring conditions such as RA (Mackey et al., 2025).

Although influenced by factors like gender, age, and plasma fibrinogen levels, an elevated baseline ESR in early Patients with RA predicts subsequent radiological joint damage in multiple studies (Lindqvist et al., 2005). CRP, an acute-phase protein synthesised by hepatocytes during inflammation, is driven by cytokine production. Active Patients with RA tend to have the most erosive damage, and CRP serves as a good measure of disease activity, predicting erosive damage regardless of rheumatoid factor presence. Unlike ESR, CRP is independent of patient age and gender, unaffected by haemoglobin concentration or plasma component levels, and measurable using stored serum samples (Siemons et al., 2014). These biomarkers indicate chronic pain conditions or responses to treatment and are used in developing targeted therapies or diagnostics for pain related to inflammation (Mackey et al., 2025).

Research indicates individual relationships between CRP and the progression of radiological damage (Pope et al., 2021). Aggressive drug treatment to control CRP has been shown to reduce radiographic progression in early Patients with RA (Siemons et al., 2014). Prospective studies have demonstrated the prognostic value of baseline CRP levels in predicting joint damage over time. However, variations in CRP levels among patients with similar radiographic scores complicate generalisation from single CRP values. Not all studies show consistent relationships; for example, some suggest that high initial CRP levels may not predict arthritis persistence in very early RA (Shrivastava et al., 2015).

Autoantibodies refer to antibodies produced by the immune system in response to and targeting an antigenic component of the individual's own tissues. Rheumatoid Factor (RF) is a critical autoimmune laboratory test conducted in arthritis patients, playing a crucial role in both diagnosing and predicting outcomes in RA. RF are antibodies that target the Fc portion of IgG immunoglobulins and are present in 75–80% of Patients with RA (Gualtierotti et al., 2014). Initially described as IgM RF by Waaler and Rose in 1940, this isotype is currently measured in clinical settings. However, other immunoglobulin types, such as IgG and IgA, have also been identified. The presence of RF in the bloodstream may precede the onset of RA by several years and can offer prognostic insight into the disease's clinical course (Gualtierotti et al., 2014). The RF titre may also decrease in response to effective clinical treatment with anti-TNFα therapy (Sakthiswary et al., 2022).

1.6 RA imaging

1.6.1 X-ray radiographs of RA

Classically, X-ray radiographs are one of the objective measures used by rheumatologists to manage pain by monitoring disease activity, thereby utilising the best available medical treatment to control the disease (Welsing et al., 2004). The utilisation of radiographs for assessing joint damage due to synovial inflammation has been a consistent aspect of clinical practice and therapeutic investigations for an extended period. This approach offers several advantages, including affordability, ease of implementation, and the ability to evaluate multiple joints of the hands and feet in a single session.
Furthermore, X-ray detects irreversible structural damage, such as erosions and narrowing of the joint space, which are often the cause of peripheral pain in the later stages of RA (Jacobson et al., 2008).

1.6.2 Magnetic resonance imaging (MRI)

MRI, an advanced imaging technique, possesses high sensitivity in evaluating various aspects of inflammation in rheumatoid joints, encompassing synovial inflammation, erosions, and bone oedema (Østergaard et al., 2019). It evaluates functional and structural brain changes related to pain. It is used to study central sensitisation, central nervous system changes in chronic pain, the effects of analgesics, and to monitor pain-related neuroplasticity in clinical trials (Mackey et al., 2025).

Notably, it avoids ionising radiation and offers multi-planar capabilities, enabling detailed assessment of specific regions of interest. Its integration into clinical studies has facilitated further validation as an outcome measure and has contributed to refining its clinical application. However, despite its significant advantages, the substantial initial costs of acquiring MRI machines limit its accessibility to more extensive, well-resourced centres. Moreover, there are constraints regarding the number of joints that can be adequately imaged within a reasonable time frame. MRI's validity against synovial histology in both knee and small hand joints (MCPs) has been demonstrated, revealing a clear correlation between MRI, such as dynamic contrast-enhanced (DCE)-MRI, and macroscopically visualised synovitis, as well as a correlation between bone changes and MRI-detected erosions (Axelsen et al., 2012). Subclinical inflammation detected solely on MRI, not clinically, has been associated with an increased risk of erosive progression (Brown et al., 2008). Furthermore, bone marrow oedema serves as a predictor of erosive disease in Patients with RA, representing an independent predictor of radiographic progression in longitudinal studies. MRI's ability to detect erosions has been shown to have superior sensitivity compared to plain radiography. The OMERACT task force has extensively examined MRI image scoring in RA, leading to the development of the Rheumatoid Arthritis Magnetic Resonance Imaging Scoring System (RAMRIS), which has been thoroughly validated and proven reliable and responsive to therapeutic interventions (Woodworth et al., 2017). MRI offers high image resolution and detects important aspects of joint inflammation and damage, including bone oedema and cartilage thinning, at all joint sites. This peripheral change is essential for identifying the peripheral inflammatory causes of pain.

The neuroimaging, such as MRI, is used as an objective biomarker for pain. Current investigations are centred on the creation and validation of imaging-based biomarkers that assess evoked pain sensitivity, as well as those that serve diagnostic, prognostic, predictive, and response-oriented roles in clinical pain management. Additionally, metrics derived from structural MRI are being employed to formulate both diagnostic and prognostic pain biomarkers (Mackey et al., 2025).

The integration of MRI into clinical trials of DMARDs and biologic agents has shown promising results, potentially reducing the required patient population for assessing disease activity and radiographic progression. While further validation with functional outcomes is needed, especially regarding neurological changes in RA, MRI offers clear advantages as an imaging modality in RA diagnosis and management (McQueen et al., 2014). The

combination of fMRI-based biomarkers with clinical evaluations has shown potential to improve the classification of chronic pain conditions (Mackey et al., 2025).

FMRI enables the investigation of pain processing networks without subjecting patients to ionising radiation. Resting-state fMRI proves advantageous for chronic pain populations by offering insights into the intrinsic connectivity among pain-related brain regions, all without the necessity for external tasks or stimuli (Tu et al., 2020; Stefanov et al., 2023). More information about the role of fMRI in RA pain is provided in section 5.7.2.3.

1.6.3 Musculoskeletal ultrasound (MSUS) of RA

Ultrasound is a non-ionising and sensitive imaging modality for identifying inflammatory joint damage and subclinical synovitis (Szkudlarek et al., 2016). Given that synovial inflammation is a central pathological feature of rheumatoid arthritis, MSUS has become an important tool for detecting disease activity that may not be apparent on clinical examination and has been shown to be more sensitive than clinical assessment in identifying minimal synovitis (Brown et al., 2008). A comprehensive discussion of the role of MSUS in rheumatoid arthritis is provided later in this thesis (Section 1.11).

1.7 Pain in Rheumatoid Arthritis

1.7.1 Introduction of pain

The International Association for the Study of Pain defines pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage (Rajaa et al., 2020). This definition recognises the subjective nature of pain, acknowledging its reality based on individual reports, even in cases where there is no evidence of physical damage. Additionally, it acknowledges that the understanding of pain is shaped by life experiences, reinforcing the influence of social and cultural factors.

Pain can be broadly classified into three categories: transient, acute, and chronic (Loeser, 2000). Transient pain can occur without local tissue damage and is typically short-lived, such as the pain experienced after receiving an injection. Acute pain is linked to tissue injury or harmful events, serving a biological function to signal potential or actual damage and prompt protective responses. Chronic pain, on the other hand, persists beyond the expected healing period or occurs in conditions where healing does not occur. It is

characterised by alterations in pain processing, leading to spontaneous pain, allodynia, and hyperalgesia (Chojnowska and Stannard, 2003).

1.7.2 Pain Mechanisms

In the realm of understanding pain, it is crucial to recognise that pain processes are plastic, i.e. neuroplasticity, which is the ability to reorganise the brain's structure, function, and connections, rather than being fixed. Prolonged pain can induce alterations in the neural structures involved in pain perception (Fornasari, 2012).

These alterations may transform pain, especially chronic pain, from simply a symptom into a distinct disease entity. Chronic pain, which persists beyond the normal healing period, has no beneficial physiological purpose and is often associated with clinical pain, which includes nociceptive and nociplastic pains reported by patients. Chronic pain can present as nociceptive, neuropathic, or nociplastic, with each type sharing certain common features.

Nociceptive pain arises from tissue injury caused by events such as trauma, inflammation, and bone erosion due to conditions such as RA, leading to the release of substances that sensitise peripheral nociceptors (Woolf, 2004). On the other hand, neuropathic pain originates from damage or pathological changes in the peripheral or central nervous system, leading to spontaneous pain and heightened sensitivity to stimuli (Malik and Stillman, 2009). Nociplastic pain, a newer concept, involves abnormal processing in the central nervous system in response to normal stimuli. It is characterised by altered pain processing in the nervous system without peripheral tissue damage, somatosensory system impairment, or activation of nociceptors (Sunzini et al., 2023). This concept has emerged from extensive research on conditions like FM and other chronic pain disorders such as irritable bowel syndrome, temporomandibular disorder, and interstitial cystitis/bladder pain syndrome (Sunzini et al., 2023).

Various pain mechanisms often coexist within individuals, particularly nociplastic pain, which frequently accompanies nociceptive or neuropathic pain. This phenomenon is likely observed in patients with RA, where initial peripheral inflammation triggers predominant nociceptive pain, which may gradually transition towards a nociplastic pain phenotype. Nociceptive pain, defined as the process of detecting and signalling the presence of a harmful stimulus, serves as an alarm system activated by noxious stimuli that stimulate primary afferent neurons. These neurons, which can be either myelinated or unmyelinated, play roles in transduction, conduction, and transmission of pain signals. Substances

released from damaged tissues activate nociceptors, leading to synaptic transmission in the dorsal horn of the spinal cord, which can involve various neurotransmitters and receptors. Primary sensory neurons come in three main nociceptors: unmyelinated C fibres, myelinated A-delta fibres and A-beta fibres. They connect with neurons in the dorsal horn of the spinal cord. A-fibre nociceptors, characterised by myelinated axons and medium to large cell bodies, conduct action potentials rapidly, while C-fibre nociceptors, with unmyelinated axons and small cell bodies, conduct action potentials slowly (Fornasari, 2012). These primary sensory neurons play three key roles in nociception: transduction, conduction, and transmission.

Transduction involves detecting and converting stimuli into electrical signals in the peripheral terminals, mediated by non-selective cation channels, such as sodium or calcium channels, leading to neuronal membrane depolarisation. This depolarisation, known as a generator potential, triggers the activation of voltage-gated sodium channels, initiating the transmission of stimuli to the central terminals of nociceptors in the spinal cord, a process called conduction. Various substances released from damaged tissues, such as histamine, bradykinin, serotonin, prostaglandins, and substance P, can activate nociceptors, contributing to inflammatory pain (Woolf, 2004).

Transmission refers to the transfer of synaptic input between neurons. Action potentials generated in primary sensory neurons trigger the release of neurotransmitters in the dorsal horn of the spinal cord, with N-type voltage-gated calcium channels playing a crucial role in regulating this release. Synaptic transmission in the dorsal horn involves both fast and slow components. Glutamate mediates fast excitatory transmission by binding to anti-modified protein antibodies (AMPA) receptors on secondary neurons. Glutamate also interacts with N-methyl-D-aspartate (NMDA) receptors, which are typically blocked by a magnesium ion under resting conditions or modest membrane depolarisation.

The central ascending pain pathways originate from projecting spinal cord dorsal horn (SCDH) neurons (Figure 1.2). These neurons include nociceptive-specific neurons, which receive inputs exclusively from C and A-delta fibres, and wide dynamic range neurons, integrating both nociceptive and sensory signals. The primary ascending pathways include the spinothalamic, spinoreticular, and spinomesencephalic tracts, which cross over in the spinal cord before reaching various regions of the central nervous system (CNS), including the thalamus, periaqueductal grey matter (PAG), parabrachial area (PB), and reticular formation (RF) (Sunzini et al., 2023).

Nuclei within the lateral thalamus project to the primary and secondary somatosensory cortices (SI and SII), which are primarily involved in pain localisation and intensity perception, respectively. Meanwhile, nuclei within the posterior thalamus project to the

posterior insula, which is crucial for integrating cognitive aspects of pain perception. Additionally, the medial thalamus integrates inputs from the RF and projects to the anterior cingulate cortex (ACC) and prefrontal cortex (PFC), regulating motor responses and emotional aspects of pain, respectively. The PB nucleus interacts with the limbic system, contributing to the integration of aversive and affective components of pain (Sunzini et al., 2023).

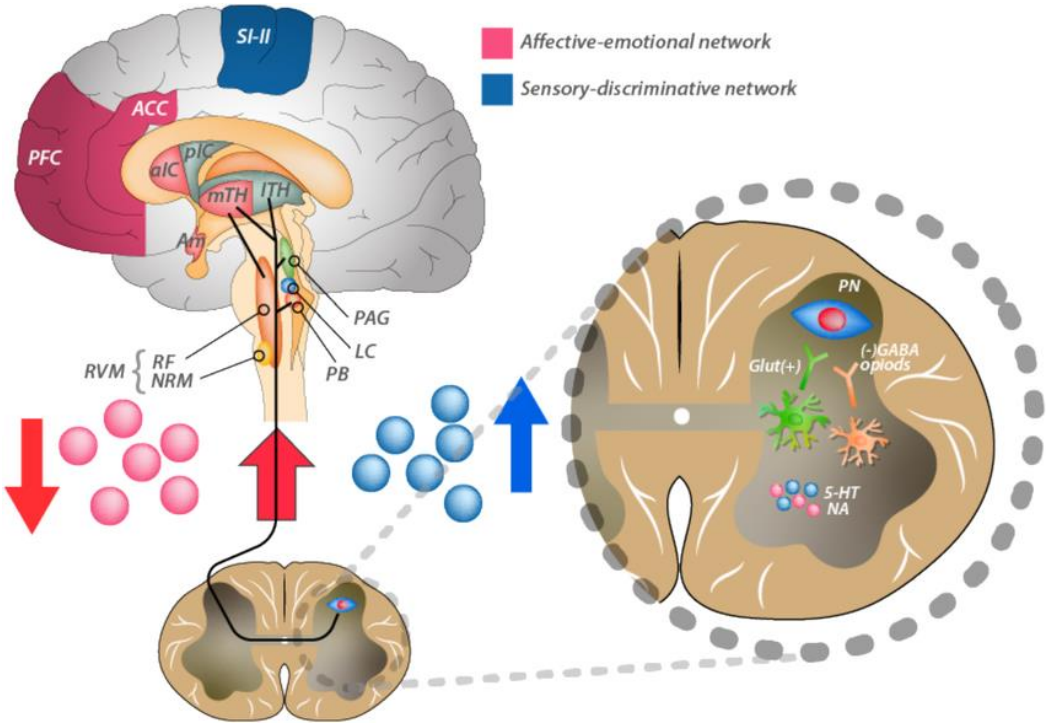

Figure 1.2: Neurologic pain sensitisation pathways. In the spinal cord, projecting neuron (PN) fibres decussate and reach different sensory areas in the central nervous system. The spinothalamic tract connects to the thalamus (TH), from which nociceptive input is relayed to key brain regions, including the somatosensory cortices I and II (SI–II), prefrontal cortex (PFC), anterior cingulate cortex (ACC), insula cortex (IC), and amygdala (Am). There are two main pain-processing networks: 1) the affective-emotional network (in red), comprising the medial thalamus (mTH), PFC, ACC, Am, and anterior IC (aIC); and 2) the sensory-discriminative network (in blue), including the lateral thalamus (lTH), SI–II, and posterior IC (pIC). Nociceptive stimuli also reach the periaqueductal grey matter (PAG), parabrachial area (PB), and reticular formation (RF) in the brainstem. The PAG modulates sensory input through the rostral ventromedial medulla (RVM), which includes the nucleus raphe magnus (NRM) and RF. Serotonergic (5-HT) and noradrenergic (NA) neurons from the RVM and locus coeruleus (LC) regulate the release of excitatory neurotransmitters such as glutamate and inhibitory mediators like endogenous opioids from spinal interneurons, creating a balance that filters sensory information sent to the brain. GABA stands for γ-aminobutyric acid. Source: (Sunzini et al., 2023).

Neuropathic pain is produced by a lesion or disease of the nervous system, specifically the somatosensory system (Bailly et al., 2020). Mechanisms involved in its maintenance also include the activation of microglia and astrocytes in the spinal cord, which promotes local inflammation in the dorsal horn (Bailly et al., 2020).

Neuropathic pain can arise from various causes, such as trauma, infection, ischemia, or cancer, leading to abnormal neuronal sprouting and heightened pain transmission. Neuroplasticity may contribute to the development of neuropathic pain, characterised by abnormal sprouting in the peripheral nervous system and dorsal horn of the spinal cord, resulting in increased pain signalling (Bak et al., 2021). More information about pain mechanisms and pathways is discussed in Section 5.7.2 in this thesis.

1.7.3 Neural Modifications in Chronic Pain

The precise mechanisms underlying the pathophysiology of chronic pain remain poorly understood; nevertheless, rapid and enduring alterations occur within the central nervous system (CNS) regions involved in pain transmission and modulation following injury. Peripheral sensitisation and central sensitisation constitute the primary factors contributing to heightened sensitivity to pain subsequent to injury (Fornasari, 2012).

1.7.4 Peripheral sensitisation

Peripheral sensitisation is evident in cases of inflammatory pain, certain types of neuropathic pain, and continuous nociceptive stimulation. Tissue injury induces significant changes in the chemical milieu surrounding the peripheral terminals of nociceptors, resulting in the release of various substances such as potassium ions, substance P, bradykinin, prostaglandins, and other inflammatory mediators (Curatolo et al., 2006). Additionally, intracellular components like adenosine triphosphatase and hydrogen ions are released from damaged cells. During peripheral sensitisation, these inflammatory mediators amplify the pain response to stimuli by lowering the threshold and prolonging the activation of nociceptors (Malik and Stillman, 2009). This process involves the phosphorylation of transducers and Nav 1.8 sodium channels. For example, prostaglandin E2 reduces the activation threshold of nociceptor terminals by binding to prostaglandin E receptors linked to intracellular kinases. Bradykinin and leukotrienes can also directly sensitise nociceptors (Woolf, 2004). Furthermore, interleukin-1b and tumour necrosis factor-alpha (TNF-alpha) induce the expression of cyclooxygenase 2 (COX-2) at the injury site, resulting in the production of prostaglandin E2 (Malik and Stillman, 2009). Since the induction of COX-2 occurs several hours after the initiation of inflammation, non-steroidal anti-inflammatory drugs (NSAIDs) or COX-2 selective inhibitors have no immediate effect; however, they exhibit prompt analgesic effects in chronic inflammatory conditions, such as RA, where COX-2 expression is persistent due to ongoing inflammation (Woolf,

2004). Additionally, repeated activation of peripheral nociceptors contributes to the neurological changes that increase pain sensitivity in chronic pain. Peripheral sensitisation is recognised as a fundamental process underlying hyperalgesia (Fornasari, 2012).

1.7.5 Central sensitisation

Central sensitisation is defined as an amplified responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input (Welsh and McWilliams, 2014). It is observed in inflammatory, functional, and neuropathic pain conditions (Fornasari, 2012). It results from heightened excitability of central nociceptor transmission neurons within the spinal cord (Schaible and Richter, 2004) and progresses through several stages.

Activation stage: Initially, intense nociceptive input to the secondary afferent neurons in the dorsal horn, triggered by acute injury, peripheral sensitisation during inflammation, or chronic pain disorders, leads to a significant release of glutamate and co-regulatory peptides (Malik and Stillman, 2009). This activation of AMPA receptors induces robust plasma membrane depolarisation and removes the magnesium block from NMDA receptors, leading to their activation.

Modulation stage: NMDA receptors on secondary afferent neurons in the dorsal horn (or spinal nucleus of the trigeminal) play a pivotal role in central sensitisation. Highly permeable to calcium ions, these receptors contribute to the depolarisation of second-order neurons and act as second messengers that activate calcium/calmodulin-dependent kinases (Malik and Stillman, 2009). This activation subsequently phosphorylates postsynaptic proteins, including NMDA receptors, thereby modifying neural transmission (Woolf, 2004).

Modification stage: The most significant changes occur during the final stage of central sensitisation, where second-order neurons undergo substantial modifications in their genetic program. This phenomenon, responsible for neural plasticity, remains incompletely understood in terms of its complete reversibility (Woolf, 2004). Nociceptor sensory neurons and low-threshold sensory fibres terminate in the superficial and deep laminae of the dorsal horn, respectively (Malik and Stillman, 2009).

1.8 Pain rating scales

1.8.1 The McGill Pain Questionnaire

The McGill Pain Questionnaire (MPQ) is an early tool for pain assessment, stemming from a study where individuals with pain categorised pain-related words into sensory, affective, and evaluative classes. Then, the intensity values assigned to these words, creating a questionnaire with sensory, affective, and evaluative words, each rated on a scale of 1 to 5 (Sokka et al., 2003). The questionnaire includes a pain diagram and asks patients to circle words that describe their pain, as well as queries about changes in pain over time and the intensity levels. There was debate over whether a research assistant or self-reporting was preferable; however, self-reporting generally proved more reproducible and easier to administer. However, its completion time of 15-20 minutes, even with a shortened version, makes it challenging for busy clinical settings. Thus, the time required to complete the MPQ is a major limitation (Sokka et al., 2003).

1.8.2 The Pain Visual Analogue Scale (VAS)

The Pain VAS is extensively utilised worldwide as a method for assessing pain intensity (Begum et al., 2019). Research indicates that the pain VAS is both valid and reliable, functioning on an interval and continuous scales. The interval scale exhibits high test-retest reliability and repeatability. The VAS comprises a continuous scale featuring both vertical and horizontal formats. While a strong correlation exists between the two, scores on the horizontal scale tend to be slightly lower. This tool finds widespread application in epidemiological and clinical research, particularly in RCTs, to gauge treatment effectiveness. Patients rate pain intensity by marking a point on a line between descriptors such as "no pain" and "worst imaginable pain". The VAS, typically 100 mm in length, can be horizontal or vertical and does not require sophisticated equipment for administration. It demonstrates high sensitivity in detecting treatment effects and permits analysis through parametric tests (Begum et al., 2019; Birnie et al, 2012). Pain VAS is considered the ‘gold standard’ for assessing clinical and experimental pain, and changes in VAS scores are regarded as significant evidence of individual response to treatment or experimental manipulation (Yarnitsky et al., 1996; Bendinger et al., 2016). Research has shown that the pain VAS is a superior scale for assessing pain in patients with RA compared to the Short

Form-36 (SF-36), a tool designed to measure an overall view of health-related quality of life experienced by the patient (Wolfe and Michaud, 2007).

There are limitations to using the pain VAS that could affect its validity and usefulness in research and clinical settings. The measurement's validity can be challenging for patients with motor or perceptual impairments, who may struggle to understand the instructions or complete the scale accurately. Furthermore, non-inflammatory factors such as fibromyalgia and anxiety can influence the use of pain VAS in patients with RA for measuring RA-related pain. Non-inflammatory pain can significantly affect functional status and quality of life, and may confound pain outcomes, resulting in ineffective and inappropriate treatment strategies (Boyden et al., 2016).

Furthermore, using retrospective recall to compare pain intensity before and after interventions introduces potential bias, and the requirement for immediate scoring may not be feasible in clinical settings where real-time measurement of patients' responses is not possible. Collectively, these factors highlight limitations in the generalisability of the pain VAS, particularly in populations with cognitive or functional impairments (McMahon et al., 2013). In addition, McMahon et al. (2013) reported that elderly patients with chronic pain made fewer errors when using pain verbal rating scales (VRSs) compared with pain VAS.

1.8.3 The Pain Numeric Rating Scale (NRS)

The Pain Numeric Rating Scale (NRS) is a validated 11-point scale widely utilised across diverse patient populations. NRS data are easily recorded and straightforwardly interpreted, fulfilling regulatory requirements for pain assessment and documentation (Thomas et al., 2008). Research demonstrates that even during the tumultuous prehospital phase, most acute care patients can reliably assess their pain levels using a simple "zero-to-10 scale" or NRS. Similar to VAS, the NRS exhibits minimal language translation challenges, making it suitable for use across various cultures and languages. The NRS offers advantages over the VAS in its versatility, being usable both verbally (including over the telephone) and in written form, as well as its straightforward scoring system (Karcioglu et al., 2018). However, like the VAS, the NRS solely evaluates one aspect of the pain experience, pain intensity and thus fails to capture the complexity and individual variability of pain experiences or improvements resulting from symptom fluctuations. The NRS entails patients rating their pain on a scale from 0 to 10, with 0 representing no pain and 10 denoting the worst imaginable pain. Pain scores on the NRS are typically

interpreted as follows: 0 = no pain, 1–3 = mild pain, 4–6 = moderate pain, 7–10 = severe pain (Karcioglu et al., 2018).

The NRS has disadvantages similar to the VAS in that both methods attempt to capture the pain experience with a single numerical value. They both exhibit a ceiling effect, meaning that if a patient selects a score of "10" and their pain increases, there is no official way for them to convey this change. Likewise, research on the VAS has sought to establish what constitutes a significant change in the NRS. A meaningful relief of pain for patients has been identified as at least a 30% reduction or a decrease of at least 2 points on the scale. However, it is improbable that these scales are truly linear, as the numbers and their differences hold various meanings for different individuals (Waldman, 2011).

1.9 Pain Patterns in RA

Pain is one of the most challenging symptoms for patients with RA. Sánchez-Flórez et al. (2022) highlight that 97% of Patients with RA reported pain at the early stages of the disease. Dueñas and colleagues (2024) found that 18.1% of Patients with RA experienced chronic pain, defined as pain occurring at least four times a week and lasting for at least three months.

Lee (2013) highlights that pain is probably the most important patient-reported outcome in RA, as patients with RA rate their pain as one of the top three priorities. Lee et al. (2011) and Sánchez-Flórez et al. (2022) reported that persistent pain persists despite inflammation control, affecting around 12% of Patients with RA. In addition, Vergne-Salle et al. (2020) highlight that 38.4% of patients with RA continue to report moderate to severe pain despite biological DMARD treatment. Mathias et al. (2021) highlight that patients with RA are more likely to have secondary pain syndromes, such as FM, as around 13–25% of patients with RA have concomitant FM.

Pain is often viewed as a marker of inflammation, although there is a limited connection between pain intensity and peripheral inflammation measures (Studenic et al., 2012). Nonetheless, pain is linked to disease activity, and future pain may be associated with radiographic changes (Sarzi-Puttini et al., 2014). Pain progression in Patients with RA mirrors typical disease activity patterns. While pain scores may show initial improvement, studies indicate that this progress may not be sustained over time. Interestingly, research has shown that initial pain severity does not always accurately predict long-term pain levels, with some studies even suggesting that baseline pain in the early stages of the

disease can be a more reliable predictor of cumulative pain over a year (Sokka et al., 2003). Long-term follow-up studies of five or more years show varying changes in pain levels. Generally, patients with early-stage disease experience a more significant improvement in pain over five years compared to those with longer disease duration at the outset of follow-up (Sokka et al., 2003).

Inflammation leads to pain, stiffness, and joint damage, but it is increasingly feasible to completely suppress it, aiming for clinical remission, which could enhance long-term outcomes (Schipper et al., 2010). Clinical trials demonstrate that early aggressive treatment with disease-modifying anti-inflammatory drugs (DMARDs) and corticosteroids improves pain outcomes, particularly when coupled with regular disease activity monitoring. While effectively suppressing inflammatory disease in the initial years after RA diagnosis tends to reduce pain levels, it may not eliminate it entirely. It could resurge later (Studenic et al., 2012). RA-related pain can be evoked spontaneously or with joint movement, sometimes extending to surrounding tissue (Atzeni et al., 2011). Referred pain syndromes are also observed, as symptom severity does not always correlate with underlying disease severity, persisting even during remissions. Joint damage exacerbates RA-related pain, either from inflammatory disease or concomitant osteoarthritis (OA). In contrast, the prevalence of non-inflammatory pain syndromes like fibromyalgia (FM) is higher among Patients with RA than in the general population (Wolfe et al., 2011). Patients with both inflammatory arthritis and FM experience higher disease activity and lower quality of life (Boyden et al., 2016). Consequently, pain not only directly affects patients but also contributes indirectly to the psychological and social impact of RA, underscoring the ongoing need for improved analgesic interventions (Lee et al., 2013).

Pain significantly predicts poor outcomes (Rupp et al., 2006). In early RA, patients presenting with elevated levels of bodily pain are more prone to experiencing increased disability within one year. Patients articulate their joint pain intensity, nature, and recurrence patterns diversely. While some describe it as "gnawing" or aching, indicative of nociceptive mechanisms directly influenced by inflammation or joint damage, others use terms like "burning" or "shooting," suggestive of potential nerve damage associated with neuropathic pain (Sarzi-Puttini et al., 2014). Moreover, the prevalent descriptions of widespread pain linked with disruptions in sleep, fatigue, and mood hint at abnormal central pain processing. DAS28 is commonly employed to evaluate joint inflammation in randomised controlled trials (RCTs) and guide treatment strategies in clinical settings. Intensive "treat-to-target" protocols necessitate treatment escalation for patients with active disease, as defined by their DAS28 score. Specific national guidelines, such as those in the

United Kingdom, limit the use of biological treatments for patients with high DAS28 scores (Sarzi-Puttini et al., 2014). However, the correlation between DAS28 and inflammatory disease activity is confounded by other variables (Sarzi-Puttini et al., 2014). Pain VAS and tender joint counts typically increase with inflammation and are closely associated with reported bodily pain; they may also be elevated by concurrent painful conditions like osteoarthritis (OA) or changes in pain processing, such as central sensitisation, which often accompanies joint inflammation and can complicate DAS28 interpretation (Pollard et al., 2010). For instance, individuals meeting diagnostic criteria for both RA and FM report heightened pain levels and exhibit higher DAS28 scores compared to those with RA alone, suggesting potential influences of central sensitisation or painful comorbidities on scoring accuracy (Ranzolin et al., 2009).

1.10 RA treatment

The pharmacological management of RA can be broadly categorised into two main approaches: alleviating underlying symptoms like pain using non-steroidal anti-inflammatory drugs (NSAIDs) or targeting the inflammatory process with Disease Modifying Anti-Rheumatic Drugs (DMARDs) (Upchurch et al., 2012). Historically, there have been significant shifts in RA treatment strategies. In the 1980s, a pyramidal approach was commonly employed, focusing on symptom management and escalating drug doses and numbers as the disease progressed. This approach aimed to minimise disease burden while mitigating the adverse effects of potent medications such as steroids and early DMARDs like Gold and ciclosporin (SOKKA et al., 1999). In addition, DMARDs medications, particularly sulfasalazine and methotrexate, were shown through randomised controlled trials (RCTs) to yield better clinical and radiological outcomes. This emphasised the concept of a "Window of Opportunity" in the early stages of RA when treatment is most effective (O'Dell et al., 2002). Furthermore, the biologic DMARDs, which target specific pro-inflammatory cytokines, have demonstrated superior efficacy compared to single DMARD therapy, especially when combined with methotrexate.

Nevertheless, due to the high cost per patient, their use in the UK is currently limited to cases of moderate disease (Emery et al., 2008). Currently, RA management follows a Treat-To-Target (T2T) approach, as recommended by an international task force in 2010 (Smolen et al., 2016). Similar to chronic illnesses like hypertension and diabetes, this approach emphasises predefined treatment targets using biomarkers/markers of disease activity to minimise the risk of organ damage. Remission, defined as the absence of

significant inflammatory disease activity, is advocated as the primary treatment goal for all Patients with RA (Smolen et al., 2016). However, the common use of low disease activity as the primary target in clinical trials has led to some scepticism regarding the attainment of remission. Hence, while remission remains the ultimate objective, low disease activity may be considered a viable alternative in some instances. Advances in DMARD therapy, particularly in combination with other agents like methotrexate, have made remission or at least low disease activity achievable in the majority of RA cases, becoming the target for clinicians (Tanaka et al., 2016). However, defining remission or low disease activity poses challenges, especially in severe cases unresponsive to conventional DMARDs, where biologic DMARDs may be prescribed to achieve remission or low disease activity at a higher cost.

Glucocorticoids serve various roles in controlling RA disease activity. They may be administered in low to moderate doses to achieve rapid disease control before the onset of fully effective DMARD therapy or as a short-term burst for acute flares. Chronic low-dose prednisone therapy may also be necessary to manage disease activity in patients with inadequate responses to DMARD therapy. However, the benefits must be weighed against risks such as osteoporosis. High-dose glucocorticoids may be required for treating severe extraarticular manifestations of RA (Ankoor et al., 2015). Intra-articular glucocorticoid injections may be considered for localised inflammation, after careful exclusion of joint infection. Osteoporosis is a significant long-term complication of chronic prednisone use, necessitating primary prevention with bisphosphonates in patients receiving five mg/d or more of prednisone for over 3 months (Ankoor et al., 2015).
Conventional DMARDs, including hydroxychloroquine (HCQ), sulfasalazine, methotrexate, and leflunomide, typically take 6–12 weeks to show efficacy (Ankoor et al., 2015). Methotrexate is the preferred choice and remains the benchmark for efficacy and safety (Friedman et al., 2019). Other DMARDs, such as leflunomide and sulfasalazine, are also effective. Hydroxychloroquine, while slow-acting, is not considered a true DMARD as it does not delay radiographic disease progression (Ankoor et al., 2015). Biological DMARDs, targeting cytokines and cell-surface molecules, have transformed RA treatment. TNF inhibitors are the first biologics approved for RA, reducing signs/symptoms, slowing joint damage, and improving quality of life. They are often combined with methotrexate (Rein and Mueller, 2017). Anakinra, a less frequently used IL-1 receptor antagonist, may be effective for certain RA cases but is not recommended with anti-TNF therapy due to increased infection risk (Salliot et al., 2009). Abatacept, rituximab, and tocilizumab are newer biologics with proven efficacy in RA treatment. These agents target specific

pathways involved in inflammation and immune response (Gottenberg et al., 2019). Rituximab, a monoclonal antibody against CD20, depletes B cells, thereby reducing inflammation (Cohen and Keystone, 2015). Tocilizumab inhibits IL-6 receptor signalling, mitigating joint inflammation and damage (Scott, 2017).

Tofacitinib inhibits JAK1 and JAK3, reducing inflammation by blocking cytokine signalling (Dhillon, 2017). Although effective, tofacitinib may cause liver injury, neutropenia, elevated cholesterol, and infections, necessitating careful monitoring during therapy (Dhillon, 2017).

Some randomised clinical trials have found that JAK inhibitors are highly effective at reducing pain and other patient-reported outcomes (Rocha et al., 2021; George et al., 2020). The JAK/STAT pathway appears to play a significant role in the pathophysiology of central sensitisation mechanisms associated with chronic pain. This pathway is also present in the dorsal root ganglia and the spinal cord, potentially contributing to nociceptor sensitisation caused by joint inflammation (Vieira et al., 2016; Salaffi et al., 2022).

1.11 Musculoskeletal Ultrasound

1.11.1 Introduction

MSUS is increasingly favoured by rheumatologists, particularly in assessing RA joints, due to its non-invasive nature and lack of radiation exposure, making it suitable for clinical settings.

There is a lack of objective measures for pain assessment. MSUS is a valuable tool for evaluating peripheral changes at joints associated with increased pain intensity, as it is sensitive in identifying synovitis (Lage-Hansen et al., 2017).

MSUS plays an essential role in evaluating disease severity, particularly in RA, where small hand joints are frequently affected. MSUS provides crucial insights into vascularity, synovial thickening, and erosions, helping confirm the presence of synovitis and associated joint damage. This information is essential for assessing joint conditions and identifying peripheral inflammatory changes that may contribute to nociceptive pain, especially when combined with other factors (Pereira et al., 2015).

Although this role is important, there is still debate about the relationship between inflammatory changes observed in MSUS, especially ultrasound power Doppler (USPD), and articular pain (Pereira et al., 2015). These debates relate to factors affecting the sensitivity of power Doppler (PD), such as the type of machine, probe pressure, required

training, operator skill, patient positioning, weather conditions, and the duration of the examination as potential influences on PD detection (Lage-Hansen et al., 2017; Robin, 1999).

Thus, this thesis aims to determine whether there is a correlation between the presence of inflammatory changes detected by MSUS and pain in participants with inflammatory arthritis. This highlights the importance of using MSUS as an evaluation tool for pain in inflammatory arthritis. Therefore, it could serve as an objective method for detecting changes in joints that contribute to this pain.

While ultrasound's reliance on operator skill and concerns regarding reproducibility are acknowledged, adopting consensus-based scoring systems and standardised definitions of joint inflammation in RA has been demonstrated to enhance its reliability as an outcome assessment tool. The technique involves utilising grayscale (GS) imaging and Doppler modalities, with GS imaging capturing anatomical structures and Doppler visualising blood flow. These modalities are recommended for evaluating peri- and intra-articular structures and for precisely depicting soft-tissue and bony-cortex alterations across all disease stages.

The illustrative MSUS images included in this chapter were graded according to internationally validated consensus definitions. Synovial hypertrophy and power Doppler (PD) signal were assessed using the EULAR–OMERACT semi-quantitative scoring system (0–3 scale) (D'Agostino et al., 2017). Synovial hypertrophy was defined as abnormal hypoechoic intra-articular tissue that is non-displaceable and poorly compressible, with PD signal reflecting intra-synovial vascularisation. Joint effusion was defined according to OMERACT criteria as abnormal anechoic or hypoechoic intra-articular fluid that is displaceable and compressible, without a Doppler signal (Wakefield et al., 2005). Bone erosions were identified and graded based on OMERACT ultrasound definitions as intra-articular discontinuity of the bone surface visible in two perpendicular planes (Szkudlarek et al., 2003). All grading was performed for illustrative purposes in accordance with these standardised consensus criteria. In this thesis, ultrasound inflammatory findings were graded using internationally validated consensus-based scoring systems to ensure methodological rigour, reliability, and reproducibility. Synovial hypertrophy, joint effusion, and power Doppler (PD) activity were assessed using the EULAR–OMERACT semi-quantitative 4-grade scoring system (0–3 scale) (D'Agostino et al., 2017). This system provides standardised definitions for grayscale and Doppler abnormalities in inflammatory arthritis and has demonstrated strong interobserver

reliability, thereby facilitating comparability across studies and strengthening outcome assessment.

Joint effusion was defined according to OMERACT criteria as abnormal anechoic or hypoechoic intra-articular fluid that is displaceable and compressible, without a Doppler signal (Wakefield et al., 2005). Synovial hypertrophy was defined as abnormal hypoechoic intra-articular tissue that is non-displaceable and poorly compressible, with PD signal reflecting intra-synovial vascularisation (D'Agostino et al., 2017).

Bone erosions were evaluated using the Ultrasound Structural Erosion Score (ScUSSe) system (Sommier et al., 2006). This scoring method was selected for its feasibility and practicality in both clinical and research settings. Unlike alternative approaches that require direct measurement of erosion width with callipers or rulers, the ScUSSe system provides structured categorisation based on erosion size thresholds, thereby enabling efficient, standardised application without additional measurement tools and reducing operator dependency.

The definition of bone erosion was based on established ultrasound criteria describing an intra-articular cortical break visible in two perpendicular planes (Szkudlarek et al., 2003; Wakefield et al., 2005). However, unlike later grading frameworks in which cortical surface irregularities without clear cortical discontinuity may be classified as grade 1 erosions (Szkudlarek et al., 2016), a more conservative interpretative approach was adopted in this thesis. Isolated cortical irregularities were not automatically classified as erosions, as such irregularities may arise from mechanical stress, degenerative change, or normal anatomical variation rather than inflammatory pathology (Wakefield et al., 2005; D'Agostino et al., 2017). Only definite cortical discontinuities fulfilling consensus definitions were graded as erosions. This approach was implemented to minimise misclassification and avoid overestimation of structural damage.

All ultrasound images presented in this thesis, including the illustrative examples in this introductory chapter, were graded in accordance with these consensus-based definitions and scoring systems to ensure consistency between descriptive content and methodological application. Furthermore, these standardised grading protocols were systematically applied across the primary research studies conducted within this thesis, including the CENTAUR, SOAR, and TEMPO studies in chapter five, to ensure methodological uniformity, internal consistency, and reproducibility across all ultrasound assessments.

1.11.2 Grey-scale ultrasound (US)

Grey-scale ultrasound (US) involves using high-frequency sound waves to generate images of internal body structures, utilising waves beyond the audible range for humans. These waves, generated by electrical stimulation of a piezoelectric crystal, are directed towards specific body areas and reflect back when encountering changes in tissue density, such as at cartilage-bone borders. Reflected echoes are received by an electronic device, determining echo intensity and tissue position, enabling the creation of static or dynamic images of the body's interior. Grey-scale US, the most basic form, does not utilise Doppler effects.

Grey scale ultrasonography has long been utilised for detecting joint and soft tissue inflammation, relying on reflected high-frequency sound waves to assess structures. Variations in reflected sound wave intensities, or echoes, are represented in shades of grey, with the technique capable of revealing early erosions in RA, a crucial prognostic indicator in patients with arthritis. Greyscale ultrasound exhibits good interobserver agreement and may surpass MRI in detecting synovitis and tenosynovitis, accurately delineating synovial thickening in the hands' small joints in active Patients with RA. However, the analysis of these images may not consistently correlate with clinical assessments of disease activity. This discrepancy might arise from the ultrasound's ability to detect synovial thickening without distinguishing between actively inflamed or fibrous tissue, or it could underscore ultrasound's heightened sensitivity in detecting joint inflammation compared to clinical examination. Notably, a study comparing clinical evaluation with ultrasound assessment in early Patients with RA found ultrasound detected signs of joint inflammation in a higher percentage of joints with good agreement between readers, indicating its superior sensitivity over clinical examination (Rizzo et al., 2013).

1.11.3 Colour Doppler ultrasound

Colour Doppler ultrasonography combines the Doppler effect with real-time imaging, superimposing Doppler information onto grayscale images as colour signals. This allows simultaneous visualisation of anatomy and flow dynamics, with blood flow direction indicated by red or blue colours denoting flow towards or away from the ultrasound transducer, respectively. This technique is beneficial for assessing arterial blood flow.

1.11.4 Power Doppler ultrasound (USPD)

Power Doppler ultrasonography (USPD) quantifies the amplitude of the power spectral density of the Doppler signal, serving as a sensitive method for detecting slow blood flow in small vessels. The power Doppler signal reflects the density of moving reflectors at a specific level, representing fractional vascular volume. However, PD is less sensitive to flow in vessels smaller than a millimetre, serving as an indirect measure of vessel flow. The total integrated power Doppler signal is displayed in colour and incorporated into grey-scale images.

The Doppler effect, named after Christian Doppler, refers to the alteration in wave frequency due to the motion of the source or receiver. This phenomenon is exemplified by the change in pitch of a police siren as it approaches (higher frequency) and moves away (lower frequency). Doppler ultrasound imaging measures blood flow, primarily relying on red blood cells as reflectors. The Doppler shift is determined by the transmitted acoustic wave frequency, blood velocity, tissue's speed of sound, and the angle between the sound beam and blood flow direction (Naredo and Monteagudo, 2014).

Modern equipment selectively filters out high-amplitude, low-frequency Doppler signals generated by tissue movement, which can arise from vessel wall motion or slight musculature shifts, notably in major vessels like the carotid arteries. Although these signals can be harnessed for Power Doppler imaging, various forms of Doppler imaging are available to sonographers, including continuous-wave, pulsed-wave, colour, duplex, and power Doppler ultrasonography. Power Doppler imaging, of particular interest to rheumatologists, differs from colour flow imaging in that it displays intensity based on the overall Doppler shift frequencies rather than individual frequency signals. While directional information is sacrificed, this method enhances Doppler detection sensitivity at low flow rates. It improves the signal-to-noise ratio, allowing for increased receiver gain with minimal background interference. However, it also amplifies noise from probe-related mechanical movements, necessitating careful adjustment of gain and pulse repetition frequency (PRF). The accurate evaluation of the USPD holds significant importance in clinical studies utilising ultrasound as a measure of synovitis. Various methods have been employed in the literature for both qualitative and quantitative assessment, which are briefly outlined below (Robin, 1999).

The semi-quantitative scoring method is the most commonly utilised approach for grading USPD, offering a relatively rapid assessment with moderate inter-observer variability. This method involves using predefined criteria or reference image atlases for scoring, mirroring the Likert scoring system established by the OMERACT group for MRI images in RA

clinical trials (Strunk et al., 2006). While this approach allows for real-time scoring during patient imaging, it discretely categorises the continuum of USPD, thus posing limitations. It is considered an interval scale, providing relevant information to researchers regarding the order and distance between values on the scale. However, it exhibits weaknesses such as overlap at the extremes of each category and deviation from the assumption that each step along the interval scale reflects the same quantified difference in Doppler signal or synovial thickness. USPD offers high sensitivity in detecting low velocity in small vessels, making it a vital tool for identifying the vascularity involved in inflammatory processes, which are key areas in rheumatic diseases (Naredo and Monteagudo, 2014).

Figure 1.3 is an example that demonstrates a real-time USPD of a joint with grade two (moderate). It shows the third proximal interphalangeal joint of the left hand, demonstrating synovial hypertrophy of grade three (severe) with a USPD signal of grade two (moderate).

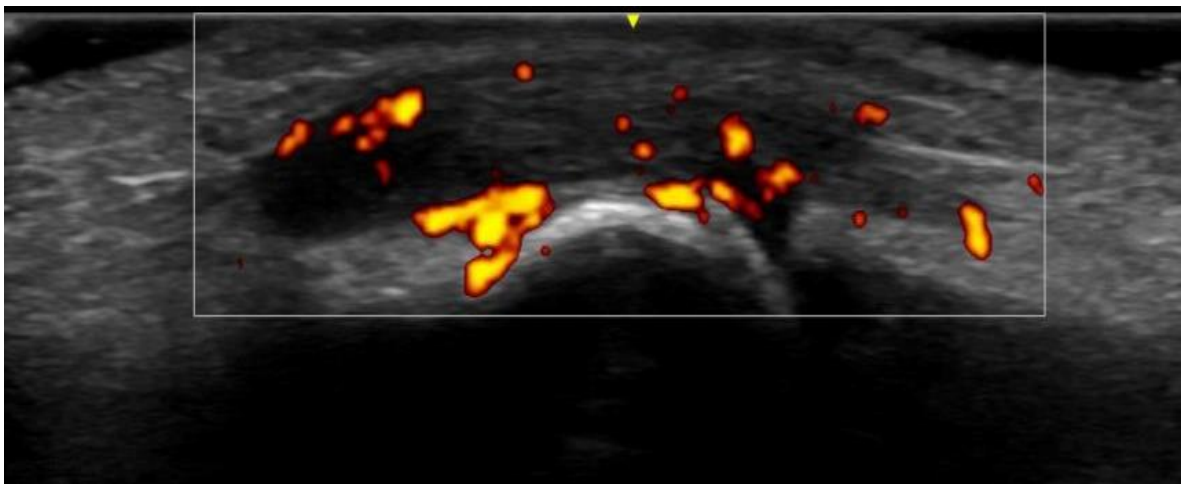

Figure 1.3: Longitudinal dorsal scan of the third proximal interphalangeal joint of the left hand showing synovial hypertrophy grade three with power Doppler signal graded two (Author's own, 2025).

1.11.5 Ultrasound Role in RA

1.11.5.1 Introduction

MSUS holds promise as a diagnostic and prognostic tool for RA. It offers ease of use, low operational costs, non-invasiveness, and interactive patient engagement (Naredo et al.,

2005). Moreover, it does not involve ionising radiation, provides multiplanar visualisation, and enables real-time imaging.

Furthermore, MSUS plays a crucial role in assessing disease severity, particularly in RA, where the involvement of small hand joints is common. Due to their shallow depth, these joints are easily assessable using ultrasound with higher frequencies, resulting in high-resolution images (Naredo et al., 2005).

While the diagnosis of RA involves multiple factors, including patient history, clinical examination, and serological tests, the MSUS can provide valuable information on vascularity, synovial thickening, joint effusion and erosions, aiding in confirming the presence of synovitis and associated joint damage. Despite ongoing standardisation and validation efforts, the MSUS is widely utilised for investigating joint inflammation due to its ability to enhance diagnostic accuracy (Naredo et al., 2005). MSUS examination of normal and pathological structures in joints encompasses imaging of cartilage, bone, and various pathologies. These pathologies include effusions, synovitis, cartilage damage, and bone erosions, each assessable through ultrasound. The definitions of normal structures (joint, cartilage, and bone) and pathology (joint effusion, synovitis, and bone erosion) pertinent to ultrasound imaging are discussed herein.

A joint is a structure separating two or more adjacent elements of the skeletal system. Joints like the metacarpophalangeal joints (MCPJs), where separated elements articulate, exhibit a visualisable joint capsule profile on ultrasound, demarcating the joint's outer margin. Articular surfaces are coated with cartilage (Delle Sedie et al., 2008). Within MCPJs, a hypoechoic intra-articular (IA) fat pad is often observed, presenting as an inverted triangular area with uniform echogenicity, known as the triangular structure. Its boundaries include the metacarpal head, phalangeal base, and superior joint capsule. Articular cartilage appears on ultrasound as a homogeneously anechoic layer with well-defined outer and inner margins. Bone cortex manifests on ultrasound as a continuous, sharp hyperechoic line, accompanied by an acoustic shadow (Filippucci et al., 2006).

Several studies have explored the potential of MSUS to aid in the diagnosis of RA and distinguish it from other inflammatory arthritis. US, particularly when combined with USPD, has shown superiority over clinical evaluation in detecting joint inflammation, such as effusions and synovitis, with better interobserver reliability observed for US findings. In the Szkudlarek et al. study (2001), they conducted USPD and dynamic MRI on the metacarpophalangeal (MCP) joints of 15 patients with active RA and 12 controls. Compared to dynamic MRI, USPD exhibited a sensitivity of 88.8% and a specificity of 97.9%, whereas USPD and clinical assessment of joint swelling showed a weak correlation. Additionally, grey-scale ultrasound has effectively detected ongoing synovial

hypertrophy in 84% of a sizable patient cohort considered clinically in remission by their treating physician. Among these patients, 60.4% showed increased USPD signals, confirming active synovitis through rising PD signals, which underscores ultrasound's superior sensitivity in detecting synovial inflammation compared to clinical examination. Notably, subclinical inflammation identified by grey scale and power Doppler ultrasound predicted joint damage progression in Patients with RA. The utilisation of microbubble-based ultrasound contrast agents may enhance intra-articular vascularisation detection in the finger joints of Patients with RA; however, this finding lacks consistency, increases examination cost, time, and invasiveness and limits the number of assessable joints per examination.

Moller et al. (2009) utilised grey-scale US to measure cartilage thickness in metacarpophalangeal (MCP) and proximal interphalangeal finger (PIP) joints, successfully differentiating early symptomatic osteoarthritis (OA) from early RA based on reduced cartilage thickness in OA joints compared to RA. They also found that US cartilage thickness scores correlated with the duration of treatment-resistant progressive RA, suggesting potential utility in early arthritis clinics for distinguishing RA from OA. Wakefield et al. (2000) compared the US with conventional radiography for detecting erosions in MCP joints of early Patients with RA, revealing that the US detected significantly more erosions than radiography, with all sonographic erosions corresponding to MRI abnormalities. This highlights the MSUS as a reliable technique for detecting erosions in early RA. Agrawal et al. (2009) conducted a retrospective study on the use of clinic-based musculoskeletal US, demonstrating its potential to improve the early diagnosis of inflammatory arthritis. US findings, combined with clinical evaluation and serological tests, aided in confirming or changing diagnoses in a significant percentage of new patients and contributed to diagnostic revisions in follow-up cases.

Moreover, a reduction in the PD signal has been observed following therapeutic intervention in a randomised, placebo-controlled study of anti-tumour necrosis factor (anti-TNF) therapy in early RA and other small uncontrolled studies. Consequently, ultrasonography may be a feasible imaging modality for monitoring treatment response in Patients with RA, facilitating accurate disease activity monitoring in clinical settings (Agrawal et al., 2009).

1.11.5.2 Joint effusion MSUS

A joint effusion, a key indicator of joint pathology, can cause capsular distension and pain or signify intra-articular derangement (Hunt, 2022). On musculoskeletal ultrasound,

effusion appears as compressible, anechoic or hypoechoic intra-articular fluid without a Doppler signal (Naredo et al., 2005). These findings include anechoic widening of the joint space and compressible fluid within synovial recesses (Figure 1.4). However, effusion alone does not necessarily indicate active synovitis and must be interpreted in conjunction with synovial hypertrophy and Doppler activity (Wakefield et al., 2005; D'Agostino et al., 2017). Effusions may also occur secondary to mechanical factors, including repetitive microtrauma, degenerative joint changes, or biomechanical stress, particularly in load-bearing or frequently used joints. Therefore, they should not be considered synonymous with synovitis or active rheumatoid arthritis, as accurate assessment of inflammatory activity requires evaluation of synovial hypertrophy in combination with Doppler signals (Wakefield et al., 2005; Filippucci et al., 2013).

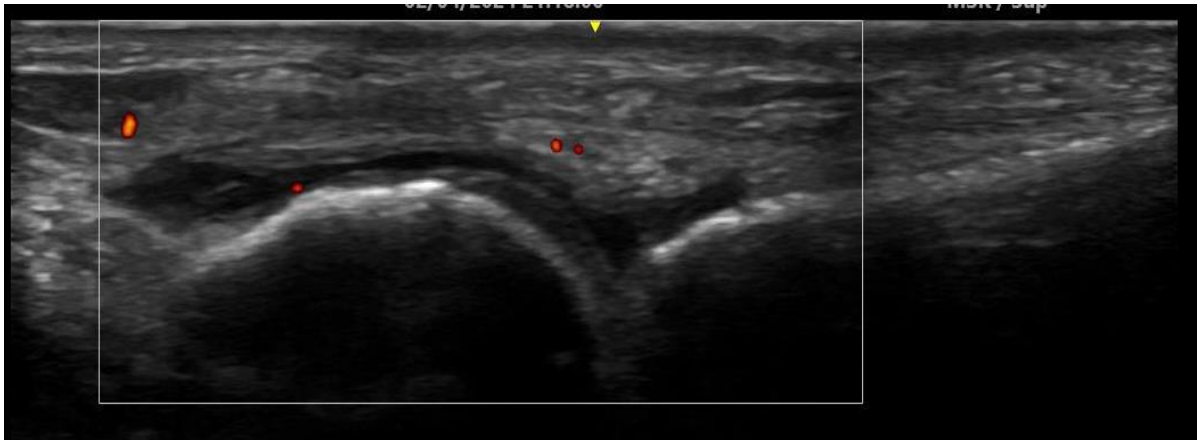

Figure 1.4: Longitudinal dorsal scan of the second metacarpophalangeal joint of the right hand showing joint effusion grade one (mild) (Author's own, 2025).

1.11.5.3 Appearance of synovitis in MSUS

Synovitis, characterised by synovial proliferation, presents on ultrasound as clusters of soft echoes with a bushy or villous appearance and/or homogeneous synovial hypertrophy. This pathological tissue, hypoechoic or isoechoic relative to subdermal fat, may exhibit a Doppler signal and joint effusion (Filippucci et al., 2019). Synovitis represents a pivotal aspect of RA, characterised by inflammatory changes at the joint level, including synovial effusion, hypertrophy, and increased local vascularisation. Power Doppler (PD) and colour Doppler (CD) techniques aid in distinguishing between active and inactive inflammation in the presence of synovial hypertrophy. According to OMERACT, synovitis on MSUS is characterised by abnormally thickened, hypoechoic intra-articular tissue that is poorly compressible and may show increased Doppler signals (Wakefield et al., 2005).

The OMERACT Task Force recommends a standardised scoring system combining grayscale (GS) and PD for assessment. Ultrasound characteristics of synovitis include homogeneous echoic joint space widening indicative of synovial proliferation, thickening of the synovial membrane visualised as hypo- or hyperechoic structures within effusion-affected regions, non-compressible hypoechoic intracapsular areas, echogenic non-compressible intra-articular tissues within synovial recesses, abnormally hypoechoic joint spaces reflecting synovial hypertrophy, and joint space widening with clusters of soft echoes or homogeneous synovial thickening (Figure 1.5)(Rizzo et al., 2013).

Another crucial aspect of ultrasound in RA is its ability to detect subclinical synovitis, which is often more sensitive than clinical examination in identifying inflamed joints. Subclinical inflammation, particularly in symptom-free joints, is common in RA, particularly in hand, wrist, knee, and foot joints. Subclinical synovitis detected by ultrasound with PD is more likely to progress to structural damage, such as bone erosions and joint space narrowing (Rizzo et al., 2013).

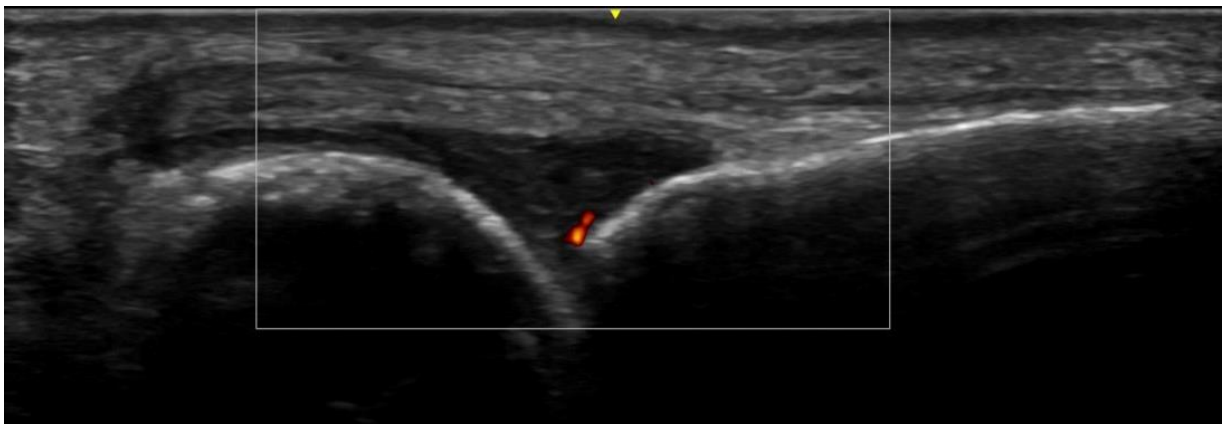

Figure 1.5: Longitudinal dorsal scan of the fourth metacarpophalangeal joint of the right hand, showing synovial thickening grade two (moderate), no joint effusion, and grade one (mild) power Doppler (Author's own, 2025).

1.11.5.4 Bone erosion MSUS

Bone erosion in inflammatory arthritis is defined on ultrasound as an intra-articular discontinuity of the bone surface that is visible in two perpendicular planes (Wakefield et al., 2000; Szkudlarek et al., 2003). This criterion is essential to distinguish true erosions from physiological cortical irregularities. Ultrasound has demonstrated superior sensitivity compared with conventional radiography for detecting erosions in the small joints of the hands and feet, particularly in early RA. Wakefield et al. (2000) illustrated this by

recording erosion sites detected by radiography and ultrasound at the metacarpophalangeal (MCP) joints of 100 Patients with RA. In early disease, ultrasound detected 6.5 times more erosions than radiography, and in late disease, a 3.4-fold difference was observed. Most erosions were located at the second MCP joint, predominantly on the radial and ulnar aspects, and showed strong agreement with MRI findings, supporting their validity. More recent comparative studies using computed tomography (CT) as a reference standard have confirmed the high specificity of ultrasound-detected erosions, suggesting that radiographically occult erosions identified by ultrasound represent true structural damage. Bone erosion is a key prognostic marker in RA and contributes to the classification of disease into erosive and non-erosive phenotypes. The presence of early erosive disease is considered a poor prognostic factor and influences therapeutic decision-making, including escalation to biologic or targeted synthetic DMARDs according to EULAR recommendations (Aletaha et al., 2010; Smolen et al., 2020). Careful technique is essential when assessing erosions, as anisotropies, vascular channels, and physiological cortical irregularities may mimic pathological defects. Accurate identification requires confirmation of cortical discontinuity in at least two perpendicular scanning planes to avoid false-positive findings (Wakefield et al., 2000; Szkudlarek et al., 2003). Cartilage damage also contributes significantly to functional impairment in RA. On ultrasound, normal hyaline cartilage appears as a homogeneous anechoic band with well-defined margins. Cartilage damage manifests as loss of margin sharpness, thinning, or complete loss of cartilage, often in association with adjacent bone erosion (Rizzo et al., 2013) (Figure 1.6).

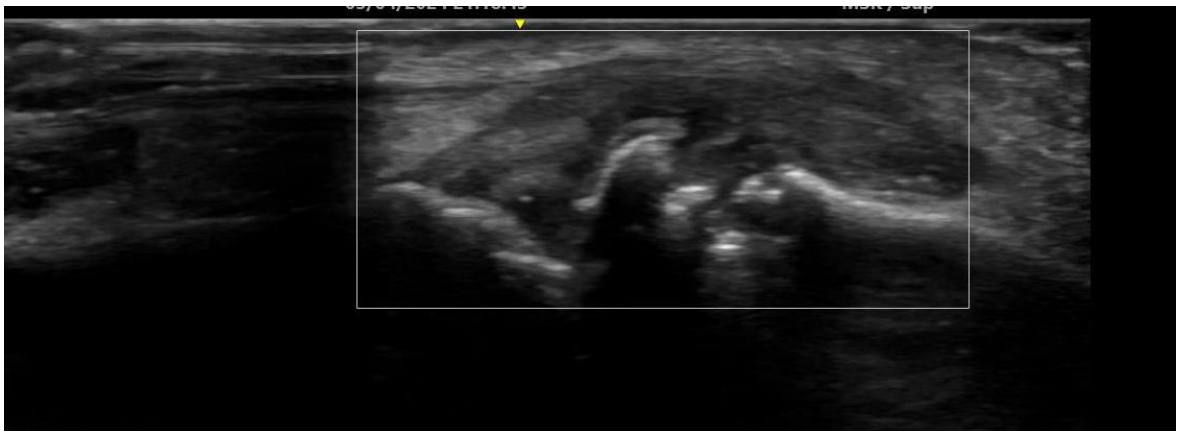

Figure 1.6: Longitudinal dorsal scan of the first metacarpophalangeal joint of the left hand showing bone erosion grade three (severe) and synovial hypertrophy grade two (moderate) with no power Doppler that can be detected (Author's own, 2025).

1.11.6 MSUS scoring in RA

Following the establishment of the first international consensus on MSUS definitions for joint pathologies in RA by the Outcome Measures in Rheumatology (OMERACT) US Working Group, there has been increased uniformity in defining RA synovitis in published literature (Wakefield et al., 2005). Grey-scale (GS) and USPD have demonstrated sensitivity to change and predictiveness of arthritis development and radiographic structural damage. However, consensus is lacking regarding how to grade the observed changes and the extent to which both features of the sonographic inflammatory spectrum should be monitored, namely, morphological changes in GS (effusion and synovial hypertrophy) and hypervascularity shown by PD. The most commonly utilised approach for scoring synovitis is a semiquantitative (SQ) severity grading on a scale from 0 to 3 (Filippucci et al., 2019). Some scoring systems focus on hypervascularity using USPD without considering grayscale changes, particularly hypertrophy. The SQ scoring method, frequently used to grade PD signals in the literature, is relatively quick and has reasonable inter-observer variability. It can utilise pre-defined criteria or reference images for scoring. This Likert scoring system mirrors the SQ score for MRI images developed and validated by the OMERACT group. While this type of scoring can be conducted in real-time imaging, it artificially segments a continuum of PD signals. It is considered an interval scale, with weaknesses including overlap at the extremes of each category and a deviation from the notion that each step along the interval scale represents the same quantified difference. This tool may be too insensitive to detect small changes in US signals. Nonetheless, several studies have shown that this score detects change and possesses predictive value for disease flare and erosive outcomes at the cohort level (Filippucci et al., 2019).

The EULAR-OMERACT US group recently proposed a combined scoring method based on USPD signal and synovial hypertrophy (SH) on grayscale ultrasound (GSUS) (Filippucci et al., 2019). This combined score demonstrated improved reliability compared to usual scanning practices, particularly when assessing MCPJs. However, reliability was slightly lower when evaluating other joints in real time compared to static images. Using MSUS to detect joint and tendon abnormalities offers significant diagnostic and prognostic value, which varies depending on the clinical context, whether confirming or predicting a diagnosis in the early stages or revealing subclinical synovitis in established disease. While a simple presence-absence analysis is insufficient for short-term

monitoring, developing scoring systems capable of capturing reductions in US signs of synovitis is necessary.

Several scoring systems have been developed to semiquantitatively assess ultrasound findings in Patients with RA (Tables 1.2-1.6). Grayscale and Doppler findings are typically graded independently for synovitis at the joint level, with various scoring systems introduced for each elementary component. Notable among these are the scoring systems proposed by Szkudlarek et al. (2003), Scheel et al. (2005), and the Leeds score (Healy and Helliwell,2008). The EULAR-OMERACT recently established a combined semiquantitative scoring system for synovitis in RA, incorporating grayscale and power Doppler modes (Table 1.2). Different approaches have been described for bone erosion, including measuring the maximal diameter of erosive craters or counting the number of erosions in a joint. Zayat et al. (2015) introduced a novel method of dividing joints into quadrants and parts, scoring erosions semiquantitatively using a transverse view. For cartilage damage, grading systems are predominantly based on qualitative pathological findings detected at metacarpal head cartilage, with Mandl et al. (2011) presenting a three-grade semiquantitative score to enhance reliability. At the tendon level, while tendon involvement is common in RA, many studies do not include tendon examination, and when they do, the focus is often on tenosynovitis. The heterogeneity of tenosynovitis morphology and difficulty standardising quantitative scoring systems necessitate subjective qualitative grayscale scoring for tenosynovitis and a consensus-based semiquantitative scoring system for Doppler findings. Filippucci et al. (2019) conducted one of the first studies on the prevalence and distribution of tendon involvement in RA, describing three grades of tendon damage. Subsequently, the OMERACT US task force agreed on a scoring system for tendon damage, utilising a scale from 0 to 3 for B-mode, PD and combined grading (Table 1.2). Furthermore, Szkudlarek and his colleagues (2003)(Tables 1.3), Scheel et al. (2005)(Tables 1.4), Brown et al. (2006)(Tables 1.5), and Terslev et al. (2017)(Tables 1.6) developed their MSUS scoring using 0-3 grades for joint effusion, synovial hypertrophy and PD. Developing a scoring system for tenosynovitis poses challenges due to local anatomical factors, highlighting the complexity involved in this endeavour (Filippucci et al., 2019).

Various scoring systems have been established for evaluating bone erosions. There are two primary methods. The first method involves measuring the maximal diameter of the erosive crater; its key drawbacks include the lack of agreement on the smallest size for a definitive bone erosion and the inability to demonstrate progression once the maximum score is achieved (typically a diameter exceeding 4 mm). The second method counts the number of bone erosions present in a joint. A significant issue arises when two or more

erosions merge into a larger erosion, causing a situation where a deterioration is interpreted as an improvement (Filippucci et al., 2019). Table 1.7 compares the MSUS scoring for bone erosion.

Table 1.2: The proposed OMERACT semi-quantitative score. Adopted from Elangovan and Tan. (2020).

B-mode	
Grade 0:	Normal joint (no synovial hypertrophy and joint effusion).
Grade 1:	Minimal synovitis (minimal synovial hypertrophy with or without minimal joint effusion).
Grade 2:	Moderate synovitis (moderate synovial hypertrophy with or without minimal or moderate joint effusion).
Grade 3:	Severe synovitis (severe synovial hypertrophy with or without severe joint effusion).
PD	
Grade 0:	No vessel in the synovium.
Grade 1:	Up to 3 single-spot signals or one confluent spot + up to 2 single spots.
Grade 2:	Vessel signals are present in less than half of the area of the synovium (<50%).
Grade 3:	Vessel signals are present in more than half of the synovium area (>50%).
Combined	
Grade 0:	No SH and PD signal.
Grade 1:	Grade 1 hypoechoic SH and ≤ grade 1 PD signal.
Grade 2:	Grade 2 SH and ≤grade 2 PD signal; or grade 1 SH and grade 2 PD signal.
Grade 3:	Grade 3 SH and ≤ grade 3 PD signal; or grade 1-2 SH and a grade 3 PD signal.

Table 1.3: Szkudlarek US scoring of synovitis (2003). Adopted from Filippucci et al. (2019).

Joint effusion	
Definition	A compressible anechoic intra-capsular area.
Grade 0:	No effusion.
Grade 1:	Minimal effusion.
Grade 2:	Moderate effusion.
Grade 3:	Extensive effusion.
Synovial hypertrophy	
Definition	A non-compressible hypoechoic intra-capsular area.
Grade 0:	No synovial thickening.
Grade 1:	Minimal synovial thickening (fills the angle between periarticular bones without bulging over the line linking the tops of the bones).
Grade 2:	Synovial thickening bulging over the line linking the tops of the periarticular bones, but without extension along the bone diaphysis.
Grade 3:	Synovial thickening bulging over the line linking the tops of the periarticular bones and extending to at least one of the bone diaphyses.
Power Doppler	
Definition	Flow signal in the synovium.
Grade 0:	No flow in the synovium signals.
Grade 1:	Single vessel.
Grade 2:	Confluent vessel signals are present in less than half of the area of the synovium.
Grade 3:	Vessel signals are present in more than half of the area of the synovium.

Table 1.4: (Scheel et al., 2005) US scoring. Adopted from Filippucci et al. (2019).

Scheel et al. (2005). US scoring	
Grade 0:	No effusion/synovial hypertrophy.
Grade 1:	Minimal effusion/synovial hypertrophy.
Grade 2:	Moderate effusion/synovial hypertrophy.
Grade 3:	Extensive effusion/synovial hypertrophy.

Table 1.5: (Brown et al., 2006) US scoring. Adopted from Filippucci et al. (2019).

Synovial hypertrophy	
Grade 0:	No synovial hypertrophy.
Grade 1:	Mild hypertrophy.
Grade 2:	Moderate hypertrophy.
Grade 3:	Severe hypertrophy.
Power Doppler	
Grade 0:	Normal/minimal vascularity.
Grade 1:	Mild hyperaemia.
Grade 2:	Moderate hyperaemia.
Grade 3:	Marked hyperaemia.

Table 1.6: (Terslev et al., 2017) US scoring. Adopted from Filippucci et al. (2019).

Synovitis	
Grade 0:	**No synovitis** There is no synovial hypertrophy and no power Doppler signal within the synovium.
Grade 1:	**Minimal synovitis** Grade 1 synovial hypertrophy and power Doppler signal ≤ grade 1.
Grade 2:	**Moderate synovitis** Grade 2 synovial hypertrophy and power Doppler signal ≤ grade 2 or Grade 1 synovial hypertrophy and power Doppler signal grade 2.
Grade 3:	**Severe synovitis** Grade 3 synovial hypertrophy and power Doppler signal ≤ grade 3 or synovial hypertrophy ≤ grade 2 and power Doppler signal grade 3.

Table 1.7: Bone erosion US scoring.

Wakefield et al. (2000). Adopted from Filippucci et al. (2019).	
Grade 0:	No definite erosion.
Grade 1:	< 2 mm.
Grade 2:	2–4 mm.
Grade 3:	> 4 mm.
Szkudlarek et al. (2016). Adopted from Filippucci et al. (2019).	

Grade 0:	Regular bone surface.
Grade 1:	Irregularity without formation of a defect is seen in two planes.
Grade 2:	Formation of a defect in the surface of the bone is seen in two planes.
Grade 3:	A bone defect is creating extensive bone destruction.
Ohrndorf et al. (2014). Adopted from Filippucci et al. (2019).	
Grade 0:	No erosion.
Grade 1:	< 1 mm.
Grade 2:	1 to < 2 mm.
Grade 3:	2 to ≤ 3 mm.
Grade 4:	> 3 mm.
Grade 5:	Multiple bone erosions.
ScUSSe Score. Adopted from Sommier et al. (2006)	
Grade 0:	No erosion.
Grade 1:	Single erosion < 2 mm in diameter.
Grade 2:	One erosion between 2–3 mm, OR Two erosions each < 2 mm.
Grade 3:	One erosion > 3 mm, OR Multiple erosions present.

1.12 Psoriatic Arthritis (PsA)

1.12.1 Introduction

Psoriasis (Ps) is a prevalent chronic inflammatory skin disorder affecting approximately 1–3% of the global population. Studies suggest that up to 30% of Ps patients also experience PsA (Michalek et al., 2017).

Investigating pain using MSUS in different inflammatory populations, such as PsA and RA, holds clinical significance, especially in diagnosing pain. This is because pain in these conditions often results from diverse mechanisms, including inflammation, structural damage, and central sensitisation, which may not be fully reflected by patient-reported measures alone, such as pain VAS. MSUS provides a more precise assessment of the biological origins of pain, particularly at peripheral sites in both RA and PsA. It could help differentiate inflammatory from non-inflammatory sources of pain in these populations, which is crucial for tailoring treatment strategies, avoiding overtreatment, and enhancing

patient outcomes in RA and PsA. Furthermore, examining pain across various inflammatory arthritis groups improves understanding of disease-specific pain patterns. PsA is a chronic inflammatory condition that often co-occurs with psoriasis; however, its exact prevalence remains uncertain, and its underlying causes are not fully understood (Duarte et al., 2012). Genetic, environmental, and immunologic factors are all implicated in its development.

The onset of arthritis may precede, follow, or coincide with skin manifestations. Although sometimes perceived as mild, PsA has a significant impact on patient well-being and functionality.

In the UK, the prevalence of PsA is approximately 19 cases per 10,000 individuals (Ogdie et al., 2012). Several factors, including the severity and duration of psoriasis, as well as obesity, are significantly linked to the occurrence of PsA. Pain is a prevalent symptom among those with PsA, with 19% of patients in the UK receiving pain management medications (Ogdie et al., 2012).

Treatment goals include alleviating symptoms, preventing joint damage, enhancing quality of life, and reducing mortality. Treatment strategies are tailored based on disease severity, with immunobiological agents reserved for cases resistant to conservative therapies.

PsA is characterised by diverse musculoskeletal and non-musculoskeletal symptoms, leading to significant morbidity for those affected. Musculoskeletal symptoms encompass arthritis, enthesitis, dactylitis, and axial involvement, with the recognition that these conditions may arise from various immune mechanisms. Dactylitis is characteristic of spondyloarthropathies, especially PsA, and can be defined by swelling of an entire digit related to articular and periarticular inflammation (Kavanaugh and McHugh, 2007). Spondyloarthritis is a group of various disorders that share certain genetic predisposing factors and clinical features, including psoriatic arthritis, arthritis related to inflammatory bowel disease, reactive arthritis, a subgroup of juvenile idiopathic arthritis, and ankylosing spondylitis (Dougados and Baeten, 2011). Enthesitis is a key pathological characteristic of spondyloarthritis, affecting synovial joints, cartilaginous joints, syndesmoses, and other entheses outside the joints (D'Agostino and Olivieri, 2006).

Non-musculoskeletal manifestations extend beyond skin and nail issues to include uveitis, inflammatory bowel disease (IBD), metabolic syndrome, cardiovascular disease, and psychological conditions like anxiety and depression (Stober, 2021).

Complications arising from joint damage induced by PsA not only impair joint function and increase mortality rates but also impact patients' ability to work and their social interactions. Recent research suggests that early diagnosis and treatment contribute to the

remission of PsA symptoms. However, PsA often goes undiagnosed in individuals with psoriasis, possibly due to insufficient recognition of PsA symptoms and ineffective screening methods (Liu et al., 2014).

1.12.2 The prevalence of PsA

The prevalence of psoriasis in the general population ranges from 2% to 3%, affecting both men and women equally. However, the exact prevalence of PsA is uncertain, with rates varying widely from 20 to 420 cases per 100,000 individuals in Western countries and only 1 case per 100,000 individuals in Japan (Duarte et al., 2012). This discrepancy in prevalence, particularly in Japan, where other forms of spondyloarthropathy are less common, may be attributed to ethnic differences. The considerable variation in reported prevalence across different populations stems from variations in the studied cohorts, including community samples and hospitalised patients, as well as the utilisation of various diagnostic criteria. These criteria, such as Moll and Wright, Bennet, Vasey and Espinoza, Fournié, and CASPAR, exhibit varying levels of sensitivity and specificity (Khan et al., 2003; Espinoza et al., 1982). Among patients with psoriasis, the prevalence of PsA ranges from 6% to 42%. Severely destructive and disfiguring forms of PsA are observed in up to 20% of affected patients.
Furthermore, Zhang and colleagues (2018) associated obesity with an increased risk of developing PsA, noting a higher prevalence of PsA in overweight or obese patients (5.3%) compared to those with an average weight.

1.12.3 Clinical features of PsA

The peak incidence of PsA typically occurs between the ages of 30 and 50 (Duarte et al., 2012). Clinically, it is characterised by joint, ligament, and tendon inflammation, presenting symptoms such as swelling, pain, tenderness, and stiffness. Enthesitis most commonly affects the plantar fascia, Achilles tendon, ligaments around the pelvis, ribs, and vertebral spine. The co-occurrence of synovitis and enthesitis in the same digit is termed dactylitis, also known as a 'sausage-digit', and is observed in approximately 30% of patients with PsA (Liu et al., 2014). Arthritis manifests in periods of exacerbation and remission; however, untreated inflammation can persist. Arthritis may precede, follow, or coincide with skin lesions. In most patients, the onset of skin disease precedes the onset of arthritis. Conversely, in about 15% of individuals, the development of arthritic

manifestations coincides with the skin disease, while in 17% of patients, arthritis precedes the appearance of dermatological symptoms (Tiwari et al., 2024).

Typically, there is no correlation between the type or severity of skin lesions and the presence, type, or extent of joint involvement. The majority of patients with PsA exhibit plaque psoriasis. About 10-30% of patients with psoriasis will develop PsA within 7-12 years from the diagnosis (Mease and Armstrong, 2014). Diagnosis confirmation usually relies on the presence of psoriasis, given the lack of specific clinical, laboratory, and radiological findings. Nail changes are present in up to 80% of Patients with PsA, compared to only 40% of those with psoriasis alone (Sobolewski et al., 2017). These changes can include pitting, thickening, onycholysis, and subungual hyperkeratosis. Rheumatoid factor positivity is observed in only 13% of Patients with PsA. Additional features aiding in differential diagnosis include involvement of the distal interphalangeal joints and a lower frequency of symmetric bilateral involvement. PsA is classified as a spondyloarthropathy due to the occurrence of spondylitis, is a chronic progressive inflammatory rheumatic disorder mainly impacting the sacroiliac joints and the axial skeleton, in up to 40% of cases, as well as the presence of common extra-articular manifestations such as urethritis, diarrhoea, mucous membrane involvement, aortic dilation, and association with HLA-B27 (Liu et al., 2014).

1.12.4 PsA classification

The classification of PsA remains a subject of debate. While the Moll and Wright criteria are commonly used, the five subgroups within this classification often overlap, and patients may transition between subgroups over time. These subgroups encompass asymmetric oligoarthritic, symmetric polyarthritis resembling RA, distal interphalangeal involvement, spondylitis affecting the spine, and involvement of the sacroiliac or coxofemoral joints (Kyle et al., 2005).
In 2006, the Classification of Psoriatic Arthritis (CASPAR) group established highly sensitive and specific diagnostic criteria, facilitating diagnosis even in cases of PsA without evident psoriasis or in patients positive for rheumatoid factor (Tylor et al., 2006). Additionally, the Psoriatic Arthritis Screening and Evaluation (PASE) questionnaire, a symptom screening tool for arthritis, has been developed to aid in the detection of PsA by dermatologists, demonstrating promising sensitivity and specificity (Husni et al., 2007).

1.12.5 PsA diagnosis

PsA is a multifaceted condition characterised by musculoskeletal manifestations, including arthritis, enthesitis, dactylitis, and axial involvement, as well as potential skin and nail manifestations. The diverse patterns of PsA involvement can mimic various inflammatory arthropathies. When assessing a patient with inflammatory arthritis, rheumatologists consider a range of differential diagnoses, including RA, crystal arthropathies, and other forms of inflammatory arthritis. Particularly in polyarticular PsA, differentiating from RA involves identifying key features such as psoriasis, nail disease, dactylitis, and negative serology, as outlined in the CASPAR (Classification Criteria for Psoriatic Arthritis) criteria.

Table 1.8: CASPAR criteria for PsA diagnosis adopted from (Duarte et al., 2012).

CASPAR criteria for PsA diagnosis
Inflammatory musculoskeletal involvement (inflammatory arthritis, enthesitis, or lumbar pain) combined with at least 3 points.
Evidence of current psoriasis (2 points), personal history of psoriasis (1 point), and family history of psoriasis (1 point) in an unaffected patient.
Affected nails (onycholysis, pitting) – 1 point.
Dactylitis (current or in history, recorded by a rheumatologist) - 1 point.
Negative rheumatoid factor - 1 point.
Radiographic evidence of new juxta-articular bone formation (excluding osteophytes) - 1 point.

1.12.5.1 Radiological Findings

Radiological assessment of peripheral PsA typically reveals asymmetric joint distribution, involvement of distal interphalangeal joints, periostitis, bone density preservation, bone ankylosis, and characteristic bone proliferation (Duarte et al., 2012). Axial involvement is

characterised by findings such as paravertebral ossification, syndesmophytes, ligament calcification, and sacroiliitis. Imaging modalities such as ultrasonography and magnetic resonance imaging (MRI) play crucial roles in detecting subclinical enthesopathy and synovial inflammation, aiding in differentiation from RA and guiding treatment decisions (Schwenzer et al., 2010).

1.12.5.2 Musculoskeletal ultrasound (MSUS)

Musculoskeletal ultrasound has been utilised for several years to evaluate joint pathology and may offer value in assessing disease activity in individuals with inflammatory joint conditions, including PsA. Employing high-frequency transducers (10 MHz or higher) facilitates excellent tissue resolution. Ultrasound enables the evaluation of synovial tissue, joint effusions, and erosions, and, when coupled with Doppler interrogation, provides a qualitative assessment of hyperaemia, potentially indicating inflammation indirectly. Doppler may also be beneficial in evaluating tenosynovitis and specific features of PsA, such as enthesitis. Enthesitis is often detected with ultrasonography more frequently than through clinical examination in patients with psoriasis and PsA at various entheseal sites such as the lateral epicondyles of the humerus, the medial condyles of the femur, the superior and inferior poles of the patella, the tibial tuberosity, the Achilles tendon, and the plantar aponeurosis. The appearance of enthesitis in MSUS is characterised by a loss of normal fibrillar echogenicity at the tendon insertion, especially during the acute inflammatory phase. This appears as hypoechoic, with increased thickness of the enthesis insertion close to the bone (within 2 mm of the bony cortex) and possibly intralesional focal changes, such as calcific deposits, fibrous scars, and periosteal modifications (D'Agostino, 2018).

Structural damage has been a key outcome measure in RA and Patients with PsA, traditionally evaluated through scoring methods applied to plain film radiography. An international Outcome Measures in Rheumatology Clinical Trials (OMERACT) MRI in RA working group has been devising a scoring system to assess synovitis, bone oedema, and erosions in hands and wrists, meeting the OMERACT criteria (Ostergaard et al., 2022). Given the shared clinical features between patients with PsA and RA, this MRI scoring system could also serve as an outcome measure in patients with PsA. MRI may offer the advantage of detecting some of these features earlier than plain radiography, allowing for the measurement of treatment response and disease activity before structural damage occurs.

MRI has been utilised to assess synovial vascularity in the RA wrist following therapy initiation, a method currently employed in a PsA trial with anti-TNF therapy. In a study of infliximab in PsA (Grdner et al., 2003), MRI was utilised to observe changes in inflammatory activity, indicated by a significant reduction in gadolinium uptake post-treatment. However, akin to ultrasound, as some of these measured features are nonspecific, it is imperative to obtain histopathological correlation whenever feasible and enrol patients in longitudinal studies to validate this modality as a disease outcome measure. In summary, alongside plain radiographs, these novel imaging techniques, once validated, may aid in the early detection of changes in peripheral joints, periarticular tissues, and spinal structures in individuals with PsA (Ory et al., 2005).

Table 1.9: PsA radiographic findings adopted from (Duarte et al., 2012).

X-Ray	MSUS	MRI
Bone proliferation	Tendinitis	Effusions
Periostitis	Tendon rupture	Synovitis
Calcification	Peritendinitis	Erosions
Ankylosis	Bursitis	Tenosynovitis
Erosions	Detection of enthesopathy	

1.12.6 PsA treatment

The objectives of managing PsA include alleviating disease symptoms, preventing joint deterioration, enhancing patient well-being, and reducing mortality rates. Patients should receive comprehensive education about the nature of the disease and may benefit from psychological counselling and physiotherapy interventions. Mild forms of PsA may respond to nonsteroidal anti-inflammatory drugs (NSAIDs), often administered alongside intra-articular glucocorticoid injections (Nash et al., 2005). For moderate to severe cases, initial treatment is similar to that for mild disease, with the addition of disease-modifying antirheumatic drugs (DMARDs) (Gottlieb et al., 2008). While methotrexate, sulfasalazine, and leflunomide have been studied, evidence supporting their efficacy in axial disease presentation is lacking. Antimalarial agents, gold salts, and cyclosporine are generally not recommended due to limited evidence of effectiveness. Refractory cases, defined as those failing to respond to DMARD therapy after at least three months, may require treatment escalation to anti-tumour necrosis factor (TNF) drugs. Adalimumab, etanercept, and

infliximab are commonly used anti-TNF agents that demonstrate efficacy in promoting remission and improving various disease parameters. Golimumab is another cost-effective option for PsA treatment (Rodgers et al., 2011). Studies have shown that adalimumab, etanercept, and infliximab effectively improve PsA symptoms, inhibit radiographic progression, and enhance quality of life (Mease et al., 2004). Rituximab, an anti-CD20 agent, exhibits moderate efficacy, particularly in patients who have not previously received anti-TNF therapy (Tak et al., 2011). Furthermore, Daclizumab, an anti-CD25 agent, has shown promise in reducing PsA severity with minimal adverse effects.

1.13 Role of Ultrasound in Evaluating Pain in Rheumatoid Arthritis: A Systematic Review of the Literature

1.13.1 Abstract

Introduction

RA is a chronic autoimmune disorder characterised by significant pain and diminished quality of life. Traditionally, pain in RA has been attributed to nociceptive mechanisms associated with joint inflammation. MSUS has emerged as a sensitive tool for detecting inflammatory changes in RA. This systematic literature review (SLR) aims to evaluate the association between MSUS-detected peripheral joint inflammation and pain in RA, and to explore whether discordance between inflammatory findings and reported pain suggests alternative pain mechanisms.

Methods

A comprehensive literature search was conducted in PubMed and Web of Science for studies published between 1 January 2019 and 31 December 2023. Original research articles published in English that investigated rheumatoid arthritis (RA), musculoskeletal ultrasound, Doppler imaging, and pain assessment or management were included. Data extracted from eligible studies included study design, participant characteristics, ultrasound protocols, Doppler parameters, pain assessment methods, and reported outcomes. Methodological quality was appraised using the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies-2) tool.

Results

After applying inclusion and exclusion criteria, 15 studies were selected for review. Synovitis scores from MSUS, pain VAS scores, Disease Activity Score 28 (DAS28), and treatment regimens were consistently assessed across the included studies. Most included studies in this SLR showed that synovitis's severity reflects the pain's severity. However, few studies highlight that pain VAS did not improve despite the effective treatment.

Conclusion

MSUS proves valuable in assessing synovitis severity in RA, thus providing insight into pain intensity. However, the persistence of pain in patients with improved synovitis warrants further investigation into the underlying pain mechanisms in RA.

1.13.2 Introduction

RA is a systemic autoimmune disease marked by chronic synovial inflammation. It leads to joint damage, deformity, decreased quality of life, and reduced life expectancy (Sarzi-Puttini et al., 2014). While patients with RA endure various symptoms like joint swelling, tenderness, and morning stiffness, pain remains the primary concern, prompting medical attention. Addressing pain management is paramount as it stands out as the foremost aspect of health where patients with RA seek improvement (Sokka, 2005). Synovial RA inflammation causes pain and stiffness and can progressively damage the affected joints. Modern RA drug treatment, including biological therapies, aims to improve the short-term and long-term outcomes of the disease by suppressing inflammation. Effectively suppressing inflammation enhances pain outcomes (Walsh and McWilliams, 2011).
The International Association for the Study of Pain (IASP) defines pain as an unpleasant sensory and emotional experience with actual or potential tissue damage. Pain has become a vital element of the core sets utilised for classifying the severity of rheumatic disease. Hence, how pain should be effectively measured has become increasingly important (Englbrecht et al., 2012). The pathogenesis of pain in RA is multifactorial, as it is traditionally linked to synovitis and joint destruction. The pain in RA results from a combination of many interacting pain mechanisms, including nociceptive, nociplastic and neuropathic causes. Nociceptive pain is a response to damage to body tissues. This tissue damage can include joint inflammation, resulting in inflammatory or nociceptive pain (Paice, 2002). Nociceptive pain originates from activating nociceptors, which serve as primary afferent neurons, as highlighted by Prescott and Ratté (2017).
This activation triggers protective withdrawal reflexes, serving as a crucial alarm system. Nociceptive pain is typically well-localised and consistent with the underlying tissue damage, as noted by Duarte et al. (2009). On the other hand, nociplastic pain, also known as centralised pain, refers to pain that arises from changes in nociception without clear evidence of tissue damage. This phenomenon leads to the activation of the peripheral nociceptor or somatosensory system, as described by Kosek et al. (2021). Central pain sensitisation can occur, wherein neural signals are amplified in response to peripheral nociceptive input within the central nervous system. Neuropathic pain, distinct from nociceptive and nociplastic pain, is caused by lesions or diseases affecting the nervous system, particularly the somatosensory systems, as Bailly et al. (2020) highlighted. Mechanisms contributing to the maintenance of neuropathic pain involve the activation of

microglia and astrocytes in the spinal cord, leading to local inflammation within the dorsal horn of the spinal cord.

Pain is regarded as "an objective" based on patient data and objective tests such as physical examinations, laboratory tests, and radiological procedures. Then, these tests are reviewed by clinicians for diagnosis and management (Sokka, 2005). In chronic rheumatic disease management, evaluating pain longitudinally lacks feasibility without quantitative data to track changes in a patient's condition over months to years. To address this challenge, a clinical methodology for pain assessment employing patient self-report questionnaires has evolved in recent decades. These tools enable both qualitative and quantitative evaluation of pain status. Despite inherent limitations in scientific measurement, pain questionnaires have emerged as valuable tools for investigating the underlying mechanisms and management of pain (Sokka, 2005).

The pain VAS originated in psychology in the early 1900s and was later adapted for use in rheumatology by Huskisson and colleagues in the late 1970s. They emphasised the subjective nature of pain assessment, stating that only the patient can accurately gauge pain severity. Various types of VAS were described, including vertical and horizontal scales, each indicating degrees of pain intensity without numerical values. Initially, assistance from a healthcare professional was recommended for first-time completion, but subsequent self-reporting was deemed sufficient. The standard VAS consists of a 10 cm line bordered on each side. On the left, "0" indicates "No pain at all", and on the right, "10" indicates "Pain as bad as it could be". Numerous studies have confirmed the reproducibility of data obtained from self-report pain VAS (Sokka, 2005).

MSUS is a valuable objective tool for assessing inflammatory changes in RA (Mandl et al., 2011). MSUS can provide information about joint conditions such as synovial thickening, joint effusion, increased blood vessels, and bone erosion. These findings are used for diagnosis and may be used to guide therapeutic decisions. Synovial thickening and joint effusion are evaluated primarily on grey-scale (GS) ultrasound. At the same time, Power Doppler is utilised to demonstrate the activity related to synovial thickening and detect microvascular blood flow at the synovial and entheseal inflammation (D'Agostino, 2017).

1.13.3 Aim

This systematic literature review aims to investigate the relationship between MSUS-detected peripheral joint inflammation and pain in RA and to examine whether persistent pain in the absence of active inflammatory findings indicates alternative, non-inflammatory pain mechanisms.

1.13.4 Methods

To systematically extract data on ultrasound evaluation of synovitis in RA and pain, we implemented a rigorous 4-step approach: (1) Clarifying the review's objective, (2) defining selection criteria, (3) selecting relevant articles, and (4) extracting data. Our selection criteria encompassed original English-language articles published between January 2019 and December 2023, focusing on ultrasound assessment and pain measurement in RA.

1.13.4.1 Search strategy and study selection

For the search process, we utilised PubMed and Web of Science databases. Articles were searched using specific keywords such as “Ultrasound,” “Rheumatoid Arthritis,” and “Pain,” with filters applied to restrict results to English-language and human studies published between January 2019 and December 2023. These keywords were matched with MeSH Terms where available or with terms in titles and abstracts. Screening of titles, abstracts, and full articles was conducted by one author (NA) against predefined inclusion and exclusion criteria, with verification by a second reviewer (YM). Articles were excluded if they were not in English, involved healthy participants, or were abstracts from conferences or review articles. A manual reference search of the included studies was also performed, with no date restrictions, to identify any additional relevant primary research not captured through database queries. The exclusion criteria are outlined in Table 1.10. The decision to use a limited set of core search terms, “ultrasound”, “rheumatoid arthritis”, and “pain” was made to maintain alignment with the central research aim, which was to investigate the relationship between MSUS findings and pain perception in patients with RA. These keywords were selected for their direct relevance to the key variables in this study. While broader search strategies with multiple synonyms and Boolean logic can enhance sensitivity, the use of targeted terms, supported by MeSH indexing where applicable, was considered sufficient to identify the relevant clinical and imaging-focused literature. Furthermore, to mitigate the risk of missing eligible studies, a manual search of reference lists was conducted. This focused approach also helped reduce the retrieval of studies outside the scope of the review, such as those on unrelated imaging modalities (e.g., MRI) or different forms of arthritis (e.g., osteoarthritis or psoriatic arthritis), thereby improving specificity. This approach is consistent with accepted systematic review methods, where search strategies are guided by the specificity and structure of the research question (Higgins et al., 2022).

To ensure the relevance and currency of evidence, the electronic database search was restricted to studies published between January 2019 and December 2023. This five-year window was selected to capture the most recent and clinically applicable research in the field of RA. During this period, significant progress has been made in the application and clinical integration of MSUS in rheumatology practice, particularly in relation to its role in assessing disease activity, monitoring treatment response, and supporting diagnostic decisions (Mandl et al., 2019). Moreover, recent years have seen the widespread adoption of updated therapeutic guidelines and biologic treatment strategies for RA, which have shifted the focus of disease management from structural preservation alone to comprehensive patient-centred outcomes, including pain control and quality of life (Smolen et al., 2020). Importantly, literature published within this timeframe also reflects the growing recognition of pain in RA as a complex, multidimensional phenomenon no longer viewed solely as a byproduct of synovial inflammation but increasingly understood in terms of nociplastic and central sensitisation mechanisms (Taylor et al., 2016). By focusing on studies from this contemporary period, the review ensures that the included evidence is aligned with current clinical perspectives, imaging practices, and conceptual models of pain in RA.

Conversely, no date restrictions were applied during manual searching of reference lists. This decision aligns with recommendations in the Cochrane Handbook (Higgins et al., 2022), which supports manual citation searching to capture foundational or seminal studies that may not be indexed using current terminology. Manual searches help address indexing bias and ensure methodological completeness (Greenhalgh & Peacock, 2005; Booth, 2016).

Table 1.10: Summary of inclusion and exclusion criteria used in this review.

	Inclusion	Exclusion
Population	• Adult patients with RA	• Paediatric patients • Patients with osteoarthritis and psoriatic arthritis
Index test / Exposure	Musculoskeletal ultrasound (MSUS) assessment of peripheral joint inflammation/synovitis (grey scale and power Doppler).	Other imaging modalities (e.g., MRI) or studies without musculoskeletal ultrasound assessment.
Outcome	Pain intensity assessed using pain VAS (0–10). Clinical disease activity measures (e.g., DAS28) were extracted where reported.	Studies that did not include pain VAS or did not report pain outcomes.
Study design	• Quantitative studies • Cohort studies • Randomised controlled trials	• Systematic reviews • Case reports • Qualitative studies
Other	• English language studies published in 2019-2023	• Non-English language • Studies published before 2019 are deemed out of date

1.13.4.2 Data extraction

During data extraction, particular attention was paid to the “Patients and Methods” and “Results” sections of each included article. A summary table was created to compile the relevant data from all studies included in this review. The table includes details such as

study aim, design, participant characteristics, ultrasound protocols, scoring systems, pain VAS measurements, and key outcomes.

Selected articles were further evaluated to determine ultrasound protocols, scoring systems, system characteristics, and pain VAS scores at various time points. Methodological quality was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool. QUADAS-2 is a validated instrument used to evaluate the risk of bias in diagnostic accuracy studies and comprises four domains: patient selection, index test, reference standard, and flow and timing. Each domain was assessed for risk of bias in all included studies.

1.13.5 Results

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart outlines the study selection process from various databases (Figure 1.6). As described in the methodology, 2189 studies were initially recorded electronically. After applying the inclusion and exclusion criteria and screening the titles and abstracts of the remaining studies, 15 studies were selected for inclusion in the review. Table 1.11 presents the design and demographic features of the 15 included studies.

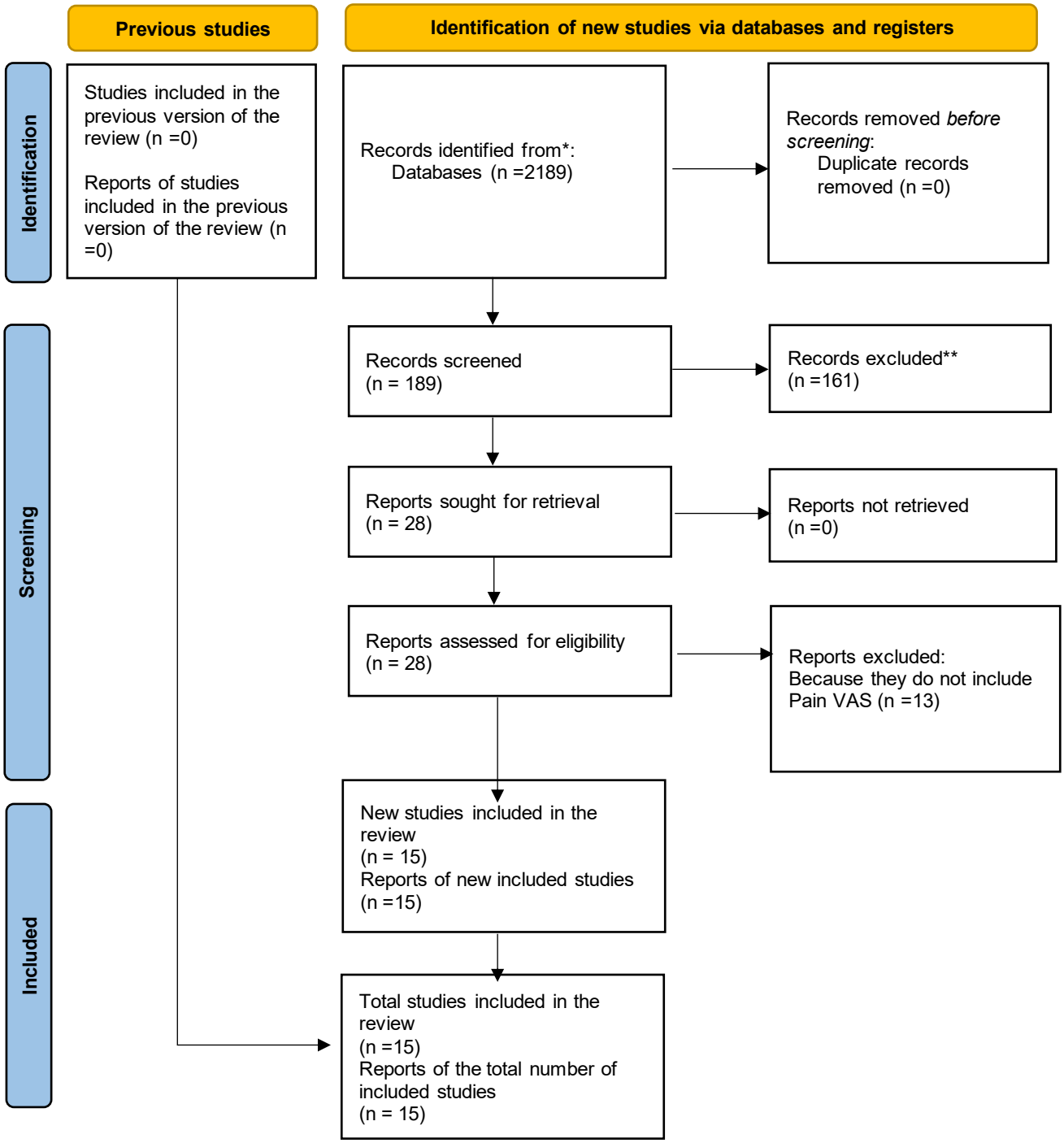

Figure 1.7: The PRISMA flowchart demonstrates the research selection process in this systematic review, adapted from Page et al. (2021).

Table 1.11: Design and demographic characteristics of included studies

Paper	Sample size	Age (years)	Gender	RA disease duration (years)	Study design	Patient group	Control group	Treatment drug	Session
Abdelghani et al. (2022)	Pt: 30 Control: 37	Intervention: 48 Control: 52.4	Gender ratio: Pt: 0.2 Control 0.15	6.1 ± 2.4	Cross-sectional observational	Yes	Yes	Joint steroid injection	1
Abdellah et al. (2021)	100	44.1	M/F 14/86	8.7 ± 5.3	Cross-sectional observational	Yes	No	Steroid (74) Methotrexate (46) hydroxychloroquine (HCQ) (84) Leflunomide (48)	1
Blanco et al. (2020)	65	53.7	M/F 17/48	9.8 (2–28)	Prospective observational cohort	Yes	Yes	DMARDs CZP	2
Ciurtin et al. (2019)	101	43.5	M/F 22/79	7.8	Prospective observational	Yes	Yes	DMARDs	2
Hammer et al. (2021)	110	55.6	M/F 19/91	12.8	Prospective observational	Yes	No	DMARDs	4
Inamo et al. (2019)	59	58.8	M/F 9/50	9 (2–18)	Cross-sectional observational	Yes	Yes	DMARDs	1
Kuettel et al. (2020)	29	64.8	M/F 9/20	10.1 ± 9.4	Prospective observational	Yes	No	DMARDs	2
Lin et al (2022)	139	52.0	M/F 38/101	5 [2–10]	Cross-sectional observational	Yes	Yes	DMARDs	1
Morris et al. (2021)	54	51.9	M/F 5/49	10 ± 10	Open-label prospective clinical trial	Yes	No	IV-Tocilizumab (TCZ) DMARDs	6
Nawata et al. (2021a)	30	65.4	M/F 6:24	11.5 ± 9.6	Retrospective observational	Yes	Yes	DMARDs	1
Nawata et al. (2021b)	300	65.4	M/F 60:240	8.6	Retrospective observational	Yes	Yes	DMARDs	1
Sifuentes-Cantú (2020)	94	67.04	M/F 7 / 87	11 (5–15)	Randomised	Yes	Yes	DMARDs	2

					controlled trial				
Sami et al. (2023)	100	44.82	M/F 12/88	6.88 ± 5.77	Cross-sectional observational	Yes	Yes	Methotrexate (53 %), leflunomide (39 %), hydroxychloroquine (32 %), steroid (49 %), azathioprine (2 %), sulfasalazine (3 %) and biological treatment (TNF inhibitor) (4 %).	1
Stein et al. (2020)	171	58.4	M/F 49/122	8.6	Prospective observational	Yes	Yes	non-biologic or biologic DMARDs	2
Tesei et al. (2021)	43	56.09	M/F 6/37	10.3 ± 8.9	Prospective observational	Yes	Yes	csDMARDs and bDMARDs	4

All included studies utilise MSUS to investigate synovitis in the joints, and they include pain VAS and DAS28 to measure pain and disease activity, respectively. Five longitudinal studies were included, while the remaining only investigated synovitis and RA pain at baseline. All studies included DAS28 to indicate how synovitis is active, except for four studies (Table 1.12). Eleven studies included control patients. The sample size ranged from 24 to 278 patients, aged 34.5 to 67 years (Table 1.12). The majority of patients were female. One study concluded that the pain VAS was improved at the follow-up visit. However, the author did not provide their values (Morris et al., 2021).

No agreement was found on a preferred ultrasound modality for evaluating possible arthritis. All included studies evaluated arthritis using both GS and PD. The MSUS examinations in the included studies involved grey scale (GS) and power Doppler, and the severity was measured using different scoring systems. Still, the majority scored semi-quantitatively on a four-point scale (0: no, 1: minor, 2: moderate, 3: the significant presence of GS or Doppler) (Table 1.12). Differences in the numbers and types of joints evaluated were also found. In most of the included studies, the sonographers were blinded to clinical assessments and pain measures.

Table 1.12: Characteristics related to ultrasound, scoring and pain VAS.

Paper	MSUS		Component studied	MSUS scoring system	Pain VAS		DAS28	
	BL	Follow-up			BL	Follow-up	BL	Follow-up
Abdelghani et al. (2022)	GS 14% PD 7%	N/A	GS+ PD	Semi-quantitative scale	6	N/A	2.03	N/A
Abdellah et al. (2021)	7.2	N/A	GS+ PD	GUESS	6	N/A	4.3	N/A
Blanco et al. (2020)	GS 14.3 PD 8.9	GS 7.7 PD 4.6	GS+ PD	Semi-quantitative scale	6.68	2.76	N/A	N/A
Ciurtin et al. (2019)	GS 7 PD 1.8	N/A	GS+ PD	Semi-quantitative scale	5.1	N/A	3.64	N/A
Hammer et al. (2021)	GS 19 PD 5	GS 5 PD 0	GS+ PD	Semi-quantitative scale	6	2.3	N/A	N/A
Inamo et al. (2019)	24	N/A	GS+ PD	Semi-quantitative scale	3	N/A	3	N/A
Kuettel et al. (2020)	8.3	10.04	GS+ PD	Semi-quantitative scale	1.67	2.58	2	2.6
Lin et al. (2022)	GS 20.2 PD 4.6	N/A	GS+ PD	Backhaus US7	6.2	N/A	6.9	N/A

Morris et al. (2021)	GS 43.6 PD 29.6	GS 32.3 PD 16.5	GS+ PD	Semi-quantitative scale	High	Reduced significantly	6.4	4
Nawata et al. (2021a)	GS 2.1 PD 0.3	N/A	GS+ PD	Semi-quantitative scale	5.6	N/A	N/A	N/A
Nawata et al. (2021b)	GS 3.1 PD 1.3	N/A	GS+ PD	Semi-quantitative scale	3.1	N/A	N/A	N/A
Sifuentes-Cantú (2020)	GS 94 PD 35	N/A	GS+ PD	GUS scoring	1.3	N/A	2.4	N/A
Sami et al. (2023)	GS 69% PD 7%	N/A	GS+ PD	Simplified 12-joint scoring + GUESS	6	N/A	4.3	N/A
Stein et al. (2020)	GS 5.9 PD 6.3	GS 2.1 PD 2.3	GS+ PD	US7 score	6.1	N/A	5	N/A
Tesei et al. (2021)	GS 9.5 PD 8	GS 4.1 PD 4.55	GS+ PD	US7 score	6.8	2.9	5.27	3.5

The baseline MSUS values reported in this table represent either the number of affected joints, semi-quantitative scores based on a 0–3 scale, or the percentage of scanned joints showing grey scale or Doppler activity. These metrics vary depending on how each study reported its findings. MSUS = Musculoskeletal Ultrasound; GS = Grey Scale; PD = Power Doppler; BL = Baseline; VAS = Visual Analogue Scale for Pain (0–10); DAS28 = Disease Activity Score using 28 joints; GUESS = Glasgow Ultrasound Enthesitis Scoring System; US7 = 7-joint ultrasound score; N/A = Not Available.

Abdellah et al. (2021) and Sami et al. (2023) highlight that MSUS synovitis and PD were detected at various entheseal sites in Patients with RA. They used the Glasgow Ultrasound Enthesitis Scoring System (GUESS) score to grade the joints. These MSUS findings were associated with high pain VAS (6) and DAS28 (4.3). Lin and colleagues (2022) used the Backhaus US7 score system to grade synovitis in Patients with RA. MSUS examinations

were blinded to all other measures and assessments. The results reveal that pain VAS and DAS28 are high, and MSUS synovitis (6.2, 6.9, and 31.4, respectively). Kuettel et al. (2020), Tesei et al. (2021), Hammer et al. (2021), Morris et al. (2021), and Blanco et al. (2020) conducted longitudinal studies on patients with RA. The results showed high MSUS synovitis and pain VAS at the baseline. On the follow-up, pain VAS scores and MSUS synovitis are improved in these studies (Table 1.12). Curtin et al. (2019) conducted MSUS on the hand and foot joints of the RA and non-RA patient groups. In the RA group, MSUS synovitis was higher than in the non-RA group. However, the pain VAS was high in both groups.

Abdulghani and colleagues (2021) highlight that MSUS examination showed PD signals in 57% of patients. A total of 26 patients were in remission, and a Doppler signal was detected in 58% of those cases. Pain VAS was high in both groups (5.7 and 6, respectively). The remission group reported high pain VAS in contrast to MSUS and DAS28. Sifuentes-Cantú (2020) emphasised that pain VAS was worsened at the baseline for patients in remission, although power Doppler synovitis was detected in up to 37% of Patients with RA. Nawata and colleagues (2021) conducted an MSUS study to investigate the subjective residual symptoms that persist after clinical remission of RA. They showed that the pain VAS was increased in patients with clinical remission, although the MSUS synovitis score was not.

1.13.6 Quality assessment

The quality of the included studies was assessed using the QUADAS-2 tool, which is designed to evaluate risk of bias and applicability in diagnostic accuracy studies. QUADAS-2 includes four key domains: Patient Selection, Index Test, Reference Standard, and Flow and Timing. For each domain, risk of bias was judged as either low (L), high (H), or unclear (?). While QUADAS-2 was originally developed for diagnostic accuracy studies, it was applied pragmatically in this review to structure and report potential sources of bias relevant to the review aim, which was to evaluate the association between MSUS-detected peripheral joint inflammation and pain in rheumatoid arthritis. In practical terms, QUADAS-2 helped to judge whether participant recruitment could introduce selection bias, whether MSUS assessment and interpretation were described clearly and carried out independently of clinical assessment results, whether the clinical disease activity assessment was described clearly, and whether the timing/flow of assessments was appropriate for interpreting study findings.

For the purposes of this review, the index test was musculoskeletal ultrasound (MSUS), specifically grey scale (GS) and power Doppler (PD) assessment of synovitis/inflammatory activity. The reference standard was treated as the clinical disease activity assessment (clinical comparator/reference assessment), such as DAS28 and/or clinical remission criteria, where reported. This approach was adopted because MSUS was the imaging method being evaluated for how well it reflects inflammatory status, whereas clinical assessment measures represent the established clinical approach used to define disease activity/remission in routine practice.

Pain VAS was not treated as a reference standard. Instead, pain VAS was extracted as the pain outcome measure (patient-reported pain intensity) used to examine concordance/discordance with MSUS inflammatory findings. Unless explicitly stated otherwise in individual studies, pain VAS was treated as a global/overall pain score rather than joint/region-specific pain at the scanned sites, consistent with the reporting notes used in this review.

The rationale for this classification is consistent with the review framework, where pain VAS is the primary outcome measure used to assess whether MSUS-detected inflammation corresponds with (or differs from) reported pain.

Table 1.13 summarises the QUADAS-2 appraisal for each included study. Overall, most studies demonstrated low risk of bias across domains. However, five studies were judged as unclear in the index test domain because they did not clearly report whether MSUS interpretation was performed without knowledge of the clinical comparator/reference assessment. No major applicability concerns were identified across the included studies.

Table 1.13: QUADAS-2 appraisal of the included studies.

Study	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Abdelghani et al. (2022)	L	L	L	L	L	L	L
Abdellah et al. (2021)	L	?	L	L	L	L	L
Blanco et al (2020).	L	?	L	L	L	L	L
Ciurtin et al (2019).	L	?	L	L	L	L	L
Hammer et al. (2021)	L	L	L	L	L	L	L
Inamo et al. (2019)	L	L	L	L	L	L	L
Kuettel et al. (2020)	L	L	L	L	L	L	L
Lin et al (2022)	L	L	L	L	L	L	L
Morris et al. (2021)	L	L	L	L	L	L	L
Nawata et al. (2021a).	L	L	L	L	L	L	L
Nawata et al. (2021b).	L	L	L	L	L	L	L
Sifuentes-Cantú (2020)	L	L	L	L	L	L	L
Sami et al. (2023)	L	?	L	L	L	L	L

Stein et al. (2020).	L	?	L	L	L	L	L
Tesei et al. (2021)	L	L	L	L	L	L	L

For the purposes of this review, MSUS (GS/PD synovitis assessment) was treated as the index test, and clinical disease activity assessment (e.g., DAS28 and/or remission criteria, where reported) was treated as the reference standard/clinical comparator. Pain VAS was extracted as the pain outcome measure (typically overall pain unless a study specified joint/region-specific pain). Keys: L = low risk of bias; H = high risk of bias;? = unclear risk of bias.

1.13.7 Discussion

This SLR summarises and evaluates evidence from the literature on the possibility of MSUS to reflect the level of pain in patients with RA objectively. However, there is limited research investigating the MSUS as a factor for pain in RA.

This SLR highlights a gap in the literature regarding the use of MSUS in evaluating pain mechanisms in RA, as most of the included articles did not employ MSUS to explore the nature of pain in RA. Additionally, investigating pain with MSUS was not their primary aim. Instead, they mainly used MSUS to monitor remissions and treatments in RA.

From the included articles in this review, pain VAS is the most effective measure for demonstrating overall pain intensity in RA clinically. However, pain VAS has limitations, including the difficulty in providing information about the source of pain because it is a subjective measure that relies on patients' reporting of pain. Therefore, MSUS offers an objective, sensitive, and non-invasive method for detecting peripheral changes at the joints, including synovitis, enthesitis, and tenosynovitis, thereby enabling a more accurate assessment of the biological factors underlying pain.

Furthermore, SLR highlighted the discrepancies among the included studies regarding the sensitivity of MSUS in assessing synovitis in RA and whether defining the severity of synovitis indirectly determines pain intensity in RA. Synovitis, characterised by synovial hypertrophy, joint effusion, and increased vascularity, is readily detected by MSUS. It enables clinicians to directly assess synovial inflammation, a classic key contributor to pain in RA. Most included studies in this SLR showed that synovitis severity reflects pain severity. Higher levels of synovial inflammation detected on ultrasound are associated with increased pain intensity reported by patients (Walsh and McWilliams, 2012). The clinical

manifestations of RA typically involve ongoing joint and systemic inflammation, as well as elevated levels of inflammatory markers in the bloodstream. Patients with RA commonly suffer from acute pain during episodes of inflammation and in the early phases of the condition, with a tendency to develop chronic pain as the disease progresses. Both local and systemic inflammation can influence how pain is perceived and processed. In RA, peripheral inflammation and resulting tissue damage contribute to the nociceptive aspect of pain (Sunzini et al., 2023). Initially, RA pain arises from inflammation, characterised by tenderness and swelling of the joint. Laboratory findings, such as increased C-reactive protein, and radiological procedures, including MSUS, can confirm this. Furthermore, rheumatoid factor is consistent with inflammation (Pisetsky and McCleane, 2009). Then, RA progresses, leading to erosion in bone and cartilage, which causes pain.

Few studies in this SLR showed that the pain worsened either in follow-up visits or at the remission stage. Patients continued to report high pain intensity despite advancements in treatment modalities, including disease-modifying anti-rheumatic drugs (DMARDs) and biological therapies. Further investigation is required in future research to understand chronic pain in RA, especially with effective management. However, according to previous research in the literature, the persistence of pain in Patients with RA despite effective treatment can be attributed to various biological mechanisms (Lee et al., 2011; Bailly et al., 2020). Chronic inflammation also leads to neuroplastic changes in the peripheral and central nervous systems, increasing pain sensitivity and amplifying pain signalling (Bailly et al., 2020). Central sensitisation in RA can occur due to ongoing peripheral inflammation and joint tissue damage. Persistent nociceptive input from inflamed joints leads to the activation and sensitisation of central pain pathways, contributing to the development of chronic pain and hyperalgesia in Patients with RA (Meeus and Nijs, 2007). However, the reasons for persistent pain in the included studies are unknown; therefore, additional investigation is needed to identify the definitive pain mechanism in this population.

In this SLR, most participants in the included studies were female. RA exhibits a striking gender bias, with women being two to three times more likely to develop the disease compared to men (Alamanos and Drosos, 2005). This gender disparity is evident across various populations and persists across different age groups. While the exact mechanisms underlying this phenomenon remain incompletely understood, several factors, including hormonal influences and genetic factors, have been proposed to contribute to the increased susceptibility of women to RA. The gender disparity in RA has significant implications for pain management. Female patients with RA tend to report higher levels of pain intensity,

more significant pain-related disability, and poorer quality of life compared to male patients (Chancay et al., 2019). The reasons for these differences in pain perception and management are multifactorial and may include biological, psychological, and sociocultural factors. Differences in pain processing and neuroimmune interactions between men and women may contribute to variations in pain perception and response to treatment in RA (Fillingim et al., 2009). Hormonal fluctuations, such as those associated with the menstrual cycle and menopause, can also influence pain sensitivity and the efficacy of pain medications (Chancay et al., 2019). Psychosocial factors, including depression, anxiety, and stress, are more prevalent in women with RA and can exacerbate pain perception and coping mechanisms (Nicassio et al., 2011).

In the included studies, different treatment drugs were used, and these drugs could play a role in the intensity of pain experienced by patients with RA. Effective management of RA involves a comprehensive approach that includes pharmacological interventions aimed at controlling inflammation, alleviating pain, and improving overall quality of life. The treatment drugs used in RA play a crucial role in pain management by addressing both the underlying inflammation and the nociceptive component of pain. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) provide immediate relief from pain and stiffness by reducing inflammation and inhibiting pain mediators. DMARDs, including both conventional synthetic and biological agents, help to control disease activity, prevent joint damage, and ultimately reduce pain over the long term (Singh et al., 2016). In addition to controlling inflammation, DMARDs have improved pain and physical function in patients with RA, leading to better quality of life outcomes. Biologic DMARDs, in particular, have demonstrated efficacy in reducing pain and improving joint symptoms in patients with moderate to severe RA who have failed to respond to conventional therapies (Taylor et al., 2016). By optimising treatment strategies and addressing patients' needs, healthcare providers can improve pain management outcomes and enhance the overall quality of life for individuals with RA.

Clinical studies focused on pain in RA are crucial for advancing our understanding of the disease, optimising treatment strategies, and improving patient outcomes. These studies encompass various aspects, including patient characteristics, drugs used, inflammation markers, central sensitisation, and imaging techniques.

This SLR suggests conducting further research to fully understand the pain mechanisms in RA. MSUS is a sensitive tool for detecting peripheral joint changes. It could be used to investigate the nature of pain in RA, especially causes related to peripheral inflammation

and damage. This SLR highlights the importance of examining pain in RA at different time points. Therefore, analysing the relationship between MSUS and patient characteristics at various time points, such as baseline, including demographics, disease duration, disease activity scores (e.g., DAS28), and pain intensity scores (pain VAS), would provide information about disease activity and inflammation status, especially when correlated with clinical inflammation biomarkers, when relating pain measures to MSUS. This information could enhance understanding of the nature of pain in RA. Inflammation might be linked to changes in the joints, or the absence of inflammation could indicate a non-inflammatory source of pain. In this context, MSUS will be crucial in confirming the presence of inflammatory changes in the joints. Biomarkers such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and pro-inflammatory cytokines (e.g., tumour necrosis factor-alpha - TNF-α, interleukin-6 - IL-6) are commonly measured to quantify disease activity and assess treatment responses. Additionally, longitudinal evaluation of inflammation markers allows researchers to correlate changes in inflammatory status, including MSUS findings, with pain outcomes and clarify the mechanisms underlying pain in RA. Furthermore, it is essential to investigate the contribution of central sensitisation in chronic RA, characterised by heightened pain sensitivity and abnormal pain processing within the central nervous system.

Furthermore, MSUS proves to be a valuable tool for identifying inflammatory peripheral changes in RA that correlate with disease activity. Therefore, MSUS is a useful instrument for monitoring changes in Patients with RA over time. This SLR supports the classical understanding of pain, as inflammation decreases in response to treatment, and therefore, pain levels tend to improve. However, some included studies in this SLR have noted that patients may still report pain even during the remission stage despite MSUS indicating either no synovitis or improved synovial inflammation. These observations regarding pain in RA require further investigation. Although subjective pain measures provided a complete understanding of the ongoing pain mechanism, a gap remains to be filled by introducing objective pain measures. This is necessary to understand the pain mechanism, as this SLR suggests that more than one pain mechanism may contribute to persistent pain in RA. Addressing this discrepancy requires further investigation into the underlying pain mechanisms in RA. MSUS provides a reliable and sensitive method for detecting inflammatory changes, encompassing both structural issues such as synovitis, enthesitis, and tenosynovitis, as well as disease activity through the use of USPD. This capability enhances the accuracy of assessing the biological causes of pain. Consequently, MSUS can help identify peripheral sources of pain, making it a potential peripheral marker for

inflammatory arthritis. However, further research is needed due to inconsistencies in the reported relationship between MSUS and pain VAS measures in the literature. More studies exploring this relationship across different inflammatory arthritis groups could enhance understanding of pain mechanisms.

In conclusion, this SLR highlights the lack of research investigating the correlation between pain measures and MSUS. There was a lack in the research in exploring pain in RA using MSUS. Most of the included articles focused on the role of MSUS-monitored remission and treatments in RA. None of the included articles mainly focused on investigating pain mechanisms in RA using MSUS. This investigation is crucial for understanding the nature of pain in RA, whether inflammatory or non-inflammatory factors cause it. MSUS could play a significant role in identifying the nature of pain, either directly by confirming the presence of peripheral changes at the joints or indirectly by confirming their absence. This information is crucial for understanding the characteristics of pain in RA. Further research is necessary to clarify the role of MSUS in understanding pain in RA.

1.13.8 Limitations

Despite the systematic approach adopted in this review, several limitations must be acknowledged. Firstly, the heterogeneity among the included studies posed challenges for consistent comparison. Differences were observed in ultrasound protocols (e.g., joint sites scanned, scoring systems used), pain assessment methods, and definitions of remission or clinical response. This variability restricts the ability to synthesise findings quantitatively or draw strong generalisations. Secondly, although most studies reported low risk of bias, some lacked clear reporting on whether the index test (MSUS or pain VAS) was interpreted independently of the reference standard (clinical assessment). This introduced potential for assessment bias in several cases, as identified by the QUADAS-2 evaluation. Thirdly, the primary objective of most included studies was not to investigate pain mechanisms in RA specifically. Instead, MSUS was often used to evaluate treatment effects or disease activity, while pain outcomes were secondary or descriptive. As a result, the ability to directly assess the relationship between MSUS-detected synovitis and patient-reported pain was limited. Moreover, few studies incorporated longitudinal data assessing pain and MSUS changes over time. Only a small subset examined whether persistent pain occurred despite improvement in inflammatory markers or ultrasound scores, thereby limiting insights into non-inflammatory pain mechanisms such as central sensitisation or neuropathic contributions.

Finally, although the literature search was robust and covered two major databases, language limitations (English-only) and exclusion of grey literature (e.g. unpublished theses or local journals) may have led to omission of relevant studies, particularly from non-Western contexts.

1.13.9 Future Studies

Future research should prioritise well-designed longitudinal studies that specifically investigate the relationship between MSUS findings and the different dimensions of pain in RA, including inflammatory, neuropathic, and nociplastic components. Studies should aim to recruit diverse patient populations and ensure consistent use of validated pain and ultrasound scoring systems, enabling better comparisons and meta-analysis.

Additionally, researchers should explore multimodal assessment strategies, combining MSUS with central nervous system imaging (e.g., fMRI) or pain sensitisation measures to better differentiate inflammatory from non-inflammatory pain mechanisms.

More studies are also needed to examine persistent pain in patients in clinical or ultrasound-defined remission, with attention to psychosocial, hormonal, and gender-based factors that may modulate pain experience.

Finally, future systematic reviews could expand their scope to include grey literature and non-English studies, potentially uncovering underreported findings and reducing publication bias. Establishing international consensus on MSUS pain-specific protocols would also enhance standardisation across studies.

1.13.9.1 SLR Summary

This chapter presents an SLR exploring the role of MSUS in evaluating pain in patients with RA. While MSUS is widely used to assess joint inflammation and monitor treatment response, its potential to reflect or explain patient-reported pain remains underexplored. Pain in RA is multifactorial, encompassing both inflammatory and non-inflammatory mechanisms, and may persist even in states of clinical or ultrasound-defined remission.

A systematic search strategy was applied across key databases (PubMed and Web of Science), identifying 15 eligible studies published between January 2019 and December 2023. The included studies were evaluated for methodological quality using the QUADAS-

2 tool and summarised in terms of design, population, ultrasound protocol, pain measures, and clinical outcomes.

Despite the growing use of MSUS in RA management, findings across studies were inconsistent in linking ultrasound-detected synovitis with pain intensity. In some cases, pain persisted even as synovitis improved, suggesting possible roles for central sensitisation or other non-inflammatory mechanisms.

MSUS has proven useful for assessing synovitis severity in RA and providing insights into pain intensity. However, the persistent presence of pain in patients showing improvement in synovitis requires further investigation into the underlying mechanisms of pain in RA. There is a need for more targeted research exploring the biological basis of pain in RA, using both imaging techniques and patient-reported outcomes.

Chapter 2 Exploring the prevalence of pain and quality of life in patients with early rheumatoid arthritis

2.1 Abstract

Introduction

Pain is the hallmark of RA, and it has long been classically believed that this pain originates from the inflammation present in the joints. Typically, this inflammation is linked to pain that tends to improve with effective treatment. However, recent studies indicate that many patients continue to experience pain even after their inflammation has been successfully managed. Research shows that higher pain levels profoundly affect the quality of life for those living with RA.

Objectives

To investigate the prevalence of persistent pain in patients with early RA and assess the impact of chronic pain on their quality of life. Furthermore, this study seeks to examine the clinical measures associated with persistent pain in participants with RA.

Methods

A secondary retrospective analysis was conducted based on the original prospective and observational data from the Scottish Early Rheumatoid Arthritis (SERA) study. Descriptive statistics were conducted at baseline and the 12-month follow-up visits. This analysis was performed using the IBM SPSS Statistics software package (version 29.0.2.0). Continuous variables were analysed, including pain VAS, DAS28, and EQ-5D.

Then, participants were divided into two groups based on their 12-month pain VAS scores: non-persistent pain and persistent high pain, using a cut-off of ≥ 34. Those with consistently high pain at baseline, 6 months, and 12 months were classified as persistent high pain, while those who improved at any point were classified as non-persistent pain. Then descriptive statistics were conducted for each group. An independent samples t-test was performed at the 12-month follow-up visit to determine whether there were statistically significant differences in the mean values of the outcome variables (DAS28, ESR, TJC, SJC, EQ-5D, and Pain VAS) between the two groups experiencing different types of pain (persistent high vs non-persistent). Additionally, changes in clinical measures were calculated to account for baseline values and to assess the impact of standard care on these clinical variables. Another independent samples t-test was conducted to evaluate whether there were statistically significant differences in the changes to the outcome variables. Finally, the clinical measures in the persistent high pain group were assessed for

inflammation markers, and Mann-Whitney rank tests were conducted to determine significant differences.

Results

A total of 723 participants (70.06%) out of 1039 reported experiencing significant pain at baseline (pain VAS ≥ 34), with a mean pain VAS of 52.3, and the EQ-5D score, which assesses health-related quality of life, was relatively low at 0.48, indicating poor quality of life at baseline.

At the 12-month follow-up visit, 268 (35%) out of 757 participants reported persistent high pain with a mean of 59.34, and the EQ-5D score increased to 0.69 at the 12-month follow-up visit.

A total of 134 participants (12.98%) reported experiencing high levels of pain that persisted at all visits, while 623 participants in the non-persistent pain group indicated lower pain intensity. The average score on the pain VAS for the persistent high pain group was 61.34, in contrast to 21.79 for the non-persistent group. Quality of life, as assessed by the EQ-5D scale, was substantially lower in the persistent high pain group, with a mean score of 0.39, compared to 0.75 in the non-persistent group. There was a significant difference in EQ-5D scores between the groups at the 12-month follow-up visit; however, no significant difference was observed in the change over time.

Out of 134 participants, 4.48% achieved remission according to the DAS28 criteria at the 12-month follow-up. 16.42% showed a negative SJC, while 36.56% had a high TJC, defined as greater than 11. 44.04% of participants demonstrated a normal ESR of less than 20. The Mann-Whitney tests showed that the normal ESR varied significantly in this population.

Conclusion

The research revealed that 70.05% of participants experienced high pain levels at baseline, a common occurrence in RA. By the 12-month follow-up, pain intensity had improved due to effective treatments targeting inflammation; however, 35% of participants continued to report high pain levels. Quality of life, as measured by the EQ-5D scale, demonstrated improvement from baseline to the 12-month follow-up. Nonetheless, those with persistent high pain reported lower scores, underscoring the detrimental impact of ongoing pain on overall quality of life. Furthermore, 12.8% of participants experienced chronic pain consistently throughout all visits, suggesting that non-inflammatory factors may play a role.

Although some clinical measures indicated joint inflammation, these findings were not statistically significant. Therefore, additional assessment tools, such as musculoskeletal

ultrasound (MSUS), are necessary to gain a clearer understanding of inflammation and pain mechanisms in this RA population.

2.2 Introduction

RA is a chronic autoimmune disease that affects multiple joints and is often associated with pain, which can limit patients' daily activities. The goal of managing RA is to reduce the disease's impact on disability and to improve the patient's quality of life. Healthcare professionals consider persistent pain and loss of function to be the most critical effects of RA on patients. These challenges stem from ongoing inflammation of the joints and the gradual deterioration of joint health. However, RA influences numerous aspects of a person's life, reaching beyond the typical scope of medical treatment. It can be challenging to provide a concise summary of how pain in RA affects patients, as its effects vary widely based on numerous personal factors.

2.2.1 Pain in RA

Pain is the primary reason patients seek medical care. Nearly all medications used to treat arthritis, including analgesics, anti-inflammatory drugs, disease-modifying anti-rheumatic drugs (DMARDs), and biological therapies, are designed to provide varying degrees of pain relief. However, many patients continue to experience significant pain despite these treatments (Walsh and McWilliams, 2014).

Patients with RA report higher pain levels compared to the general population, with pain levels similar to those experienced by patients with non-inflammatory pain. However, Patients with RA often face greater disability (Sokka, 2003).

Traditionally, it has been believed that pain in RA originates from inflammatory changes in the joints. These changes are associated with pain, which can be alleviated when patients receive treatment to control the inflammation. Research indicates that higher pain levels are linked to increased disability and a higher incidence of depression, all of which significantly affect the quality of life for Patients with RA (Rupp et al., 2006).

Chronic pain in RA is a multifaceted issue influenced by various factors. Some studies have indicated that patients continue to report pain even when this inflammation has been effectively treated (Basu et al., 2018).

It stems from peripheral inflammation and non-inflammatory pain mechanisms, including central sensitisation (Lee et al., 2018; Vladimirova et al., 2015). Chronic pain may lead to

more persistent functional impairment and disability, affecting activities of daily living and overall quality of life.

By addressing the complexities of pain in early RA, researchers can inform tailored treatment strategies, optimise patient care, and improve quality of life outcomes.

2.2.2 Prevalence of pain in RA

Estimates indicate that the prevalence of RA among adults in the USA and Europe ranges from 0.4% to 1.0% (Alamanos et al., 2006). In the UK, the disease affects 0.81% of the adult population, with a female-to-male ratio of nearly 3:1 (Symmons et al., 2002). In Norway, the prevalence is reported at 0.44% (Madsen et al., 2016), while lower rates are observed in Southern Europe and developing countries (Alamanos et al., 2006).

Gossec and colleagues (2009) and Hewlett and colleagues (2005) identified pain as one of the two most critical patient outcomes, alongside physical functioning. In a study of patients with early RA after a six-month treatment period, it was found that 40.2% did not achieve a meaningful improvement in pain, defined as a reduction of 30 mm or more on the pain VAS (Ten Klooster et al., 2015). Additionally, approximately 20% of Patients with RA experience pain that has non-inflammatory characteristics (Koop et al., 2015; Rifbjerg-Madsen et al., 2017).

2.2.3 Quality of life in RA

Historically, the World Health Organisation has defined the impact of chronic diseases, such as RA, on patients' lives through three levels: impairment, disability, and handicap.

Impairment is described as the loss of physical or mental function. Disability refers to the inability to perform usual activities because of an impairment. Handicap refers to an individual's challenges because of their impairment or disability, which restricts their ability to participate in normal life roles (West and Jonsson, 2005).

As a progressive condition, RA leads to persistent pain that can severely restrict an individual's daily activities. Consequently, the quality of life (QoL) for those suffering from RA is significantly impacted across various domains, including physical health, independence, environmental factors, and personal beliefs (Jakobsson et al., 2002).

In clinical research, patient-reported outcomes and QoL assessments are typically collected using health-related quality of life (HRQoL) instruments to evaluate the effectiveness of treatments on Patients with RA. Several generic tools are available for measuring QoL,

such as the EuroQoL Five-Dimensional Questionnaire (EQ-5D), Short Form 6D (SF-6D), and the Health Utilities Index, in addition to disease-specific questionnaires like the RA Quality of Life (RAQoL) (Haridoss et al., 2021).

Among these, the EQ-5D is one of the most widely used HRQoL instruments. It is the preferred method for assessing health state utilities in health technology assessments (HTA), as endorsed by the National Institute for Health and Care Excellence (NICE)(Haridoss et al., 2021). The EQ-5D employs both descriptive elements and a visual analogue scale (EQ-5D-VAS) to evaluate health status across five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (Brooks et al., 2003). Each dimension includes five response levels (the EQ-5D-5L, which has replaced the earlier EQ-5D-3L with three levels). The scores for these dimensions are combined into a single summary index number (utility), which ranges from 0 (indicating death) to 1 (indicating perfect health), with values below 0 representing health states perceived as worse than death (Bernfort et al., 2018). The EQ-5D-VAS, measured on a scale from 0 to 100, reflects the patient's health self-assessment (Haridoss et al., 2021).

2.2.4 Aim

This research aims to investigate the prevalence of persistent pain in patients with early RA using the SERA dataset and to assess its impact on their quality of life. Additionally, this research aims to explore the clinical measures associated with persistent pain in RA.

There is a lack of studies in the literature focusing on the persistent pain in early RA and its impact on the quality of life, since most of the chronic pain data exists in the RA population. Therefore, exploring the prevalence of persistent pain in early RA would lead to tailored treatment strategies, optimise patient care, and enhance quality of life outcomes.

2.2.5 Hypothesis

I hypothesise that the prevalence of persistent pain in patients with early RA is significantly high, with a majority reporting persistent pain despite standard treatment interventions in the Scottish early RA cohort.

I hypothesise that persistent pain in early Patients with RA is associated with a significantly lower quality of life compared to patients without persistent pain.

2.3 Methods

In this chapter, a secondary retrospective analysis of the original SERA study (a prospective and observational study; Dale et al., 2016) is described below. This analysis aims to investigate the prevalence of chronic pain in patients with early RA and assess its impact on the quality of life. Additionally, it explores the differentiation between inflammatory and non-inflammatory chronic pain in early RA.

2.3.1 The original SERA study

The SERA Study was launched by the Scottish Collaborative Arthritis Research (SCAR, www.scarnetwork.org) network, which involves a partnership between the Universities of Aberdeen, Dundee, Edinburgh, and Glasgow, NHS Scotland, Healthcare Improvement Scotland, the Chief Scientist's Office Scotland, and Pfizer Ltd. The study's protocol and procedures received a favourable review from the West of Scotland Research Ethics Committee, and all participating patients provided written informed consent to take part (Dale et al., 2016).

Rheumatology units from across Scotland participated in the SERA study. Patients with a new clinical diagnosis of RA or undifferentiated arthritis (UA) and who have at least one swollen joint are invited to participate. The diagnosis of RA was made based on the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) Classification Criteria for RA (Aletaha et al., 2010). Patients were classified as having UA if they exhibited clinical evidence of inflammatory arthritis but did not meet the criteria for RA or any other specified rheumatic disease baseline. Patients are excluded if their joint swelling can be explained by an alternative diagnosis (e.g. psoriatic arthritis) or if they are carriers of blood-borne viruses. Duration of symptoms up until diagnosis is not an exclusion criterion. A short duration of treatment was permitted to enhance recruitment efforts. In most cases, this means that participants likely had their study recruitment visits shortly after their initial patient visit, during which they may have begun treatment.

Potential participants are referred to local research nurses for screening and baseline assessments. Treatment decisions (including initiation and escalation) and clinical follow-up remain the responsibility of the local rheumatology department, which follows standard local practice. Patients are not excluded if treatment with steroids or DMARDs has already started prior to recruitment (for example, by the General Practitioner) as long as the diagnosis of UA/RA is new and treatment has commenced within the last 6 months. The

design of the SERA dataset was practical and aligned with clinical practices at the time of recruitment. The goal was to identify new diagnoses of RA as they presented in clinics, creating a population with a disease presentation and progression similar to "real-life" cases. The inclusion of some patients who had already started on DMARDs and steroids prior to recruitment also reflects actual clinical practice.

All participants provide generic and enduring consent that allows the collection of demographic and outcome data, retrieval and linkage of routine health care data, and long-term storage of data and samples for future research projects.

Research nurses conducted evaluations of participants every six months during the first two years and then annually thereafter. They were responsible for the assessment and collection of all outcome data. Demographic and clinical outcome information were gathered in a standardised manner at both baseline and follow-up. This data includes age, gender, DAS28 score, tender joint count (TJC), swollen joint count (SJC), erythrocyte sedimentation rate (ESR), patient global VAS, pain VAS, rheumatoid factor (RF), and responses from the EQ-5D questionnaire, along with its VAS. The standardised SJC and TJC assessment for RA includes 28 specific joints, such as shoulders, elbows, wrists, MCPs, PIPs, and knees. Additionally, plain radiographs of both hands and feet will be taken at the beginning of the study and again after 12 months of follow-up.

Recruitment started in September 2011, with patients gathered from 16 rheumatology departments across ten Scottish NHS Health Boards. By April 2015, 1,073 patients had provided complete baseline data.

Access to the SERA dataset was obtained through a formal data request submitted to the SERA study management group. The application included demographic data, clinical variables such as DAS28, TJC, SJC, ESR, patient global VAS, and pain VAS. Serological status (RF), quality of life, and EQ-5D (including its VAS) were measured to assess the prevalence of pain in early RA and to investigate the clinical variables and quality-of-life factors associated with reported pain in patients with early RA.

2.3.2 Descriptive statistics of the SERA dataset

To characterise and summarise the study population and the measures of interest, descriptive statistics were employed at baseline and at the 12-month follow-up visits. This analysis was performed using the IBM SPSS Statistics software package (version 29.0.2.0). For continuous variables, which include pain VAS, DAS28 scores, and EQ-5D, the descriptive statistics consisted of means and standard deviations (SD) for data that

followed a normal distribution, and medians and interquartile ranges (IQR) for data that did not at the baseline visit, 12-month visit and the change. The change is achieved by calculating the difference between 12-month and baseline visits. In addition, the age and gender of participants were represented.

2.3.3 Evaluation of clinical and quality of life outcomes in pain subgroups

Participants were divided into two groups for a comparative statistical analysis based on their pain VAS scores from baseline through the 12-month visits: non-persistent and persistent high-pain groups (Waldheim et al., 2013). This analysis used a pain VAS cutoff of ≥ 34 because this cut-off tends to interfere more with daily functioning and quality of life. It also provides the best balance between sensitivity and specificity in differentiating mild pain from more clinically significant pain levels (Boonstra et al., 2014). Pain VAS scores less than 34 were classified as low pain, while scores of 34 or higher were categorised as high pain. Participants who continued to report high pain at baseline, as well as at the 6-month and 12-month follow-up visits, were classified as having high persistent pain. In contrast, participants who reported an improvement in pain intensity at any time point were assigned to the non-persistent pain group.

Descriptive statistics using standardised mean difference (Cohen's d) were conducted for each group. The Cohen's threshold (small: $d \approx 0.2$, medium: $d \approx 0.5$, large: $d \geq 0.8$) was used (Cohen, 2013).

The mean and standard deviation for each outcome variable were calculated for both the non-high-persistent and high-persistent groups. Also, the Sample sizes (N) for each group were reported.

Effect size analysis was conducted to measure the strength of the relationship between variables or the magnitude of the difference between the non-high-persistent and high-persistent groups.

The following variables were investigated: DAS28 as an indicator of disease activity, SJC, TJC and ESR as clinical markers of inflammation. In addition, the frequency and percentage for each measure were calculated using SPSS. An independent-samples t-test was conducted to assess whether there were statistically significant differences in the mean values of the outcome variables (DAS28, ESR, TJC, SJC, EQ5D, and Pain VAS) between the two pain groups (persistent vs non-persistent).

2.3.4 Evaluating the clinical variables changes in non-persistent and persistent high pain groups.

This analysis was performed to account for baseline differences that could have influenced the interpretation of changes in clinical variables at the 12-month visits. The longitudinal effects can be assessed by calculating the change score (12-month values minus baseline values) while controlling for these baseline differences.

Descriptive statistics were carried out for each group. The sample sizes (N), means, and standard deviations for each variable change were determined for both the non-high-persistence and high-persistence groups.

An effect size analysis was conducted to evaluate the strength of the relationship between the changes in variables and to measure the extent of the difference between the non-high-persistent and high-persistent groups.

An independent-samples t-test was conducted to determine whether there were statistically significant differences in the mean values of the outcome variables (DAS28 change, ESR change, TJC change, SJC change, EQ5D change, and Pain VAS change) between the two pain groups (persistent vs non-persistent).

2.3.5 Explore the clinical measures of persistent high pain in RA.

Clinical measures, including negative SJC, high TJC, normal ESR, and DAS28 remission, were examined among participants experiencing persistent high pain. DAS28 Remission, defined as a DAS28 score of less than 2.6, indicating minimal disease activity (Fransen et al., 2004); a negative SJC, which indicates the absence of swollen joints and reflects a lack of inflammation; and a normal ESR, with values less than 20, suggesting no active inflammation (Sokka et al., 2009). Finally, a TJC greater than 11 indicates non-inflammatory pain (Pollard et al., 2010).

The descriptive analysis, including frequency and percentage of each measure, was calculated using SPSS software. Mann-Whitney rank tests were conducted to identify any significant differences between these variables.

2.4 Results

2.4.1 Descriptive statistics

The results showed that 1039 participants were included in this study, with a higher proportion of females compared to males (64.6% and 35.4%, respectively) (Table 2.1). The baseline mean age was 60.3 years for females and 56.7 years for males (Table 2.1).

Table 2.1: The demographic characteristics of study participants.

Gender	Frequency	Age at BL (mean±SD)
Male	**368 (35.4%)**	**60.3 ± 0.66 yrs**
Female	**671 (64.6%)**	**56.7 ± 0.55 yrs**

At baseline, the mean pain VAS score was 52.3, with a median value of 54, indicating moderate to severe pain levels across the cohort. In addition, 723 participants (70.06%) reported high pain at the baseline (pain VAS ≥34) with a mean Pain VAS of 59.34. The mean scores for the SJC and TJC were 7.25 and 8.21, respectively, reflecting significant joint involvement. Inflammatory markers, such as ESR, were elevated, with a mean of 30.3. Additionally, disease activity, measured by DAS28, was high, with a mean of 5.93 (Table 2.2).
The EQ-5D score, which assesses health-related quality of life, was relatively low at 0.48, indicating poor quality of life at baseline.

At the 12-month follow-up, significant improvements were noted across all parameters. The pain VAS scores demonstrated a marked decrease, with a mean of 28.79 and a median score of 21, indicating a substantial reduction in pain levels. Additionally, 268 participants (35%) reported high pain during the 12-month follow-up visit. Likewise, both SJC and TJC showed notable reductions, with mean values dropping to 3.92 and 6.26, respectively. Additionally, ESR exhibited a significant improvement, with a mean of 17.68, and DAS28 decreased considerably, with scores falling to a mean of 3.71, reflecting enhanced disease control. Finally, the EQ-5D score increased to 0.69 at the 12-month follow-up visit, up from 0.48 at baseline, indicating a significant improvement in quality of life (Table 2.2).

Table 2.2: Descriptive statistics at baseline and the 12-month follow-up visits.

Baseline						
	Pain VAS	**SJC**	**TJC**	**ESR**	**DAS28**	**EQ5D**
N	1032	1037	1039	700	695	1038
Missing	7	2	0	339	344	1
Mean ± Sd	52.3±27.64	7.25±6.75	8.21±6.7	30.3±23.8	5.93±1.5	0.48±0.38
Median	54	5	6	23	5.95	0.62
IQR	43	8	8	30	2.1	0.5
12-month Follow-up						
N	757	770	770	477	469	766
Missing	282	269	269	562	570	273
Mean ± Sd	28.79±25.8	3.92± 5.84	6.26±8.47	17.68±17.16	3.71±1.65	0.69±0.31
submissionMedian	21	1	2	12	3.52	0.76
IQR	43	5	9	17	2.43	0.3

VAS = Visual Analogue Scale for Pain (0–10); DAS28 = Disease Activity Score using 28 joints; SJC= swollen joint count, TJC= tender joint count, ESR=Erythrocyte Sedimentation Rate, EQ5D=EuroQo Five-Dimensional Questionnaire to measure the quality of life related to RA.

2.4.2 Evaluation of clinical and quality of life outcomes in pain subgroups

Participants were classified into two subgroups based on their pain VAS scores at the 12-month follow-up (cutoff≥34). The results indicate differences in outcomes between participants experiencing non-persistent pain and those with persistent high pain at the 12-month follow-up. Participants in the persistent high-pain group reported markedly poorer outcomes across all assessed measures.

In the persistent high pain group, 134 participants reported experiencing significant pain levels, while 623 participants in the non-persistent pain group reported lower pain intensity. The mean score on the pain VAS was 61.34 in the persistent high-pain group, compared with 21.79 in the non-persistent group (Table 2.3). This considerable difference in the mean of pain VAS scores highlights a notable disparity in pain intensity between the two groups.

There was a notable difference in joint involvement between the two groups. In the persistent high pain group, the average SJC was higher, at 5.01, compared to 3.69 in the non-persistent group. Additionally, the average TJC was almost twice as high in the persistent high pain group, with a mean of 10.26, in contrast to 5.42 in the non-persistent group.

The mean ESR values were higher in the persistent high pain group, averaging 23.0, compared to the non-persistent group, which had a mean ESR of 16.22 (Table 2.3). The decrease in ESR values within the non-persistent group suggests an improvement in inflammation among the participants.

The disease activity, as measured by the DAS28 score, was higher in the persistent high pain group, with a mean of 4.72. In contrast, the non-persistent pain group had a lower mean DAS28 score of 3.47 (Table 2.3). Therefore, participants in the non-persistent group did not meet the remission threshold of 2.6.

Table 2.3: Comparisons of clinical and quality of life measures at the 12-month follow-up visit between non-persistent and persistent high pain groups.

	Pain Groups	N	Mean	Std. Deviation
Pain VAS 12-month	Non-persistent	623	21.79	21.95
	Persistent high	134	61.34	16.02
SJC 12-month	Non-persistent	636	3.69	5.83
	Persistent high	134	5.01	5.79
TJC 12-month	Non-persistent	636	5.42	8.031
	Persistent high	134	10.26	9.37
ESR 12-month	Non-persistent	386	16.22	14.43
	Persistent high	91	23.9	24.87
EQ5d 12-month	Non-persistent	633	0.75	0.25
	Persistent high	133	0.39	0.41
DAS28 12-month	Non-persistent	378	3.47	1.57
	Persistent high	91	4.72	1.61

The quality of life, as measured by the EQ-5D scale, was significantly lower in the persistent high pain group, with a mean score of 0.39, compared to 0.75 in the non-persistent group (Table 2.3). These results highlight the severe impact that persistent high pain has on physical health and overall quality of life. This emphasises the necessity for targeted interventions aimed at managing and alleviating chronic pain in those affected.

For SJC, results indicated more swelling in the persistent high-pain group ($p = 0.018$). There was a notable difference in TJC ($p < 0.001$), reflecting significantly more tender joints in the persistent high-pain group.

ESR results also showed significant differences ($p < 0.001$), indicating higher inflammation in the persistent high-pain group. For DAS28, the persistent high pain group had higher scores ($p < 0.001$). In the EQ-5D assessment, the non-persistent group performed better, with a statistically significant result ($p < 0.001$).

Table 2.4: Effect size estimates and confidence intervals for the pain VAS, SJC, TJC, DAS28, ESR and EQ-5D at a 12-month follow-up visit.

				95% Confidence Interval	
		Standardizer[a]	Point Estimate	Lower	Upper
Pain VAS 12-month	Cohen's d	21.03	-1.88	-2.08	-1.67
SJC 12-month	Cohen's d	5.82	-0.22	-0.41	-0.03
TJC 12-month	Cohen's d	8.28	-0.58	-0.77	-0.39
ESR 12month	Cohen's d	16.91	-0.45	-0.68	-0.22
DAS28 12month	Cohen's d	1.58	-0.79	-1.02	-0.55
EQ5d 12month	Cohen's d	0.28	1.28	1.09	1.48

VAS = Visual Analogue Scale for Pain (0–10); DAS28 = Disease Activity Score using 28 joints; SJC= swollen joint count, TJC= tender joint count, ESR=Erythrocyte Sedimentation Rate, EQ5D=EuroQo Five-Dimensional Questionnaire to measure the quality of life related to RA.

The effect sizes between participants in the persistent high pain and non-persistent groups at the 12-month visit across several clinical outcomes showed significant differences.

In the context of the pain VAS, the effect sizes were found to be large and negative (Cohen's $d = -1.88$) based on traditional Cohen's thresholds (small: $d \approx 0.2$, medium: $d \approx 0.5$, large: $d \geq 0.8$)(Cohen, 2013), with confidence intervals ranging from -2.08 to -1.66. This large negative effect size on Pain VAS indicates a substantial reduction in reported pain in the non-persistent pain group compared to the persistent pain group. Since pain VAS is a direct patient-reported outcome measure, this demonstrates that persistent pain status is clinically meaningful.

Additionally, the outcomes related to joint involvement reveal smaller but statistically significant differences. For SJC, the effect size is small and negative (Cohen's $d = -0.22$, CI: -0.41 to -0.03), indicating that the persistent high-pain group has slightly more swollen joints. In contrast, for TJC, the effect size is moderate (Cohen's $d = -0.58$, CI: -0.77 to -

0.39), suggesting that the persistent high-pain group reports greater joint tenderness (Table 2.4).

The results show that the ESR indicates a moderate negative effect size (Cohen's d = -0.45, CI: -0.68 to -0.22), suggesting that the persistent high pain group exhibits higher inflammatory activity. Additionally, the DAS28 reveals a large negative effect size (Cohen's d = -0.79, CI: -1.02 to -0.55), indicating significantly worse disease activity in the persistent high-pain group.

The quality of life, evaluated using the EQ-5D, demonstrated a substantial positive effect size (Cohen's d = 1.28), with confidence intervals ranging from 1.08 to 1.48 (Table 2.4). This result highlights a significantly better quality of life for the non-persistent pain group, in contrast to the poorer quality of life experienced by participants in the persistent high-pain group.

2.4.3 Evaluating the clinical variables changes in non-persistent and persistent pain groups.

The results emphasise the differences in clinical outcome changes over time between the non-persistent and persistent high-pain groups.

In the analysis of pain VAS change scores, the persistent high pain group showed a smaller decrease in pain levels, with a mean change of -9.45, compared to a mean change of -25.81 in the non-persistent pain group (Table 2.5).

Regarding the SJC change, the persistent high pain group exhibited a more significant reduction, with a mean change of -65.79 compared to -44 in the non-persistent group. This difference was statistically significant ($p < 0.001$), indicating a greater improvement in swollen joints for the persistent high-pain group. Additionally, participants in the non-persistent group demonstrated more improvement in TJC change, with a mean change of -2.70 compared to 0.91 in the persistent high-pain group (Table 2.5). This significant difference ($p < 0.001$) showed greater outcomes for tender joints in the non-persistent group.

For the DAS28 change, the mean was -2.27 in the non-persistent pain group and -2.15 in the persistent high pain group. This difference was not statistically significant ($p = 0.38$), indicating similar reductions in disease activity across both groups.

For the ESR change, the non-persistent pain group experienced a mean change of -13.50, compared to -10.65 in the persistent high pain group (Table 2.5). However, this difference was not statistically significant ($p = 0.23$).

Finally, the EQ5D change was similar between the two groups, with a mean change of 0.20 in the non-persistent pain group and 0.17 in the persistent high pain group (Table 2.5). This difference was not statistically significant (p = 0.51).

Table 2.5: Comparisons of the change in clinical and quality of life measures between non-persistent and persistent high-pain groups.

	Pain Groups	N	Mean	Std. Deviation
Pain VAS Change	Non-persistent	618	-25.81	35.13
	Persistent high	134	-9.45	24.30
SJC Change	Non-persistent	631	-44	28.45
	Persistent high	134	-65.79	18.75
TJC Change	Non-persistent	636	-2.70	10.33
	Persistent high	134	0.91	11.43
DAS28 Change	Non-persistent	367	-2.27	1.86
	Persistent high	90	-2.15	1.87
ESR Change	Non-persistent	377	-13.50	21.13
	Persistent high	90	-10.65	29.36
EQ5D Change	Non-persistent	632	0.20	0.35
	Persistent high	133	0.17	0.51

VAS = Visual Analogue Scale for Pain (0–10); DAS28 = Disease Activity Score using 28 joints; SJC= swollen joint count, TJC= tender joint count, ESR=Erythrocyte Sedimentation Rate, EQ5D=EuroQo Five-Dimensional Questionnaire to measure the quality of life related to RA.

The t-test results indicate differences in clinical outcome changes between the non-persistent and persistent high-pain groups. The SJC improvement (change) was greater in the persistent pain group compared to the non-persistent pain group, with significant differences noted in SJC changes (p < 0.001). While TJC improvement (change) was greater in the persistent pain group, a significant difference was also observed between the non-persistent and persistent high pain groups (p < 0.001).

In contrast, no significant difference in DAS28 change was found between the groups (p = 0.573). Similarly, ESR changes did not differ significantly between the non-persistent and persistent high-pain groups (p = 0.291). Finally, there was no significant difference in EQ-5D change (p-value = 0.382).

Table 2.6: Effect size estimates and confidence intervals for change in pain VAS, SJC, TJC, DAS28, ESR and EQ-5D.

		Standardizer[a]	Point Estimate	95% Confidence Interval	
				Lower	Upper
SJC Change	Cohen's d	27.01	0.80	0.61	0.99
TJC Change	Cohen's d	10.53	-0.34	-0.53	-0.15
DAS28 Change	Cohen's d	1.86	-0.06	-0.29	0.16
ESR Change	Cohen's d	22.94	-0.12	-0.35	0.10
EQ5D Change	Cohen's d	0.39	0.08	-0.10	0.27

VAS = Visual Analogue Scale for Pain (0–10); DAS28 = Disease Activity Score using 28 joints; SJC= swollen joint count, TJC= tender joint count, ESR=Erythrocyte Sedimentation Rate, EQ5D=EuroQo Five-Dimensional Questionnaire to measure the quality of life related to RA.

Table 2.6 highlights the effect size differences between participants in persistent high pain and non-persistent pain groups across several clinical outcome changes.

Significant differences were observed in the change of SJC, with a large effect size (Cohen's d = 0.80, 95% CI: 0.61 to 0.99). This indicates that the group experiencing persistent high pain showed greater improvement in SJC compared to the non-persistent group.

There is a moderate effect size for TJC change (Cohen's d = -0.34, 95% CI: -0.53 to -0.15), suggesting that the non-persistent group had better improvement in tender joint counts.

In contrast, the DAS28 change showed an insignificant effect size (Cohen's d = -0.06, 95% CI: -0.29 to 0.16), indicating no significant difference in disease activity improvements between the groups. Additionally, for ESR Change, the effect size was small and insignificant (Cohen's d = -0.12, 95% CI: -0.29 to 0.16), indicating minimal differences in the reduction of inflammation between the two groups.

Finally, for EQ5D Change, the effect size was not significant (Cohen's d = 0.08, 95% CI: -0.10 to 0.27), showing no significant difference in quality of life improvements between the groups.

2.4.4 Evaluating the clinical measures in non-persistent and persistent pain groups

The results indicate that 134 out of 1039 participants (12.9%) were categorised in the persistent high pain group. They reported high pain VAS at all visits (pain VAS ≥34). Out

of 134 participants, six achieved DAS28 remission. Twenty-two participants showed a negative SJC, while forty-nine participants had a high TJC (greater than 11). Additionally, fifty-four participants demonstrated a normal ESR (<20), indicating the absence of inflammation within this subgroup (Table 2.7).

Table 2.7: Clinical variables in the persistent high pain groups.

Item	Participants	P value
Frequency	134 (12.8%)	-
DAS28 < 2.6	6 (4.48%)	> 0.05
SJC=0	22 (16.42%)	> 0.05
TJC>11	49 (36.56%)	> 0.05
ESR<20	59 (44.03%)	<0.05

DAS28 < 2.6 indicates remission, SJC= 0 indicates the absence of swollen joints and reflects a lack of inflammation; normal ESR <20 suggests no active inflammation, a TJC greater than 11 indicates non-inflammatory pain.

The results of the Mann-Whitney U test revealed no statistically significant difference between the negative and positive SJC groups, with a p-value of 0.138 (Figure 2.1). The frequency and the mean rank for the negative SJC group (22 and 56.27, respectively) indicate that pain in participants with persistent high pain and negative SJC tends to derive from a non-inflammatory source.

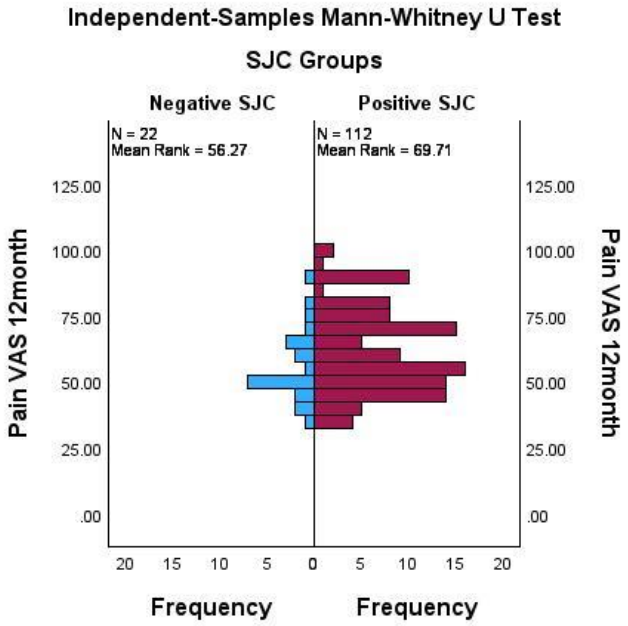

Figure 2.1: Distribution of 12-month pain VAS scores in the persistent high-pain group, stratified by SJC groups (Negative: n = 22; Positive: n = 112); groups compared using an independent-samples Mann–Whitney U test.

The results of the Mann-Whitney U test revealed no statistically significant difference between the high and low TJC groups (p-value = 0.091) (Figure 2.2). The mean rank for the low TJC group was 63.20, while the high TJC group had a slightly higher mean rank of 74.96. However, this suggests a trend that pain experienced by participants with higher TJC (greater than 11) and persistent high pain may have originated from non-inflammatory sources.

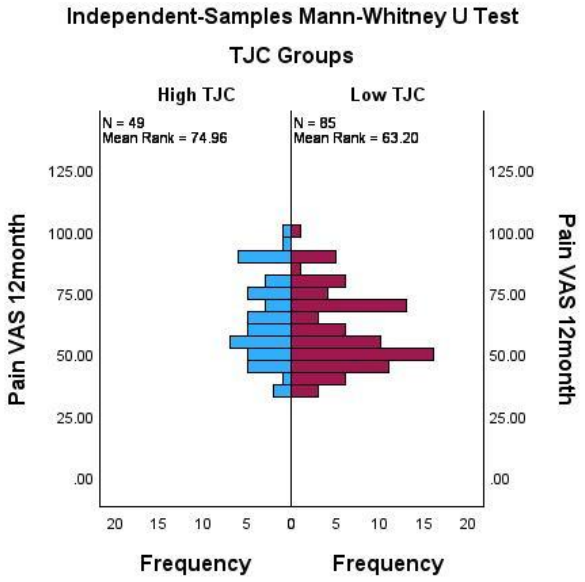

Figure 2.2: Distribution of 12-month pain VAS scores in the persistent high-pain group, stratified by TJC groups (High: n = 49; Low: n = 85); groups compared using an independent-samples Mann–Whitney U test.

The results of the Mann-Whitney U test revealed no statistically significant difference between the DAS28 remission and the no DAS28 remission group (p-value 0.287)(Figure 2.3).

The mean rank for the DAS28 remission group was 34.32, while the mean rank for the no DAS28 Remission group was 46.76.

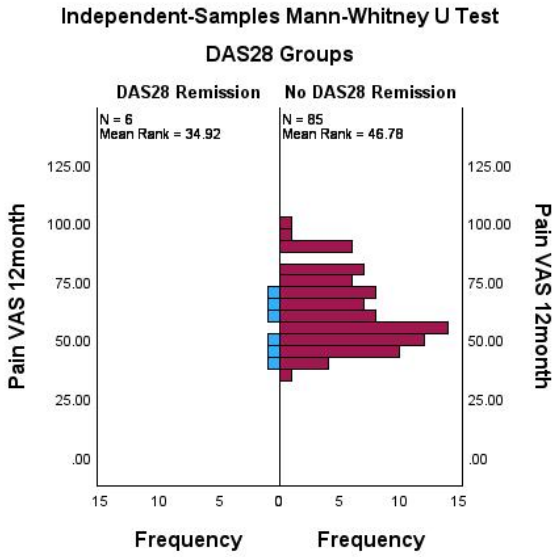

Figure 2.3: Distribution of 12-month pain VAS scores in the persistent high-pain group, stratified by DAS28 remission status (remission: n = 6; no remission: n = 85); groups compared using an independent-samples Mann–Whitney U test.

The results of the Mann-Whitney U test revealed a statistically significant difference between high ESR and normal ESR, with a p-value of 0.018, which is below the threshold of 0.05 (Figure 2.4). Moreover, the mean rank of the normal ESR group (41.19) indicates that the pain mechanism in participants with normal ESR levels and persistent high pain is likely due to non-inflammatory sources.

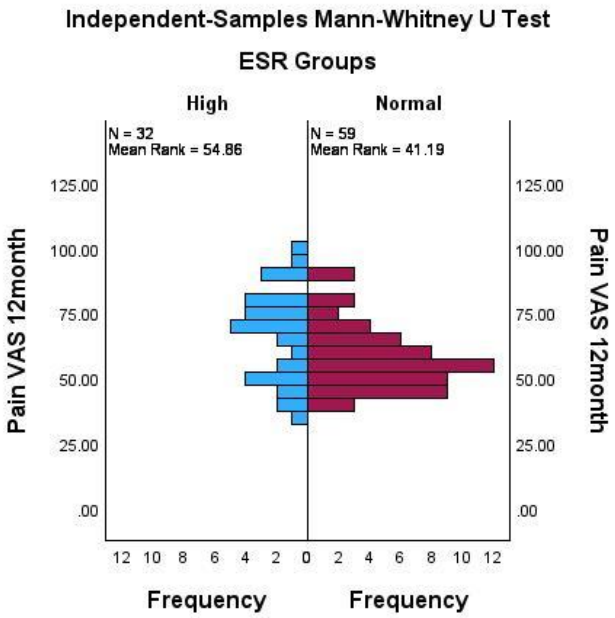

Figure 2.4: Distribution of 12-month pain VAS scores in the persistent high-pain group, stratified by ESR groups (High: n = 32; Normal: n = 59); groups compared using an independent-samples Mann–Whitney U test.

2.5 Discussion

This research underscores the prevalence of pain in patients with RA, shedding light on pain as their most significant issue and the highest need for improvement.

This research leveraged the comprehensive SERA dataset to achieve its main objectives. The dataset provided a reliable and comprehensive source of data for examining the prevalence of pain, assessed using the pain VAS, and the quality of life, measured by the EQ-5D, in the early RA population at baseline and during 12-month follow-up visits. Subsequently, these measures were also analysed in patients with chronic pain and those experiencing reduced pain. Finally, clinical measures were investigated among patients with RA who are suffering from chronic persistent pain to better understand putative pain mechanisms in this population.

2.5.1 The prevalence of pain in early RA

The results of the research reveal that the prevalence of high pain at the baseline is high (70.05%), and participants experienced significant levels of pain. Participants are expected to report a high intensity of pain at the beginning of this research, as pain is a hallmark of RA. These results are consistent with McWilliams and colleagues (2012), who highlighted

that patients with early RA continue to experience pain after one year. They state that approximately 58% report that their resistant pain is better than baseline but still not fully improved; 15% of the patients recorded pain intensity similar to that at baseline; and 27% reported worse pain than at baseline. Furthermore, the results of this research align with Altawil et al. (2016), who emphasise that patients with early RA continue to experience pain after three months of effective treatment, even though 40% showed a good clinical response. They also reported that persistent pain in early RA was observed in one-third of patients who had a positive EULAR response to treatment and in two-thirds of those with a moderate or poor response.

The majority of the pain is attributed to inflammation, as evidenced by clinical and inflammatory markers. The disease activity, measured by DAS28, indicates that RA is active. Additionally, an abnormal ESR and positive SJC further confirm inflammation in participants with RA. These findings suggest that the pain experienced at baseline is likely due to inflammatory causes. This result aligns with Studenic et al. (2012), who emphasise that pain serves as an indicator of inflammation, and its severity reflects the level of peripheral inflammation. The high prevalence of pain in early RA is because it is considered one of the initial signs in early RA diagnosis (Jutley et al., 2017). Furthermore, Tylor (2023) highlights that pain is the major issue requiring improvement in RA. Therefore, joint pain compels Patients with RA to pursue treatment.

At the 12-month follow-up visit, pain intensity was found to have improved over time. This observed improvement is likely attributable to effective treatment strategies that targeted inflammation, which was the primary source of pain in this population. However, the wide range of pain VAS detected by the percentile results suggests persistent pain, possibly due to another pain mechanism, such as non-inflammatory causes. Additionally, 35% of participants in this cohort reported high pain at the 12-month follow-up despite the standard management of RA. These findings are in line with Ten Klooster and colleagues (2015), who highlighted that 41% of participants with RA reported pain at the follow-up. Furthermore, McWilliams and colleagues (2019) highlight that 59%–79% of patients with RA have persisting pain. These findings indicate that the effective treatment of RA did not address all causes of pain in RA, leading to persistent pain at follow-up among some participants. The persistent pain experienced by patients with RA negatively affects their quality of life. Therefore, further investigation into the nature of pain in RA is essential to tailor treatment and address all potential causes of pain. This research further explores persistent pain in RA, and the subsequent sections provide more discussion to enhance our understanding of the pain mechanisms involved.

2.5.2 Quality of life in RA

The results reveal that the quality of life in RA, measured by the ED-5D, improved from 0.48 at baseline to 0.69 at the 12-month follow-up. This finding aligns with the research conducted by West et al. (2005), which emphasises that the quality of life significantly improved after a two-year follow-up. This improvement suggests that the treatment has a positive impact on the quality of life for participants with RA. Gerhold and colleagues (2015) noted that the baseline quality of life for participants with RA was impaired, but it improved by 12 months following DMARD treatment.

When participants were categorised based on their pain VAS scores at the 12-month follow-up visit, it was found that those in the high-pain group had a worse quality of life, as measured by the EQ-5D. This indicates that persistent pain in RA negatively impacts quality of life. Therefore, identifying the nature and mechanisms of this pain would enable better management, ultimately leading to an improved quality of life. Hernández Alava and colleagues (2013) emphasise that the EQ-5D is particularly sensitive to the direct effects of pain on quality of life because it explicitly includes pain/discomfort as one of its five dimensions. This feature enables the EQ-5D to effectively capture the subjective experience of pain. As a result, it can reflect the multidimensional impact of pain on the overall quality of life (Hernández Alava et al., 2013).

Additionally, Strand and Khanna (2010) emphasise that pain significantly impacts patients' quality of life. Due to the importance of this matter, new therapies are increasingly assessed based on their ability to improve quality of life, productivity, and participation. This will enable patients to work, thus reducing the socioeconomic burden of disease (Strand and Khanna, 2010).

2.5.3 Evaluation of clinical and quality of life outcomes in pain subgroups

In this analysis, participants were divided into two groups: those with persistent high pain and those with non-persistent pain. This categorisation was based on pain intensity, measured using the VAS during the 12-month visit. It focuses on identifying participants with chronic pain who experience high pain consistently at all visits (from the baseline to the 12-month visits). The majority of the participants were in the non-persistent pain group. All clinical measures improved in the non-persistent pain group, indicating a reduction in inflammatory changes due to RA treatment, consequently leading to pain

relief. On the other hand, approximately 12.9% of participants (134 out of 1039 participants) experienced chronic pain, which remained high during all visits despite the standard treatment. T-test results showed statistically significant differences in SJC, TJC, ESR, DAS28, and EQ5D between the two groups at the 12-month visit. The clinical measures changes were calculated to correct the baseline values. Significant differences between the groups were observed only for SJC and TJC, while DAS28, ESR and EQ5D were no longer significant. This finding suggests that the alterations in DAS28 and ESR are less influenced by persistent pain in early RA. Altawil et al. (2016) emphasise that the presence of residual pain in RA was significantly correlated with the ESR at baseline. In contrast, no such correlation was observed between residual pain and either the DAS28 or the SJC at baseline. These findings regarding DAS28 are consistent with the current research, suggesting that changes in DAS28 are less affected by persistent pain in early RA. However, this study indicates that, unlike the findings of Altawil et al. (2016), ESR also demonstrates a weaker association with persistent pain in early RA. Furthermore, McWilliams et al. (2012) utilised a newly developed index called the DAS28-P, which includes only the patient-reported elements of the DAS28, specifically TJC28 and PGA, to act as a marker for patient-reported pain. Their findings showed that a significant number of patients with early RA experienced incomplete pain relief at the 12-month follow-up, which aligns with the results of this research.

2.5.4 Explore the clinical measures of persistent high pain in RA

The 134 participants with persistent high pain were investigated further to understand the behaviour of the clinical measures in this population.

Negative SJC was observed in 16.4% of participants, indicating the absence of inflammation. Thus, the few participants who reported negative SJC are likely associated with non-inflammatory changes in this sub-population.

Additionally, ESR, which serves as a marker of inflammation, was assessed in this population. An ESR level below 20 indicates a normal ESR (Sokka et al., 2009). Normal ESR was observed in 44% of participants, suggesting that the pain experienced is not caused by inflammation. These findings align with those of Altawil et al. (2016), who reported that persistent pain persisted even at low ESR scores, suggesting non-inflammatory reasons behind it.

Moreover, TJC was observed among participants with persistent pain within the early RA cohort. High TJC (greater than 11) was observed in 36.5% of the participants. These

findings corroborate the assertions of Pollard et al. (2010), who contend that TJC may serve as a marker for non-inflammatory conditions. However, TJC could represent sub-clinical inflammation. Therefore, an MSUS investigation is needed to identify any inflammatory changes among patients with early RA.

Additionally, the DAS28 was investigated in this population to identify how many participants with persistent high pain achieved remission. Firstly, the DAS28 measures disease activity, and remission indicates a minimum level of inflammation, which is the intended goal of treatment aimed at addressing inflammation. The cut-off value for DAS28 indicating remission is <2.6 (Fransen et al., 2004). Based on this criterion, this analysis evaluated patients with persistent pain who reached remission. 4.48% of participants achieved remission based on DAS28. These results are not in line with McWilliams et al. (2012), who emphasise that a high DAS28 score at baseline is linked to greater pain and a reduced improvement in pain over the course of one year in patients with early RA despite traditional disease-modifying therapy. Additionally, this finding contradicts the finding of Altawil et al. (2016), who reported high pain associated with higher DAS28 remission.

Furthermore, the low number of participants who achieved DAS28 remission in this subgroup may be attributed to physiological or methodological factors. The physiological perspective includes the contribution of non-inflammatory conditions that can have different pain mechanisms.

On the other hand, the methodological approach that employs the DAS28 as an indicator of remission may lack reliability for several critical reasons. First, DAS28 is a clinical measure composed of four distinct components. Two of these components, namely the TJC and the PGA, may be significantly influenced by the non-inflammatory pain perception. Specifically, non-inflammatory conditions such as FM can manifest symptoms such as an elevated TJC and an increased global health assessment score, which may impede the DAS28 score from falling beneath the remission threshold despite ongoing therapeutic interventions (Das et al., 2023).

Additionally, the global health assessment, which is another integral component of DAS28, may not solely reflect peripheral pain. It serves as a subjective measure that non-inflammatory conditions can impact. These conditions can exacerbate pain severity, thereby hindering the DAS28 score from accurately indicating remission (Lee et al., 2011).

In addition, the results of this analysis are in line with previous studies that emphasise that DAS28 remission is not commonly achieved by early Patients with RA who suffer from persistent pain and can also be misinterpreted (Pollard et al., 2010; Lee et al., 2011).

Therefore, DAS28 may not be a reliable measure of disease activity in this early RA population.

Additionally, negative SJC, high TJC and DAS28 remission were not statistically significant in this population. Therefore, they could not be solid measures of non-inflammatory pain. Also, these measures could be subject to variability due to discrepancies in data collection among different assessors. Such variability underscores the necessity for employing a more reliable tool, namely MSUS, to validate the presence of inflammatory changes. Furthermore, MSUS serves as a crucial tool for diagnosing subclinical inflammatory changes, including subclinical synovitis, which may not be adequately detected through SJC assessments or conventional inflammatory markers, such as the ESR. MSUS could be employed to elucidate the underlying joint status further and clarify the clinical implications of the TJC findings.

Therefore, MSUS measures can be used as a marker for local joint inflammation to confirm the contribution of peripheral pain.

2.5.5 Limitations

One limitation of this research is the missing data at both the baseline and the 12-month follow-up visit. For instance, 339 participants had missing ESR values at baseline, which could lead to incomplete DAS28 calculations, as ESR is one of the components of the DAS28. A large amount of ESR data was missing because some departments participating in SERA did not routinely measure ESR. This lack of data may negatively impact the accuracy of disease activity assessments at baseline.

Additionally, at the 12-month follow-up visit, 269 participants had missing values for the SJC and the TJC, and 562 participants had missing ESR data. This missing data could introduce bias, reduce statistical power, and limit the generalizability of the results.

Another limitation of this research is that clinical examinations, such as SJC and TJC, were performed by multiple rheumatologists across various locations. This variability could introduce the potential for inter-rater differences due to varying levels of expertise, clinical judgment, and interpretation of joint abnormalities. Such differences could impact the reliability. While standardised protocols have been implemented, the inherent subjectivity in clinical examinations could still lead to measurement bias.

Another limitation of this research is that the duration of symptoms up until diagnosis is not an exclusion criterion. The symptom duration of RA is considered a prognostic factor,

as longer durations are linked with poor clinical outcomes, while shorter symptom durations tend to be associated with better treatment responses (Finckh et al., 2006; Van Der Linden et al., 2010; Rosa et al., 2020).

Therefore, patients tend to respond better to treatment during the initial three months following the onset of the disease (Van Der Linden et al., 2010). Therefore, limiting the duration of symptoms prior to diagnosis to three months could better reflect the experiences of pain in early RA, excluding those patients who have transitioned to chronic RA. Furthermore, participants who had already begun treatment with steroids or DMARDs prior to recruitment were not excluded. This could influence the baseline clinical scores, which reflect clinical outcomes responsive to treatment. In contrast, participants who had not received prior treatment had clinical measurements that accurately depict the actual state of the disease at baseline.

2.6 Conclusion

The research showed that 70.05% of participants had high pain levels at the baseline, which is common in RA. By the 12-month follow-up, pain intensity improved due to effective treatments targeting inflammation. However, 35% of participants still reported high pain levels despite this management at the 12-month follow-up visit.

The quality of life for patients with RA, as measured by the EQ-5D scale, improved from baseline to the 12-month follow-up, indicating a positive impact of the treatment. Participants with persistent high pain showed lower EQ-5D scores, suggesting that persistent pain in RA negatively affects quality of life. 12.9% of participants experienced chronic pain that persisted during all visits. This pain was not affected by inflammatory suppression treatment, suggesting that non-inflammatory causes may be involved. The clinical measures among these participants indicated signs of missing inflammation, but were not statistically significant except for normal ESR. Thus, another valid tool, such as MSUS, is required to assess both clinical and subclinical inflammation, thereby better understanding pain mechanisms in this RA population.

Chapter 3 Exploring the correlation between ultrasound power Doppler and pain in patients with early rheumatoid arthritis using the TaSER dataset

3.1 Abstract

Introduction:

Despite improvements in clinical and laboratory measures, such as ESR and SJC, in patients with early RA, a substantial proportion of patients with early RA continue to experience persistent pain. This creates questions about the pain mechanisms in RA. In the previous chapter (SERA), the results highlight that a high prevalence of patients with early RA reported persistent pain despite effective treatment. The clinical biomarkers in the SERA dataset were limited in their ability to identify all causes of pain within the RA population. This highlights the necessity for imaging tools, namely MSUS, to offer further insights into potentially overlooked inflammation, such as subclinical synovitis, which could be contributing to the pain experienced by patients with early RA. This imaging tool could indicate the involvement of additional factors contributing to pain experiences in this patient population. Ultrasound Power Doppler (USPD) is an advanced imaging modality that offers high sensitivity for evaluating and quantifying synovitis. USPD can effectively confirm the presence or absence of peripheral subclinical inflammation, while also exploring the relationship between Pain VAS and USPD to shed light on the underlying mechanisms of pain. USPD can effectively confirm the presence or absence of peripheral subclinical inflammation, while also exploring the relationship between Pain VAS and USPD to shed light on the underlying mechanisms of pain.

Objectives

Investigating the role of USPD in the pain mechanism in patients with early RA. Additionally, it is to identify patients experiencing persistent pain and to explore the clinical biomarkers associated with inflammation among them. This investigation aimed to confirm or exclude the role of peripheral inflammatory changes as contributing factors to pain in patients with early RA.

Methods

This study was a secondary retrospective analysis of the original Targeting Synovitis in Early Rheumatoid Arthritis (TaSER) study, a multiple-centre study (Dale et al., 2016). The original study included 111 patients recruited at the time of their first-ever diagnosis of RA or undifferentiated arthritis (UA) and with <1 year of symptom duration. In the original TaSER study, patients were divided into two groups: a control group based on the Disease Activity Score (DAS28-ESR) without MSUS, and an intervention group based on the

DAS28-ESR with musculoskeletal ultrasonography (MSUS) assessment, specifically ultrasound power Doppler assessment.

USPD assessments were conducted under two conditions: if the DAS28 score was greater than 3.2 with fewer than two swollen joints or if the DAS28 score was below 3.2.

Secondary analyses have been conducted on the TaSER dataset to explore the relationship between pain VAS and USPD in this cohort. The relationship between pain VAS and USPD was examined using appropriate correlations cross-sectionally and longitudinally.

This study utilised USPD as a marker for peripheral inflammation, while the pain VAS measured pain intensity in patients with RA. The relationship between these variables is analysed to demonstrate how nociceptive pain from inflamed joints affects the overall pain experienced in RA.

In this analysis, participants were systematically categorised into two distinct cohorts based on pain VAS assessments from their three-month visit until their 12-month visit: the persistent pain group and the non-persistent pain group. Both cohorts underwent thorough evaluation for clinical biomarkers indicative of inflammation, including DAS28, ESR, SJC, TJC, and USPD. Chi-square tests were performed to evaluate the relationships between pain VAS (categorised into pain groups) and various clinical biomarkers.

Results

Fifty-four participants were in the intervention group who underwent the USPD assessment. No significant correlation was observed between the pain VAS and USPD at any follow-up visit. Forty-five participants (83.3%) were in the non-persistent pain group, and five participants were in the persistent pain group (9.3%).

In the persistent pain group, three participants (60%) achieved DAS28 remission, and three (60%) had a negative SJC. Only one participant (20%) exhibited ultrasonographic active synovitis (USPD ≥2), with two participants (20%) reporting a high TJC and four participants (80%) showing elevated ESR.

In the non-persistent pain group, thirty-five participants (78%) achieved DAS28 remission, while twenty-seven participants (60%) had a negative SJC, indicating no joint inflammation. Six participants (13%) showed ultrasonographic evidence of active synovitis (USPD ≥2), and six (13%) reported a high tender joint count (TJC > 11). Additionally, thirty-six participants (80%) had elevated ESR (≤20).

The Chi-square analysis test results identified statistically significant relationships between pain VAS and clinical measures, such as DAS28 remission, ESR, SJC, and TJC (TJC > 11). However, no significant association was seen between pain VAS and USPD.

Conclusion

Some patients with RA continue to experience pain despite effective control of inflammation, prompting further investigations into its nature. The investigation revealed no discernible association between USPD and pain VAS. This lack of correlation may be attributed to methodological limitations, notably the insubstantial sample size and suboptimal MSUS protocol utilised in this study, which incorporated a limited number of MSUS measurements and scanned only a limited number of joints. Alternatively, the absence of a significant relationship could also stem from biological factors, particularly the potential influence of non-inflammatory pain mechanisms. These findings highlight the necessity for further research with a larger sample size and a wider range of scanned joints using various MSUS measurements to better understand the relationship between pain VAS scores and MSUS findings.

3.2 Introduction

RA is a chronic autoimmune disorder associated with significant pain and joint damage. It may lead to deformities if untreated or inadequately treated (Firestein and McInnes, 2017). Synovitis is the clinical hallmark of RA, and it can be defined as an inflammation of the synovium characterised by soft tissue swelling and tenderness of the joint, which results in pain and loss of joint function (Pisetsky and McCleane, 2009).

3.2.1 MSUS roles in RA

Ultrasound is a non-invasive, cost-effective, and radiation-free imaging technique that allows for a quick and sensitive assessment of soft tissue inflammation (Sun et al., 2019). Generally, the MSUS in rheumatology can be applied in five aspects (Grassi et al., 2005). First, MSUS can assess regional pain disorders in RA. For patients with these disorders, MSUS provides crucial information, which, when combined with clinical data, enhances diagnostic accuracy by identifying specific anatomical targets associated with the condition.

Secondly, detecting anatomical changes in the early stages of RA is critically important. As there is an increasing focus on early and aggressive treatment strategies, it becomes essential to utilise a sensitive and specific imaging technique to identify anatomical damage resulting from persistent inflammation. MSUS is also more sensitive than X-rays in detecting joint bone erosion, and this sensitivity is particularly pronounced in minor erosion associated with RA (Wakefield et al., 2000). MSUS has shown greater sensitivity in synovitis evaluation compared to X-rays and offers several advantages, making it the preferred first-line imaging method for assessing early RA. Although MRI also demonstrates high sensitivity, its cost and availability present significant obstacles to broader implementation (Grassi et al., 2005).

Furthermore, assessing inflammatory activity is crucial. In RA, MSUS has a significant role in detecting synovitis and making therapeutic decisions (Naredo et al., 2005; Wakefield et al., 2012). The remarkable sensitivity of MSUS, particularly USPD, positions it as the most effective tool for detecting increased blood flow in soft tissues related to inflammation. At the same time, USPD enables the detection of synovial tissue hyperaemia, which allows assessment of tissue vascularity, hence differentiation between active synovitis, which is associated with the presence of USPD signals and inactive synovitis, which has no USPD signals (D'Agostino, 2017). The use of USPD in inflammatory conditions has significantly increased in recent years. It is now employed to

identify synovial changes in RA and has been validated as an effective measure of hyperaemia associated with inflammation in RA. Prior studies have demonstrated that USPD can effectively detect synovitis in small joints (Hau et al., 1999; Grassi et al., 2014). The extent of inflammation can be assessed using either colour or power Doppler techniques, and fluctuations in inflammatory activity can be monitored by observing changes in the number of colour pixels within the region of interest (Terslev et al., 2016). Additionally, greyscale images in ultrasound (GS) can delineate synovial thickening and joint effusion, allowing for the assessment of the size and shape of synovial hypertrophy.

Additionally, it serves as a valuable method for monitoring short-term responses to therapy. The combination of high-resolution ultrasound and Power Doppler offers a progressive approach to evaluating the immediate effects of treatment. Although robust evidence supporting its role in therapy monitoring is still emerging, recent studies suggest that the use of MSUS for this purpose is poised for significant growth in the coming years. Finally, in cases where patients present with pain but demonstrate no imaging findings suggestive of RA or secondary osteoarthritis (OA), MSUS and MRI can be employed as effective negative tests. These modalities aid in investigating non-inflammatory mechanisms of pain, including FM (Grassi et al., 2005).

3.2.2 Concordance of MSUS and clinical assessments in RA

For many years, rheumatologists have used clinical assessments such as SJC, TJC, and DAS28 as the gold standard for evaluating RA activity. Although these assessments demonstrate effective disease monitoring, they are limited in detecting subclinical synovitis, underscoring the need for an additional diagnostic tool to identify this condition. Ultrasound has been shown to effectively detect minimal synovitis (Brown et al., 2008). MSUS is a sensitive tool for identifying inflammatory joint damage and subclinical synovitis (Szkudlarek et al., 2016). It can reveal residual disease activity even in patients who are in clinical remission according to the DAS28, highlighting its role in monitoring ongoing inflammation. Furthermore, MSUS is valuable for tracking changes in RA in response to treatment (Wakefield, 2007).

Numerous studies have demonstrated that MSUS is more effective than clinical joint assessments in detecting synovitis, as it increases the identification of early RA in patients from 31% to 61% (Prado et al., 2018). Additionally, many cases of synovitis were detected through MSUS diagnosis, even though clinical joint examinations classified these cases as non-arthritic joints. Furthermore, a study reported less concordance between MSUS and

clinical joint examination in detecting synovitis at the MTP joints, wrists, and shoulders, while higher concordance was observed at other joints (Garrigues et al., 2013).

3.2.3 Pain in RA

Pain represents one of the most significant challenges for patients with RA. Although it is commonly believed that this pain arises mainly from joint inflammation, recent research has revealed that multiple mechanisms contribute to this pain experience (Basu et al., 2018). The International Association for the Study of Pain (IASP) defines pain as an unpleasant sensory and emotional experience with actual or potential tissue damage. Pain has become a vital element of the core sets utilised for classifying the severity of rheumatic disease. Hence, how pain should be effectively measured has become increasingly important (Englbrecht et al., 2012).

Historically, pain in RA has been primarily associated with inflammatory changes in the joints (Walsh and McWilliams, 2012). However, recent research suggests that this traditional understanding is evolving. It has become clear that factors beyond peripheral inflammation significantly contribute to the overall pain experienced in RA. Notably, neurochemical changes in the sensory nervous system and the mechanisms of pain processing in the central nervous system may play crucial roles in the pain experienced by patients with RA. Patients with RA may experience pain that not only manifests as nociceptive or inflammatory but also includes characteristics of non-inflammatory pain, such as neuropathic pain. Furthermore, this type of pain is independently associated with poorer self-reported physical and mental health outcomes (Koop et al., 2015). Current management guidelines for RA advocate the use of anti-inflammatory DMARDs. While this treatment is effective for many patients and helps them achieve remission, specific subpopulations continue to experience pain despite adequate control of inflammation (Walsh and McWilliams, 2012).

Concerning inflammatory arthritis (IA), it is likely that pain will comprise various characteristics, including frequency, duration, intensity, and location. The pathogenesis of pain in RA is multifactorial, as it is traditionally linked to synovitis and joint destruction. The pain in RA results from a combination of many interacting pain mechanisms, including inflammatory mechanisms, namely nociceptive pain and non-inflammatory mechanisms. Nociceptive pain is a response to damage to body tissues. This tissue damage can include joint inflammation, resulting in inflammatory or nociceptive pain (Paice, 2002). MSUS is a valid tool for capturing these peripheral changes (Di Mattio et al., 2020);

therefore, it could evaluate the nociceptive pain resulting from these changes. This pain type is initiated by the activation of nociceptors, which are considered the primary afferent neurons (Prescott and Ratté, 2017). Nociceptor activation initiates protective withdrawal reflexes, a vital alarm system. Nociceptive pain is well-localised and consonant with the underlying lesion (Duarte et al., 2009).

On the other hand, non-inflammatory pain is defined as pain arising from nociception changes despite no clear evidence of tissue damage. This causes activation of the peripheral nociceptor or somatosensory system (Kosek et al., 2021). This occurs when the neural signals are amplified to peripheral nociceptive input within the central nervous system (Bailly et al., 2020).

3.2.4 Aim

This chapter is based on a retrospective analysis of existing data. The data used in this chapter were specifically gathered to assess the relationship between MSUS and pain VAS in patients diagnosed with early RA. As mentioned in the SLR section of Chapter 1, there is a lack of research on the nature of pain evaluation using MSUS in the literature. Investigating pain mechanisms through MSUS is an innovative approach that may provide valuable insights into the nature of pain in RA, thereby enhancing our understanding of its underlying mechanisms and improving pain management.

The study aimed to assess peripheral joint inflammation in early Patients with RA by correlating USPD signals with pain VAS. The objective is to determine whether ultrasonographic synovitis or subclinical synovitis is the primary contributor to pain in patients with RA. This research also explores the potential role of USPD in indirectly identifying the various mechanisms of pain in early RA by confirming or excluding peripheral joint changes.

3.2.5 Hypotheses

In this research, I hypothesise that USPD can be used to evaluate pain mechanisms in early RA by assessing changes in joint inflammation, including subclinical inflammation, which may be the source of pain.

I also hypothesise that the absence of USPD signals indicates no inflammation. Therefore, any reporting pain in the absence of USPD in early Patients with RA could be linked to a non-inflammatory source.

3.3 Methods

In this chapter, a secondary retrospective analysis based on the original TaSER study, a multiple-centre study (Dale et al., 2016), is described below. This analysis aimed to use the USPD assessment to investigate potential explanations for the persistent pain that is reported in early Patients with RA. The USPD assessment evaluates peripheral joint inflammation and damage by correlating the USPD signal with the pain VAS to determine whether synovitis is the primary contributor to pain in early Patients with RA.

3.3.1 The original TaSER study

The original TaSER study was a randomised controlled trial conducted from September 2009 to April 2013 at three teaching hospitals in Scotland (Dale et al., 2016). The primary objective of the original study was to examine the effect of using MSUS within a treat-to-target approach in patients with early RA, compared to conventional clinical assessment. The original study included 111 patients recruited at their first-ever diagnosis of RA or undifferentiated arthritis (UA) and had <1 year of symptom duration. In the original TaSER study, participants were divided into two distinct cohorts: a control group, in which the escalation of DMARDs was guided solely by the Disease Activity Score in 44 joints using the erythrocyte sedimentation rate (DAS28-ESR) without the inclusion of MSUS evaluation, and an intervention group, where both DAS28-ESR and comprehensive MSUS assessments informed the escalation of DMARDs. The dividing was performed to ensure that the groups were well-balanced regarding the severity of the disease and other essential patient factors.

This was an open-label, randomised, controlled trial with outcome assessments conducted by investigators who were blinded to group allocation and treatment.
Patients were monitored through follow-up appointments approximately every month over 18 months. The evaluations were conducted by a rheumatologist who was kept unaware of the patient group allocations, thereby reducing the likelihood of bias. This study also collected comprehensive data, including clinical measures such as swollen and tender joint counts, ESR, CRP, and patient-reported outcomes, including pain VAS and global VAS. At baseline and after 18 months, imaging studies, including MRI and radiographs, were conducted to evaluate the improvement of joint erosion and structural damage.

The primary outcomes of the original TaSER study focus on changes in DAS28 and Rheumatoid Arthritis MRI Scoring System (RAMRIS) erosion score, reflecting disease activity and joint progression. Various statistical methods were employed to compare the clinical and imaging data findings of the two groups, including t-tests and Wilcoxon rank-sum tests. With a broad approach, the original TaSER study aimed to determine if using the MSUS ultrasound device in conjunction with standard clinical methods would enhance the effectiveness of RA management options, potentially leading to a more tailored treatment approach and improved long-term outcomes for patients with early RA.
The NHS West approved the original TaSER study of the Scottish Research Ethics Committee, and all participants provided written informed consent.

3.3.2 MSUS data collection

In this research, only participants from the TaSER dataset who underwent MSUS were included for the study's purposes.

A total of Fifty-four patients were recruited in the DAS28-ESR and MSUS intervention group. MSUS assessments were conducted under two conditions: if the DAS28 score was greater than 3.2, the cutoff indicated active disease that may require a change in medication, with fewer than two swollen joints or a DAS28 score below 3.2. A single ultrasound operator carried out all MSUS assessments.

The MSUS assessments were conducted at three Glasgow hospital sites using a portable ultrasound machine (Voluson I, GE Healthcare) and a 10–16 MHz linear array probe (SP 10–16RS, GE Healthcare). Power Doppler (USPD) examinations were obtained using the following settings: frequency high, pulse repetition frequency 0.9 kHz, wall filter low, and gain adjusted to below the level at which Doppler artefact appeared beneath bone. Bilateral examinations were performed on the dorsal recesses of the index and middle proximal interphalangeal and metacarpophalangeal joints, radiocarpal joints, and the second and fifth metatarsophalangeal joints.

Intra-articular USPD activity was graded using a semiquantitative scale from 0 to 3 (Szkudlarek et al., 2003). The MSUS joint set utilised in this study was pragmatically developed by combining the common peripheral joints from two previously proposed sets (Backhaus et al., 2009; Naredo et al., 2008). Any benefits of using a more comprehensive joint set or performing a more detailed examination (for example, including tendons)

would need to be balanced against the additional time and expertise required (Dale et al., 2016).

In this study, MSUS defines active disease as the presence of a USPD signal in at least two joints. This criterion was established as a pragmatic approach to minimise unnecessary treatment escalation, while acknowledging the potential risk of inadvertently excluding certain patients from achieving genuine MSUS remission (Dale et al., 2016). Detecting USPD in two or more joints indicates a positive finding for that participant.

The MSUS assessments were conducted monthly starting from the 3-month follow-up until the 18-month visit. No MSUS assessment was performed at baseline.

3.3.3 Descriptive statistics of the TaSER dataset

Descriptive statistics were used to describe and summarise the study population and the measures of interest. They were specifically utilising the IBM SPSS Statistics software package (version 29.0.2.0) for that purpose (Field, 2024). For continuous variables, such as pain VAS, DAS28, HAQ scores, and ultrasound (e.g., power Doppler activity), descriptive statistics included means and standard deviations (SD) for normally distributed data and medians and interquartile ranges (IQR) for non-normally distributed data. The normality of continuous variables was assessed using statistical tools, including histograms and the Shapiro-Wilk test. Finally, categorical data such as gender have been illustrated with percentage frequencies.

3.3.4 Correlation between USPD and pain VAS

3.3.4.1 Cross-Sectional Correlation of USPD and Pain VAS

The correlation between USPD and pain VAS scores at several time points (3, 6, 9, 12, and 15 months) was evaluated. Pearson's correlation coefficient was used for normally distributed data, and Spearman's correlation coefficient was used for non-normally distributed data. The correlation was conducted using IBM SPSS Statistics (version 29.0.2.0) to calculate the correlation coefficients and their associated p-values. The rationale for this analysis is to determine whether ultrasound-detected joint inflammation correlates with patient-reported pain levels at various time points. The cross-sectional

analyses at different visits are crucial for assessing the temporal consistency of the association between USPD and pain VAS during treatment.

3.3.4.2 Correlation of Change in USPD and Change in Pain VAS

The relationship between changes in USPD scores and pain VAS throughout the study was analysed. The change was calculated by subtracting the scores at the 3-month visit (the first USPD assessment) from those at the 15-month visit for each participant. Due to significant missing data at the 18-month visit, the 15-month visit data were utilised to assess the observed changes.

Pearson's or Spearman's correlation, depending on the distribution of the change scores, was used to analyse the correlation between changes in USPD and changes in pain VAS. The rationale for this analysis is to explore the longitudinal relationship between reductions in inflammation, as detected by USPD, and pain, as measured by the pain VAS. This analysis addresses whether improvements in ultrasound-detected joint activity are associated with a clinically meaningful reduction in pain.

Scatterplots were created for visual examination of relationships, both at cross-sectional time points and for change data. All statistical analyses were performed using IBM SPSS Statistics (version 29.0.2.0), with significance set at $p < 0.05$.

3.3.4.3 Evaluation of USPD and pain VAS in low and high pain subgroups

Participants who underwent the MSUS assessment were divided into two groups for comparative statistical analysis based on their pain VAS score at the 15-month visit: a low-pain group and a high-pain group (Waldheim et al., 2013). This allows investigation of inflammatory changes in participants who reported high pain cross-sectionally despite treatment, compared to those who show a good response to therapy.

The USPD data at this time point are greater than those recorded during the 18-month visits, which is when the most missing USPD data occur. Pain VAS <34 was classified as low pain, and pain VAS ≥34 was considered high pain (Boonstra et al., 2014). The USPD signal in the joints of these groups was assessed at every point, from 3 to 15 months, if the DAS28-ESR was <3.2 or the DAS28-ESR was 3.2-5.1 with SJC <2, and if at least three months had passed since the last treatment escalation (Dale et al., 2016).

Then, the number of patients with active synovitis at each time point was calculated in both groups. The USPD signal was neglected if it was present in fewer than two joints, because

active RA is typically associated with two or more swollen joints. Therefore, patients with fewer than two USPD joint counts were not considered to have active synovitis (Dale et al., 2016). The number of patients was calculated across the time points in the low-pain groups.

DAS28 measures disease activity as an indicator of remission, indicating minimal inflammation due to the treatment intended to address it. The cut-off value for DAS28 indicating remission is <2.6 (Fransen et al., 2004). An ESR of less than 20 is used as an indicator of remission, which signifies a normal ESR level (Sokka et al., 2009); TJC values greater than 11 were examined among participants, as this serves as a marker for non-inflammatory conditions (Pollard et al., 2010).

A chi-square test of independence was conducted using SPSS software (version 29.0.2.0) to evaluate the relationship between pain VAS (categorised into pain groups) and various clinical measures, including DAS28 remission, ESR, SJC, USPD, and TJC. Crosstabulations were conducted for each variable pairing, and the Pearson chi-square test was utilised to determine the statistical significance of observed associations.

3.3.4.4 Evaluation of USPD and pain VAS in persistent and non-persistent pain subgroups

Participants who completed the MSUS assessment were divided into two groups for comparative statistical analysis based on their pain VAS scores. Those with consistently high VAS scores at all visits up to 12 months were categorised as the high persistent pain group. This subgroup allows the investigation of inflammatory changes in participants who reported persistent pain at all visits despite treatment. It compares them to those who reported pain improvement at any visit during the study. This categorisation confirms that pain in the persistent pain group was chronic rather than a transient flare during a specific follow-up visit. The 12-month visit was selected for consistency with the previous chapter. A VAS pain score of 34 or higher is considered indicative of high pain levels (Boonstra et al., 2014). Conversely, the non-persistent group includes participants who did not score high on the pain VAS at any visit up until the 12-month visit. The same statistical tests and procedures used in the previous analysis were repeated for these two groups.

3.4 Results

One hundred and eleven participants with clinical diagnoses of UA or RA were recruited for this study. Fifty-four participants underwent an ultrasound. Sixty-one per cent were female and thirty-nine per cent male, with an average age of 58 years.

3.4.1 Descriptive statistics of the TaSER dataset

The results of descriptive statistics demonstrate that the number of participants who completed pain VAS at baseline, 3 months, 15 months, and 18 months in the intervention group was 53, 51, 48, and 49, respectively (Table 3.1). The results also demonstrate that the number of participants who conducted the DAS28 at the baseline, 3-month, 6-month,9-month,12-month,15-month, and 18-month time points in the intervention group was 53, 52, 47, and 49, respectively (Table 3.2). In addition, the results show that the number of participants who conducted USPD at the 3-month, 6-month, 9-month, 12-month, 15-month and 18-month intervals in the intervention group were 35, 33, 34, 32, 33 and 11, respectively (Table 3.1).

The results of descriptive statistics also show that pain intensity, measured using the pain VAS, decreased consistently over time (Table 3.1). At baseline, the mean score of pain VAS was 46.79 (SD = 19.67). By 3 months, this had declined to 25.27 (SD = 25.75), and by 15 and 18 months, the mean pain score further reduced to 14.64 and 14.71, respectively (SD = 21.23 and 19.46, respectively) (Table 3.1). The results of the Shapiro-Wilk tests indicate that the pain VAS was normally distributed only at the baseline and not at any follow-up visits (Figure 3.1 and Table 3.1).

Table 3.1: Descriptive statistics of pain VAS.

	Frequency	Missing	Mean	SD	Shapiro-Wilk (P value)
Pain VAS BL	53	1	46.79	19.67	0.72
Pain VAS 3M	51	3	25.27	25.75	< 0.001
Pain VAS 6M	52	2	21.32	23.74	< 0.001
Pain VAS 9M	50	4	19.56	23.40	< 0.001
Pain VAS 12M	50	4	22.96	27.59	< 0.001
Pain VAS 15M	48	6	14.64	19.46	< 0.001
Pain VAS 18M	49	5	14.71	21.23	< 0.001

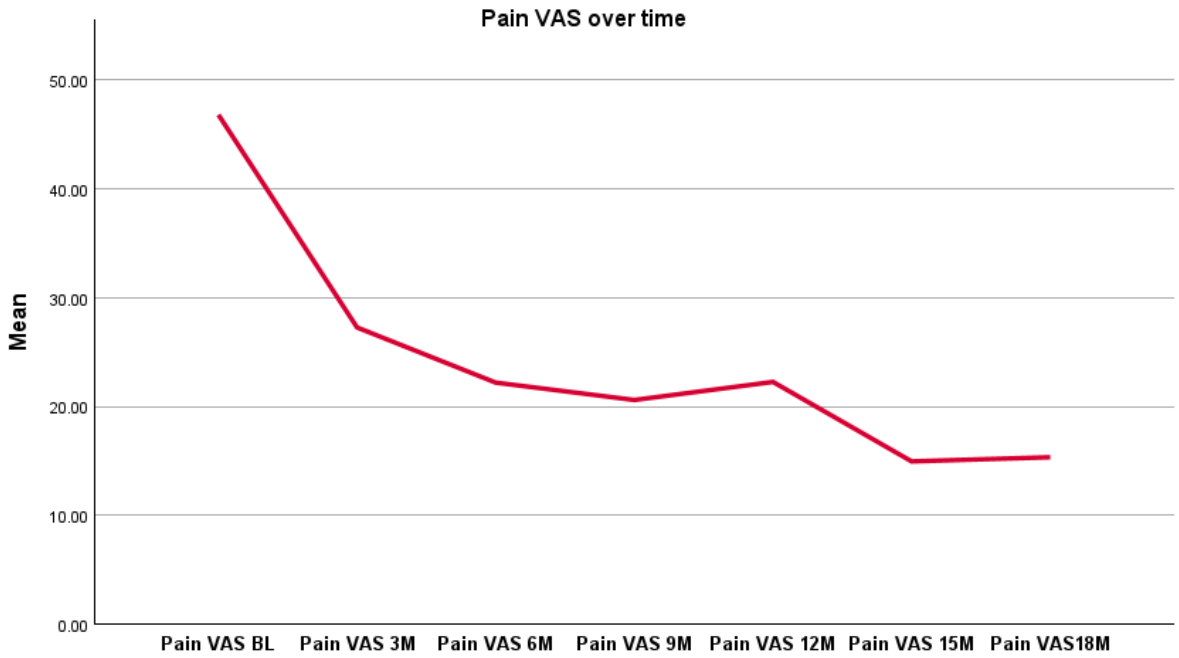

Figure 3.1: The Line chart shows the pain VAS scores over time.

The descriptive statistics indicate that DAS28, a measure of disease activity, exhibited a similar trend of improvement to the pain VAS (The cut-off value for DAS28 indicating remission is <2.6). The mean score of DAS28 decreased from 4.41 (SD = 1.03) at baseline to 2.33 (SD = 1.19) at 3 months. At 18 months, the mean score further reduced to 1.59 (SD = 1.12) (Table 3.2).

Table 3.2: Descriptive statistics of DAS28.

	Frequency	Missing	Mean	SD	Shapiro-Wilk (P value)
DAS28 BL	53	1	4.41	1.03	0.46
DAS28 3M	52	2	2.33	1.19	0.68
DAS28 6M	52	2	2.30	1.43	0.008
DAS28 9M	50	4	1.97	1.41	< 0.001
DAS28 12M	50	4	1.88	1.35	< 0.001
DAS28 15M	47	7	1.66	1.08	< 0.001
DAS28 18M	49	4	1.59	1.12	< 0.001

Furthermore, descriptive statistics results indicate that USPD scores, which measure inflammatory changes at the joints, have notable reductions throughout the study. At 3 months, the mean USPD score was 2.68 (SD = 5.63), which decreased to 2.15 (SD = 5.44) by 6 months and to 2.00 (SD = 3.00) by 18 months (Figure 3.2 and Table 3.3).

Table 3.3: Descriptive statistics of USPD.

	Frequency	Missing	Mean	SD	Shapiro-Wilk (P value)
USPD 3M	35	19	2.68	5.63	< 0.001
USPD 4M	21	33	2.38	4.28	< 0.001
USPD 5M	20	34	2.10	4.21	< 0.001
USPD 6M	33	21	2.15	5.44	< 0.001
USPD 7M	24	30	1.66	4.64	< 0.001
USPD 8M	26	28	2.26	4.85	< 0.001
USPD 9M	34	20	2.17	5.63	< 0.001
USPD 10M	23	31	1.73	4.49	< 0.001
USPD 11M	29	25	2.06	5.15	< 0.001
USPD 12M	32	22	1.81	5.41	< 0.001
USPD 13M	32	22	2.06	5.41	< 0.001
USPD 14M	30	24	1.66	5.29	< 0.001
USPD 15M	33	21	1.57	5.52	< 0.001
USPD 16M	29	25	1.55	5.13	< 0.001
USPD 17M	33	21	1.93	5.47	< 0.001
USPD 18M	11	43	2.00	3.00	< 0.001

The frequency indicates the number of participants who underwent USPD.

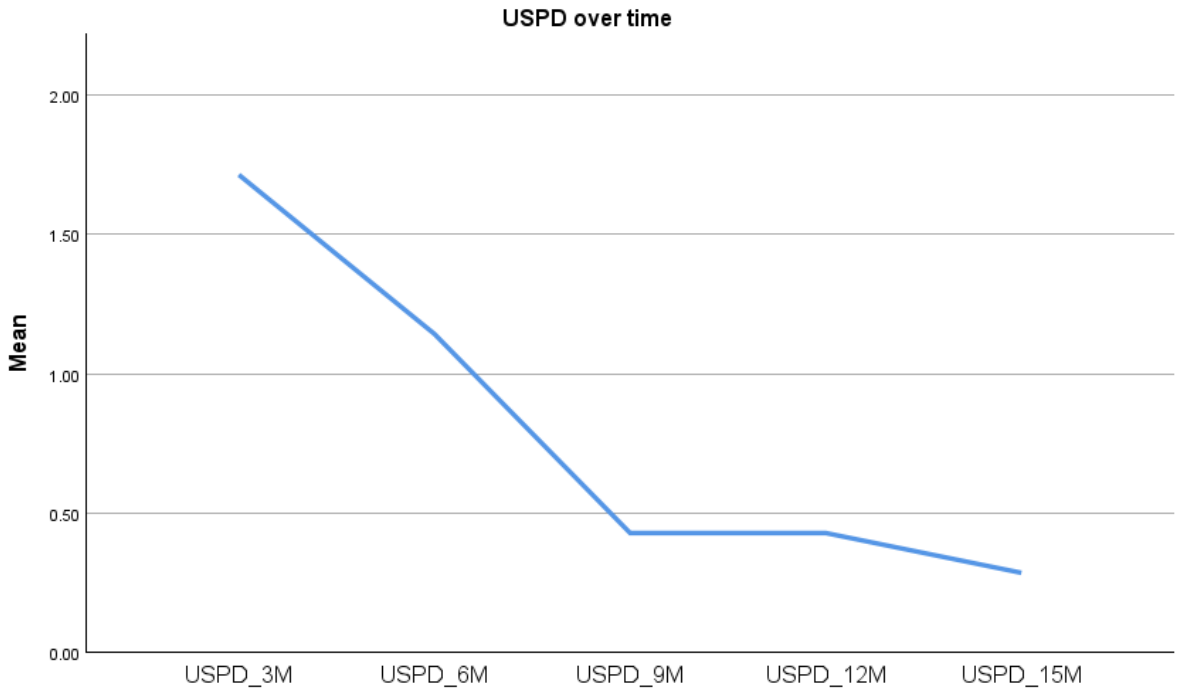

Figure 3.2: The line chart shows the USPD scores over time.

3.4.2 Cross-Sectional Correlation of USPD and Pain VAS

The 3-month correlation analysis between pain VAS and USPD reveals a significant negative correlation ($r = -0.35$, $p < 0.05$) (Figure 3.3). However, this negative relationship does not make sense clinically, as more inflammation in the joints is associated with more pain and vice versa.

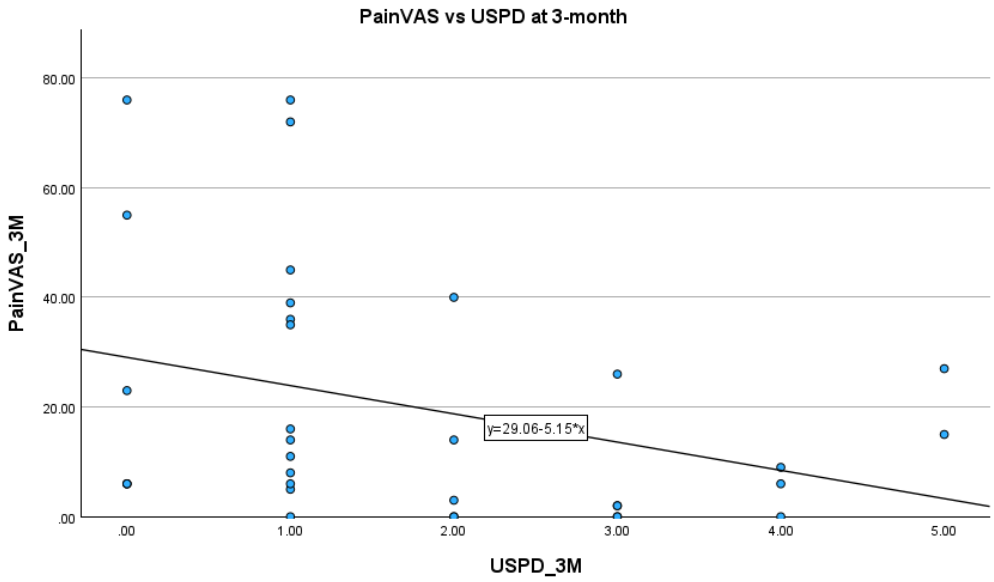

Figure 3.3: The scatter plot shows the correlation between pain VAS and USPD at the 3-month time point.

At the 6-month follow-up, no significant correlation was observed between pain VAS and USPD (r = 0.09, p > 0.05) (Figure 3.4).

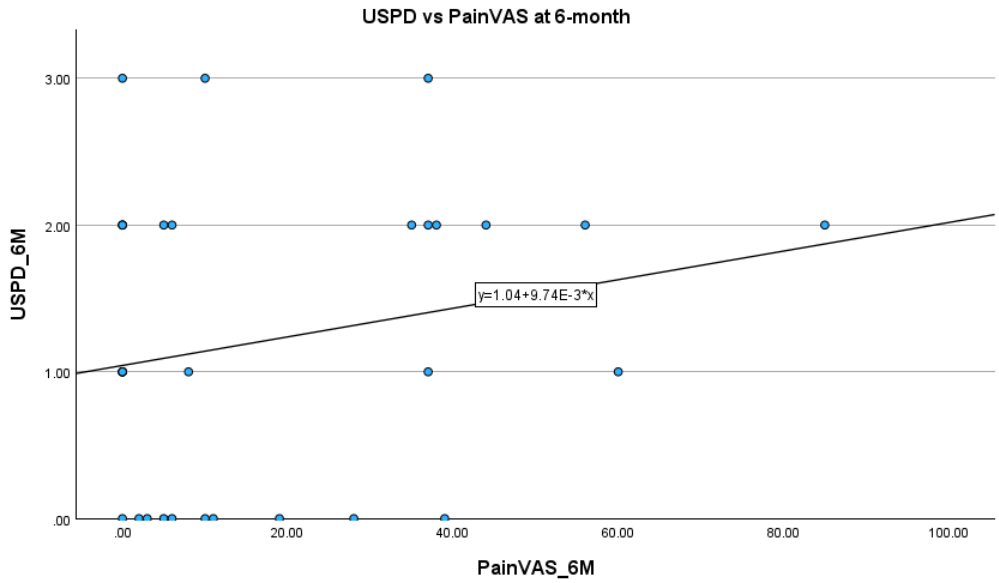

Figure 3.4: The scatter plot shows the correlation between pain VAS and USPD at the 6-month time point.

At the 9-month follow-up, no significant correlation was observed between pain VAS and USPD (r = -0.05, p > 0.05) (Figure 3.5).

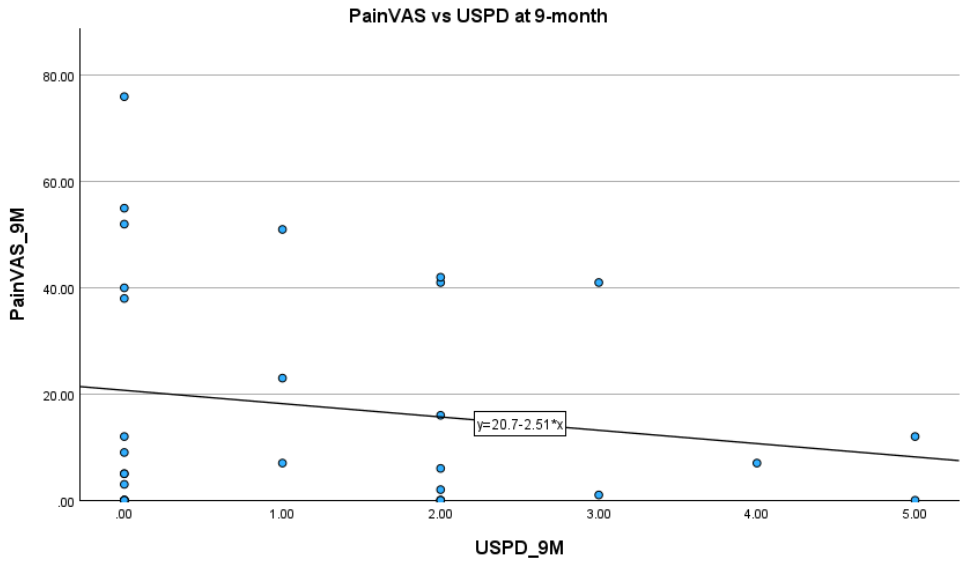

Figure 3.5: The scatter plot shows the correlation between pain VAS and USPD at the 9-month time point.

At the 12-month follow-up, no significant correlation was observed between pain VAS and USPD (r = 0.08, p > 0.05) (Figure 3.6).

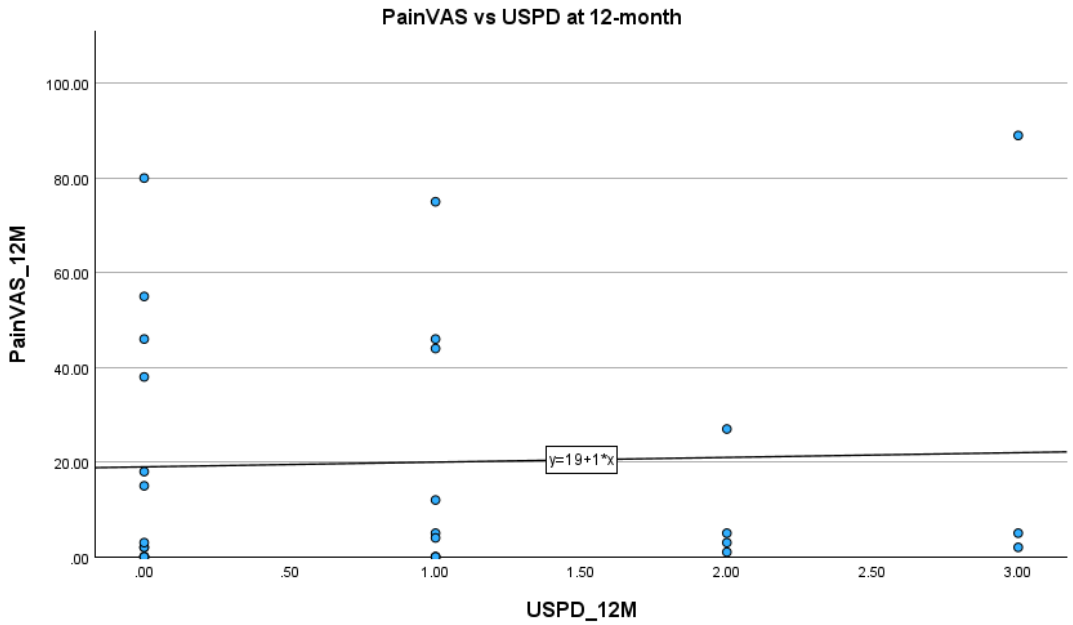

Figure 3.6: The scatter plot shows the correlation between pain VAS and USPD at the 12-month time point.

At the 15-month follow-up, no significant correlation between pain VAS and USPD was seen (r=0.14, p >0.05 (Figure 3.7).

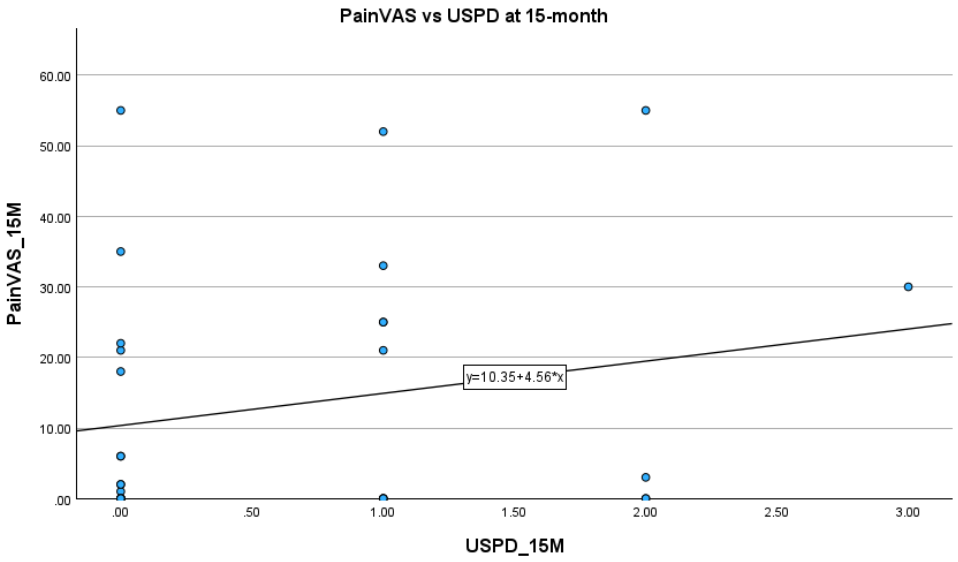

Figure 3.7: The scatter plot shows the correlation between pain VAS and USPD at the 15-month time point.

3.4.3 Correlation of Change in USPD and Change in Pain VAS

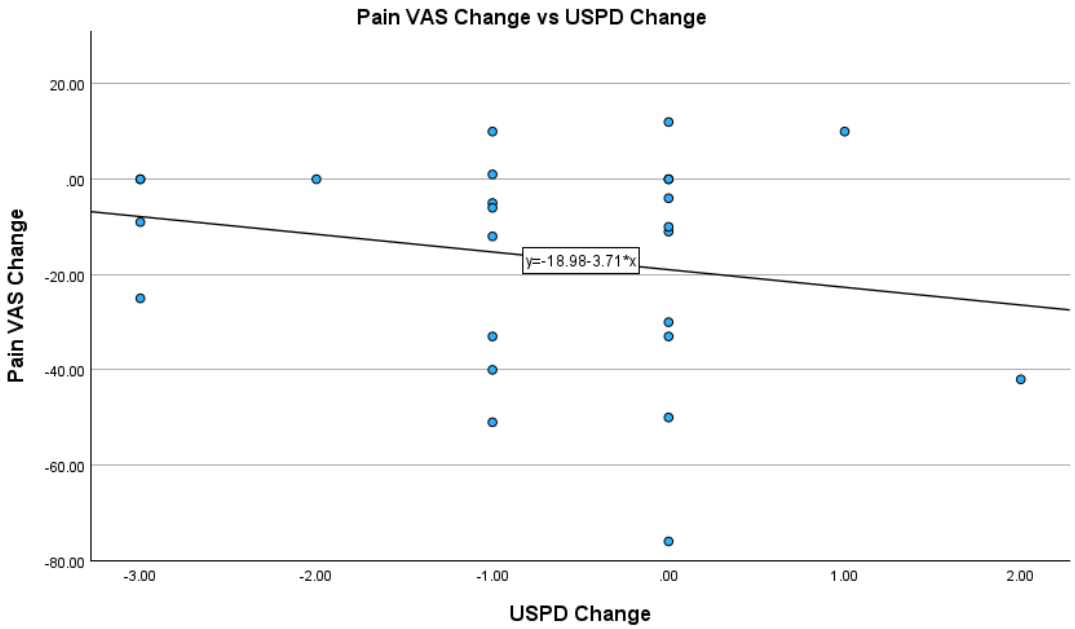

Figure 3.8: The scatter plot shows the correlation between pain VAS change and USPD change.

There is no significant correlation between pain VAS change and USPD change (r=-0.21, p >0.05) (Figure 3.8).

3.4.4 Evaluation of USPD and pain VAS in low and high pain subgroups

Participants were classified into two subgroups based on their pain VAS scores at the 15-month follow-up (cutoff≥34): 42 participants (79%) were in the low pain group, and 6 participants (11.32%) were in the high pain group.

In the low-pain group, 39 participants had a DAS28 remission, and 32 participants had a negative swollen joint count (SJC), indicating the absence of joint inflammation. Four participants showed ultrasound active synovitis (USPD ≥2) in the low-pain group (Table 3.4).

Table 3.4: Clinical variables and USPD at low and high pain subgroups at a 15-month time point.

15-Month follow-up	Low pain group	High pain group
Pain VAS ≥34	42 (79.25%)	6 (11.32%)
USPD ≥2	4 (9.52%)	1 (16.67%)
DAS28<2.6	39 (92.86%)	0
SJC=0	32 (76.19%)	4 (66.67%)
TJC>11	0	3 (50%)
ESR<20	24 (57.14%)	5 (83.3%)

DAS28 < 2.6 indicates remission, SJC= 0 indicates the absence of swollen joints and reflects a lack of inflammation; normal ESR <20 suggests no active inflammation, and a TJC greater than 11 indicates non-inflammatory pain.

Conversely, in the high-pain group, 6 participants (11.32%) had high pain. Only one participant showed ultrasound active synovitis (USPD ≥2), and no participant achieved DAS28 remission at a 15-month timepoint. Negative SJC characterised 4 participants, and 3 participants scored high TJC (TJC > 11). Finally, 5 participants (ESR < 20) had a low ESR, indicating the absence of inflammation in this subgroup (Table 3.4).

3.4.5 Evaluation of USPD and pain VAS in persistent and non-persistent pain subgroups

Participants in this analysis were classified into two subgroups, persistent and non-persistent, based on their pain VAS scores (cutoff≥34). Based on the pain VAS cut-off at all visits through the 12-month follow-up, participants with persistent high pain VAS were assigned to the persistent pain group: 5 participants (9.3%). Only one participant showed ultrasound active synovitis (USPD ≥2), and 3 participants achieved DAS28 remission. Three participants exhibited negative SJC, while two participants had a high TJC (TJC > 11). Additionally, four participants showed an elevated ESR (ESR ≤ 20), indicating the absence of inflammation in this subgroup (Table 3.5).

Table 3.5: Clinical variables and USPD in the persistent and non-persistent pain groups.

12-Month follow-up	No persistent pain group	Persistent pain group
Pain VAS	45 (83.3%)	5 (9.3%)
USPD ≥2	6 (11.1%)	1 (1.85%)
DAS28<2.6	35 (64.8%)	3 (5.56%)
SJC=0	27 (50%)	3 (5.56%)
TJC>11	6 (11.1%)	2 (3.7%)
ESR< 20	36 (66.67%)	4 (7.41%)

DAS28 < 2.6 indicates remission, SJC= 0 indicates the absence of swollen joints and reflects a lack of inflammation; normal ESR <20 suggests no active inflammation, and a TJC greater than 11 indicates non-inflammatory pain.

On the other hand, participants with non-persistent high pain were assigned to the non-persistent group; 45 participants (83.3%) were in the non-persistent pain group (Table 3.5). 6 participants demonstrated ultrasound-active synovitis (USPD ≥ 2), and 35 participants reached DAS28 remission. Twenty-seven participants showed a negative SJC, while 6 participants had a high TJC (TJC > 11). Additionally, 36 participants had low ESR (ESR < 20), indicating the absence of inflammation in this subgroup (Table 3.5).

The chi-square test reveals a statistically significant relationship between pain VAS groups and DAS28 remission status ($\chi^2 = 54.842$, df = 4, $p < 0.001$) (Table 3.6). Participants with non-persistent pain were more likely to achieve remission, with 35 out of 45 cases in remission, whereas participants with high persistent pain showed minimal remission, as indicated by a DAS28 score. Additionally, a significant association exists between the pain VAS group and ESR levels ($\chi^2 = 54.000$, df = 4, $p < 0.001$). The participants in the non-persistent group predominantly had normal ESR values, whereas participants in the high-persistent pain group had abnormal ESR.

In addition, a significant relationship was seen between pain VAS and SJC ($\chi^2 = 54.000$, df = 4, $p < 0.001$) (Table 3.6). Patients with non-persistent pain have shown negative SJC compared to those with persistent pain.

Furthermore, no significant association was detected between pain VAS and USPD active synovitis ($\chi^2 = 0.825$, df = 4, p = 0.935). Moreover, a significant relationship was observed between pain VAS and TJC ($\chi^2 = 56.571$, df = 4, $p < 0.001$) (Table 3.6). Participants with persistent pain had higher TJC, whereas participants with non-persistent pain exhibited lower TJC.

Table 3.6: Summary of Chi-square test results for the pain VAS and the clinical variables.

Variable pair	Chi-square value	Degree of freedom (df)	p-value
Pain VAS vs DAS28 remission	54.84	4	<0.001
Pain VAS vs USPD	0.83	4	0.94
Pain VAS vs negative SJC	54	4	<0.001
Pain VAS vs high TJC	56.57	4	<0.001
Pain VAS vs normal ESR	54	4	<0.001

3.5 Discussion

The previous chapter emphasised the necessity of using a more reliable tool, namely USPD, to validate the presence of synovial abnormalities detected by clinical variables such as SJC and ESR. In this research, the nature of pain in early RA using USPD was investigated. The traditional belief about the nature of pain in early RA is that joint inflammation is the source of pain. Clinical inflammatory markers, such as ESR and SJC, can help detect this inflammation. Additionally, USPD could be used to validate the findings of these clinical measures, as the presence of a USPD signal is associated with active inflammation in early RA (Hall et al., 2014; Dale et al., 2016), and consequently, it may cause potential pain in the affected joints.

3.5.1 USPD correlation with pain VAS

The correlation between the presence of USPD and pain in the early RA population is controversial (Pereira et al., 2014). While USPD can measure peripheral changes at the joints, it does not necessarily indicate the pain intensity associated with these changes (Pereira et al., 2015).

In the current research, the correlation between pain VAS and USPD was first conducted at the 3-month visit due to the absence of USPD at the baseline. Initially, a relationship is expected between pain intensity, as measured by the pain VAS, and inflammation changes, as measured by USPD, given that the primary source of pain in RA arises from peripheral inflammatory changes.

The findings reveal a significant negative correlation between pain VAS and USPD at the 3-month visit. This result does not make sense clinically, as more inflamed joints typically lead to greater pain intensity (Scanzello and Goldring et al., 2012), and changes in synovitis are associated with changes in pain (Hill et al., 2007). This negative correlation is clinically not sensible; therefore, this significant negative association could indeed be a spurious correlation. Spurious correlations often occur when the statistical relationship does not reflect a reasonable causal connection between the variables and can result from various factors such as sample selection bias and sample size variability (Haig, 2003). At the 3-month visit, 51 participants with pain VAS were correlated with 35 participants with USPD, which may not represent the actual relationship and produce a spurious correlation due to sample bias (Haig, 2003). Additionally, the sample size is small and imbalanced, which can introduce noise into the data and lead to spurious correlations due to sample variability (Haig, 2003). As a result, the correlation between pain VAS and USPD is neglected, suggesting no correlation between these variables at this point.

In addition, no significant correlation was observed at the 6-, 9-, 12-, or 15-month follow-up visits. These results align with those of Pereira and colleagues (2014), who reported no significant association between pain and USPD. They highlighted in their study that the presence of USPD did not differ significantly between the low pain group and the high pain group.

The findings from their study were based on the USPD assessments of the MCP joints in both hands. However, the pain VAS score is not restricted to the joints assessed by ultrasound. It may also reflect pain intensity originating from joints that were not included in the USPD assessments. Bhasin and Cheung (2015) emphasise that the small joints of the hands are the most commonly studied in ultrasound for the assessment of inflammatory conditions. While the reliability of image interpretation for these joints is good, the variability in image acquisition is notable. In contrast, the knee joint shows the highest image quality and interpretation reliability. Therefore, incorporating additional joints, such as the knee, into the ultrasound protocol could enhance the diagnostic capabilities of

ultrasound, particularly in detecting inflammation that may be responsible for the pain experienced in RA.

Disease activity in RA is associated with pain, especially pain arising from peripheral changes (Pereira et al., 2015). Furthermore, Fjellstad and colleagues (2020) highlight that synovitis is associated with pain, and its intensity increases with the progression of inflamed joints. Several research studies have highlighted that pain VAS is correlated with disease activity, as measured by DAS28. Also, several studies showed that a change in DAS28 correlates well with a change in USPD (Freestone et al., 2010; Wakefield et al., 2003). Based on the literature research, the USPD may be capable of detecting inflamed joints, which could subsequently indicate a portion of the pain contribution in RA (Goldenberg et al., 2019). Therefore, further research is needed to investigate that correlation using wider joint sets and larger sample sizes.

3.5.2 Evaluation of USPD and pain VAS in low and high pain subgroups

This analysis divided participants into low-pain and high-pain subgroups based on their pain VAS scores at the 15-month follow-up. The 15-month data were chosen because more patients underwent USPD assessments at this time point compared to the 18-month visit, where the number of assessments is lowest. This variation is also influenced by whether patients undergo MSUS assessments based on their SJC scores, while the Pian VAS is measured every three months. At this point, the pain VAS was used to identify participants with low pain intensity (pain VAS is less than 34) (Boonstra et al., 2014). For the high-pain group, every participant who scored high pain VAS (pain VAS ≥34) was assigned to this group (Boonstra et al., 2014). This pain categorisation would help to understand the effects of pain characteristics on the RA population and enable the identification of pain mechanisms in RA. This method of categorising pain was consistent with the method used in the SERA research. Dividing participants with RA into subgroups based on the pain intensity was introduced in the literature. For instance, Lee and colleagues (2014) categorised their participants into high and low pain subgroups to identify which participants share similar inflammatory or non-inflammatory symptoms, thereby illustrating the characteristics of pain in RA.

In this study, the majority of participants (79%) reported experiencing low pain at the follow-up visit, indicating that pain caused by peripheral inflammatory changes had improved after treatment. This pattern aligns with nociceptive pain as the predominant

mechanism, even though a low pain VAS score by itself does not exclude contributions of other pain pathways.

This finding was further supported by the high number of participants who achieved DAS28 remission and exhibited a negative SJC. Inflammatory biomarkers such as the SJC, ESR, and USPD are indicators of inflammation control. Improvements in these inflammatory markers are linked to pain relief in patients with RA (Walsh and McWilliams, 2012). These objective biomarkers are utilised to assess the inflammatory disease associated with pain in Patients with RA (Walsh and McWilliams, 2014). Therefore, a reduction in these inflammatory biomarkers is correlated with improvements in pain resulting from inflammatory changes. However, it is essential to note that this type of pain represents only one component of the overall pain experienced by those with RA (Walsh and McWilliams, 2012).

On the other hand, about 9% of participants in this research reported high pain despite the RA treatment. Unlike participants in the other group, the pain did not improve due to DMARD treatment. Only one of six participants exhibited active ultrasound synovitis, as measured by USPD, indicating that the experienced pain is unlikely to stem from subclinical inflammation; therefore, a different mechanism may be the source of pain in this group.

To investigate the nature of this kind of pain in the high-pain group, inflammatory biomarkers and USPD were examined to exclude the presence of inflammatory changes. Druce and colleagues (2016) indicated that the absence of peripheral inflammatory changes suggests the occurrence of non-inflammatory pain. Only one of six participants showed ultrasound-active synovitis; four showed no swollen joints, and five had a normal ESR. All these inflammatory markers confirm the absence of inflammation in most of the participants in the persistent pain group. Therefore, this could be evidence of the presence of non-inflammatory pain, namely, nociplastic pain.

Furthermore, high TJC was investigated in persistent pain, as Walsh and McWilliams (2014) highlight that high TJC is a marker of non-inflammatory pain in RA. High TJC (more than 11) was observed in 3 participants (50%), indicating the presence of non-inflammatory pain in them. This finding aligns with Pollard et al. (2010), who emphasise that TJC could be a marker for non-inflammatory conditions such as fibromyalgia.

3.5.3 Evaluation of USPD and pain VAS in persistent and non-persistent pain subgroups

Further analysis was conducted to ascertain whether the high pain VAS scores observed at the follow-up visit indicated chronic persistent pain rather than temporary flare pain. Participants were divided into two groups: those experiencing persistent pain and those with non-persistent pain. This categorisation was based on the pain VAS scores recorded during the 12-month visit, selected for consistency with the methods outlined in the previous chapter. To maintain consistency, the same pain VAS cutoff (≥34) used in the prior analysis was applied to this analysis. Participants who experienced high levels of persistent pain during follow-up visits up until the 12-month visit were categorised into the persistent pain group. In contrast, participants without persistent pain were assigned to another group.

Forty-five participants (83.3%) experienced non-persistent pain, while five participants reported persistent pain at the 12-month visit. Among those with persistent pain, only one participant exhibited active synovitis on ultrasound, compared to five participants in the non-persistent pain group. Thus, four participants exhibited negative USPD, indicating an absence of joint inflammation. Consequently, the persistent pain experienced is unlikely to arise from subclinical inflammation; therefore, an alternative mechanism could be the source of pain in this group.

Regarding disease activity, three participants in the persistent pain group achieved remission, as measured by the DAS28 scale, while 35 participants in the non-persistent pain group reached remission. Additionally, three participants in the persistent pain group had no swollen joints, unlike the 27 participants in the non-persistent group, who also had no swollen joints. Furthermore, 4 participants in the persistent pain group had a normal ESR, compared to 36 participants in the non-persistent group. The negative SJC and normal ESR indicate the absence of inflammation in the persistent pain group, suggesting that a non-inflammatory source could be responsible for the experienced pain in this subgroup.

The inflammatory markers clearly demonstrate that the majority of participants in the persistent pain group show no signs of inflammation. This evidence could indicate the presence of non-inflammatory pain.

The Chi-square test results indicated statistically significant relationships between pain levels, measured by the pain VAS, and various clinical indicators, including DAS28

remission, ESR, SJC, and TJC. This highlights a strong link between subjective pain levels, namely pain VAS, and markers of disease activity and inflammation. However, the absence of a significant association with USPD suggests that ultrasound may not fully capture the underlying sources of pain in this RA population. Therefore, the lack of an association between pain and USPD suggests that other non-inflammatory pain mechanisms may be involved and warrant further investigation.

The results of this research align with those of the SERA study discussed in the previous chapter. SERA findings indicated that some participants with early RA experienced persistent pain despite receiving excellent treatment. The current research reports a negative SJC, normal ESR, and a high TJC, which is consistent with the SERA findings.

These intriguing observations underscore the need for further investigation to enhance the understanding of pain mechanisms in RA.

3.5.4 Impact of the absence of USPD at the baseline

In this dataset, the ultrasound assessment was carried out in the interventional group. However, the ultrasound time points were not aligned with other clinical variables, as there was no baseline ultrasound in this dataset.

Furthermore, the USPD did not follow the same temporal protocol, as USPD assessments were conducted monthly starting at 3 months, unlike other variables, which began at the baseline and were repeated every 3 months until the 18-month follow-up visit.

Therefore, the absence of a USPD assessment at baseline in this longitudinal study could introduce challenges to data interpretation and analysis.

In addition, variables such as pain VAS and DAS28, collected at baseline and monitored longitudinally, cannot be directly correlated with USPD until the 3-month visit. This could create a gap in exploring how early changes in the clinical variables align with USPD inflammation. The descriptive statistics at the baseline and 3-month visits indicate a reduction in pain VAS and DAS28 values compared to the baseline values, suggesting an improvement in treatment. Therefore, the presence of USPD at baseline is crucial for reflecting inflammation at the joints prior to treatment intervention.

The absence of baseline data could bias the interpretation of longitudinal outcomes. To illustrate, an improvement in USPD scores from 3 to 12-month time points could be underestimated if the baseline inflammation was severe or overestimated if it was low.

Moreover, the absence of USPD at the baseline makes it challenging to assess the true extent of changes in synovial inflammation over time. Therefore, it is unable to correlate with the changes in pain VAS or DAS28 unless the change in these variables is calculated, and the initial visit is set to be 3 months instead of the baseline to align with the USPD data. Therefore, there is a gap in the interpretation of early inflammation changes at the baseline.

3.5.5 Limitations

The limitations identified in this research, encompassing biological and methodological aspects, could influence the outcomes.

From a biological perspective, a key limitation is the lack of correlation between the USPD joint count and overall pain levels. The source of pain may stem from different origins; for instance, the pain could be centralised while its origin remains peripheral, as seen in conditions like synovitis.

From a methodological standpoint, the study had a very small sample size and focused solely on one specific ultrasound measure (USPD) performed on a limited number of joints. In contrast, the pain VAS evaluates widespread pain based on patients' perceptions of pain intensity. As a result, the lack of a comprehensive MSUS might dilute the association between joint inflammation and pain.

Moreover, many USPD assessments were missing at various time points, such as at the 18-month mark, which could compromise the validity of the findings (Jelicic et al., 2010). The absence of a baseline USPD assessment in this longitudinal study may also introduce challenges to data interpretation and analysis.

In the Chi-square test, a considerable percentage of cells in the contingency tables had expected counts below 5 (ranging from 66.7% to 77.8%). This limitation could impact the validity of the Chi-square test results, indicating that larger sample sizes are needed to validate these findings.

Moreover, the lack of non-inflammatory measures forces researchers to rely on indirect measures, such as the absence of inflammatory markers and negative USPD, to exclude pain originating from peripheral inflammatory changes, including subclinical inflammation, thereby providing evidence of non-inflammatory pain, such as nociplastic pain.

Due to the reliance on the original TaSER dataset, the available USPD data were not well-suited to address our specific research aim of evaluating pain intensity in early rheumatoid arthritis using MSUS. The original TaSER study was not designed to prioritise MSUS as the primary method for monitoring inflammation. As a result, MSUS assessments were not consistently performed at every visit; they often depended on the clinical status of the patients, such as being conducted when participants achieved DAS28-defined remission, rather than being collected proactively to track inflammatory changes alongside pain at all time points. This led to gaps in MSUS data, including a missing baseline MSUS measurement, which hinders the ability to model within-patient trajectories and to correlate changes in pain with MSUS findings during follow-up. Moreover, the relatively small sample size reduces the statistical power to detect longitudinal links between pain and MSUS outcomes, especially when the number of observations per time point is diminished due to intervention criteria affecting MSUS assessments. Overall, these methodological choices in the original TaSER study compromise the completeness and temporal resolution of the MSUS data, thereby limiting the dataset's ability to address the research questions posed in this chapter.

3.5.6 Recommendations for future study

Future research should aim to address the limitations identified in the current study to clarify the relationship between synovitis and pain types in patients with RA. Key recommendations for future studies include increasing the sample size to establish a robust foundation for examining the connection between pain VAS scores and USPD results. Such enhancements could improve the reliability of the findings, making them more applicable to diverse RA populations and yielding valuable insights into broader implications.

Additionally, future research should incorporate a broader range of joints scanned using various MSUS metrics, such as ultrasound hypertrophy and joint effusion, in conjunction with USPD to determine which metric most effectively correlates with pain measures.

Moreover, it is recommended to include non-inflammatory measures to address the clinical and biological limitations observed. These measures could encompass convenient methods that serve as indirect assessments of non-inflammation in RA. One example is the swollen-to-tender ratio (STR), which emphasises the neurobiological components of pain, particularly focusing on centralised pain.

3.6 Conclusion

Patients with RA continue to report pain despite excellent inflammation control. This has led to an investigation into the nature of their pain. USPD, as a marker for peripheral inflammatory change, is associated with pain VAS, which is used to assess the pain intensity originating from joint inflammation. The findings indicate no significant association between pain VAS and USPD during follow-up visits.

The observed lack of correlation may be attributed to methodological issues, specifically the ineffective MSUS protocol employed in this study. This protocol utilised a limited number of MSUS measurements and examined only a small selection of joints. Furthermore, biological factors may also influence the absence of a meaningful relationship, particularly the potential role of non-inflammatory pain mechanisms.

Then, patients with persistent pain were identified in this research. Furthermore, the findings of this analysis identify patients with RA who are experiencing persistent pain despite excellent treatment in the early RA population. This subgroup was investigated for a better understanding of pain mechanisms. The results indicate that the percentage of absence of inflammation biomarkers is high in this subgroup. This evidence suggests that the persistent pain in this subgroup could arise from non-inflammatory sources. More research is needed to understand the pain mechanism in this population, ideally with a larger sample size, to examine the relationship between pain VAS and USPD.

Chapter 4 Exploring the relationship between ultrasound power Doppler and pain in patients with early rheumatoid arthritis using the Spanish RA cohort (Naredo)

4.1 Abstract

Introduction

Despite advancements in controlling joint inflammation, a significant proportion of Patients with RA (40-50%) still experience persistent pain, suggesting the involvement of pain mechanisms beyond inflammation. This discrepancy indicates that pain mechanisms beyond peripheral inflammation may play a role. MSUS can be used to confirm the existence or absence of peripheral inflammation, which could provide evidence about the nature of pain.

Objectives

In this study, MSUS was utilised to identify inflammatory changes in joints that may cause nociceptive pain and investigate the relationship between joint inflammation and pain in RA. The goal was to quantify the contribution of inflammatory nociceptive mechanisms in explaining the totality of pain in RA.

Methods

This study was a secondary analysis of a prospective study (Naredo et al., 2008) of Patients with RA who met the 1987 American College of Rheumatology criteria. The study was conducted on 367 participants starting treatment with a tumour necrosis factor-alpha (TNFα) blocking agent. The participants underwent assessments, including clinical, laboratory, MSUS, pain VAS (100mm), and DAS28, at baseline, 3 months, 6 months, 9 months and 12 months of treatment. MSUS examination involved evaluating 86 sites across 28 joints to assess several metrics: ultrasound power Doppler (USPD) signals, ultrasound synovial hypertrophy (USSH), and ultrasound synovial effusion (USSE). These metrics were scored on a semi-quantitative scale from 0 to 3, where 0 indicates "absent", 1 "mild", 2 "moderate", and 3 "marked". Participants were divided into subgroups based on pain VAS, the swollen-to-tender joint count ratio (STR)and negative ultrasound power Doppler (USPD). The relationship between pain VAS and MSUS metrics in RA was examined using appropriate correlations at baseline and longitudinally in each subgroup.

Results

A moderately significant correlation with a minor effect size was observed between pain VAS and MSUS metrics, namely USPD, USSE and USSH at baseline ($r = 0.154$, $p = 0.003$; $r = 0.123$, $p = 0.018$; $r = 0.111$, $p = 0.034$, respectively). Furthermore, a strong, statistically significant correlation with a small effect size was observed between

longitudinal changes in pain VAS and MSUS metrics, namely USPD, USSE, and USSH ($r = 0.197$, $p < 0.001$; $r = 0.254$, $p < 0.001$; $r = 0.241$, $p < 0.001$, respectively). There was no significant correlation between pain VAS and USPD at baseline and 12 months in the low STR group (p-values of 0.531 and 0.144, respectively). A significant correlation was observed between pain VAS and USPD at baseline and at the 12-month visit ($p = 0.005$ and $p < 0.001$, respectively) in the high STR group. Finally, 14 participants (18.4%) reported high pain VAS in the negative USPD group.

Conclusion

MSUS is a valuable tool for identifying nociceptive pain as it demonstrates a correlation with pain intensity measured by VAS but accounts for a minor portion of pain experienced by patients with RA. This suggests that nociceptive pain mechanisms do not predominate as classically considered and that other pain mechanisms have existed. When MSUS shows no correlation with pain VAS at low STR, it may indicate the presence of nociplastic pain. Additionally, MSUS could indirectly suggest the presence of nociplastic pain in RA by confirming the absence of inflammation. This supports the possibility that high levels of pain in RA may be attributed to central sensitisation. These findings underscore the significance of MSUS in evaluating pain in RA, thereby enhancing the understanding of The nature of pain and facilitating improved pain management strategies for RA.

4.2 Introduction

This chapter builds on the previous, addressing the same research question but utilising a different dataset. This chapter uses a new dataset with several noteworthy enhancements. In contrast, the previous chapter examined pain types in RA using only the pain VAS and USPD for assessment of the pain. This dataset has a greater sample size, covers a wider variety of joints in the investigation, and incorporates a broader range of ultrasound techniques that offer comprehensive imaging of joint structures and vascularity. These methodological developments aim to provide us with more detailed insights and knowledge of RA's underlying pain mechanisms.

MSUS is now a commonly used tool for RA diagnosis. It provides a comprehensive visualisation of joint structures and improves clinical evaluation by detecting conditions such as tenosynovitis, synovitis, and erosions that might not be visible on physical examination alone. While colour Doppler (CD) and power Doppler (USPD) provide information on the vascularisation within the inflamed synovial tissue, indicating the level of active inflammation, greyscale US (GS) aids in assessing the degree of synovitis. Since fluctuations in disease activity can be reflected in changes in Doppler activity, this visualisation of hypervascularity inflammation is beneficial.

This study differs from the previous chapter because it uses a much larger sample size, improving the findings' validity and reliability. Although the previous chapter provided significant preliminary insights, the small sample size may limit the study's power and prevent generalisation of the findings (Serdar et al., 2021). A more comprehensive range of variability within the RA patient population can be captured by increasing the study's participant pool, enabling more reliable statistical analyses and more conclusive findings. In addition to enhancing the study's ability to identify clinically significant differences and associations, a larger sample size also increases confidence in the repeatability of the findings. Furthermore, providing a comprehensive understanding of pain in RA may lead to better RA management.

Studying RA using different ultrasound techniques, including power Doppler ultrasound (USPD), synovial thickening (USSH), and ultrasound joint effusion (USJE), has many benefits. Every method provides distinct information that improves the RA diagnosis. For example, USPD plays a role in identifying synovial vascularity, a crucial sign of active inflammation. High levels of pain intensity, especially nociceptive, may be associated with increased pain due to higher inflammatory activity (Hammer et al., 2018).

Furthermore, USSH can identify chronic synovitis by providing details about the disease's prognosis. Moreover, USJE is another indicator of inflammation that can be found by evaluating joint fluid accumulation. Merging these methods could provide a comprehensive evaluation of joint conditions, including chronic alterations and active inflammation. Walsh and McWilliams (2014) highlight that pain is associated with active inflammation as it results from the interplay between joint pathology and the processing of pain signals by peripheral nerves, spinal and supraspinal pain pathways. These techniques could provide evidence of nociceptive pathway activity, which could lead to better RA evaluation of pain mechanisms, especially pain arising from classic spinothalamic.

Including additional joint counts for MSUS is yet another benefit of this research. For several reasons, including the inclusion of more joints in RA studies, it is essential. To begin with, RA is a systemic disease that can impact several joints in the body. A comprehensive assessment of a larger number of joints yields a more accurate picture of the disease impacts (Naredo et al. 2004). More accurate evaluations result from this inclusiveness and improved capacity to identify disease activity and severity differences among various joints. While previous reports usually focused on a few joints, such as the knee, MCP, and PIP joints, this study evaluated 28 joints per patient for USSH, USJE, and USPD. Considering its practicality, the 28-joint count is frequently employed in clinical practice and research (Naredo et al. 2005). In rheumatological practice, the 28-joint count helps strike a balance between thoroughness and efficiency. The MSUS investigation focusing on 28 joints can significantly reduce scanning duration to about 15 minutes, making it feasible for routine use without compromising the accuracy of inflammation assessment, even though effusion and synovitis can occur in other periarticular locations (Naredo et al. 2005).

A combination of patient-reported measures and advanced imaging techniques may be helpful for effective pain management in Patients with RA. Patients can self-evaluate their level of pain using the widely used Pain VAS, which uses a scale that is usually anchored from ‘no pain’ to ‘the worst pain imaginable’. The subjective measure provides valuable insight into the patient's pain perception, helping medical professionals assess the condition's severity and functional impact. Nevertheless, the pain VAS does not provide objective measurements of the underlying pathophysiology of pain. The MSUS offers a thorough, impartial assessment of the impacted joints, thereby complementing the pain VAS. The synovitis that causes RA pain can be identified and measured by MSUS. Power Doppler (USPD) evaluates the vascularisation of the inflammatory synovial tissue, offering

information on the degree of active inflammation, while GSUS measures the extent of synovial thickening and joint effusion. An improved method for assessing pain in RA is enabled by combining the pain VAS and MSUS.

Pain in rheumatic diseases plays a crucial role in clinicians' diagnostic process, as its accurate interpretation can significantly impact patient management. Patients with RA often experience high levels of pain regardless of the specific pathological condition, making pain control a significant challenge for both patients and healthcare providers (Sheane et al., 2008). The complexity of pain in RA stems from its multifactorial nature involving peripheral nociception and central sensitisation (Katz and Rottenberg, 2005). Clinically, RA pain can be divided into nociceptive and nociplastic components. Nociceptive pain arises from tissue damage and is mediated by nociceptors that respond to mechanical, chemical, or thermal stimuli, often accompanied by pro-inflammatory mediators (Pinho-Ribeiro et al., 2017). Emerging evidence suggests that not all pain in RA correlates with inflammatory markers, suggesting a role for non-inflammatory mechanisms. Nociplastic pain results from the activation of peripheral nociceptors without actual or potential tissue damage, typically due to central sensitisation, which heightens the responsiveness of nociceptive neurons in the central nervous system, leading to pain hypersensitivity (Kosek et al., 2016).

With the development of more effective disease-modifying drugs, joint inflammation, a primary source of RA pain, has become more manageable, often preventing joint damage. Despite the suppression of inflammation, the long-term pain prognosis remains unfavourable for a significant proportion of Patients with RA, affecting 40-50% of patients (McWilliams and Walsh, 2017). The inconsistency between improvements in inflammation and pain relief suggested that mechanisms beyond peripheral inflammation may contribute to the situation. One such mechanism is central sensitisation, linked to dysfunctional central nervous system pain processing and commonly associated with fibromyalgia (FM), a condition found in 13–25% of patients with RA (Basu et al., 2018).

MSUS techniques have been crucial in identifying peripheral inflammation features in RA. MSUS outperforms clinical examination in detecting synovitis and joint effusion, which are linked to nociceptive pain, a type of pain mechanism in RA. However, there have been no studies exploring the use of MSUS as an indirect measure of co-occurring central sensitisation, specifically fibromyalgia, in Patients with RA. Besides the advantage of MSUS as a marker of peripheral changes, it can be used to confirm the absence of active

inflammation in patients who have effectively managed their inflammation but continue to experience persistent pain.

4.2.1 Objectives and hypotheses

This research utilised MSUS as a measure of nociceptive pain to examine the relationship between joint inflammation and pain in RA. The primary objective was to quantify the contribution of inflammatory nociceptive mechanisms in explaining the overall pain in RA.

In this research, I hypothesise that MSUS metrics statistically correlate with pain VAS scores, reflecting nociceptive pain due to inflammatory joint changes.

I also hypothesise that MSUS can be used to indirectly assess pain related to non-inflammatory nociplastic pain if it shows no signs of inflammation in participants with persistent pain.

4.3 Methods

A retrospective secondary analysis was performed to explore the relationship between MSUS metrics and pain severity in patients with RA. This analysis was based on previously collected data from a prospective study conducted by Naredo and colleagues in 2008. The original study aimed to assess the efficacy of MSUS in evaluating synovial inflammation and monitoring treatment responses in Patients with RA receiving anti-TNF therapy. The findings from this retrospective analysis intend to provide further insights into the utility of MSUS metrics as a diagnostic tool to explain pain in patients with RA.

4.3.1 Participants

Participants with RA were enrolled in the study based on the American College of Rheumatology's 1987 criteria, which were designed to identify patients with RA. All patients started therapy with a TNF blocking agent, following Spanish and international consensus guidelines on biologic agent use for RA treatment. The study adhered to the Declaration of Helsinki and obtained approval from local ethics committees. Informed consent was obtained from all patients prior to enrolment.

4.3.2 Data collection

Patients underwent clinical, laboratory, and MSUS evaluations at multiple time points: baseline (within one week before initiating anti-TNF therapy), one month, three months, six months, and 12 months. MSUS scanning was taken at baseline and after 12 months of follow-up. The patient's clinical progress guided treatment decisions throughout the follow-up without knowledge of MSUS findings.

Clinical and laboratory assessments were conducted at each visit by the same rheumatologist, with one rheumatologist assigned per centre, except for one centre where two rheumatologists were involved. The rheumatologist remained blinded to MSUS findings. Patient data collected at enrolment included age, gender, duration of symptoms, prior use of DMARDs and biologic agents for RA, and rheumatoid factor (RF) status. Drug usage for RA was recorded at each visit. At each visit, tenderness and swelling of 28 joints were evaluated, with tender and swollen joint counts recorded. Participants self-assessed their pain and overall disease activity using a 100-mm pain VAS at each visit. Functional ability was evaluated using a Spanish version of HAQ. Serum markers of inflammation

(CRP and ESR) were obtained from laboratory tests performed within 48 hours of each clinical visit. RF levels were measured at enrolment and the 12-month visit. Disease activity was quantified at each visit using the Disease Activity Score in 28 joints (DAS28).

MSUS assessments, including power Doppler (USPD), joint effusion (USJE) and synovial thickening (USSH), were conducted during each clinical visit. Each patient was consistently evaluated by the same rheumatologist at all visits to ensure consistency (one rheumatologist at 23 centres and two rheumatologists at two centres, all proficient in ultrasonography). These rheumatologists were blinded to the clinical, laboratory, and radiographic findings and were not involved in treatment decisions. To minimise bias, the rheumatologists were not given access to the MSUS results from previous visits. Participants were instructed not to discuss their clinical symptoms with the ultrasound.

The MSUS examinations were carried out in a darkened scanning room. A systematic USJE, USSH, and PD examination of the 28 clinically assessed joints was performed using commercially available real-time scanners (Logiq 5 Pro by GE Healthcare in 23 centres and Logiq 7 by GE Healthcare in 2 centres) equipped with multifrequency linear array transducers (7–12 MHz). The 28-joint MSUS assessment encompassed the evaluation of intra-articular synovitis, tenosynovitis, bursitis, and synovial PD signals at 86 anatomical sites.

Before the study, all investigators standardised the ultrasound scanning techniques, grey-scale and USPD machine settings, and abnormality definitions. Synovitis, tenosynovitis, and bursitis were defined according to the published definitions and descriptions in Outcome Measures in Rheumatology Clinical Trials.

During the grey-scale ultrasound examination, USSH and USJE within intraarticular recesses, tendon synovial sheaths, and bursae were graded semi-quantitatively on a scale of 0–3 (0 indicating absence, one mild, two moderate, and three marked). Synovial, tenosynovial, and intrabursal blood flow at each joint was evaluated using USPD. USPD imaging involved selecting a region of interest that included the bony margins, the synovial site, and variable views of the surrounding tissues. The pulse repetition frequency (PRF) was set to the lowest permissible value to maximise sensitivity, typically ranging from 500 Hz to 750 Hz, depending on the anatomical area scanned. Low-wall filters were applied, the dynamic range was set to 20–40 dB, and colour gain was adjusted just below the level at which colour noise appeared on the underlying bone (no flow should be visualised on

bony surfaces), resulting in gains of 18-30 dB. Flow was demonstrated in two planes and confirmed by pulse wave Doppler spectrum to exclude artefacts.

Intraarticular, tenosynovial, and intrabursal PD signals were graded on a semi-quantitative scale of 0–3 during the USPD examination (0 indicating no synovial flow, one mild with fewer than three isolated signals, two moderate with more than three isolated signals or a confluent signal in less than half of the synovial area, and three marked with signals in more than half of the synovial area). A score ranging from 0 to 3 was assigned to each joint for USSH, USJE, and USPD signals based on the highest scores recorded from the evaluated synovial sites within each joint. The counts of joints displaying USSH, USJE, and USPD signals at any synovial site were recorded at each visit. An overall joint index for USSH, USJE, and USPD signals was also calculated at each MSUS assessment. These overall joint indices were determined by summing the USSH, USJE, and USPD signal scores, respectively, for each joint.

4.3.3 Data Analysis

Descriptive statistics aim to summarise the central tendencies, variability, and distribution patterns of these measures over time. They involve calculating means, standard deviations (SD), frequency distributions, and histograms and conducting normality tests using the Shapiro-Wilk test at various time points.

The first step in the analysis involved computing descriptive statistics for USPD, pain VAS, and DAS 28 at each time point. Descriptive statistics summarise the data in terms of central tendency and variability. The mean and standard deviation for USPD, pain VAS, and DAS28 were calculated for each time point. The mean provides the average value of the data, offering insight into the central tendency, and the standard deviation indicates the degree of dispersion or variability around the mean. Frequency distributions for USPD, pain VAS, and DAS 28 scores were examined. This analysis involved counting the number of occurrences of each score within predefined intervals or categories. Frequency distribution tables were generated to summarise the data, providing a clear overview of the distribution patterns.

Histograms were constructed for USPD, pain VAS, and DAS 28 scores at each time point. They provide a visual representation of the data distribution, allowing for the identification of skewness, kurtosis, and potential outliers. Then, they were plotted using statistical

software, ensuring accurate and reproducible visualisations. The Shapiro-Wilk test played a crucial role in assessing the normality of USSH, USJE, USPD, pain VAS, and DAS 28 scores at each time point. This test, which evaluates whether the data follow a normal distribution, is a critical step in the analysis. A p-value less than 0.05 indicates a significant deviation from normality, prompting consideration of appropriate transformations or non-parametric methods for further study.

After conducting normality tests, namely the Shapiro-Wilk, to determine the appropriate statistical tests, we proceeded with statistical analysis using SPSS. Normality was assessed using the Shapiro–Wilk test; p-values greater than 0.05 indicated that the data did not significantly deviate from normality. A t-test was used for normally distributed variables. However, the Mann-Whitney U test, an essential alternative for non-normally distributed data, was applied when necessary. These tests were instrumental in understanding differences between variables at different time points.

4.3.4 Univariate correlation between MSUS metrics and pain VAS

The relationship between MSUS metrics and pain VAS was investigated using univariate correlation, which assesses relationships between two variables. Pearson's correlation was used for normally distributed continuous variables, while Spearman's correlation was used for ordinal or non-normally distributed variables. These methods provided insights into the strength and direction of the relationships between USPD and pain VAS at baseline and 12 months.

Multiple regression models analysed the relationship between the pain VAS as the dependent variable and various independent variables such as USSH, USJE, and USPD. They aimed to identify which MSUS metric is the most significant predictor of pain and to determine the variable or combination of variables that best explains and forecasts pain levels. This analysis was carried out using SPSS (Statistical Package for the Social Sciences) version 28.0, IBM.

4.3.5 Categorising participants into two subgroups based on their pain VAS score

Pain VAS is a widely used tool for quantifying pain, with scores ranging from 0 (no pain) to 10 (worst pain). For this analysis, a pain VAS score of 34 or lower was classified as the

"low pain" group, and a score of 34 or higher as the "high pain" group (Boonstra et al., 2014). This cutoff allowed for the comparative analysis of variable outcomes and participants' characteristics between those experiencing reduced versus higher pain levels. This cutoff aligns well with functional interference assessments and patient self-reports. It effectively distinguishes between mild scores with low impact and moderate pain that begins to significantly affect daily functioning. Additionally, this cutoff is a simple, clinically measurable cutoff reflecting significant remaining pain, sensitive enough to indicate potential pain above an acceptable level.

This analysis investigates the relationship between pain and MSUS matrices among patients with reduced pain and consistently high pain at follow-up. At the follow-up visit, participants were categorised into two subgroups according to their pain intensity, measured by pain VAS.

Descriptive statistics were conducted to summarise the distribution of each variable, including measures of central tendency and dispersion. Frequency distributions, histograms, and Shapiro-Wilk normality tests were conducted at various time points in these subgroups. Statistical analysis using SPSS included t-tests for normally distributed data and the Mann-Whitney U test for non-normally distributed data to understand differences between variables at different time points in these subgroups. Correlation analyses were used to assess relationships between USPD and pain VAS, and multiple regression models were employed to identify significant predictors of pain levels.

4.3.6 Categorising participants into two subgroups based on whether they completed the 12-month visit or not

At the 12-month visit, a comprehensive assessment was conducted to identify participants who did not complete the study. This process involved collecting and analysing follow-up data. The purpose of this analysis was to evaluate whether the dropouts during follow-up visits affected attrition bias, a form of selection bias caused by systematic differences between study groups in the number and manner in which participants are lost from a study (Nunan et al., 2018). Participants were classified into two groups: completers, who attended the 12-month visit and fulfilled all study requirements, and non-completers, who did not. To understand the potential impact of non-completion on study results, the baseline characteristics of both completers and non-completers were investigated, explicitly focusing on their pain VAS and USPD scores.

Baseline data were extracted and analysed using descriptive statistical methods. This analysis aimed to identify any significant differences between the groups in pain and USPD scores at baseline. The Shapiro-Wilk test was used to evaluate the normality of the USPD and Pain VAS at baseline and 12-month visits for the completers and non-completers groups. This test determines whether the data are normally distributed or not, with a p-value of less than 0.05 indicating a significant deviation from normality. If the data are not normally distributed, appropriate transformations or non-parametric methods will be considered for further analysis. Following the normality tests, statistical analysis using SPSS was conducted. T-tests were used to compare means between two groups when the data were normally distributed, while the Mann-Whitney U test was applied to non-normally distributed data. These tests helped to understand the differences between variables at different time points.

Univariate correlations assessed relationships between two variables at baseline and 12-month visits for the completers and non-completers groups. Pearson correlation was utilised for normally distributed continuous variables, whereas Spearman correlation was applied for ordinal or non-normally distributed variables. These methods provided insights into the strength and direction of the relationships between variables, such as USPD and pain VAS and USPD and DAS28 at baseline and 12-month visits for completers and non-completers groups.

4.3.7 Evaluating pain VAS among participants with negative USPD

This investigation aims to evaluate USPD scores at the baseline and 12-month visits to identify participants with negative USPD and subsequently examine their pain VAS scores to determine the source of pain, whether it is peripheral or centralised in patients with RA. If the USPD score was zero, this suggests that it is unlikely there was a peripheral inflammatory cause for their ongoing pain.

Negative USPD is defined as the absence of USPD, indicating no synovitis activity, while positive USPD is defined as the presence of a USPD signal, indicating synovitis activity. The participants with negative USPD were then grouped separately from those with positive USPD. Descriptive statistics were used to summarise both groups' USPD and pain VAS scores at baseline and the 12-month visit. Additionally, correlation analysis was performed to evaluate the relationship between USPD and pain VAS scores at both time points. This analysis aimed to determine whether a significant association existed between

negative USPD and high pain VAS scores and measure its strength. The analysis focused on comparing the pain VAS scores between the negative USPD group and the positive USPD group. This will determine if participants with negative USPD, indicating no synovitis, had higher pain levels, potentially indicating central pain mechanisms.

4.3.8 Categorising participants into two subgroups based on STR

This analysis aimed to assess the swollen-tender joint count ratio (STR) to identify Patients with RA with abnormal central nervous system (CNS) pain regulatory mechanisms (Lee et al., 2014).

The SJC and TJC for each participant in the Naredo dataset were identified. Then, the STR was calculated by dividing the number of SJC by the number of TJC. This ratio provided insight into the balance between inflammation and pain sensitivity, which could indicate CNS pain regulatory dysfunction. Based on their STR, participants were categorised into two groups: Low STR Group, comprising participants with a lower STR (STR < 0.5), indicating a higher number of tender joints than swollen ones (Lee et al., 2014). This group was hypothesised to have abnormal CNS pain regulatory mechanisms.

High STR Group (STR ≥ 0.5): Participants with a higher STR indicate a higher number of swollen joints than tender joints. This group was considered to have a more typical inflammatory response. This analysis then compared the USPD and pain between the low STR and high STR groups to determine if the STR could predict the nature of pain measured by ultrasound.

Statistical analyses were conducted to summarise participants' characteristics in each STR group. SPSS was used for statistical analysis, which encompassed t-tests and univariate correlation. T-tests were employed to compare means between two groups when the data exhibited a normal distribution; in contrast, the Mann-Whitney U test was used for non-normally distributed data. These analyses facilitated the comprehension of variations between variables at different time points.

Additionally, univariate correlations were employed to evaluate the associations between both USPD and pain VAS at baseline and 12-month visits for low and high STR groups. Pearson correlation was utilised for normally distributed continuous variables, while Spearman correlation was applied for ordinal or non-normally distributed variables. These

methodologies provided insights into the relationships between variables, such as USPD and pain VAS, at baseline and 12-month visits for both low and high STR groups.

4.4 Results

A total of 367 patients with RA, diagnosed according to the American College of Rheumatology 1987 criteria, were enrolled in the study, including 295 women and 72 men. The recruitment occurred at outpatient rheumatology clinics across 25 Spanish centres between October 2004 and March 2006. The mean age of the participants was 53.7 years, and the disease duration was 9.1 years (Naredo et al., 2008).

4.4.1 Descriptive statistics

The descriptive statistics results (Table 4.1) showed that all variables had high mean scores at baseline among participants with RA. However, over 12 months, these values consistently decreased.

Table 4.1: Clinical features of participants at all time points in the RA study.

	Baseline (mean ± SD)	3-month (mean ± SD)	6-month (mean ± SD)	9-month (mean ± SD)	12-month (mean ± SD)
Pain VAS	(58.86 ±24.32)	(38.40 ±24.22)	(36.12 ±25.38)	(34.06 ±22.61)	(30.70 ± 24.36)
PGA (Patient Global Assessment)	(60.14 ±24.38)	(38.08 ±23.55)	(35.55 ±24.54)	(34.42 ±23.08)	(31.05 ±24.19)
TJC	(10.95±6.39)	(6.38 ±4.99)	(5.72 ±5.45)	(4.67 ±4.71)	(3.99 ±4.95)
SJC	(8.87 ±6.39)	(5.23 ±4.15)	(4.91 ±4.19)	(3.82 ±3.66)	(3.73 ±4.22)
DAS28	(5.70 ±1.10)	(4.49 ±1.21)	(4.27 ±1.34)	(3.98 ±1.26)	(3.83 ±1.37)
Joints with USPD	(6.38 ±4.71)	(4.04 ±3.58)	(3.79 ±3.93)	(3.07 ±3.66)	(2.94 ±3.41)
Joints with USSH	(11.59 ±6.33)	(8.78 ±5.98)	(8.04 ±6.06)	(7.09 ±6.01)	(6.64 ±5.89)
Joints with USJE	(11.47 ±5.94)	(8.42 ±5.66)	(7.69 ±5.76)	(6.66 ±5.45)	(6.27 ±5.60)

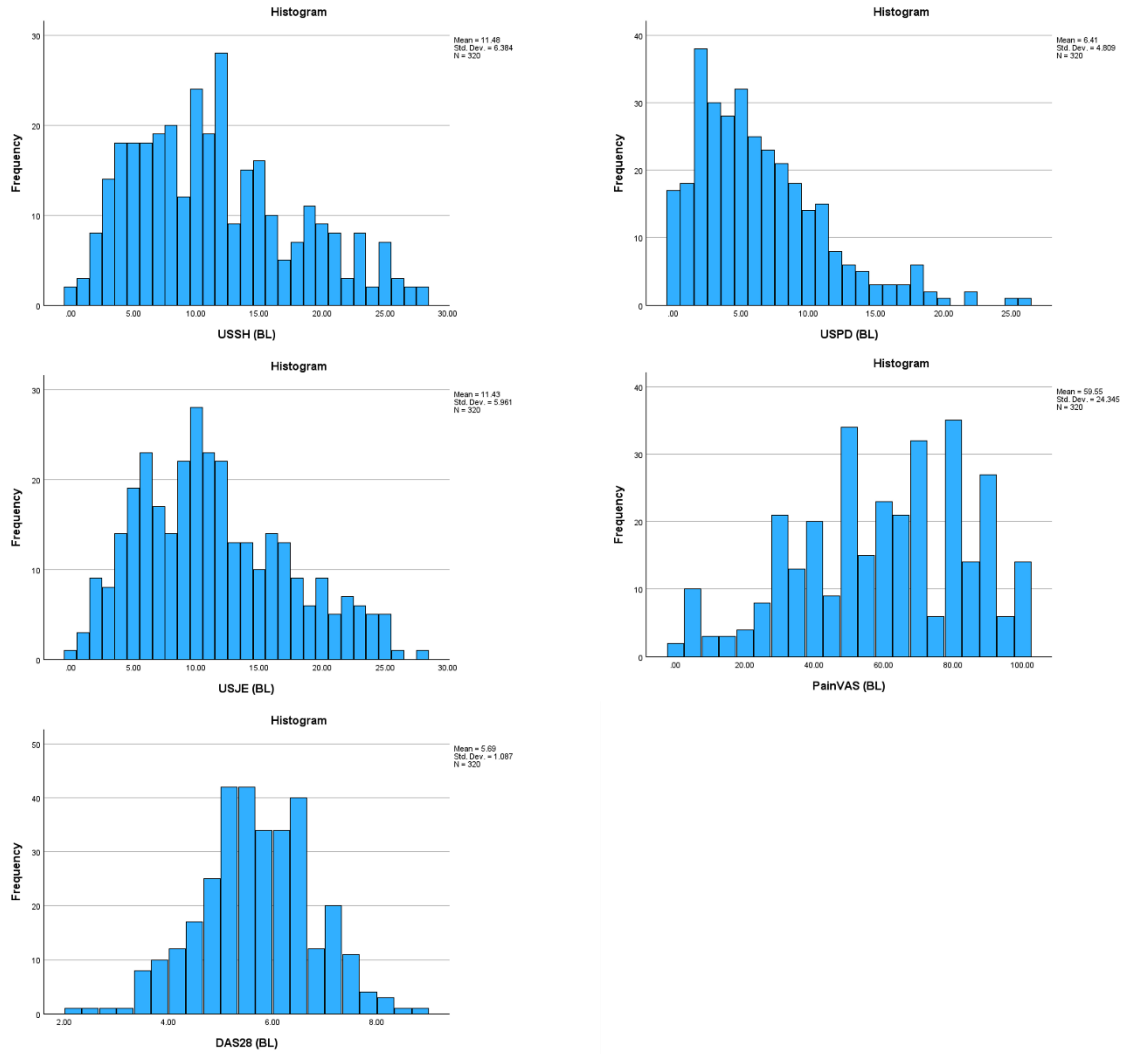

Figure 4.1: Histogram of the MSUS metrics (USSH, USSPD, USJE), Pain VAS and DAS28 at the baseline.

At baseline, the pain VAS and DAS28 histograms indicated that a large number of participants reported high levels, with most scores clustering towards the higher end of the scale. By 12 months, the histograms showed a noticeable shift towards lower scores, with fewer participants reporting high scores (Figures 4.1 and 4.2). The baseline histograms for ultrasound metrics revealed that many participants had high levels of joint inflammation. At 12 months, the histograms showed a shift towards lower scores, indicating reduced inflammation (Figures 4.1 and 4.2). Shapiro-Wilk tests reveal that all variables are non-normally distributed except DAS28 at the baseline.

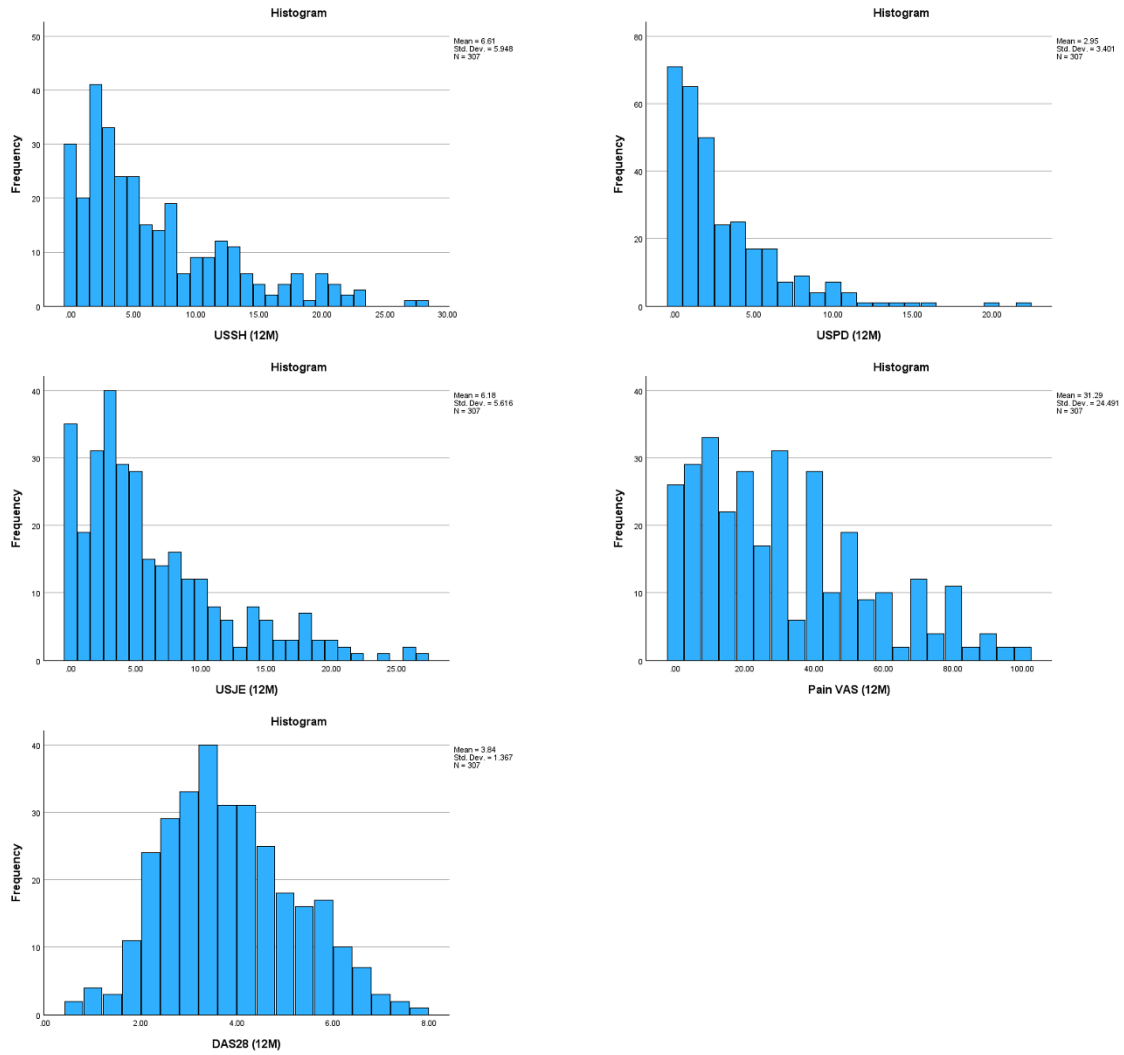

Figure 4.2: Histogram of the MSUS metrics (USSH, USSPD, USJE), Pain VAS and DAS28 at 12 months.

4.4.2 The univariate correlation between US metrics and pain VAS

The univariate correlation analysis between pain VAS and USPD at baseline and 12 months provides insight into the relationship between pain and joint inflammation at these time points. At baseline, a weak but statistically significant correlation exists between pain VAS and USPD, suggesting that higher pain levels are associated with higher joint inflammation (r = 0.15 and p value 0.003). However, this relationship becomes stronger and more pronounced at 12 months (r = 0.353 and p-value is less than 0.001) (Figure 4.3).

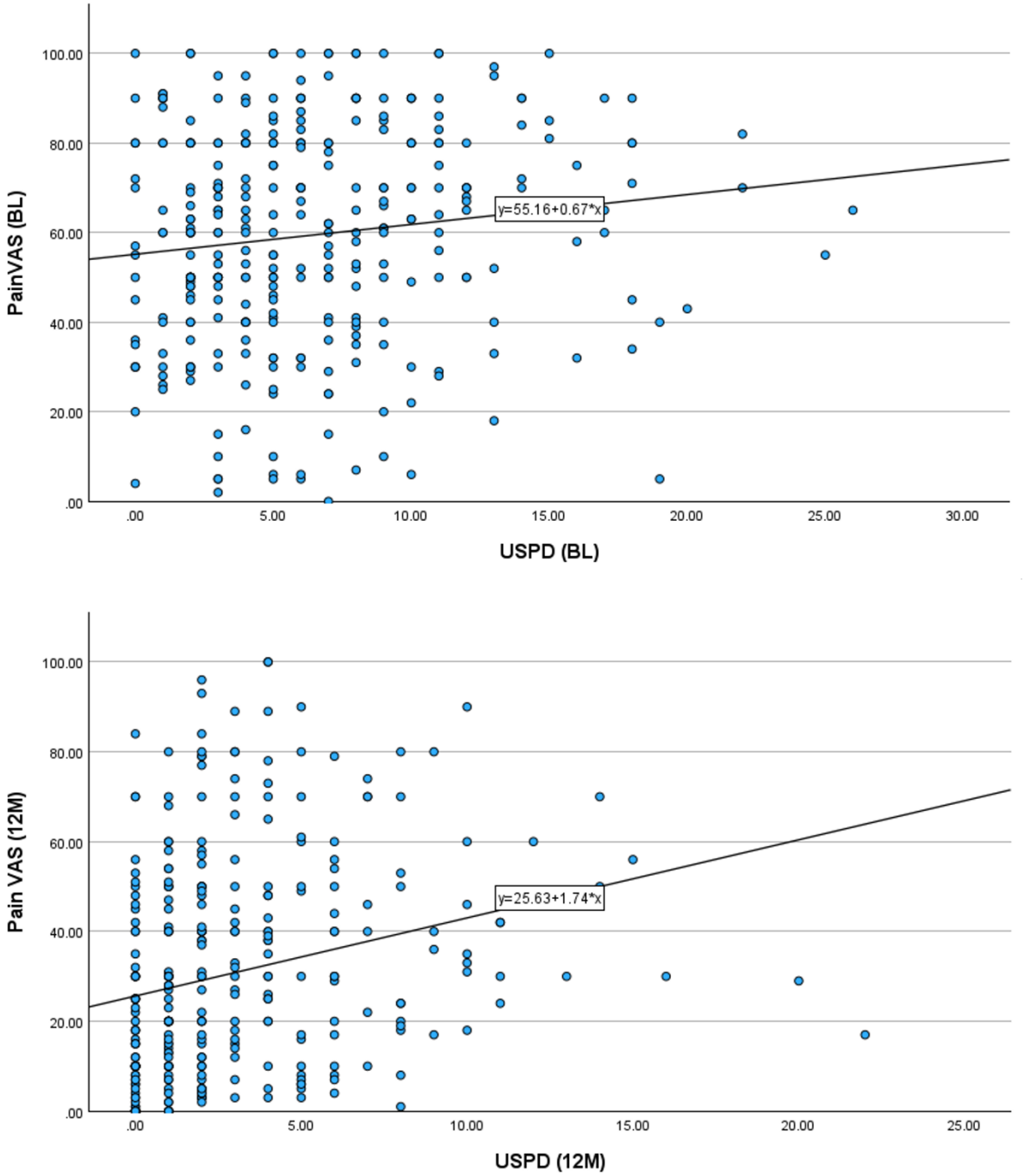

Figure 4.3: Scatter plots show the correlation between pain VAS and USPD at the baseline and at 12 months.

The correlation analysis reveals a weak yet significant relationship between baseline pain levels and joint inflammation, as measured by USSH and USJE. Higher pain was associated with higher joint inflammation ($r = 0.111$ and 0.123; p-value = 0.034 and 0.018 for USSH and USJE, respectively). However, at 12 months, this relationship became stronger and more pronounced ($r = 0.311$ and 0.349; p-value < 0.001 for USSH and USJE, respectively), as shown in Figures 4.4 and 4.5.

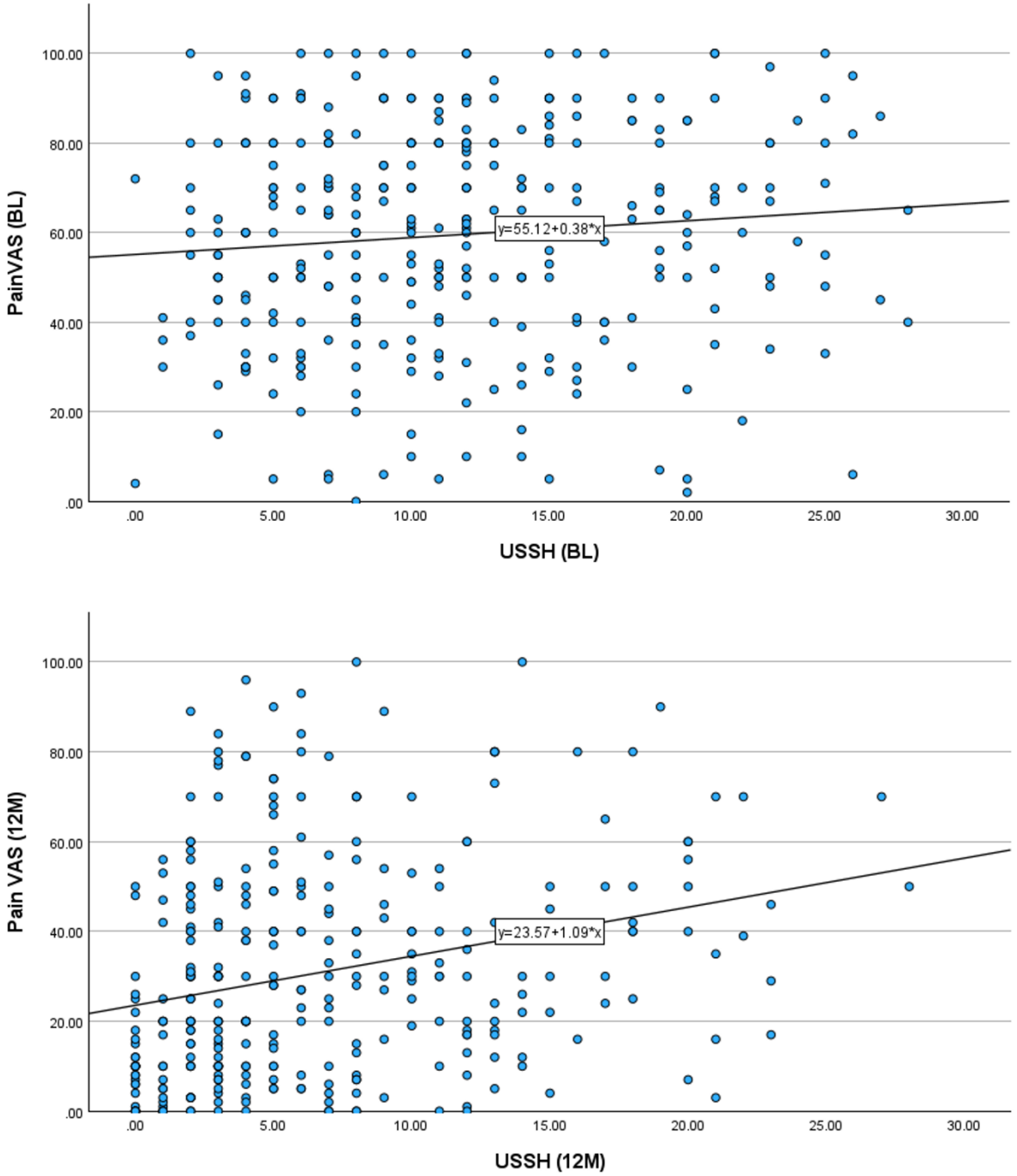

Figure 4.4: Scatter plots show the correlation between pain VAS and USPD at the baseline and at 12 months.

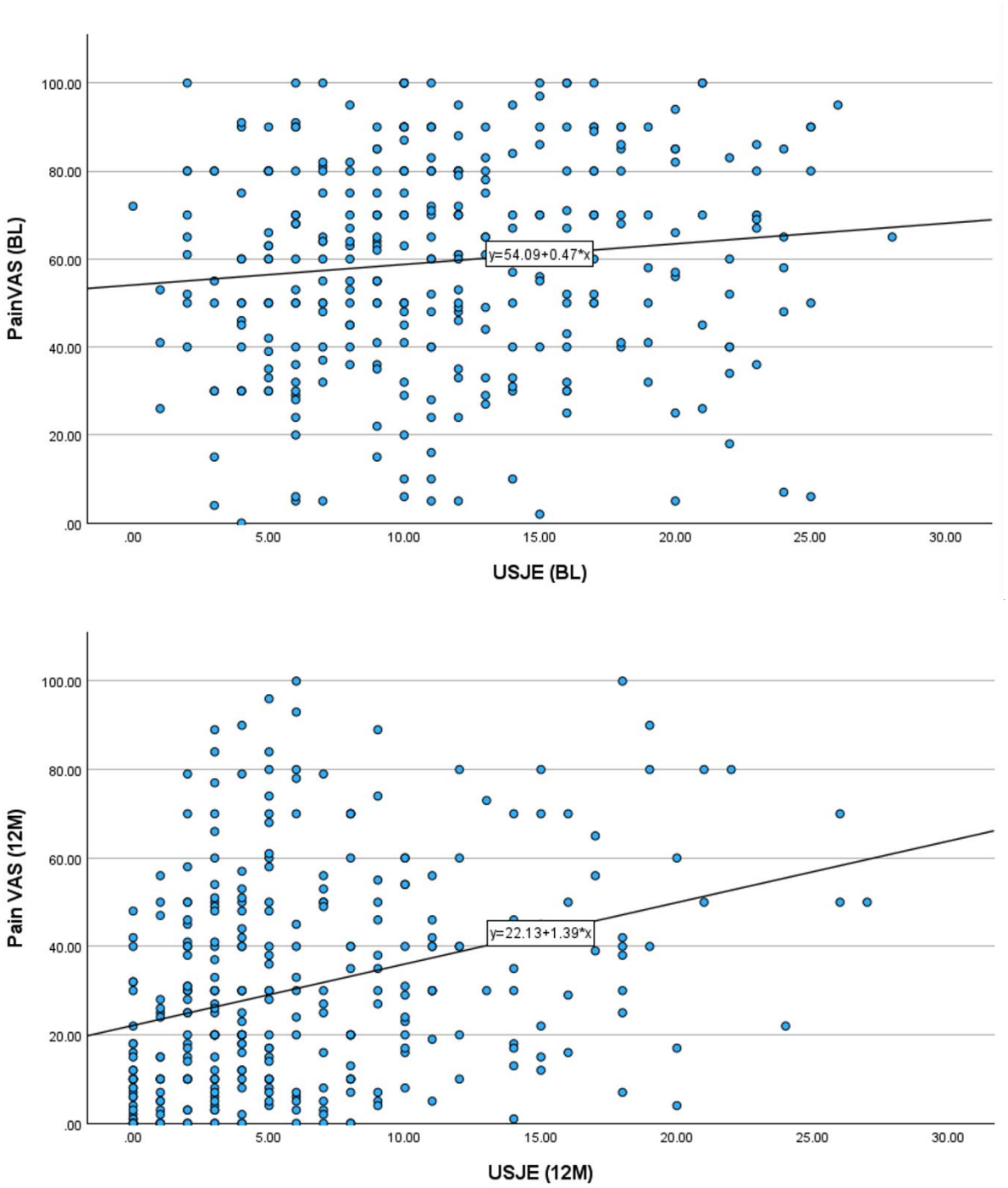

Figure 4.5: Scatter plots show the correlation between pain VAS and USJE at the baseline and at 12 months.

At the change in each variable between 12-month and the baseline, there is a weak but statistically significant correlation between pain VAS and MSUS metrics, suggesting that higher pain levels are associated with greater joint inflammation ($r = 0.197$ for USPD, $r = 0.254$ for USSH, and $r = 0.241$ for USJE, and p values are less than 0.001) (Figure 4.6).

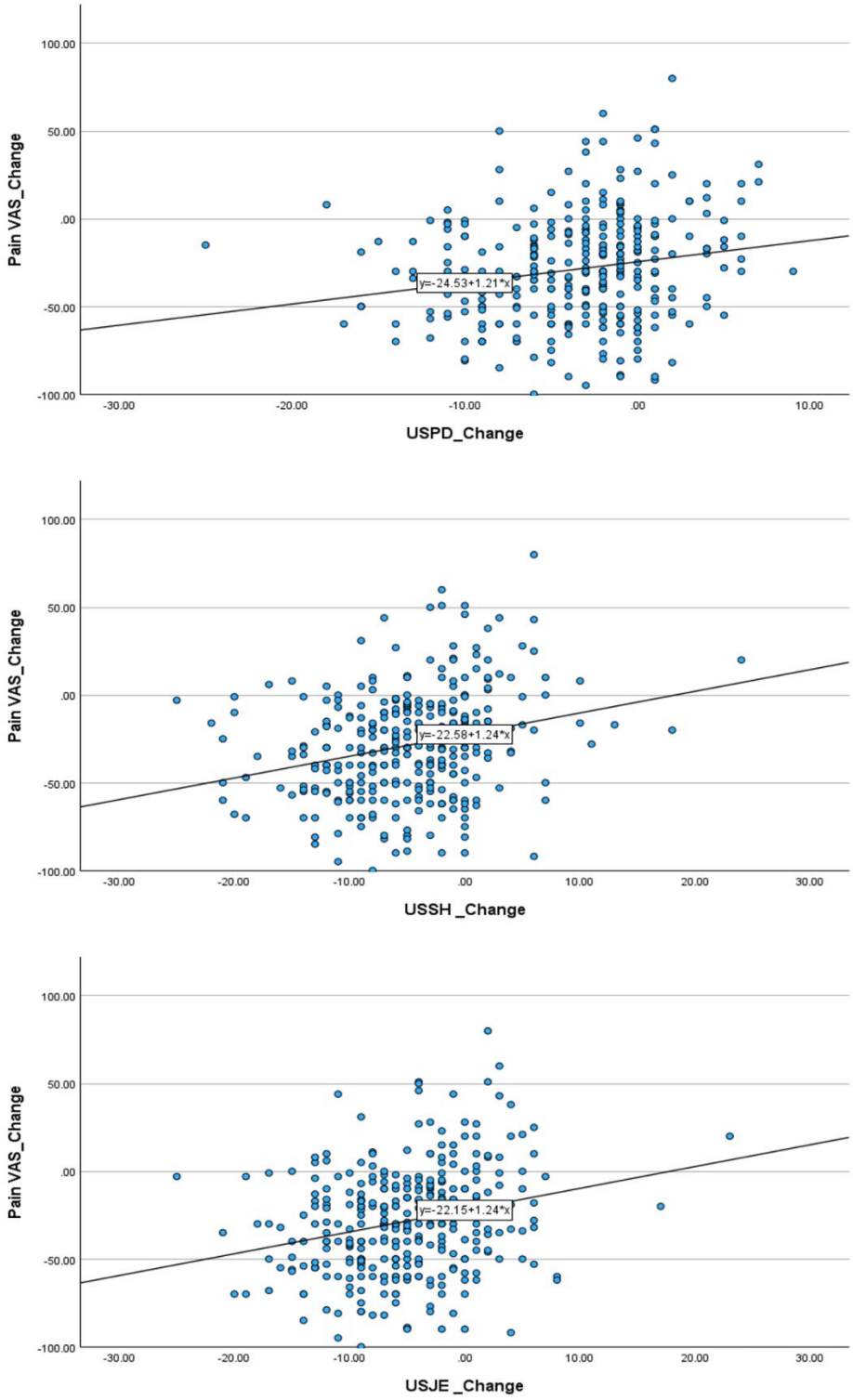

Figure 4.6: Scatter plots show the correlation between pain VAS and ultrasound metrics at the change.

This research employed linear regression models to investigate the relationship between ultrasound metrics and pain VAS. The study comprised two models: one at baseline, another at 12 months. The findings from the first model indicated a low correlation (r = 0.141) and only a 2% variance explained by the predictors (r2 = 0.02) in Pain VAS (Table

4.2). The second model revealed a moderate correlation (r = 0.328), and the predictors accounted for 10% of the variance in Pain VAS ($r^2 = 0.107$), suggesting the potential of the ultrasound metric to predict pain in RA.

Table 4.2 Multiple Linear Regression of Ultrasound Measures Predicting Pain VAS at Baseline and 12-month visits

Baseline					
Predictor	**B**	**Std. Error**	**Beta**	**t**	**p-value**
Constant	52.99	2.85	–	18.56	<.001
USPD (BL)	0.60	0.35	0.11	1.71	0.08
USSH (BL)	-0.14	0.35	-0.03	-0.41	0.67
USJE (BL)	0.32	0.33	0.08	0.98	0.32
12-month					
Constant	21.85	1.99	-	10.95	<.001
USPD (BL)	0.78	0.497	0.11	1.58	0.11
USSH (BL)	-0.29	0.434	-0.07	-0.68	0.49
USJE (BL)	1.37	0.42	0.31	3.23	0.001

At baseline, none of the ultrasound variables significantly predicted pain levels. However, at 12 months, USJE was found to significantly predict pain levels, suggesting its potential role in pain assessment for Patients with RA (Table 4.2). Throughout the study period, changes in ultrasound variables did not significantly predict changes in pain, suggesting that other factors influenced pain variations over time.

4.4.3 The influence of non-inflammatory factors

4.4.3.1 Categorising participants into two subgroups based on their pain VAS score

The study divided participants into two groups based on their Pain VAS scores: those who experienced a significant reduction in pain and those who did not. In the reduced-pain group, which included 174 participants, the average pain score decreased significantly from 61.73 to 15.08. Correspondingly, their USPD scores, which indicate inflammation,

also substantially reduced from 6.35 to 2.42 (Table 4.3 and Figure 4.7). On the other hand, the group with high pain, consisting of 150 participants, exhibited only a slight improvement. Their pain VAS scores reduced from 56.87 to 48.62, and their USPD scores decreased from 6.42 to 3.55 (Table 4.4 and Figure 4.7).

Table 4.3: Clinical features of the reduced pain group at baseline and 12-month visits.

	N	Mean	Std. Deviation
Pain VAS (BL)	174	61.7356	23.10492
Pain VAS (12m)	174	15.0805	12.24293
Pain VAS change	174	-46.6552	20.30708
DAS28 (BL)	170	5.7773	1.06963
DAS28 (12m)	166	3.3523	1.13008
DAS change	163	-2.4088	1.39813
USPD (BL)	174	6.3563	4.90011
USPD (12m)	172	2.4244	3.44210
USPD change	172	-3.8547	4.37120
USSH (BL)	174	11.7069	6.61058
USSH (12m)	172	5.7326	5.43957
USSH change	172	-5.8895	6.05670
USJE (BL)	174	11.5862	6.32008
USJE (12m)	172	5.1802	5.01309
USJE change	172	-6.3256	5.86783

BL = baseline visit, 12m = 12-month visit, change = the difference between the 12m and the baseline visits.

Table 4.4: Clinical features of the high pain group at baseline and 12-month visits.

	N	Mean	Std. Deviation
Pain VAS (BL)	150	56.87	25.35
Pain VAS (12m)	151	48.62	22.49
Pain VAS change	150	-7.99	26.48
DAS28 (BL)	149	5.59	1.11
DAS28 (12m)	147	4.37	1.42
DAS change	146	-1.22	1.42
USPD (BL)	150	6.42	4.67
USPD (12m)	150	3.55	3.31
USPD change	149	-2.84	5.19
USSH (BL)	150	11.13	5.97
USSH (12m)	150	7.59	6.20
USSH change	150	-3.47	6.38
USJE (BL)	150	11.19	5.41
USJE (12m)	150	7.42	5.94
USJE change	150	-3.67	5.85

BL = baseline visit, 12m = 12-month visit, change = the difference between the 12m and the baseline visits.

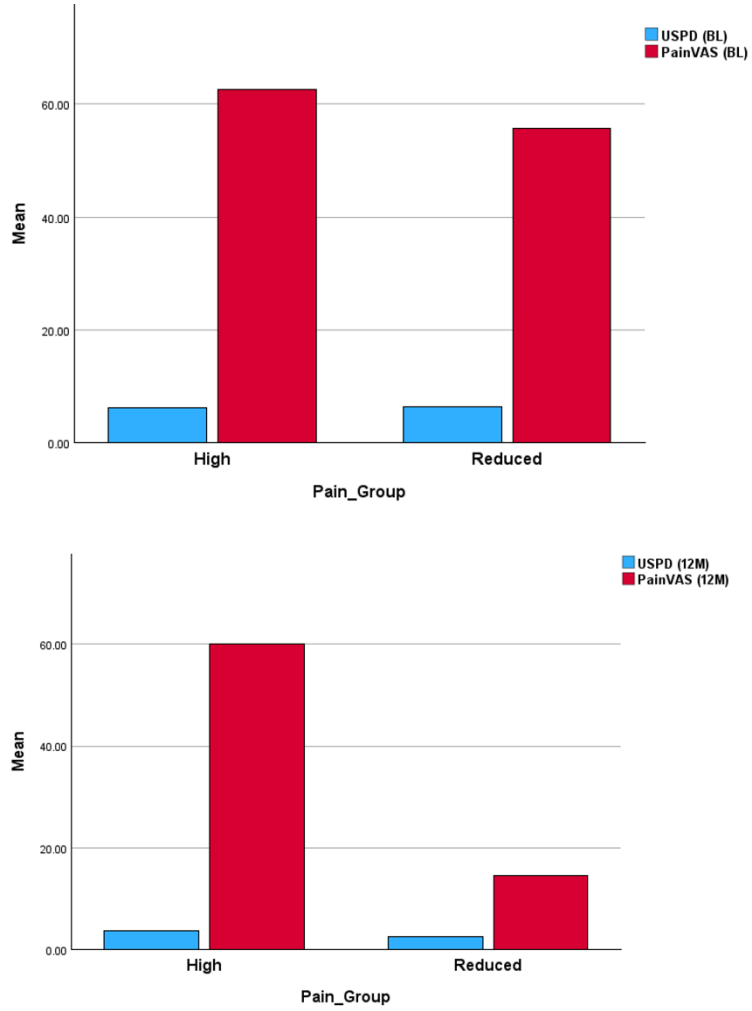

Figure 4.7 The mean of pain VAS and USPD at reduced and high pain groups at the baseline and 12-month visit.

The univariate correlation analysis reveals interesting dynamics between both groups' pain VAS and USPD scores over time. In the reduced pain group, the correlation between pain and USPD was weak but statistically significant ($r = 0.155$, $p = 0.042$) at the baseline. This suggests a slight connection between pain levels and inflammation. However, by the 12-month visit, this relationship had strengthened considerably ($r = 0.352$, $p < 0.001$) (Figure 4.8).

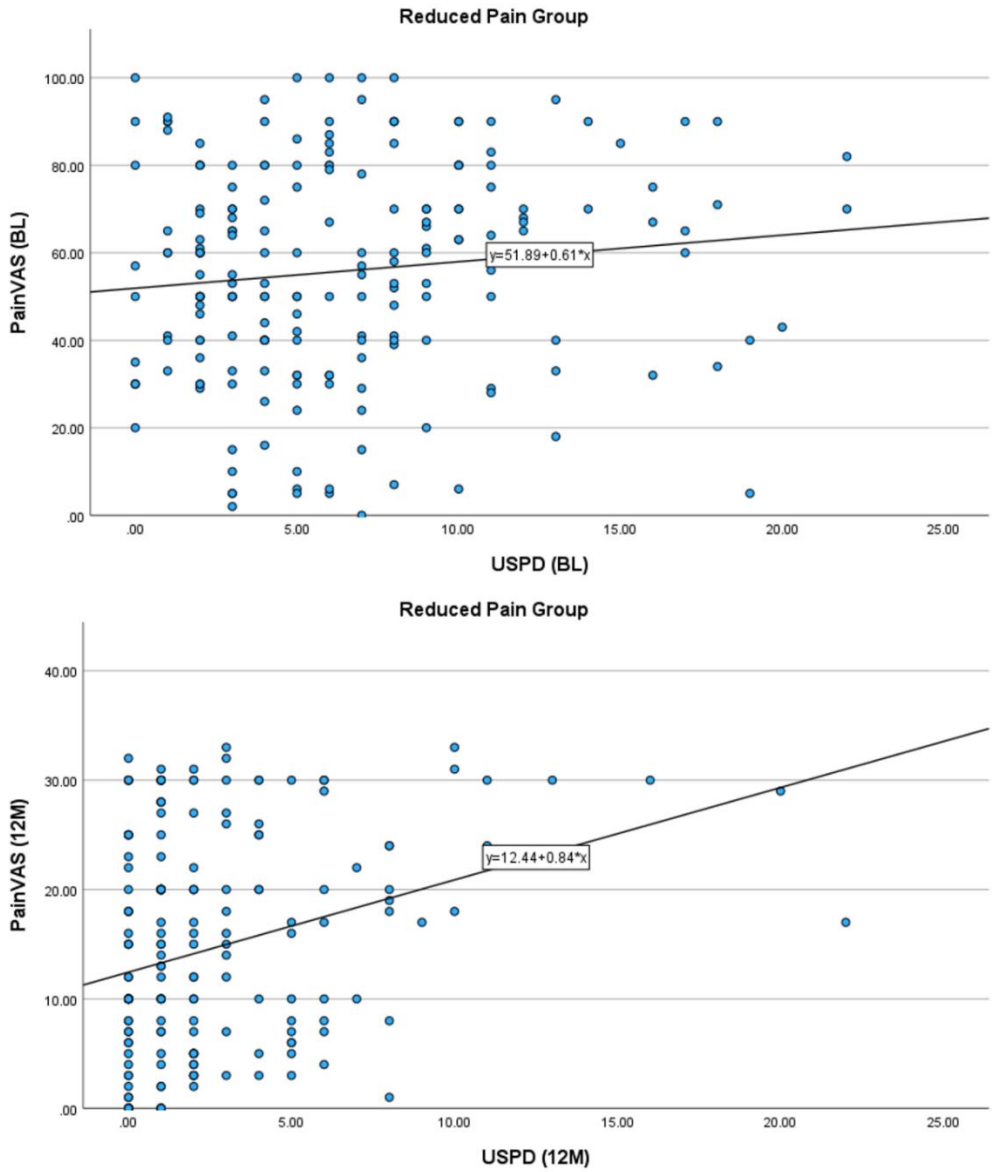

Figure 4.8: The correlation between pain VAS and USPD at the baseline and the 12-month follow-up visits in the reduced pain group.

In the high pain group, the participants had similar patterns but weaker associations. At the baseline, there was a slight but significant correlation between pain and USPD ($r = 0.180$, $p = 0.027$). At the 12-month visit, this correlation increased ($r = 0.282$, $p < 0.001$), yet it remained less intense than that observed in the reduced pain group (Figure 4.9).

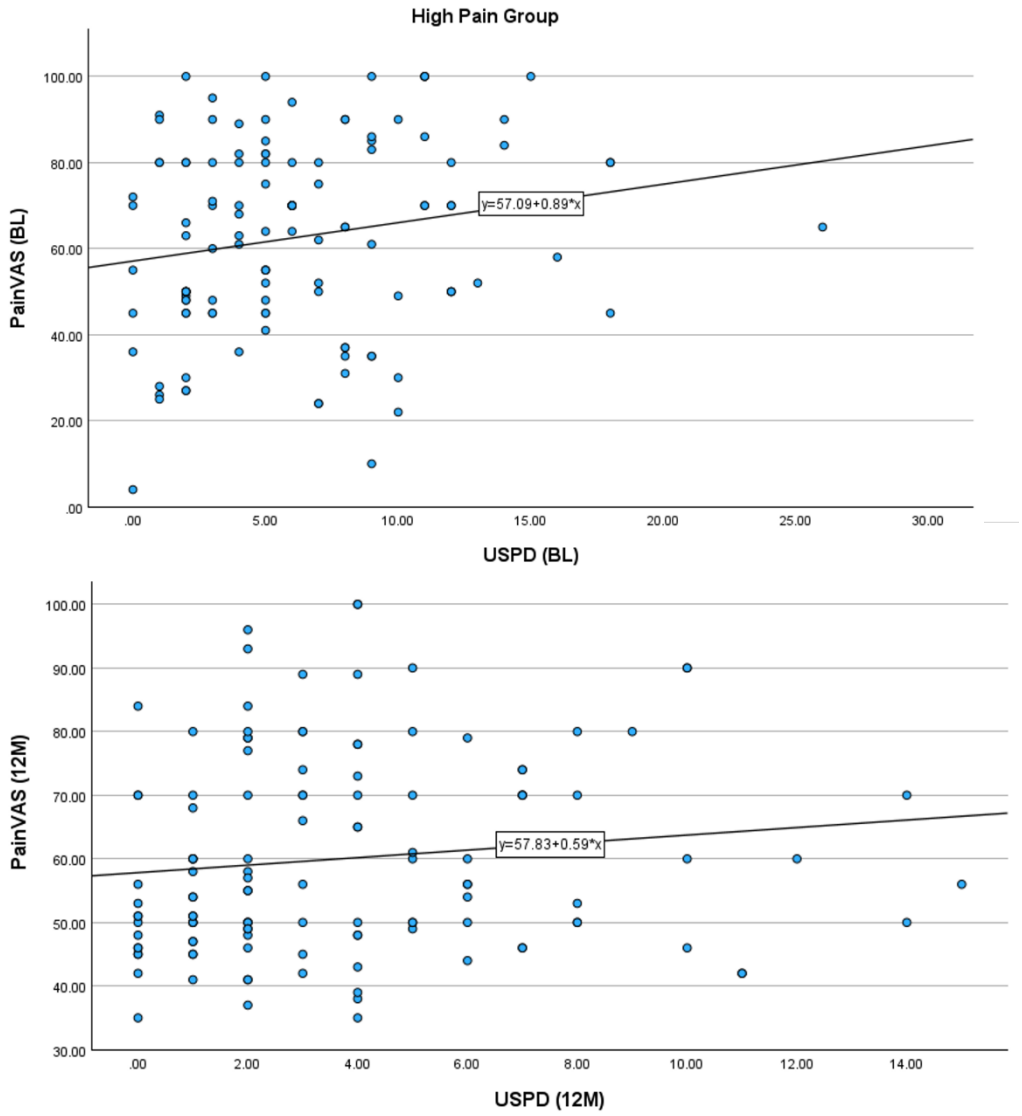

Figure 4.9 The correlation between pain VAS and USPD at the baseline and the 12-month follow-up visits in the high pain group.

In addition, participants who experienced persistent pain at all visits were examined. High pain levels were reported by these participants at baseline and persisted until the 12-month visit. It was reported that 58 participants experienced persistent pain throughout the study (Figure 4.10). Their mean pain VAS scores decreased from 73 at baseline to 58 at the 3-month visit but remained above 55 for the remainder of the study, including the 12-month visit. The mean of USPD scores for these patients decreased from 6.5 at baseline to 3.8, 4.3, 3.1, and 3.5 at subsequent visits, respectively (Figure 4.9).

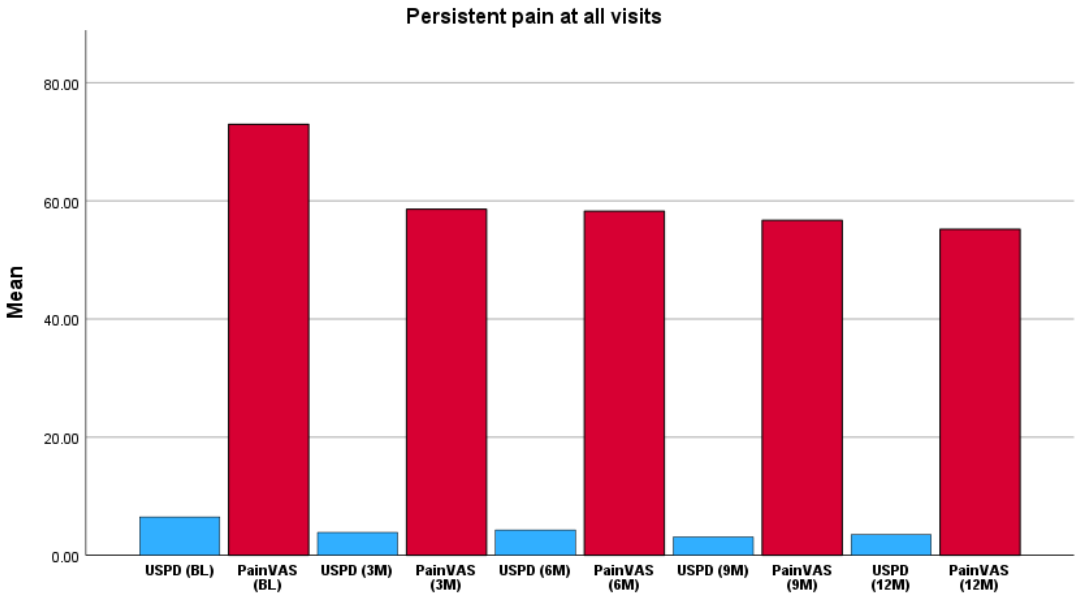

Figure 4.10: This figure shows the mean of pain VAS and USPD at all visits among patients with high persistent pain.

Moreover, the mean of USPD scores exhibited a similar trend between both groups despite the high VAS scores in the persistent pain group, as the values remained comparable during the follow-up visits. This indicates that joint inflammation has decreased. This reduction may not be related to inflammation due to effective treatment.

4.4.3.2 Categorising participants into two subgroups based on whether they completed the 12-month visit or not.

In the present analysis, participants were categorised into two groups based on their adherence to the study visits over 12 months. The complete group comprised 325 participants who attended all visits from the baseline to the 12-month visit. Conversely, the incomplete group consisted of 41 participants who participated in the baseline visit but did not fulfil all follow-up visits. Notably, the pain VAS in the complete group was measured at 59.44, with a corresponding USPD of 6.42. In contrast, the pain VAS and USPD in the incomplete group were recorded at 54.29 and 6.05, respectively (Table 4.4).

The comparison of pain VAS and USPD between these two groups using the Mann-Whitney test revealed no significant differences, with p-values of 0.219 for pain VAS and 0.907 for USPD. This indicates that, at baseline, there were no notable differences in pain

levels or inflammation between participants who completed the study and those who did not (Table 4.5).

Table 4.5: Clinical features in the complete group and the incomplete group.

	Complete group		Incomplete group		P value
	N	Mean (SD)	N	Mean (SD)	
Pain VAS	325	59.44 (24.2)	41	54.29 (24.85)	0.219
PGA	325	60.47 (24.58)	41	57.56 (22.87)	0.516
DAS28	320	5.69 (1.09)	39	5.75 (1.22)	0.614
TJC	325	10.87 (6.26)	41	11.59 (7.39)	0.635
SJC	325	8.87 (4.97)	41	8.83 (5.53)	0.906
ESR	319	59.44 (24.23)	40	42.93 (27.04)	0.209
USPD	325	6.42 (4.83)	41	6.05 (3.69)	0.907

The complete group includes participants who completed all visits; the incomplete group includes participants who failed to complete all visits.

The complete group shows a significant correlation between pain VAS and USPD ($r = 0.16$, $p = 0.004$). This suggests that pain levels were meaningfully related to inflammation in participants who completed all visits. In contrast, the incomplete group did not show a significant correlation between pain VAS and USPD ($r = 0.103$, $p = 0.52$) (Figure 4.11).

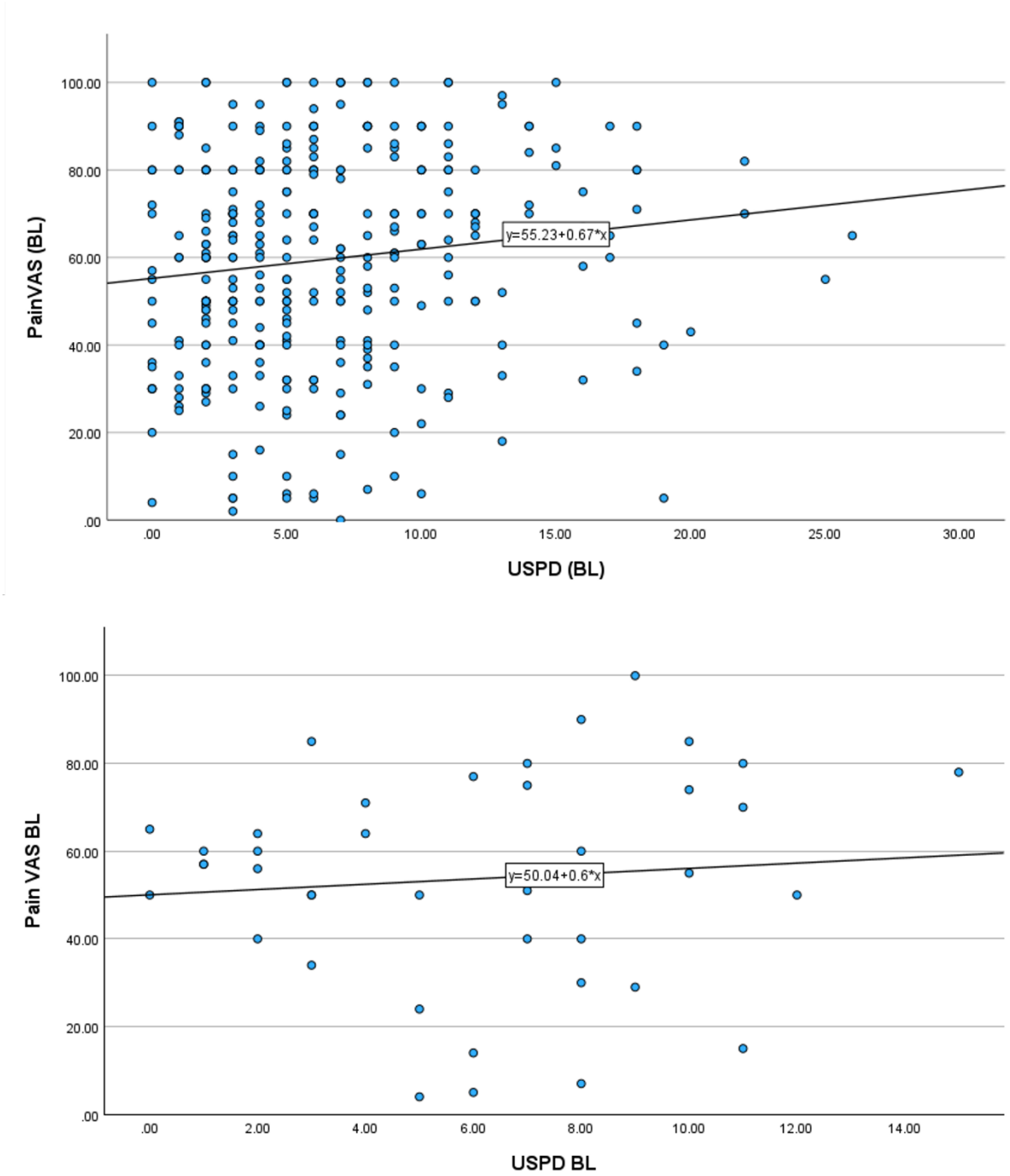

Figure 4.11: The correlation between pain VAS and USPD in complete (top figure) and incomplete groups (bottom figure).

4.4.3.3 Evaluating pain VAS among participants with negative USPD

In this analysis, participants were divided into two groups based on their USPD signal at the 12-month follow-up: negative USPD (n=75) and positive USPD (n=246). The median in the pain VAS change scores over this period was -38 in the negative USPD group, with an interquartile range (IQR) of 39.5, indicating substantial pain reduction. Despite this

improvement, participants in this group still reported pain at the 12-month visit, with a mean of their pain VAS score of 19.

In contrast, the positive USPD group had a median pain VAS change of -27.5, with an IQR of 43. This group also experienced a reduction in pain, but to a lesser extent compared to the negative USPD group.

The following analysis evaluated the persistence and frequency of high pain levels (Pain VAS ≥ 34) over 12 months in RA participants in the negative and positive USPD groups. In the negative USPD group, which indicated no detectable inflammation, 14 participants reported high pain at the 12-month visit (Table 4.6). This suggests that non-inflammatory mechanisms, such as central sensitisation, might drive pain in these patients.

Table 4.6: Frequency of participants with high pain VAS in the negative USPD group.

Timepoints	Patients with (-) VE USPD and Pain VAS ≥ 34
BL	12 (70.6%)
3MO	17 (43.6%)
6MO	20 (30.8%)
9MO	26 (35.1%)
12MO	14 (18.4%)

In the positive USPD group, the frequency of participants with high pain VAS decreased from 347 at baseline to 249 at 12 months (Table 4.7). The presence of USPD signals, indicative of inflammation, correlated with higher pain levels at the baseline. The reduction in high pain frequency suggests that RA treatment may have alleviated pain for many participants in this group.

Table 4.7: Frequency of participants with high pain VAS in the positive USPD group.

Timepoints	Patients with (+) VE USPD with Pain VAS ≥ 34
BL	300 (88.4%)
3MO	170 (54.8%)
6MO	156 (56.3%)
9MO	123 (49.2%)
12MO	110 (44.2%)

The t-test for the high-pain VAS was significant ($p = 0.001$) at baseline, indicating a substantial difference in pain levels between the negative and positive USPD groups. Mann-Whitney U tests for high pain VAS at 3, 6, 9, and 12 months were all highly significant ($p < 0.001$), highlighting differences in pain experiences between the groups across all time points. Figure 4.12 displays the number of participants with negative USPD and high pain and low pain groups, while Figure 4.13 shows the difference between low and high pain for participants with negative USPD at the 12-month visit.

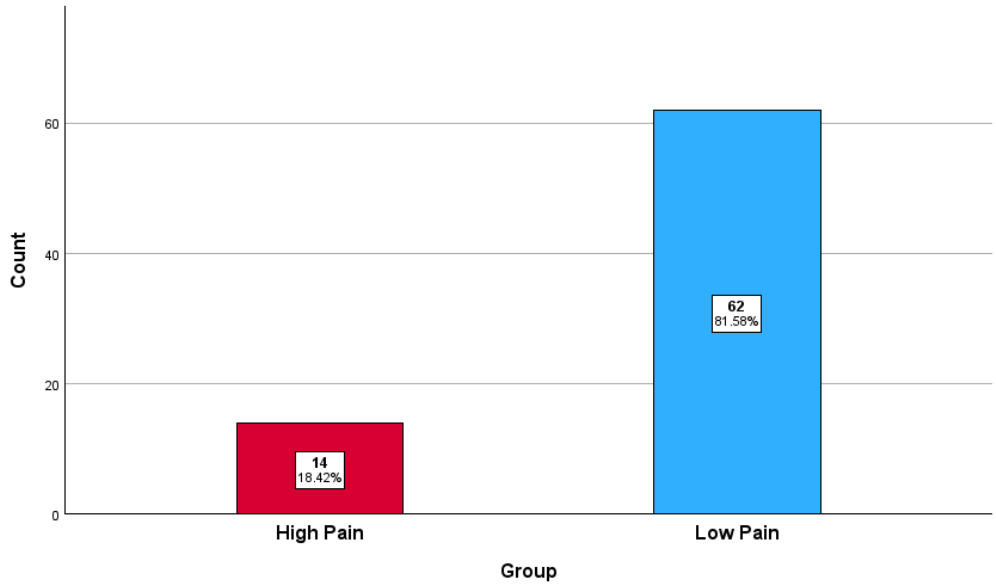

Figure 4.12: This bar chart shows the number of participants with negative USPD who have persistent and low pain VAS at the 12-month visit.

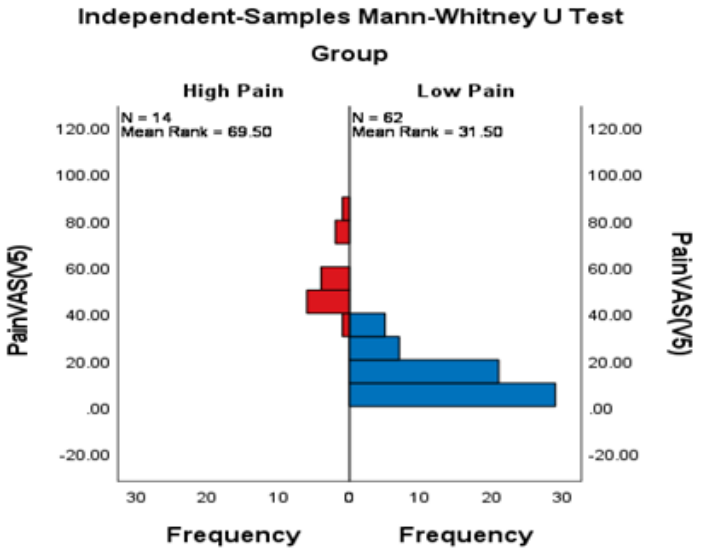

Figure 4.13: Given the non-normal distribution, the Mann-Whitney test was employed to compare pain VAS between the two groups at the 12-month visit.

4.4.4 Participants who failed to complete the follow-up of the negative USPD group

To investigate whether patients experiencing high levels of pain and negative USPD are more likely to be lost to follow-up. Fourteen participants were found to have high pain VAS and negative USPD detected at the 12-month visits. These participants were tracked at the 9-month, 6-month, 3-month, and baseline visits to monitor their pain VAS and whether they missed any visits. Among the 14 patients, three participants were found to be missing at least one follow-up visit, whereas eleven participants reported high pain VAS at all visits (Table 4.8).

Table 4.8: Frequency of high pain VAS and missing data at each time point in the (-) USPD group.

	High Pain VAS	Missing data
Baseline	11	3
3-month	12	2
6-month	12	2
9-month	11	3
12-month	14	0

Missing data indicate participants with high pain VAS ≥ 34 and negative USPD who were absent at the visits.

4.4.5 Investigating the impact of joints excluded from the MSUS scan on the reported pain.

The following analysis determines whether the reported pain in patients with negative USPD results could be attributed to joints not included in the USPD scan. A wide SJC encompassing 84 joints was compared to SJC 28. The findings demonstrated that the SJC assessed over 84 joints was similar to the SJC evaluated at the 28 joints, with mean values of 1.18 and 1.03, respectively, at the 12-month visit. The findings from the SJC results indicate that the pain levels reported for SJC28 are comparable to those associated with SJC84. This equivalence suggests that inflammation localised to the 28 assessed joints is insufficient to account for variations in experienced pain, implying that additional inflammatory processes beyond these joints are unlikely to influence the overall pain perception in this context. Therefore, pain reported by patients with negative USPD is unlikely to have originated from inflammation outside the scanned 28 joints. These findings suggest that the pain experienced by participants with negative USPD could arise from non-inflammatory sources. (see Figures 4.14 and 4.15).

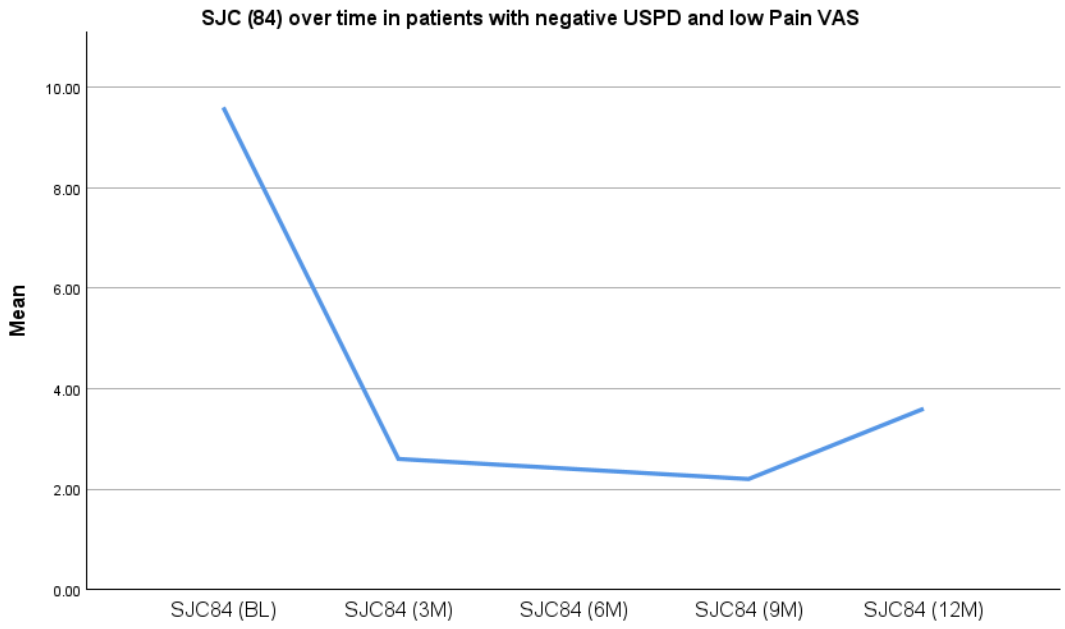

Figure 4.14 The line chart illustrates the changes in SJC (84) over time, which are negative in the USPD and associated with low pain VAS.

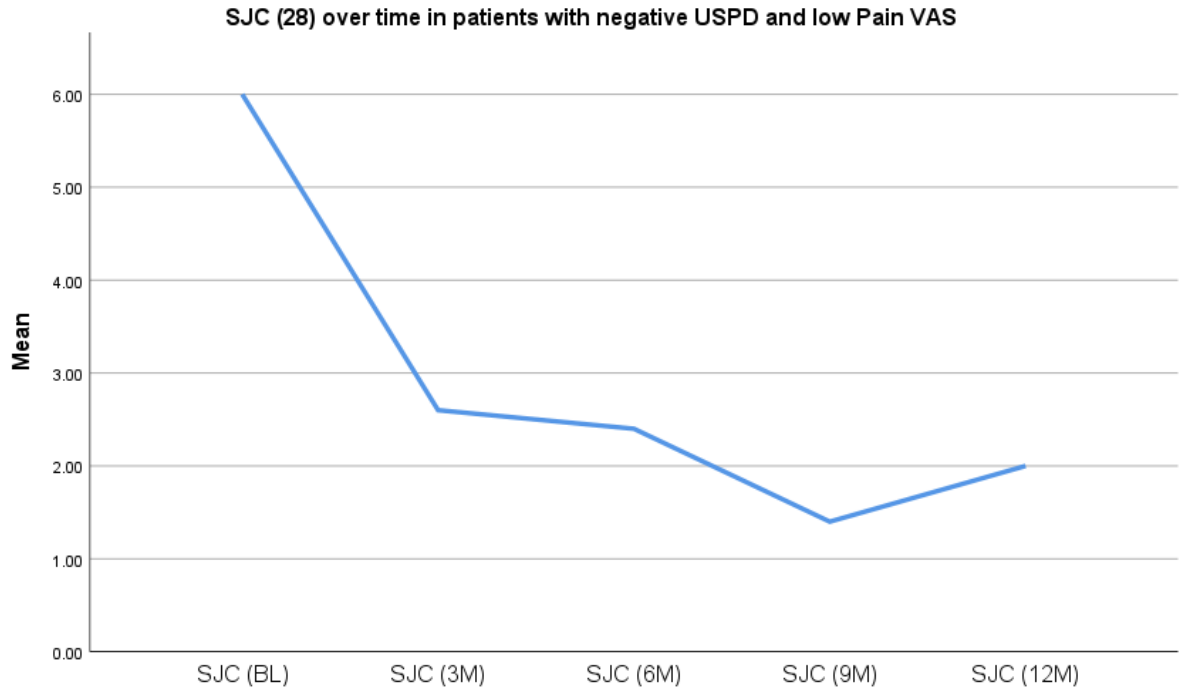

Figure 4.15 The line chart illustrates the changes in SJC (28) over time, which are negative in the USPD and associated with low pain VAS.

4.4.5.1 Categorising participants into two subgroups based on STR

In this analysis, participants were divided into two groups based on their STR: the low STR group (n=59), which indicates centralised pain, and the high STR group (n=289), which indicates peripheral pain. At baseline, USPD levels were significantly higher in the high STR group compared to the low STR group. Over time, these levels declined in both groups, as illustrated in Figure 4.16.

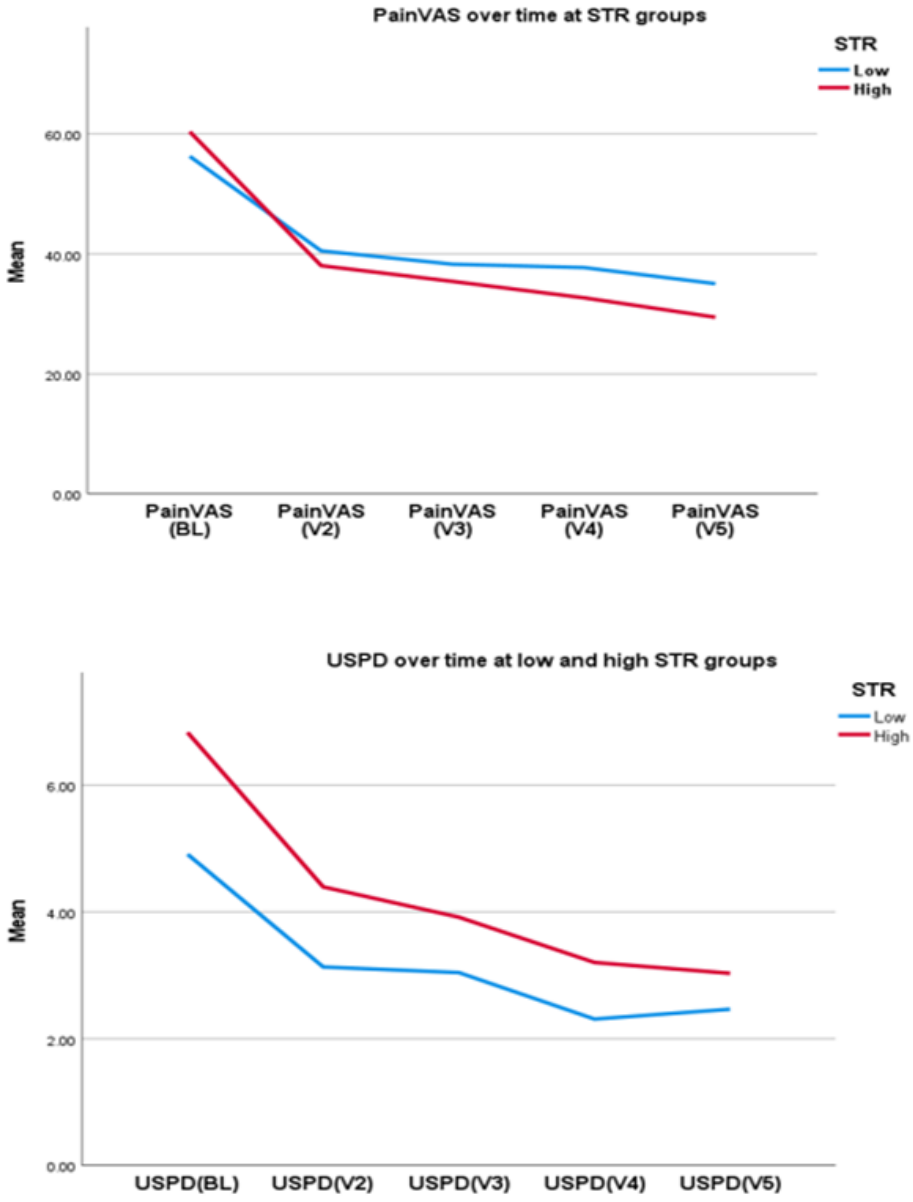

Figure 4.16: USPD over time at STR groups.

In the low STR group, at baseline, there was no statistically significant correlation between pain VAS and USPD ($p = 0.531$, $r = 0.083$), indicating a weak, non-significant relationship. Similarly, at the 12-month follow-up, the correlation remained non-significant

(p-value = 0.144; R = 0.207). Additionally, the correlation between STR and pain VAS was not significant at baseline (p = 0.236, r = 0.157); however, it became significant at the 12-month follow-up (p = 0.01, r = 0.382). There was also a significant correlation between STR and USPD at baseline (p = 0.022, r = 0.298), which was insignificant at the 12-month follow-up (p = 0.45, r = -0.09)(Figures 4.17 and 4.18).

In the high STR group, a significant correlation was observed between pain VAS and USPD at baseline (p = 0.005, r = 0.163), indicating that higher pain levels were associated with high ultrasound PD. The correlation remained significant at the 12-month follow-up (p < 0.001, r = 0.369). A negative correlation between pain VAS and STR was detected at baseline (p = 0.005, r = -0.164); however, this correlation was insignificant at the 12-month follow-up (p = 0.467, r = -0.052). The negative correlation suggests that participants experience more pain when the STR is low. Additionally, there was a significant correlation between STR and USPD at baseline (p = 0.01, r = 0.15); however, this correlation was not significant at the 12-month follow-up (p = 0.373, r = 0.062) (Figures 4.17 and 4.18).

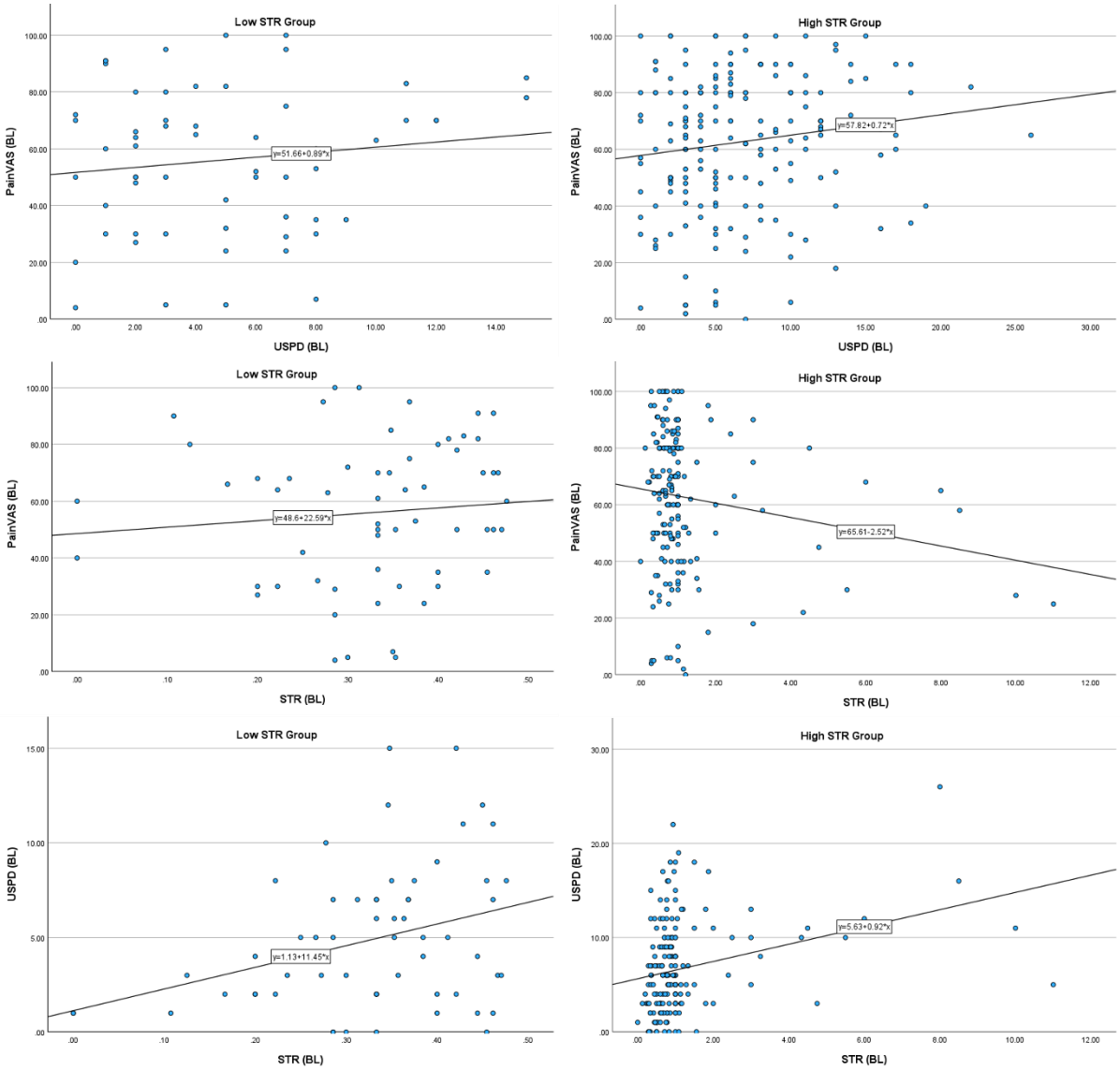

Figure 4.17: Univariate correlations at low and high STR at the baseline.

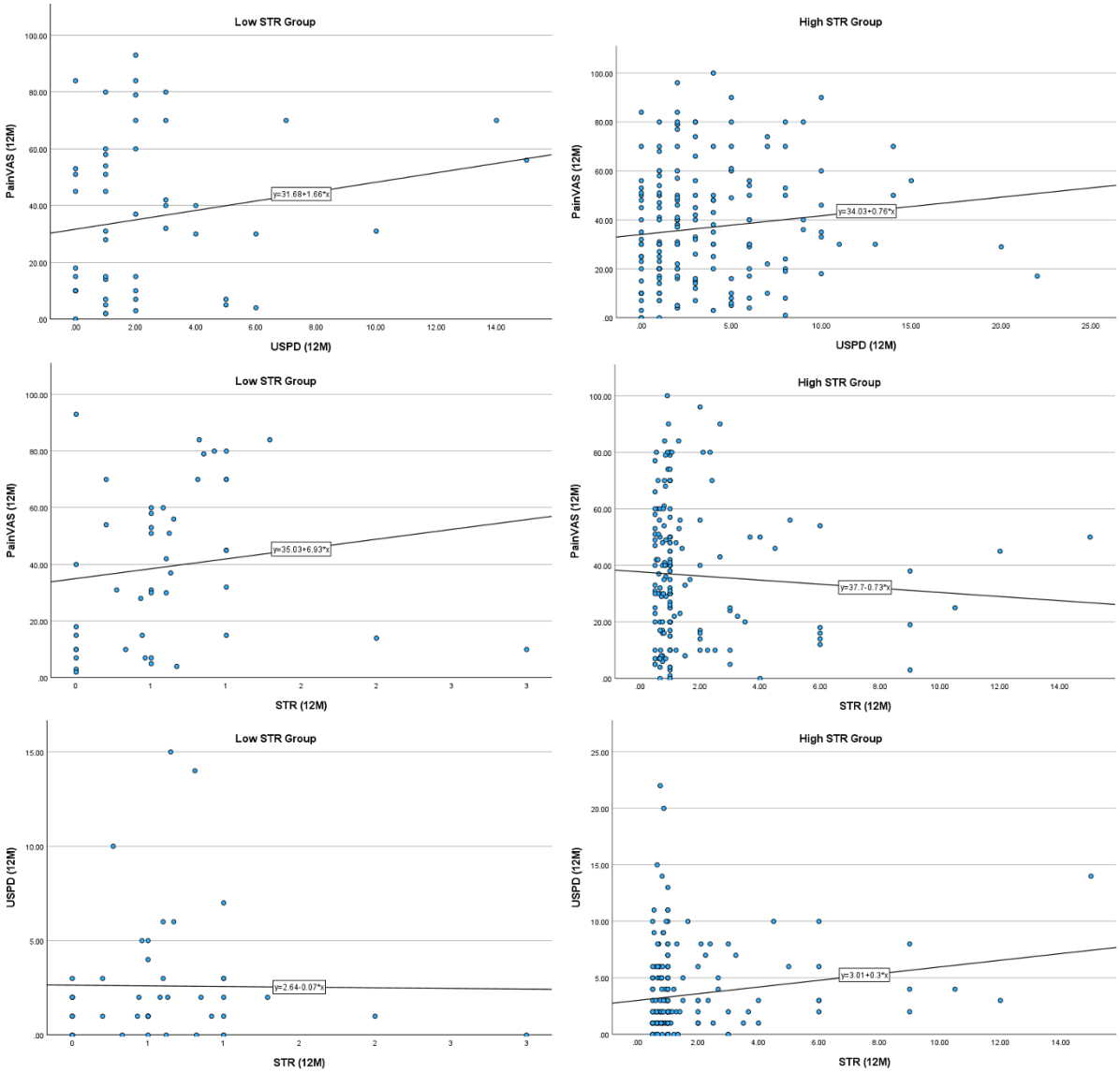

Figure 4.18: Univariate correlations at low and high STR at the 12-month follow-up.

4.5 Discussion

Many patients with RA still experience chronic pain despite improvements in treatments and management. Different pain mechanisms in RA, such as nociceptive and nociplastic pain, have been highlighted by prior research (Walsh and Williams, 2014; Sarzi-Puttini et al., 2014). The purpose of this section is to explore the relationship between pain VAS and MSUS measures in order to gather more information on the mechanisms of pain in RA. Table 4.1 shows that from baseline to the follow-up time point, there were notable improvements in the patient's well-being in essential indicators of RA. The improvement in a prominent RA symptom is indicated by the pain VAS score decreasing over time. A decline in TJC suggests a reduction in joint tenderness, representing a decrease in related pain and inflammation. Reduced joint swelling, which a lower SJC indicates, suggests better disease control. Furthermore, a reduced DAS28 score at the follow-up visits suggests an overall decrease in disease activity among patients. The results indicate a reduction in the ultrasound metrics, which means there was a reduction in synovial inflammation and blood flow within the joints. These findings aligned with the clinical findings, which showed decreased disease activity and pain among Patients with RA. These results indicate that the RA management provided to the participants in this study successfully improved both clinical and MSUS markers of RA activity, leading to enhanced overall pain levels, joint tenderness and swelling.

4.5.1 The correlation between pain and ultrasound in RA

The findings indicate a significant relationship between pain VAS scores at baseline and the 12-month follow-up visit in patients with RA and USPD, USSH and USJE. The significant association between USPD and pain VAS indicates that higher levels of pain reported by patients are closely correlated with increased joint blood flow and inflammation detected by Doppler ultrasound. This result supports the traditional belief that pain in RA is influenced by active synovitis, as it contributes to pain in RA. Furthermore, the relationship between the joint effusion measured by USJE and the pain VAS suggests that the existence of extra fluid in the joints is a major determinant of pain intensity. Joint effusion is a hallmark of inflammatory arthritis and plays a significant role in causing pain. The distension of the joint capsule due to fluid accumulation increases intra-articular pressure, which stretches the highly innervated joint capsule. This results in a deep, aching pain that worsens with joint movement (Houghton, 2007). Further evidence that thickening of the synovial membrane is a critical factor in RA pain determination

comes from the noteworthy association observed between pain VAS and synovial thickening as measured by USSH. This implies that the pain associated with RA is linked to active synovitis, which results in nociceptive pain by inflaming the peripheral joints. Additionally, a decrease in MSUS measures such as USPD, USSH and USJE can indicate a positive response to treatment. In contrast, their persistence is a poor indicator of the outcome (Pereira et al., 2015; Naredo et al., 2013; Dougados et al., 2013).

This study's results differ from earlier research results (TaSER study) as the relationship between pain VAS and USPD was insignificant in the TaSER study, unlike this study. However, although there is a significant correlation seen in this research, the results show that the correlation strength is low. These findings suggest that only a small portion of the pain experienced by Patients with RA could be explained by the US metrics used to measure joint inflammation. This implies that the prevalence of nociceptive pain mechanisms may not be as significant as previously believed and that additional pain mechanisms, such as nociplastic pain, could be involved; hence, further investigation was needed to better understand overall pain in RA.

Although pain is frequently thought of as a sign of inflammation, prior studies have shown that there is little relationship between peripheral inflammatory markers and pain severity. The multifaceted nature of pain in RA is highlighted by Walsh and McWilliams (2014), who note that it is associated with psychological distress, peripheral inflammation, central sensitisation and social functioning. These elements may lead to a rise in the use of healthcare services. Even when RA is treated as effectively as possible, the prognosis for pain is frequently not promising. Therefore, measuring it is crucial to enhance RA management and reduce pain. The results indicate that the subjective pain measures, such as pain VAS, have a weak association despite the significant p-value with objective measures of RA, such as MSUS, ESR and SJC. Nonetheless, there seems to be a stronger correlation between pain VAS and TJC, a subjective marker. Furthermore, the study's findings highlight the major benefits of USPD over other ultrasonic metrics like USJE and USSH for evaluating peripheral inflammation in Patients with RA. The regression analysis revealed that USPD was more strongly associated with pain than USJE and USSH, suggesting that USPD may serve as a more reliable marker of pain and inflammation in the long term compared to USSH and USJE. Nonetheless, the regression analysis also showed a significant impact of USSH. Comparative studies of USSH and USPD in RA reveal that synovial hypertrophy offers at least comparable and, in some cases, superior clinical usefulness. Initial validation studies indicated that USSH detects synovitis with high

sensitivity and reliability, often uncovering inflammatory tissue in joints that do not show a detectable USPD (Szkudlarek et al., 2001; Rees et al., 2007). Multicenter studies have established that USSH exhibits strong intra- and interobserver reliability, frequently matching or surpassing USPD assessments (Dougados et al., 2011; Bruyn et al., 2010). Notably, USSH serves as the structural basis for synovitis, whereas USPD activity reflects vascularisation, which can vary with machine settings and technical factors (Schmidt et al., 2015).

Longitudinal studies provide additional support for the independent prognostic significance of USSH. Scirè et al. (2009) found that both USSH and USPD could predict short-term relapse in Patients with RA in clinical remission, with USSH continuing to be present even when the USPD signal was not detectable. Likewise, Terslev et al. (2017) demonstrated that USSH without USPD remains sensitive to changes and may signify ongoing low-grade inflammation. Although USPD has been linked with radiographic progression (Naredo et al., 2007; Ikeda et al., 2013), studies assessing structural outcomes indicate that the combination of USSH rather than USPD alone enhances prognostic accuracy (Dougados et al., 2011). Altogether, these results imply that USSH captures the fundamental inflammatory structure of RA and maintains significant diagnostic and prognostic value, even in the absence of USPD activity.

Furthermore, Wakefield and colleagues (2012) emphasised that grayscale (GS) synovitis, namely US joint thickening, correlates with the duration of RA. This represents previous inflammation rather than active inflammation. On the other hand, USPD is a more accurate indicator of active inflammation because the disease duration does not influence its presence. This distinction is vital because USPD can more precisely evaluate the level of active inflammation, which is necessary for making decisions about current disease management and treatment.

4.5.2 Rise in pain VAS and USPD correlation at the follow-up

An important observation in the results is the unexpected and significant increase in the strength of the correlation between pain VAS and USPD at the follow-up. The treatment administered to Patients with RA in this cohort aims to address RA inflammation, improve disease activity and prognosis, and ultimately reduce pain. As a result, it is expected that there would be a negligible or weak correlation between pain VAS and USPD. However,

the unexpected increase in the correlation strength is an interesting finding that requires further investigation.

Even though treatment is still being administered, there are a few possible explanations for the observed increase in the strength of correlation between pain VAS and USPD at the follow-up visit, which is a crucial point in understanding the progression of the disease. Although the correlation between USPD and pain VAS increased at follow-up, its strength remains weak at all visits. Clinically, USPD reflects peripheral inflammatory changes and is unlikely to indicate non-inflammatory changes. In the next section of this discussion, the behaviour of pain VAS in the absence of USPD will be discussed. A possible explanation for the increased USPD and pain VAS at follow-up is that ultrasound may detect minor inflammation, correlating with a high pain VAS due to concomitant non-inflammatory sources, such as RA with FM.

An explanation of high pain at the follow-up that could be offered is that while the treatment has successfully decreased peripheral inflammation, the patient's pain levels are still high because of non-peripheral factors. The multifactorial nature of pain in RA may suggest that non-peripheral factors are significantly influencing the persistence of high pain levels, even in the presence of improved peripheral inflammation (Walsh and McWilliams, 2014). These factors include psychological distress, central sensitisation, and social functioning. All these factors could worsen the pain perception in Patients with RA despite the inflammation improvement (Walsh and McWilliams, 2014). One possibility that could be causing continuous pain is central sensitisation, a condition in which the central nervous system becomes sensitised to pain signals (Walsh and McWilliams, 2014). Apart from peripheral inflammation, psychological variables such as anxiety, depression and social stressors may also worsen pain perception. Additionally, methodological factors such as missing data or pain from inflamed joints not scanned by ultrasound could also impact the increase in correlation strength between pain VAS and USPD at the follow-up visit, even with active treatment. These methodological flaws may affect the data's precision and thoroughness, which could cause the correlation strength to appear to increase. The absence of data at the follow-up can lead to bias because the analysis may skew the results too heavily based on the available data. For instance, the study's observed correlation between pain VAS and USPD may have been inflated if participants with (with high non-inflammatory pain) less severe pain had dropped out at the follow-up. Several analyses were conducted to investigate the causes of the noted increase in the correlation strength between pain VAS and USPD at the follow-up visit. The purpose of these

analyses was to shed more light on the type of pain experienced by this group of people with advanced arthritis. The potential influence of methodological factors on the outcomes was also assessed by examining these factors, including the exclusion of certain joints from the ultrasound scanning protocol and the handling of missing data. These factors will be discussed further in 4.5.4 and 4.5.6.

4.5.3 Categorising participants into two subgroups based on their pain VAS score

This analysis aimed to divide the participants into two groups based on their pain VAS at the follow-up visit to compare the pain scores and determine the potential effects on these pain subgroups of variations in pain VAS and USPD at the follow-up. Study participants were divided into reduced and persistent pain groups based on their pain VAS scores. A pain VAS threshold of <34 was used to classify participants as the reduced pain group when their VAS score was low (pain VAS <34) or the persistent pain group when their pain VAS score was 34 or higher (Boonstra et al., 2014). This cutoff aligns well with assessments of functional interference and patient self-reports. It clearly distinguishes between mild scores with minimal impact and moderate pain that begins to significantly affect daily functioning. Additionally, this threshold provides a simple, clinically measurable standard indicating substantial remaining pain, showing sensitivity to levels that may surpass an acceptable limit.

Precise cutoff points encourage the classification of pain intensity in different clinical contexts and research inquiries (Boonstra et al., 2014). Furthermore, identifying various pain severity levels facilitates the creation of more accurate and successful pain management plans that are customised to meet the unique requirements of every type of pain (Boonstra et al., 2014). According to Correll (2011) and Lang-Illievich et al. (2020), low pain is defined as a pain VAS score of 30 or less and high pain is defined as a pain VAS score greater than 30. In a study by Bilberg and colleagues (2018), a pain VAS score of >40 mm is suggested to indicate clinically significant pain in patients with RA. Furthermore, Pollard and colleagues (2006) suggest that a pain VAS score of >50 mm coexists with non-inflammatory conditions in Patients with RA. Moreover, opinions differ regarding the degree of change in the VAS score, representing a significant reduction in pain from the patient's perspective. While some argue for a 30% reduction, others insist on a 50% reduction for real patient relief.

The pain VAS threshold was set at <34 in this analysis. For RA research, selecting this particular cut-off (Pain VAS at <34) has various advantages. First, these cut-offs provide a clinically relevant framework for classifying pain severity, grounded in solid research that directly links pain intensity to its effects on daily functioning. The cut-off points for pain intensities were established using receiver operating characteristic (ROC) curves, guaranteeing reflective and standardised pain assessments (Boonstra et al., 2014). Additionally, these thresholds have been confirmed by statistical analyses, which are essential for customising interventions and improving patient outcomes, as they differentiate between degrees of pain-related interference. RA research can achieve improved consistency and comparability across studies by using these established cut-offs, increasing the findings' reliability and enabling more focused and efficient treatment approaches. This strategy also aligns with the broader body of research on chronic pain, ensuring that the best available data can be used to manage pain in RA (Boonstra et al., 2014).

The univariate correlation between pain VAS and USPD using this cut-off interestingly showed how pain and inflammation in Patients with RA change over the course of a year, especially when comparing patients with reduced pain versus those with persistent pain. The pain VAS and USPD using this cutoff appear to follow a similar pattern to that found in the earlier analysis, as the correlation at follow-up is still stronger than the baseline score.

There was a weak but statistically significant correlation between pain and inflammation at baseline in the group with reduced pain. This preliminary weak correlation indicates that although inflammation plays a role in pain, its perception may also be influenced by other factors at this point. Nevertheless, during the follow-up of the study, the situation drastically shifted. This relationship had become significantly stronger over the 12 months, suggesting a closer connection between decreased inflammation and pain. It was expected to see an improvement in pain at the follow-up visit because the inflamed joints, which are classically considered the primary source of pain in RA, have been controlled by the administered treatment. This correlation was expected to become weaker or become insignificant, particularly in the reduced pain group, where pain levels have decreased. The explanation for this, as mentioned earlier in 4.5.2, is the presence of a non-inflammatory factor that hinders the improvement of pain intensity measured by the pain VAS (Walsh and McWilliams, 2014).

The group with persistent pain, on the other hand, displayed a similar pattern with generally weaker correlations. The baseline association between pain and inflammation was marginally higher than in the group with reduced pain, but it was still relatively weak. Classically, ultrasound was expected to show more peripheral inflammation in the reduced pain group at the baseline. However, in the persistent group, the presence of non-inflammatory factors could influence the pain severity (Walsh and McWilliams, 2014).

Although the correlation in the persistent pain group is not as strong as in the reduced pain group, it has increased at follow-up, indicating some alignment between inflammation and persistent pain. The weaker correlation at the follow-up visit indicates that pain for these patients is not solely caused by inflammation. Many other factors, including central sensitisation, may also play a role in persistent pain. The results suggest that the remaining pain, as measured by the pain VAS in both the reduced and persistent pain groups, may not be directly related to inflammation. The results were consistent among participants experiencing persistent pain at all visits. The USPD scores for these participants showed a similar pattern to those of participants with reduced pain. This suggests that the source of pain in participants with persistent pain is unlikely to be due to inflammatory changes in the joints.

Therefore, it may be necessary to implement additional measures that address both inflammatory and non-inflammatory pain mechanisms for individuals experiencing persistent pain.

4.5.4 Categorising participants into two subgroups based on whether they completed the 12-month visit or not

This analysis and previous analyses aimed to investigate the rise in the strength of correlation at the follow-up visit between pain VAS and USPD and provide justification for that observation. This analysis was carried out to determine whether dropouts during follow-up visits contributed to attrition bias or impacted the study results (Asendorpf et al., 2014). As stated in the study's results, the objective was to determine whether the participants who did not complete the follow-up visit (non-completers) had any impact on the observed increase in the correlation between pain VAS and USPD scores at later follow-up visits. This stage was crucial to confirming the reliability of the results and preventing participant dropout from skewing the increase in pain VAS and USPD correlation.

Based on their commitment to study visits over 12-month visits, participants were split into two groups for this analysis: the complete group, which consisted of individuals who attended all scheduled visits and the incomplete group, which included those who skipped the follow-up visit after the baseline. Regarding pain VAS and USPD at baseline, there were no statistically significant differences between the two groups. This lack of substantial difference suggests that at baseline, the participants who finished the study and those who did not had similar levels of pain and inflammation. For participants who completed all study visits, additional analysis within the entire group revealed a significant correlation between pain VAS and USPD, indicating that pain levels were significantly related to inflammation. On the other hand, there was no significant relationship found between pain VAS and USPD in the incomplete group.

These results highlight the fact that the study's overall outcomes could be unaffected by the study participants who abandoned it. The lack of baseline variations in pain and inflammation between participants who completed the study and those who did not complete the study supports the integrity of the study's findings. As a result, the substantial correlation seen across the entire group and not impacted by dropout rates accurately depicts the actual relationship between pain and inflammation over time. This demonstrates that the study's findings are reliable and highlights the significance of regular follow-ups in learning about the dynamics of pain and inflammation in RA. These results provide multiple justifications for the lack of attrition bias in the data. When the features of dropouts are systematically different from those of those who stay, attrition bias usually happens, potentially impacting the results (Asendorpf et al., 2014; Lewin et al., 2018). Because the baseline levels of pain and inflammation were comparable in this study, the dropout of non-completers did not result in a loss of participants with particular characteristics (differential loss) that could have influenced the results.

4.5.5 Evaluating pain VAS among participants with negative USPD

This analysis aimed to provide evidence of centralised pain presence in RA. Since ultrasound is a marker of peripheral changes in RA that lead to pain, its absence and presence at the same time could indicate that the nature of pain is related to the inflammatory change at the joint, but it could originate from another source. Thus, this analysis aimed to investigate the nature of pain in RA, concentrating on the lack of USPD signal as a sign of a lack of peripheral inflammation.

Any pain that occurs in the absence of a USPD signal is most likely coming from non-inflammatory sources. Nociplastic pain, which is caused by altered central nervous system (CNS) processing of pain, is the most prevalent type of pain in RA that does not result from peripheral damage or inflammation.

At the 12-month follow-up visit, 72 participants reported high pain levels (Pain VAS≥34) and no detectable inflammation based on the absence of USPD signals. The prolonged presence of elevated pain levels implies that non-inflammatory mechanisms, namely central sensitisation, are responsible for these patients' pain. The term central sensitisation describes how the central nervous system becomes more sensitive and responsive to pain stimuli, which can result in chronic pain experiences even in the absence of active inflammation. The importance of central sensitisation in RA is highlighted by this finding, which also emphasises the need for targeted treatment approaches that specifically address these central pain mechanisms.

Higher baseline pain levels, as measured by pain VAS, were observed in the positive USPD group, where USPD signals indicate inflammation. However, at the 12-month follow-up, there was a noticeable decline in the frequency of severe pain. This demonstrates how reducing inflammation affects pain management in RA, suggesting that many participants may have experienced effective pain relief from the anti-TNF treatment.

The comparison of negative and positive USPD groups could help distinguish different types of pain in RA. The significance of non-inflammatory pain mechanisms such as central sensitisation is indicated by the persistence of high pain levels in the absence of positive USPD signals. Further research was conducted to ensure that participants experiencing high levels of pain and no USPD signals at the 12-month follow-up visit were included in subsequent visits. The findings revealed that three patients had either a decrease in their pain VAS scores or were absent during at least one follow-up visit. The findings indicate that high pain levels and negative USPD at the 12-month visit were not influenced by missed visits. Furthermore, the persistent high pain levels experienced by the fourteen participants persisted despite effective treatment, suggesting that these levels may have stemmed from non-inflammatory causes.

4.5.6 The effect of joints not examined during the clinical and MSUS scanning protocols

The MSUS protocol followed during the ultrasound data collection involved 28 joints. This means that not all joints were scanned by ultrasound during the visits. This can raise questions about whether there is a possible peripheral inflammation from a joint that was not included in the MSUS protocol. To address this assumption, a further analysis was conducted to confirm that the reported pain was central and not due to peripheral inflammation from joints not covered by the MSUS scanning protocol. Due to missing MSUS data for 84 joints in this cohort, the SJC of these 84 joints was investigated to assess whether the inflammation in joints not included in the 28 joints used in the MSUS scan differs. Although the SJC is less sensitive than MSUS in assessing inflamed joints, it can be used to determine the effect of unscanned joints on pain. This is because the SJC and MSUS approximately follow a similar pattern in detecting inflamed joints in this cohort.

The SJC of 84 joints and the SJC of the 28 joints included in the MSUS scan were compared in this analysis. It would be confirmed that the pain comes from a non-inflammatory source if the patterns between the two SJCs were similar, indicating that the pain did not originate from joints excluded from the scanning protocol.

A possible study limitation would be highlighted if, on the other hand, the patterns varied and suggested that peripheral pain might be coming from joints that were not part of the MSUS scan protocol. The results showed that the SJC measured at 28 joints and the SJC measured over 84 joints were comparable. Given the similarity of these patterns, it is doubtful that inflammation in joints other than the standard 28-joint count is the cause of the pain experienced by patients whose USPD results are negative. This, therefore, lends credence to the theory that the pain in this RA population is more likely to be non-inflammatory in nature, such as centralised pain. There are various reasons why this analysis is essential. First, eliminating the chance that pain originates from unscanned joints guarantees the accuracy of the results. The study supports the theory that the pain is probably centralised by demonstrating that the extended joint count does not identify any new sources of peripheral inflammation. These findings are significant because they validate the current USPD scanning protocol, indicating that it successfully identifies the relevant inflammatory sources of pain within the 28-joint framework.

The conclusion that non-inflammatory mechanisms, such as centralised pain, are more likely to be the cause or have a considerable contribution to the reported pain is supported by the extended joint count's lack of additional diagnostic value. Participants who reported high pain also showed positive joint effusion and synovial thickening during the 12-month follow-up in the negative USPD group. These anatomical alterations are frequently connected to hypervascularity identified by USPD. It was previously mentioned that USPD revealed the presence of inflammation at the time of scanning and that structural alterations like synovial thickening may have been caused by prior inflammation (Wakefield et al., 2012). The development of central sensitisation is another possible explanation for the structural alterations in these populations. The European Alliance of Associations for Rheumatology (EULAR) has defined difficult-to-treat RA as encompassing the potential for concomitant non-inflammatory diseases such as fibromyalgia to mimic inflammatory activity (Nagy et al., 2021). Undoubtedly, USPD serves as a reliable indicator of peripheral inflammation and is superior to USSH and USJE in monitoring the effects of treatment on impacted joints. Thus, in cases of RA, USPD may be used to rule out peripheral pain. Hence, in the absence of markers of peripheral inflammation, the prevalence of non-inflammatory pain, such as nociplastic pain, is high (Druce et al., 2016).

Additionally, participants reported experiencing high pain in the absence of inflammation, as indicated by USPD as a peripheral marker. It is important to remember that throughout this study, every participant received treatment with an anti-TNF agent. When the pain levels in this group were tracked at 12-month follow-up, pain VAS scores showed a slight decrease in pain intensity. The low STR group also showed signs of this trend in the previous analysis. Therefore, the anti-TNF treatment may positively impact centralised pain, causing pain improvement among Patients with RA. These results align with those of Druce and colleagues (2016), who found that improvements in central mechanisms appear to be associated with decreased fatigue and pain after anti-TNF therapies.

4.5.7 Categorising participants into two subgroups based on STR

The previous analysis provided evidence of non-inflammatory pain in RA. This analysis aimed to validate it by investigating the nature of pain in RA using STR.

STR is an indirect measure to identify the contribution of centralised pain to the overall pain experienced in RA. Low STR is associated with centralised pain, while high STR is linked to peripheral pain in RA. Using this measure could provide information about the

nature of pain in the RA population, leading to a better understanding of the mechanism of pain and, therefore, better pain management in RA.

Using STR as a criterion, RA participants were split into two groups: low STR, which indicated central pain and high STR, which indicated peripheral pain. The analysis aimed to investigate the connections between pain levels determined by the pain VAS and USPD at baseline and 12-month follow-up. Lee and colleagues (2014) conducted a novel approach to quantifying CNS pain mechanisms and forecasting treatment outcomes using the STR concept. They classify STRs as low, moderate, or high. Their study is the first to establish suitable thresholds. Their results showed that the majority of patients' STRs fell between 0.5 and 1.0. Furthermore, it was found that 14% of patients had STRs below 0.5, which is consistent with the prevalence of centralised pain that is known to exist in patients with RA (Lee et al., 2014).

The results showed interesting results over time for participants in the low STR group, representing those with centralised pain. There was a weak and non-significant correlation between perceived pain levels and ultrasound-detected inflammation, as evidenced by the lack of a statistically significant correlation between pain VAS and USPD at the baseline and the follow-up visits. Given that low STR is associated with centralised pain, it was anticipated that there would be no significant association between inflammation and pain VAS. The results indicated that peripheral pain is not this group's leading cause of discomfort. This suggests that centralised pain, as opposed to peripheral pain, probably has a higher contribution to pain in this RA group compared to peripheral pain. These results support the theory proposed by Lee et al. (2014) that centralised pain is indicated by a low STR.

On the other hand, participants in the high STR group, which is suggestive of peripheral pain, exhibited a distinct set of relationships. Baseline data indicated a significant correlation between pain VAS and USPD, indicating that higher pain levels were linked to increased ultrasound-detected inflammation. At the 12-month follow-up, this significant relationship was still present, demonstrating a continuous relationship between these participants' perceptions of pain and inflammation as identified by ultrasound. Furthermore, a negative correlation was found at baseline between the pain VAS and STR, meaning that higher levels of centralised pain were linked to lower STR and vice versa. This suggests that participants with higher STR experienced less centralised pain. These results are unsurprising as peripheral inflammation is the leading cause of pain in the high

STR group. The 12-month follow-up revealed that the negative correlation between STR and pain levels had not persisted over time, as evidenced by the fact that it was no longer significant. Due to the treatment's successful control of the inflammation-causing pain in this group at baseline, the correlation weakened and eventually stopped being significant. The participant's perception of pain significantly improved as a result of this.

Recent studies have demonstrated the significance of central sensitisation or centralised pain in the pain that participants with RA endure. As an illustration, Joharatnam et al. (2015) found that the degree of pain experienced in RA is highly influenced by both pain sensitivity and mental health, suggesting the involvement of central sensitisation mechanisms. In addition, Clauw and colleagues (2023) emphasised that because of central sensitisation, Patients with RA frequently display diffuse pain sensitivity and increased pain responses. Minhas et al. (2023) brought to light the prevalence of fibromyalgia symptoms in Patients with RA, which are suggestive of centralised pain processing. There are various difficulties in diagnosing centralised pain in Patients with RA. Separating it from nociceptive pain is a significant challenge because Patients with RA may experience both types of pain simultaneously (mixed pain). A further difficulty in diagnosing patients is the wide range of symptoms they experience, which can be impacted by disorders such as depression, exhaustion, and coexisting medical conditions. Nonetheless, centralised pain conditions, namely fibromyalgia in RA, have been extensively studied.

STR was used in this study to detect the presence of centralised pain, even though the dataset contained no fibromyalgia measures. This study could offer substantial proof that patients with RA experience centralised pain. These results are in line with the knowledge that it is not peripheral inflammation alone, but a combination with centralised pain that persists in RA. These results might corroborate the conclusions drawn by Clauw et al. (2023) as well as Minhas et al. (2023), who highlighted how Patients with RA's pain is centralised and how this has a major influence on how pain is perceived and managed.

4.5.8 Study limitations

It is essential to take into account a few research limitations as well. First, the study's large sample size offers a solid basis for examining the relationship between Patients with RA's pain VAS scores and ultrasound metrics. A comprehensive investigation of peripheral pain and its association with objective measures of inflammation is made possible by the large sample size, which also improves the reliability of the results. As such, the findings are

generalisable to other populations of RA, providing important information about the findings' broader applicability. Nevertheless, the study's ability to examine RA-related centralised pain is constrained. Although sufficient to assess peripheral pain, the sample size indicates a smaller proportion of subjects with non-inflammatory pain. This restriction limits the generalisability of centralised pain findings to other populations affected by RA. In particular, the limited sample size for non-inflammatory pain makes it difficult to draw reliable conclusions that can be generalised to broader settings.

A further research limitation is the lack of measures such as the FM criteria, Widespread Pain Index (WPI), Symptom Severity Scale (SSS), and Quantitative Sensory Testing (QST) that are specifically intended to evaluate centralised pain. These instruments are more robust for differentiating between centralised and peripheral pain in the RA population. When direct measures are unavailable, the study employs indirect markers of centralised pain, including STR and pain VAS scores, in the absence of peripheral inflammation, as determined by USPD, which is not present. Future studies should integrate centralised pain measures with current assessments to overcome these constraints. This would enable the distinction between centralised and peripheral pain mechanisms and provide a more nuanced comprehension of the pain experienced by patients diagnosed with RA. Future research can verify the current findings and enhance their relevance to various RA populations by including metrics such as the Fibromyalgia Impact Questionnaire (FIQ), Fibromyalgia, WPI, SSS, or QST.

4.6 Study Summary

This research investigated the relationship between ultrasound metrics and pain VAS scores to explore the nature of pain in RA. The findings indicate that there was a weak but statistically significant correlation between the pain VAS scores and the ultrasound metrics at baseline and the 12-month follow-up visit. This significant correlation supports the idea that active synovitis plays a significant role in aggravating pain in RA by indicating that elevated levels of pain are closely correlated with increased blood flow and inflammation as measured by USPD. The relationship between USJE and pain VAS suggests that joints with excess fluid are important factors that affect pain levels, and the relationship between USSH and pain VAS suggests that the thickening of the synovial membrane is another crucial factor influencing pain levels. Nociceptive pain in RA is produced by inflammatory processes in the peripheral joints, which are linked to active synovitis. A reduction in MSUS measures such as USPD, USSH and USJE indicates an excellent response to RA

treatment, while the persistence of MSUS findings is an indicator of poor RA management. The strength of the USPD and pain VAS correlation is weak despite the significant correlation. These results highlight that only a small percentage of the pain that Patients with RA experienced could be explained by the joint inflammation MSUS metrics. Therefore, other pain mechanisms, such as nociplastic pain, need to be clarified, as nociceptive pain mechanisms do not predominate as is classically thought. Peripheral inflammation, central sensitisation, and psychological distress are all factors in the multifactorial pain associated with RA. The prognosis for pain in Patients with RA is still poor, even with the best management of inflammatory disease, which is one of the factors that leads to increased healthcare utilisation.

According to the study, USPD is a better ultrasound metric for measuring peripheral inflammation in Patients with RA than USJE and USSH. At baseline and follow-up, the correlation between pain VAS and USPD is stronger than the correlation between pain VAS and USJE and USSH. However, the correlation between pain VAS and USJE becomes more significant when looking at changes over time, and regression of changes indicates that USSH has a stronger correlation with pain VAS. These results imply that USPD is a reliable indicator of persistent inflammation. The study also looks at the correlation strength that increased between pain VAS and USPD during the follow-up visit. This suggests that while treatment did reduce peripheral inflammation, factors like psychological distress and central sensitisation may have contributed to the persistence of high pain levels. Participants' pain VAS scores were divided into two subgroups: those with reduced pain and those with high pain. In both groups, the correlation between pain VAS and USPD was higher at follow-up than at baseline, with the group with reduced pain demonstrating a longer-lasting relationship between pain reduction and decreased inflammation.

Additional strategies are needed to address both inflammatory and non-inflammatory pain mechanisms, as the correlation in the group with high pain remained weaker, indicating that inflammation is not the only cause of pain. An additional classification system utilising STR sought to investigate the connections between pain intensity, STR, and USPD. The results supported the theory that centralised pain is indicated by a low STR, highlighting the significance of central sensitisation in pain perception.

Another analysis was conducted to assess pain VAS among patients with negative USPD signals to determine non-inflammatory pain sources. Numerous participants reported high

pain levels in the absence of USPD signals, indicating the critical role of central sensitisation in RA.

Understanding the mechanisms and sources of pain in RA is crucial for effective pain management. Treatment strategies should focus on both inflammation and central sensitisation. Developing pain management plans that target nociplastic pain pathways in the central nervous system and peripheral inflammatory pain pathways is essential. By implementing treatments that address the multifaceted nature of pain, such as inflammation and central sensitisation, healthcare providers can improve pain management.

Chapter 5 Exploring the relationship between MSUS metrics and pain in Psoriatic arthritis

5.1 Abstract

Introduction

Psoriatic arthritis (PsA) is an inflammatory condition characterised by synovitis and enthesitis. Differentiating enthesitis from the widespread pain commonly associated with Fibromyalgia (FM), which is a prime example of central sensitisation (CS), is a particular clinical challenge. In fact, up to 30% of patients with PsA may experience this overlap. Quantitative Sensory Testing (QST) evaluates sensory processing thresholds and stimulus-responses in both normal and pathological conditions. The pressure pain threshold (PPT) is a type of QST that can assess nociplastic pain conditions. Algometry is employed in CS research to quantify the PPT, which reflects increased pain sensitivity when it is reduced. Additionally, ultrasound serves as a valuable tool for demonstrating inflammatory changes at the joints and the entheseal sites in PsA.

Objectives

This study aims to investigate the relationship between MSUS metrics, specifically ultrasound-detected synovitis and enthesitis, and various pain assessment measures, including subjective measures such as pain VAS and semi-objective measures such as QST. This study hypothesises that MSUS metrics are statistically correlated with pain VAS scores, suggesting nociceptive pain caused by inflammatory joint changes. Additionally, it will evaluate how the extent of MSUS metrics, which indicate peripheral inflammatory alterations, affects patients' overall pain levels in PsA. Furthermore, it aims to explore the relationship between central sensation (fibromyalgia; FM) and ultrasound metrics in entheses to better understand the pain mechanisms involved in enthesitis in PsA.

Methods

Patients with active PsA about to start a new immunosuppressant were recruited. The MSUS evaluations were conducted at both baseline and six-month follow-up visits. The MSUS assessments utilised a binary scale to evaluate synovial thickening and joint power Doppler findings in patients with PsA. The MSUS assessment covered a total of forty joints per patient, including bilateral MCP, PIP, DIP, and MTP joints. The MSUS also addressed enthesitis alongside the Leeds Enthesitis Index (LEI) to evaluate enthesitis. PPT was measured using algometry at the non-dominant knee, which reflects peripheral changes such as enthesitis, as well as the trapezius and calf area, which are considered CS areas. The ACR 2011 Fibromyalgia criteria score was used to determine the presence of CS. Correlations and t-tests were used to assess the associations between the collected

variables. SPSS and JASP (Jeffrey's Amazing Statistics Program) were used to analyse the data.

Results

A total of 50 patients with active PsA were recruited. Twenty participants underwent ultrasound evaluations at both the baseline and six-month follow-up visits. No significant correlation was observed between US synovitis and pain VAS ($r = 0.020$, $p = 0.934$) or between US enthesitis and pain VAS ($r = 0.191$, p value = 0.31). Thirty per cent of patients met the FM criteria and presented with higher LEI scores and lower PPT-evoked thresholds than FM-negative patients. Total FM scores significantly correlated with LEI scores ($r = 0.69$, $p < 0.001$) and calf PPTs ($r=-0.53$, $p=-0.014$), but not with knee and trapezius PPTs ($r=-0.49$, $p = 0.09$; $r=-0.30$, $p = 0.19$), or US enthesitis ($r=-0.04$, $p = 0.86$). The PPT measurements in the investigated areas did not demonstrate significant correlations with US enthesitis. Specifically, the PPT algometry at the left trapezius showed a correlation of $r = 0.01$ ($p = 0.96$), and the PPT algometry at the left knee resulted in a correlation of $r = 0.14$ ($p = 0.54$). However, an indirect association was noted between the LEI and calf PPT ($r = -0.51$, $p = 0.02$), as well as trapezius PPT ($r = -0.41$, $p = 0.06$). No significant correlation was observed between LEI and left knee US enthesitis ($r = -0.32$, $p = 0.17$).

Conclusion

The US is vital for detecting peripheral inflammatory changes, such as synovitis and enthesitis; however, this study found no significant links between US findings and pain intensity in patients with PsA. This suggests that pain may be driven more by central mechanisms than by peripheral inflammation. Additionally, there was no correlation between US enthesitis and PPT responses at the knee and trapezius sites, indicating that ultrasound does not fully account for the pain in Patients with PsA. While patients with FM, often comorbid with PsA, showed higher LEI scores, LEI did not correlate with US findings. This raises concerns about misinterpreting CS pain as active enthesitis. Using US alongside QST could better differentiate between peripheral inflammation and central sensitisation, potentially leading to improved patient care and preventing unnecessary treatment escalation.

5.2 Introduction

This chapter builds upon the previous one (Naredo's chapter), addressing the same research question while focusing on a different inflammatory arthritis: PsA. Therefore, the aim is to determine whether previous RA findings are generalisable across the spectrum of inflammatory arthritis.

RA and PsA, while distinct, share a commonality in the urgency of early diagnosis. RA is primarily characterised as an autoimmune disorder that involves autoantibodies, leading to synovial inflammation and joint damage. In contrast, PsA is an immune-mediated disorder characterised by skin and nail psoriasis, driven in part by the IL-17 and IL-23 pathways (Vecellio et al., 2021). PsA often manifests with greater enthesitis (inflammation at the sites where tendons attach to bones) and dactylitis (swelling of entire fingers or toes). Despite these differences, both conditions result in chronic joint pain due to inflammation, although the patterns of joint involvement may vary. Furthermore, they share similar treatment strategies, as many medications effective for RA are also employed in managing PsA, including TNF inhibitors. However, PsA often necessitates IL-17/IL-23 inhibitors, which are not efficacious treatment options for RA (Saalfeld et al., 2021). Moreover, patients diagnosed with RA and PsA may present a comparable phenotypic expression of a mixed pain state, which includes chronic pain that persists even when inflammation is under control. For instance, some patients with RA may still report pain despite minimal or absent inflammatory markers, such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and synovitis identified through ultrasound. This indicates that pain mechanisms extend beyond merely peripheral inflammation, as demonstrated by the findings in the previous chapter. Compared to RA, PsA often includes enthesitis, which can result in persistent pain regardless of the presence of active synovial inflammation (Kaeley et al., 2018).

The investigation into pain within this population will utilise the MSUS dataset. Additionally, the PsA data encompasses various pain measures, including the pain VAS as a subjective measure and Quantitative Sensory Testing (QST) as a semi-objective measure. QST can indicate the dominant mechanism of pain. MSUS identifies the source of nociception, while QST evaluates how the nervous system processes and amplifies these signals. Examining the link between MSUS and QST may help in categorising pain mechanisms as inflammation-driven, centrally sensitised, or a mixed type. Therefore, it could enable a better understanding of the nature of pain in inflammatory arthritis.

This study aims to provide a more comprehensive imaging perspective of joint structures and vascularity by integrating a broader array of pain measures alongside ultrasound metrics. This approach could enhance the understanding of the pain mechanisms present in this population.

5.2.1 Ultrasound in inflammatory arthritis

MSUS is an effective tool that plays a significant role in diagnosing and managing inflammatory arthritis by visualising joint inflammation and damage. The MSUS also plays a role in detecting subclinical synovitis and demonstrating bone erosion. It helps detect important features of inflammatory arthritis, such as synovitis (inflammation of the joint lining), tenosynovitis (inflammation of the tendon sheaths), and bone erosions. A comprehensive MSUS assessment provides an objective measure of actual inflammation in inflammatory arthritis, serving as a valuable comparison to subjective assessments (Filippucci et al., 2007).

Greyscale US allows for quick and precise differentiation between synovial effusion and synovial proliferation. USPD outlines the perfusion status of the synovial tissue, which indicates the level of inflammatory activity. The USPD signal provides additional differentiation, indicating blood flow within the synovial tissue when detected in the joint cavity. The distribution of the USPD signal in the joint cavity often appears irregular (Rizzo et al., 2012).

In 2001, the EULAR guidelines outlined the standard scans recommended for each joint to inspect articular and peri-articular structures. In 2005, the OMERACT released consensus definitions for common pathological lesions seen in patients with inflammatory arthritis. According to the OMERACT guidelines, synovial fluid is characterised as abnormal hypoechoic or anechoic material within the joint that is displaceable and compressible, and may contain tissue with or without fluid within the tendon sheath, observed in two perpendicular planes, which may also show a Doppler signal; finally, bone erosion is defined as an intra-articular disruption of the bone surface visible in two perpendicular planes (Rizzo et al., 2012).

Synovitis appearances on US are a uniformly echogenic widening of the joint space, indicative of synovial growth that appears as irregular clusters of soft echoes. The thickening of the synovial membrane (synovial proliferation) is seen on ultrasound as either hypo- or hyperechoic structures in the area affected by effusion (fluid accumulation). The presence of an unusually hypoechoic joint space, which indicates synovial

hypertrophy, is distinguishable from the intra-articular fat pad and remains non-compressible when the transducer is applied (Filippucci et al., 2007).

Characteristics of joint effusion in the US include anechoic, homogeneous widening of the joint space, which appears as a black, anechoic area within the joint. Additionally, a compressible anechoic area may be found within the intra-capsular space, accompanied by hypoechoic or anechoic compressible material located intra-articularly in the synovial recesses. The joint may exhibit a distinctly anechoic and compressible space alongside the anechoic widening of the joint space (Filippucci et al., 2007).

Bone erosion appearances in ultrasound include an interruption of the bone surface visible in two different planes, changes in the bone surface adjacent to the joint, and a cortical defect identifiable in two or more scanning planes. Additional US appearances involve an intra-articular discontinuity of the bone surface that can be observed in two perpendicular planes, a cortical “break” or defect with an irregular floor visible in both longitudinal and transverse planes, and an interruption of the bone margin (Filippucci et al., 2007).

An inflammatory state at the joint level is indicated by the presence of synovial effusion and/or hypertrophy, along with an increase in local vascularisation. In cases of synovial hypertrophy, the application of USPD techniques can aid in differentiating between active and inactive inflammation (Rizzo et al., 2012). The EULAR-OMERACT guidelines highlight that GS synovitis is characterised by the presence of hypoechoic synovial hypertrophy, regardless of the presence of joint effusion and USPD. The positive USPD is the presence of at least one red spot within the synovial hypertrophy (D’Agostino et al., 2017).

5.2.2 Quantitative Sensory Testing (QST)

QST is “the determination of thresholds or stimulus-response curves for sensory processing under normal and pathological conditions”(Arendt-Nielsen, 2009). It is an approach to psychophysical testing where the quantification of the stimulus occurs, which is used to measure perception. For the testing, the focus can be on tolerance, localisation, minimum perceived threshold, threshold deemed painful or differentiation of various sensory inputs (Uddin & MacDermid, 2016). This way, it is possible to detect hypersensitivity to pain using threshold tests, which assess the least amount of sensory input required to be deemed painful. The selection of various sensory inputs utilising the QST technique allows evaluation of the sensory processing of both small and large afferent nerves and other afferent pathways.

QST is a semiquantitative method that can detect abnormalities in pain processing, and it is considered a semi-objective measure for pain intensity (Bruneau, 2019). The use of QST for prediction has been previously investigated in various non-musculoskeletal pain conditions. Sensory measurements have been related to the consumption of analgesia in healthy individuals with experimental pain and patients with chronic pancreatitis, tension-type headaches, and painful temporomandibular disorder.

QST is categorised into two types, static and dynamic, based on the nature and quality of the stimuli (Geisser et al., 2008). First, static QST involves the application of controlled intensity stimuli to specific body regions, allowing for the assessment of pain thresholds and tolerance (Arendt-Nielsen and Yarnitsky, 2009). Increased sensory hypersensitivity indicates a decrease in both thresholds and tolerance. While localised hyperalgesia occurs in injured areas, diffuse hypersensitivity in otherwise healthy regions suggests the involvement of nociplastic pain mechanisms. Similarly, visual and auditory sensitivities are associated with central sensitisation processes (Marcuzzi et al., 2017).

Second, dynamic QST investigates how somatosensory processes can either amplify or inhibit pain. This involves the use of repeated or progressively larger stimuli, as well as conditioned pain modulation (CPM). Changes in pain thresholds observed during dynamic testing reflect altered sensitivity due to increased excitatory activity or diminished inhibitory control. Pain summation corresponds to the wind-up phenomenon and is frequently seen in chronic pain conditions, indicating nervous system sensitisation (Arendt-Nielsen and Yarnitsky, 2009). CPM testing evaluates the effectiveness of descending pain inhibition by measuring changes in sensory perception after applying noxious stimuli to different body areas. In healthy individuals, the second stimulus usually reduces pain, while impaired CPM is evident in a range of chronic pain conditions (Marcuzzi et al., 2017).

The QST tool can evaluate pain intensity by determining the minimum sensory input perceived as pain (Uddin et al., 2016). It can be used to assess various pain conditions, evidenced by increased pressure pain tolerance (PPTol) and thresholds (PPT), as well as enhancements in conditioned pain modulation (CPM) and temporal summation (TS) following treatments such as pregabalin and ketamine. Furthermore, both PPT and TS have proven to be reliable indicators of the effectiveness of non-pharmacological therapies, including Emotional Awareness and Expression Therapy, as well as acupuncture (Bellomo et al., 2020).

5.2.3 Psoriatic arthritis (PsA)

5.2.3.1 Introduction

Psoriasis (Ps) is a prevalent chronic inflammatory skin disorder affecting approximately 1–3% of the global population. Studies suggest that up to 30% of Ps patients also experience PsA (Ocampo et al., 2019).

PsA is a chronic inflammatory condition characterised by diverse musculoskeletal and non-musculoskeletal symptoms, leading to significant morbidity for those affected. Musculoskeletal symptoms encompass arthritis, enthesitis, dactylitis, and axial involvement, with the recognition that these conditions may arise from various immune mechanisms (Sakkas et al., 2013).

Non-musculoskeletal manifestations extend beyond skin and nail issues to include uveitis, inflammatory bowel disease (IBD), metabolic syndrome, cardiovascular disease, as well as psychological conditions like anxiety and depression (Novelli et al., 2021).

Complications arising from joint damage induced by PsA not only impair joint function and increase mortality rates but also impact patients' ability to work and their social interactions. Recent research suggests that early diagnosis and treatment contribute to the remission of PsA symptoms. However, PsA often goes undiagnosed in individuals with psoriasis, possibly due to insufficient recognition of PsA symptoms and the absence of effective screening methods.

Genetic, environmental, and immunological factors are all implicated in its development. The onset of arthritis may precede, follow, or coincide with skin manifestations. Although it is sometimes perceived as mild arthritis, PsA significantly impacts patient well-being and functionality.

5.2.3.2 The prevalence of PsA

The prevalence of psoriasis in the general population ranges from 2% to 3%, affecting both men and women equally. However, the exact prevalence of PsA is uncertain, with rates varying widely from 0.1 to 23.1 cases per 100,000 inhabitants, showing a median of 6.4 per 100,000. There are large differences between countries (Kerschbaumer et al., 2016). For example, there were 420 cases per 100,000 individuals in Italy, and only 1 case per 100,000 individuals in Japan (Kerschbaumer et al., 2016). This discrepancy in prevalence, particularly in Japan, where other forms of spondyloarthropathy are less common, may be

attributed to ethnic differences. The considerable variation in reported prevalence across different populations stems from variations in the studied cohorts. Among patients with psoriasis, the prevalence of PsA ranges from 6% to 42%. Severely destructive and disfiguring forms of PsA are observed in up to 20% of affected patients. Additionally, Zhang and colleagues (2018) noted a higher frequency of PsA in overweight or obese patients (7.81%) compared to those with average weight (5.17%, $p < 0.01$).

5.2.3.3 Clinical features of PsA

The peak incidence of PsA typically occurs between the ages of 30 and 50. Clinically, it is characterised by joint, ligament, and tendon inflammation, presenting symptoms such as swelling, pain, tenderness, and stiffness (known as dactylitis and enthesitis). Enthesitis most commonly affects the plantar fascia, Achilles tendon, ligaments around the pelvis, ribs, and vertebral spine. The co-occurrence of synovitis and enthesitis in the same digit is termed dactylitis, or 'sausage-digit', and is observed in approximately 30% of Patients with PsA (Scotti et al., 2018; Liu et al., 2014). Arthritis manifests in periods of exacerbation and remission; however, untreated inflammation can persist. In approximately 15% of individuals, arthritic manifestations develop simultaneously with skin disease, while in 17% of patients, arthritis appears before dermatological symptoms (Tiwari et al., 2024).

The majority of Patients with PsA exhibit plaque psoriasis. About 10-30% of patients with psoriasis will develop PsA within 7-12 years from the diagnosis (Mease and Armstrong, 2014). Diagnosis confirmation usually relies on the presence of psoriasis, given the lack of specific clinical, laboratory, and radiological findings. Nail changes occur in as many as 80% of Patients with PsA, whereas only 40% of those with just psoriasis experience them (Sobolewski et al., 2017). These changes can include pitting, thickening, onycholysis, and subungual hyperkeratosis. Rheumatoid factor positivity is observed in only 13% of Patients with PsA. Additional features that assist in differential diagnosis include the involvement of distal interphalangeal joints and a lower frequency of bilateral symmetric involvement. PsA is classified as a spondyloarthropathy because spondylitis occurs in up to 40% of cases, along with common extra-articular features such as urethritis, diarrhoea, mucous membrane involvement, aortic dilation, and its association with HLA-B27 (Liu et al., 2014).

5.2.3.4 Diagnosis of PsA

PsA is a multifaceted condition characterised by musculoskeletal manifestations, including arthritis, enthesitis, dactylitis, and axial involvement, as well as potential skin and nail manifestations. The diverse patterns of PsA involvement can mimic various inflammatory arthropathies. When assessing a patient with inflammatory arthritis, rheumatologists consider a range of differential diagnoses, including RA, crystal arthropathies, and other inflammatory arthritis (Kyle et al., 2005). Particularly in polyarticular PsA, differentiating from RA involves identifying key features such as psoriasis, nail disease, dactylitis, and negative serology, as outlined in the CASPAR (Classification Criteria for Psoriatic Arthritis) criteria. Classification: The classification of PsA remains a subject of debate (Tylor et al., 2006). While the Moll and Wright criteria are commonly used, the five subgroups within this classification often overlap, and patients may transition between subgroups over time (Espinoza et al., 1982). These subgroups encompass asymmetric oligoarthritic, symmetric polyarthritis resembling RA, distal interphalangeal involvement, spondyloarthritis, and sacroiliac or coxofemoral joint involvement.

5.2.3.5 Diagnostic Criteria

In 2006, the Classification of Psoriatic Arthritis (CASPAR) group established highly sensitive and specific diagnostic criteria, facilitating diagnosis even in cases of PsA without evident psoriasis or in patients positive for rheumatoid factor. Additionally, an arthritis symptom screening tool, the Psoriatic Arthritis Screening and Evaluation (PASE) questionnaire (Husni et al., 2007), has been developed to aid PsA detection by dermatologists, demonstrating promising sensitivity and specificity.

5.2.3.6 Radiological findings

Radiological assessment of peripheral PsA typically reveals asymmetric joint distribution, involvement of distal interphalangeal joints, periostitis, bone density preservation, bone ankylosis, and characteristic bone proliferation. Axial involvement is characterised by findings such as paravertebral ossification, syndesmophytes, ligament calcification, and sacroiliitis. Imaging modalities such as ultrasonography and magnetic resonance imaging (MRI) play crucial roles in detecting subclinical enthesopathy and synovial inflammation,

aiding in differentiation from RA and guiding treatment decisions (Schwenzer et al., 2010).

5.2.3.7 Ultrasound

MSUS is a valuable tool for identifying distinctive features of inflammatory arthritis, including enthesitis, cortical bone erosions, cartilage lesions, synovitis, and tenosynovitis. Notably, while clinical signs of enthesitis are a prominent indicator of PsA, the presence of MSUS enthesitis can help clinicians distinguish PsA from RA. The evaluation of LEI sites using MSUS is an effective method for assessing entheseal abnormalities. The LEI consists of six specific sites: the right and left Achilles insertions, the medial femoral condyles, and the lateral epicondyles of the humerus. In a 2005 study by De Filippis et al., 25% of psoriasis patients exhibited entheseal abnormalities identified by MSUS that were not detected by clinical examination. Zabotti and colleagues (2019) highlight that MSUS enthesitis at the proximal interphalangeal joints is detected in approximately 25% of patients with PsA, while it is typically absent in Patients with RA. This observation could sometimes be a distinguishing factor between PsA and RA.
MSUS can also effectively reveal characteristic joint involvement that differentiates PsA from RA. For instance, changes in the distal interphalangeal joints are predominantly observed in patients with PsA rather than those with RA, and dactylitis caused by flexor tenosynovitis is a hallmark of PsA. Although the overall prevalence of synovitis is higher in RA (approximately 90% of affected joints) compared to PsA (about 60% of affected joints), inflammation of the extensor digitorum tendon is significantly more common in early PsA than in early RA (54.1% versus 2.5%) (Merola et al., 2018).

In addition to entheseal assessment, inflammatory and structural joint abnormalities were systematically evaluated using standardised ultrasound definitions. Synovial hypertrophy USSH and USPD activity were assessed using the EULAR–OMERACT semi-quantitative 4-grade scoring system (0–3 scale), where 0 indicates absence of abnormality, and 3 represents severe findings (D'Agostino et al., 2017). Synovial hypertrophy was defined as abnormal hypoechoic intra-articular tissue that is non-displaceable and poorly compressible, while the USPD signal reflected intra-synovial vascularisation. Joint effusion was defined according to OMERACT criteria as abnormal anechoic or hypoechoic intra-articular fluid that is displaceable and compressible, without a Doppler signal (Wakefield et al., 2005).

Bone erosions were evaluated using the Ultrasound Structural Erosion Score (ScUSSe) system (Sommier et al., 2006). Erosions were defined in accordance with OMERACT

criteria as intra-articular cortical discontinuities visible in two perpendicular planes (Wakefield et al., 2005). A conservative interpretative approach was adopted to enhance specificity; isolated cortical surface irregularities were not automatically classified as erosions, as such changes may reflect mechanical stress or degenerative alterations rather than inflammatory pathology (Wakefield et al., 2005; D'Agostino et al., 2017). Only unequivocal cortical breaks fulfilling consensus definitions were graded as erosions to minimise misclassification and avoid overestimation of structural damage.

5.2.3.8 Magnetic resonance imaging (MRI)

Structural damage has been a key outcome measure in patients with RA and PsA, traditionally evaluated through scoring methods applied to plain film radiography. An international Outcome Measures in Rheumatology Clinical Trials (OMERACT) MRI in RA working group has been devising a scoring system to assess synovitis, bone oedema, and erosions in hands and wrists, meeting the OMERACT filter criteria (Schwenzer et al., 2010). Given the shared clinical features between patients with PsA and RA, this MRI scoring system could also serve as an outcome measure in patients with PsA. MRI may offer the advantage of detecting some of these features earlier than plain radiography, allowing for measuring treatment response and disease activity before structural damage occurs.

MRI has been utilised to assess synovial vascularity in the RA wrist following therapy initiation, a method currently employed in a PsA trial with anti-TNF therapy. In a study of infliximab in PsA, MRI was used to assess changes in inflammatory activity, as indicated by a significant reduction in gadolinium uptake post-treatment. However, akin to ultrasound, as some of these measured features are nonspecific, it is imperative to obtain histopathological correlation whenever feasible and enrol patients in longitudinal studies to validate this modality as a disease outcome measure. In summary, once validated alongside plain radiographs, these novel imaging techniques may aid in the early detection of changes in peripheral joints, periarticular tissues, and spinal structures in individuals with PsA (McQueen et al., 2006).

5.2.3.9 Treatment

The objectives of managing PsA include alleviating disease symptoms, preventing joint deterioration, enhancing patient well-being, and reducing mortality rates. Patients should

receive comprehensive education about the nature of the disease and may benefit from psychological counselling and physiotherapy interventions. Mild forms of PsA may respond to nonsteroidal anti-inflammatory drugs (NSAIDs), often administered alongside intra-articular glucocorticoid injections (De Vlam et al., 2014). For moderate to severe cases, initial treatment mirrors that of mild disease with the addition of disease-modifying antirheumatic drugs (DMARDs). While methotrexate, sulfasalazine, and leflunomide have been studied, evidence supporting their efficacy in axial disease presentation is lacking (Kingsley et al., 2012; Ritchlin et al., 2009). Refractory cases, defined as those failing to respond to DMARD therapy after at least three months, may require treatment escalation to anti-tumour necrosis factor (TNF) drugs. Adalimumab, etanercept, and infliximab are commonly used anti-TNF agents, demonstrating efficacy in promoting remission and improving various disease parameters (Kyle et al., 2005). Golimumab is another cost-effective option for PsA treatment (Voulgari et al., 2010). Studies have shown that adalimumab, etanercept, and infliximab effectively improve PsA symptoms, inhibit radiographic progression, and enhance quality of life (Kyle et al., 2005). Rituximab, an anti-CD20 agent, exhibits moderate efficacy, particularly in patients who have not previously received anti-TNF therapy (Cantini et al., 2017). Daclizumab, an anti-CD25 agent, has shown promise in reducing PsA severity with minimal adverse effects (Cohan et al., 2019). However, further research is needed to elucidate these emerging treatments' efficacy and safety profiles.

5.2.4 Pain in PsA

Ultimately, pain is a subjective experience in which peripheral sensory input interacts with emotional and cognitive factors to shape conscious perception.

Acute pain functions as a physiological response to harmful external stimuli and is essential for an organism's protection and survival. This is evident in rare genetic disorders, where heightened pain thresholds or insensitivity to pain can lead to early mortality in affected individuals. In contrast, chronic pain is characterised as pain that endures or recurs for longer than three months. It often signifies a maladaptive response that persists even after the initial harmful stimulus has been resolved.

Chronic pain is clinically characterised by increased sensory responsiveness to harmful stimuli, known as hyperalgesia, and/or an abnormal pain response to stimuli that typically do not cause pain, referred to as allodynia.

Neural plasticity is a mechanism that may mediate central sensitisation. It encompasses alterations in the chemical and molecular composition of the nervous system, leading to structural and functional adaptations in both the peripheral and central nervous systems in response to external stimuli. This intrinsic nervous system characteristic plays a crucial physiological role in adaptation. However, when maladaptive changes occur, this same neural plasticity can result in abnormal pain perception, contributing to conditions such as nociplastic pain and other pain disorders.

A hallmark clinical manifestation of PsA is the involvement of dactylitis and enthesitis. Symptoms associated with these periarticular manifestations are often characterised by pain that is difficult to localise. This widespread pain can mimic FM, particularly reminiscent of the tender points defined in the 1990 ACR FM classification criteria (Marchesoni et al., 2012). Consequently, patients with PsA who also have concurrent FM tend to exhibit significantly higher clinical scores for enthesitis. In typical clinical settings, distinguishing between FM and enthesitis can pose a challenge (Polachek et al., 2021).

The occurrence of nociplastic pain syndromes is more prevalent among patients with chronic inflammatory conditions, and they are more likely to experience persistent pain, often involving nociplastic pain mechanisms; collectively, the combination of inflammatory nociceptive and nociplastic pain defines mixed pain states. The ongoing peripheral inflammation in arthritis provides a sustained nociceptive input that can lead to neuroplastic changes in both the peripheral and central nervous systems, often resulting in sensitisation in genetically predisposed patients.

Research on nociplastic pain has employed advanced techniques to identify the specific dysfunctions underlying this condition. QST can be useful for pain modulation, while functional neuroimaging can reveal changes in how the brain processes pain (Kosek et al., 2021).

In fact, both nociceptive and nociplastic pain may play a role in the pain experienced by participants with PsA (Sunzini et al., 2025).

The Pain VAS is the gold standard for measuring pain intensity, serving as a subjective measure that allows participants to evaluate their pain levels. It effectively reflects peripheral pain, such as nociceptive or inflammatory pain, as it often corresponds with peripheral damage or inflammation occurring in the joints (Hawker et al., 2011). However, in CS such as FM, pain VAS scores can remain high despite effective control of peripheral inflammation. This could be due to the central nervous system exhibiting heightened responsiveness to pain stimuli, resulting in disproportionate pain perception (Woolf, 2004).

5.2.4.1 Comparison between RA and PsA

RA and PsA are prevalent chronic inflammatory conditions; both are marked by joint pain and swelling and exhibit considerable systemic manifestations (Merola et al., 2018). Early diagnosis is of paramount importance in managing these conditions, as it can prevent joint damage and improve function. If not identified and managed early, both conditions can lead to joint damage and reduced function. This highlights the importance of early diagnosis in developing treatment approaches that optimise both clinical and radiographic outcomes (Merola et al., 2018).

RA is an autoimmune systemic inflammatory condition characterised by joint inflammation, bone erosion, and cartilage damage. PsA is a heterogeneous autoimmune systemic disorder with various clinical and radiographic features. PsA occurs less frequently than RA, affecting about 30% of individuals with psoriasis.

For RA, the classification criteria established by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) are designed to characterise patients and facilitate clinical trials (Radner et al., 2014). A key clinical feature is the presence of definite, persistent synovitis in at least one joint (Merola et al., 2018). These criteria consider the number of affected joints, the duration of symptoms, the presence of serological markers, and elevated acute-phase reactants.

For PsA, the Classification criteria for Psoriatic Arthritis (CASPAR) play a crucial role in diagnosing patients with the inflammatory joint disease for clinical trial purposes. These criteria consider key clinical features of PsA, such as a personal or family history of psoriasis, psoriatic nail changes, and dactylitis, thereby aiding in understanding and diagnosing the disease (Tylor et al., 2006).

Joint involvement in RA is typically symmetric, whereas in PsA, it is often, though not exclusively, asymmetric (Tylor et al., 2006; Veale et al., 2015). While the majority of patients in both RA and PsA exhibit polyarthritis (with five or more affected joints), joint involvement may also present as oligoarticular or polyarticular. Monoarticular disease is relatively rare in PsA; however, approximately 5% to 10% of patients may exhibit isolated involvement of distal joints (Gladman et al., 2015). In PsA, the prognosis generally worsens, and the symmetry of joint involvement tends to become more pronounced as the number of affected joints increases (Gladman et al., 2015).

Usually, RA impacts the shoulder, elbow, wrist, metacarpophalangeal, proximal interphalangeal, hip, knee, ankle, and metatarsophalangeal joints (Mc Ardle et al., 2015).

In PsA, the distal interphalangeal joints of both hands and feet, as well as larger joints in the lower limbs, the axial spine, and the sacroiliac joints, are often involved. Additionally, the metacarpophalangeal and metatarsophalangeal joints, as well as the wrist, may also be affected (Mc Ardle et al., 2015). PsA is classified within the spectrum of spondylarthritis, as it can involve the axial skeleton (such as the sacroiliac joints and spine), unlike RA (Mc Ardle et al., 2015). Research indicates that approximately 50% of patients with PsA exhibit inflammation in the axial skeleton (Helliwell et al., 2000). This axial involvement can be a distinguishing feature of PsA, as it is infrequently observed in RA (Helliwell et al., 2000). However, it is worth noting that cervical spine involvement has been reported in up to 80% of RA cases (Baraliakos et al., 2015).

Enthesitis, which is the inflammation of entheses where ligaments or tendons attach to bone, occurs in 35% of individuals with PsA but is infrequent in those with RA (Ritchlin et al., 1998). Enthesitis is believed to play a critical role in the development of PsA and can be particularly helpful in distinguishing PsA from RA (Polachek et al., 2017). The most commonly affected entheses in patients with PsA include the plantar fascia, Achilles tendon, and ligamentous connections around the knee (Schett et al., 2017). In rare cases, enthesitis may be the only manifestation of PsA. The signs and symptoms of enthesitis can be nonspecific and difficult to distinguish from those of other inflammatory disorders (Helliwell et al., 2019). Dactylitis, which refers to the inflammation of an entire digit, is a common symptom of PsA, affecting up to 50% of patients, compared to about 5% of those with RA (Veale et al., 2015).

RA is classified as a seropositive arthropathy, with approximately 80% of patients testing positive for RF or CCP antibodies (Veale et al., 2015). While CCP antibodies offer a more specific indication of RA than RF, both biomarkers are regarded as separate yet complementary indicators of disability and joint damage (Popescu et al., 2013). In contrast, PsA is categorised as a seronegative inflammatory arthropathy. The majority of patients with PsA do not display RF or CCP, and when they do test positive, the levels tend to be relatively low (Verheul et al., 2015).

CRP and the ESR are used as indicators of acute-phase inflammatory responses in patients with both RA and PsA, although these markers are typically more pronounced in those with RA (Janssen et al., 2015). A systematic review evaluating RA disease activity metrics found that ESR and CRP levels are significant predictors of radiographic progression in most studies (Navarro-Compán et al., 2015). The acute-phase response is associated with synovial inflammation, progression of radiographic disease, and joint damage, resulting in

erosions (Navarro-Compán et al., 2015). Generally, patients with PsA exhibit significantly lower CRP and ESR levels than those with RA. Nonetheless, elevated ESR and CRP levels notably correlate with the number of swollen joints and ultrasound findings in PsA (Bandinelli et al., 2015). Specifically, ESR is considered one of the most reliable indicators of damage progression in PsA. Variations in ESR and CRP align with clinical outcomes and can be utilised to monitor treatment responses. Increased levels of ESR and CRP indicate inflammation, but these markers are not exclusive to RA (Gavrilă et al., 2016).

5.2.5 Aims and hypotheses

This study aims to evaluate whether participants with PsA and high pain levels display MSUS features similar to those seen in the RA population. Recognising that nociplastic pain may contribute to persistent pain even when inflammation is under control, this research will explore the relationship between non-inflammatory measures in PsA and MSUS findings, thereby enhancing our understanding of pain mechanisms in this condition. It is crucial to determine whether persistent pain in PsA is associated with the CS by assessing pain intensity through various methods, including the pain VAS for subjective measurement and QST for semi-objective measurement. The results from these pain assessments will be correlated with MSUS to establish whether the pain originates from peripheral sources or is linked to CS.

Furthermore, while PsA is primarily driven by inflammation, resulting in nociceptive pain, some patients may be predisposed to developing or exacerbating nociplastic pain due to chronic inflammatory processes. Given that MSUS is an effective tool for detecting entheseal inflammatory changes in PsA, this study will investigate the associations between non-inflammatory pain measures, such as pressure pain threshold (PPT) assessments, and MSUS enthesitis findings. This approach aims to elucidate further the pain mechanisms related to enthesitis in PsA.

This research utilised MSUS as a measure of nociceptive pain to investigate the relationship between joint inflammation and pain in PsA. The primary objective was to quantify the role of inflammatory nociceptive mechanisms in accounting for the overall pain experienced in PsA.

Furthermore, the study aimed to investigate the relationship between MSUS enthesitis and non-inflammatory pain measures, such as PPT, to gain insight into the underlying pain mechanisms in PsA and to determine the potential role of central sensitisation in this pain

condition. It will investigate the relationships between CS, FM, and ultrasound findings in entheses to better understand the pain mechanisms involved in enthesitis in PsA.

This study hypothesises that MSUS metrics statistically correlate with pain VAS scores, indicating nociceptive pain resulting from inflammatory joint changes. Furthermore, this study will assess how the extent of MSUS, which reflects peripheral inflammatory alterations, influences overall pain in patients with PsA, with particular attention to its association with CS pain measures, such as PPT.

5.3 Methods

A multi-centre observational study titled "Characterising Centralised Pain in Chronic Rheumatic Disease" (CENTAUR) aimed to investigate centralised pain in patients with PsA. The study has received ethical approval from the West of Scotland Research Ethics Committee. It employed various methods, including comprehensive questionnaires, QST, MSK and advanced neuroimaging techniques. These methods investigate the relationship between experienced pain and peripheral changes in the PsA population.

5.3.1 Participant recruitment

Participants diagnosed with PsA who were set to initiate a new biologic or other DMARDs for active disease as part of their regular care in NHS rheumatology outpatient clinics were identified as potential candidates by their healthcare providers. An information sheet for study participants (PIS) was provided to those who showed interest in participating in the study. The PIS contained written details about the study procedures and the principal investigator's contact information. Following the recommendations of the ethics committee, potentially eligible individuals were given a week to consider their involvement. Concurrently, inclusion and exclusion criteria were applied to verify the eligibility of the participants. Firstly, participants with PsA, who met the CASPAR criteria, were experiencing active disease and were on the verge of changing or starting a biologic or DMARDs at the point of recruitment.

The selection of participants with similarly high disease activity was preferred to ensure good homogeneity within the study population. Importantly, the level of disease activity signifies the extent of inflammation, which affects the pain experienced. Furthermore, the degree of active inflammation may be associated with sensitisation processes in the nervous system, both peripherally and centrally. Thus, including individuals with active

disease, as indicated by the clinical necessity to initiate a biologic or DMARDs, was crucial to this study. Additionally, evaluating the treatment response served as an indirect measure of inflammation. However, it was essential to acknowledge the inclusion of other variables that could influence pain mechanisms in different ways. Such variables include variations in disease duration and the initiation of various treatments, which are characteristic of cross-sectional studies.

In this investigation, participants aged 75 and older were systematically excluded from participation. However, the practice of excluding this demographic from clinical trials was not uniformly applied and is shaped by a multitude of factors. Primarily, concerns surrounding health and safety emerge due to the intricate complexities associated with age-related physiological changes, comorbid health conditions, and a variety of pharmacological treatments. Additionally, this age group was more likely to have experienced age-related structural changes, as well as alterations in vasculature and neurovascular coupling to the brain, which may complicate the MRI analyses (Tsvetanov et al., 2015).

Furthermore, challenges related to cognitive decline may introduce ethical considerations regarding participant vulnerability and the capacity to provide valid informed consent. Such considerations are crucial in the decision-making process regarding the exclusion of this age group.

Eligible participants were invited to engage in the baseline research visit at the clinical research facility affiliated with the University of Glasgow and the NHS. All participants were instructed to temporarily cease the use of current analgesic medications, including non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol, whether used alone or in conjunction with short-acting opioids, for a duration of 24 to 48 hours before the study visit, if feasible. An exception was made for participants experiencing severe pain due to ethical considerations relating to the potential exacerbation of suffering in patients with active inflammation. NSAIDs and paracetamol are commonly employed as short-acting analgesics in the management of inflammatory arthritis and chronic musculoskeletal conditions. The rationale for recommending the suspension of these short-term pain relief medications, when applicable, was to mitigate the risk that pain reduction effects could bias various study assessments, including self-reported pain levels at the time of the visit and the outcomes of QST. The prescribed interval of 24 to 48 hours allowed for a sufficient washout period for the medications of interest. The suspension of longer-acting agents was not deemed necessary, as it was unlikely to significantly influence the overall

outcome of the study, with possible implications for patient management. Notably, permitting the continuation of these medications may have introduced additional variability into the investigation results.

5.3.2 Sample size and power of the study

The initial power analysis was conducted with an assumed sample size of 50 participants, which would provide over 90% power to detect a moderate-to-large correlation effect size ($r = 0.50$) in functional neuroimaging at a significance level of $\alpha = 0.05$, utilising G*Power v3.1. However, with my current sample consisting of only 20 MSUS patients, I reevaluated the power calculation: with $n = 20$, $\alpha = 0.05$, and an anticipated larger effect size of $r = 0.60$ for MSUS measurements compared to functional neuroimaging, the statistical power is now approximately 83%. Although this was still informative, the study was somewhat underpowered relative to the original objective, and any null results would be interpreted with caution due to an increased risk of Type II error.

5.3.3 Timeline

The research consisted of three distinct visits: an initial baseline visit and two follow-up visits. During the baseline visit, participants were required to complete a consent form before any assessments were administered. This consent form granted the researchers permission to access NHS clinical records and to collect biological samples for ethically authorised secondary studies, including the current investigation. The baseline visit involved the collection of a comprehensive medical history, clinical evaluations, and multifaceted subjective and objective pain assessments. This data collection occurred prior to the initiation of the newly prescribed treatment. The baseline data alone yield robust evidence to ascertain the presence of nociplastic pain among participants diagnosed with PsA by integrating findings from questionnaires and neurobiological markers. Follow-up visits were scheduled at 3 and 6 months (+/- 2 weeks) to evaluate the participants' responses to the treatment interventions. Notably, the inclusion criteria did not specify the newly commenced immunosuppressant, resulting in variance in treatment regimens among the recruited participants. Only clinical and subjective pain assessments were conducted during the follow-up consultations, excluding multimodal-MRI and QST.

The study features a comprehensive assessment protocol for patients at baseline, 3 months, and 6 months, encompassing both clinical evaluations and subjective and objective multimodal assessments. At baseline, critical demographic and medical history data are

meticulously collected, including body mass index (BMI), past medical history, smoking and alcohol consumption, as well as specific details regarding the diagnosis of PsA. Clinical assessments encompass joint counts, dactylitis scores, enthesitis indices, and inflammatory markers (such as C-reactive protein and the Bath ankylosing spondylitis disease activity index [BASDAI]). Subjective evaluations assess pain, fatigue, emotional well-being, and coping mechanisms, utilising validated instruments such as the Patient-Reported Outcomes Measurement Information System (PROMIS), brief Pain Inventory, and McGill Pain Questionnaire. PROMIS is a collection of measures that assess various domains of health, including physical, mental, and social well-being, as experienced by patients. These health domains are considered relevant across all health conditions (Evans et al., 2018). The PROMIS Pain measures can be used to monitor RA by tracking pain levels, pain interference, and pain-related behaviours (Crins et al., 2020). The McGill Pain Questionnaire serves as a subjective instrument for evaluating an individual's experience of pain. It offers a multidimensional assessment that encompasses the severity or intensity of pain, its emotional impact, and the significance of the pain to the individual experiencing it (Main, 2016). Some assessments, including the Central Sensitisation Inventory and the PainDETECT questionnaire, are reiterated at a 6-month interval. PainDETECT is a reliable and straightforward screening questionnaire for neuropathic components of pain (Konig et al., 2021). It comprises various validated instruments that address typical comorbidities related to pain, such as function, sleep, mood, and anxiety (Freynhagen et al., 2016). Objective evaluations, comprising pressure pain sensitivity, algometry, MRI scans, and optional blood samples, are predominantly undertaken at baseline, with limited follow-ups scheduled during later phases. Throughout the study, core clinical metrics (BMI, pharmacological interventions, joint assessments, and pain scores) are systematically reassessed at 3 and 6 months to monitor disease progression and treatment efficacy.

5.3.4 Ultrasound data collection

All participants who underwent ultrasound examinations were provided written consent. Ultrasound examinations were conducted at baseline and during the follow-up visits at 6 months. The procedures were performed by a single operator, an expert in conducting MSK examinations, using a portable ultrasound machine (Voluson I, GE Healthcare) along with a 10–16 MHz linear array probe (SP 10–16RS, GE Healthcare). Power Doppler (PD) examinations were conducted with the following settings: high frequency, pulse repetition frequency of 0.9 kHz, low wall filter, and gain adjusted to a level below the threshold where Doppler artefacts appeared beneath the bone. The MSUS assessment utilised a

binary scale to evaluate synovial thickening and joint power Doppler findings in patients with PsA.

The ultrasound assessment included forty joints per patient, encompassing bilateral metacarpophalangeal (MCP), proximal interphalangeal (PIP), distal interphalangeal (DIP), and metatarsophalangeal (MTP) joints. Both synovial hypertrophy on B-mode and Doppler activity were evaluated. Scoring was performed on a binary scale, with 0 indicating the absence of findings and 1 indicating their presence, according to previously published scoring criteria (Husic et al., 2014; Gutierrez et al., 2011). In this study, a joint was classified as having active synovitis only when both B-mode synovial thickening and/or PD signal were present (Dubash et al., 2020).

In addition, bilateral assessment of four entheseal sites was carried out: the superior and inferior poles of the patella, the calcaneal insertion of the Achilles tendon, and the lateral condyle of the elbow. The USPD signal has been shown to be less prevalent in PsA than in RA (Zabotti et al., 2017; Dumitrascu et al., 2022). However, it remains a sensitive tool for detecting inflammation at entheseal sites adjacent to synovial joints in PsA (Dubash et al., 2020).

For B-mode assessment of the enthesis, abnormal thickening was defined based on site-specific thresholds adopted from Balint and colleagues (2002 and 2018) and Toprak and colleagues (2012). The mean value and two standard deviations (2 SD) were determined as the cut-off threshold (Williams et al., 2022). The cut-off threshold: >4.0 mm at the superior and inferior patellar poles, >5.29 mm at the Achilles insertion (Balint et al., 2002), and >4.05 mm at the lateral epicondyle of the elbow (Toprak et al., 2012).

Measurements were taken within 2 mm proximal to the bony cortex. MSUS enthesitis was defined by the presence of one or more of the following features: entheseal thickening, hypoechogenicity, calcifications, enthesophytes, erosions, and/or PD signal, consistent with OMERACT definitions (D'Agostino et al., 2017).

5.3.5 Quantitative sensory testing (QST)

Before each testing session, a familiarisation process was implemented to alleviate any test-related anxiety and instruct participants on how to complete the tasks more effectively. The familiarisation was conducted on the dominant right side, whereas the formal assessment was performed on the left side. Although the differences between the left and right sides within the same individual are minimal, evidence suggests that the dominant side is generally more sensitive, particularly in right-handed individuals. Consequently,

carrying out the formal test on the non-dominant side (left) contributed to improved data homogeneity and reduced potential biases associated with differing sensitivity.

The pressure pain threshold (PPT) cuff-evoked test is designed to assess pain sensitivity by applying progressively increasing pressure through a blood pressure cuff. This test is carried out on the non-dominant calf, with the cuff positioned around the widest circumference of the gastrocnemius muscle. The procedure begins with ascending pulsed pressures, starting at 20 mmHg and increasing in increments of 20 mmHg until a maximum of 400 mmHg is reached, or until the participant rates the pressure as 80/100 or higher on the Numerical Rating Scale (NRS).

Each pressure is sustained for 10 seconds, followed by a 20-second rest interval. Initially, participants are asked if the stimulus is painful; if so, they provide an intensity rating on a scale from 0 (no pain) to 100 (worst pain imaginable). Once a pain rating greater than zero is given, the yes/no questioning is discontinued, and only intensity ratings are recorded. The test concludes when the maximum pressure threshold is reached. Data is collected in real time, and interpolated pain intensity values (e.g., P10–P70) are calculated using an Excel template during a 5-minute break after the test.

The PPT Algometry assessment quantifies the minimum pressure that elicits pain at specific body locations using a handheld digital algometer featuring a 1 cm^2 probe tip. Pressure is applied at a consistent rate of 30 kPa/s, and participants indicate when they transition from feeling pressure to experiencing pain. This moment is recorded as the pain threshold. Testing is conducted at eight bilateral sites, which include: the trapezius (midpoint of the upper trapezius, typically located near the C7-T1 vertebrae), wrist (scaphoid/anatomical snuffbox), hand (thenar eminence), and hip (gluteus medius). For the trapezius, pressure is applied at a 70-degree angle towards the pelvis, with palpation used to identify the most sensitive area. Each site is tested thrice, allowing for a 15–20 second rest between trials. A fourth trial is conducted if the variance among the three readings exceeds 100 kPa. Mean values from the trials are used for analysis. The order of site testing is determined by randomisation software to minimise bias.

5.3.6 Statistical software

The analysis was conducted using IBM SPSS (Statistical Package for the Social Sciences), version 28.0. The statistical tests were considered significant if $p < 0.05$. Furthermore, JASP 0.16.2 (Jeffrey's Amazing Statistics Program) was chosen for its strong capability to manage unbalanced group distributions present in the baseline USPD data. Its ability to

conduct non-parametric tests, along with a user-friendly interface, made it particularly effective in addressing the challenges posed by unequal group sizes while upholding analytical rigour.

5.3.7 Descriptive analysis

Descriptive statistics summarise these measures' central tendencies, variability, and temporal distribution patterns. This involves calculating means and standard deviations (SDs), constructing frequency distributions, and performing normality tests using the Shapiro-Wilk test across various time points.

The initial phase of the analysis included calculating descriptive statistics for MSUS metrics, pain VAS and QST measures at each time point. For each time point, the mean and standard deviation of the selected variables were determined. Frequency distribution tables were created to condense the data, while histograms showed how the data are distributed, allowing detection of skewness, kurtosis, and potential outliers. The Shapiro-Wilk test was used to assess whether the data conformed to a normal distribution. A p-value less than 0.05 signifies a notable divergence from normality, necessitating consideration of suitable transformations or non-parametric methods for subsequent analysis.

After implementing the Shapiro-Wilk test to determine the appropriate statistical analysis, the subsequent analyses were conducted in SPSS. In instances where data were found to be normally distributed, t-tests were employed to compare the means between the two groups. Conversely, when data were not normally distributed, the Mann-Whitney U test, a crucial alternative, was utilised as necessary. These tests were crucial in elucidating the differences between variables at various time points.

5.3.8 Univariate correlation between MSUS metric and pain VAS

The relationship between MSUS metrics and pain VAS was investigated using univariate correlation, which assesses relationships between two variables. Pearson correlation was utilised for normally distributed continuous variables, while Spearman correlation was applied for ordinal or non-normally distributed variables. These methods provided insights into the strength and direction of variable relationships between MSUS metrics and pain VAS at the baseline and 6-month time points.

The MSUS metrics include USPD and US synovitis. USPD modes can detect pathological synovial blood flow, which indicates joint inflammatory activity (Naredo et al., 2013). This

capability is essential for assessing pain intensity related to peripheral joint changes in participants with PsA.

5.3.9 Univariate correlation between USPD and QST

This analysis examines the relationship between joint inflammation, as detected by MSUS metrics, including USPD and US synovitis, and QST, a semi-objective measure of non-inflammatory pain, among participants with PsA.

USPD was correlated with non-dominant cuff-evoked PPT, algometry PPT at both knees, and the trapezius. Then, US synovitis was correlated with non-dominant cuff-evoked PPT, algometry PPT at both knees and trapezium using SPSS.

5.3.10 Univariate correlation between MSUS enthesitis and QST

Non-dominant MSUS enthesitis at the left inferior poles of the patella was correlated with non-dominant cuff-evoked PPT. The left inferior pole of the patella was selected because, in patients with PsA, enthesitis at the inferior pole of the patella is observed more frequently than at the superior pole (Agache et al., 2022). Then, MSUS enthesitis at the right and left inferior poles of the patella was correlated with algometry PPT at both knees and the trapezium using SPSS.

5.3.11 Assessment of MSUS and QST among participants with psoriatic arthritis, comparing those with and without fibromyalgia (FM)

The ACR 2011 FM criteria were used to identify the presence of fibromyalgia (FM) among participants with PsA. The participants were divided into two groups: FM (+), indicating the presence of fibromyalgia, and FM (-), indicating its absence. Additionally, the cuff-evoked PPT, algometric PPT at both knees and the trapezium, along with MSUS enthesitis at the left knee and LEI scores, were compared between these two groups.

5.4 Results

A total of 50 participants diagnosed with PsA according to the CASPAR criteria were enrolled in the study. Twenty participants, comprising nine females (45%) and eleven males (55%), underwent ultrasound assessments at both baseline and the 6-month follow-up visits. The mean age is 49 ± 11.4 years, and the average disease duration is 7 ± 5.8 years (Table 5.1). Recruitment took place at the Glasgow Clinical Research Facility (GCRF) Centre, located at the Queen Elizabeth Hospital and the Glasgow Royal Infirmary, from June 2019 to April 2022.

Table 5.1 Clinical features of recruited participants

BASELINE CLINICAL CHARACTERISTICS	**N = 50**
Age (mean ± SD)	49 ± 11.4
Disease duration years (mean ± SD)	7 ± 5.8
Sex (male/female)	23/27
BMI (mean ± SD)	30 ± 4.5
TJC (mean ± SD)	21 ± 14.4
SJC (mean ± SD)	7 ± 4.5
LEI score (mean ± SD)	2.7 ± 2
Pain VAS (mean ± SD)	35.1 ± 25
BASELINE ULTRASOUND METRICS	**N = 20**
USPD (mean ± SD)	0.25 ± 0.78
US Synovitis (mean ± SD)	5.7 ± 3.72
US enthesitis (mean ± SD)	3.3 ±2.00
12-MONTH CLINICAL CHARACTERISTICS	**N = 50**
TJC (mean ± SD)	15.38 ± 17.12
SJC (mean ± SD)	2.56 ± 3.42
Pain VAS (mean ± SD)	5.34 ± 2.1
12-MONTH ULTRASOUND METRICS	**N = 20**
USPD (mean ± SD)	0.52 ± 0.71
US Synovitis (mean ± SD)	7.88 ± 3.91
US enthesitis (mean ± SD)	35.11 ±1.96

5.4.1 Descriptive analysis

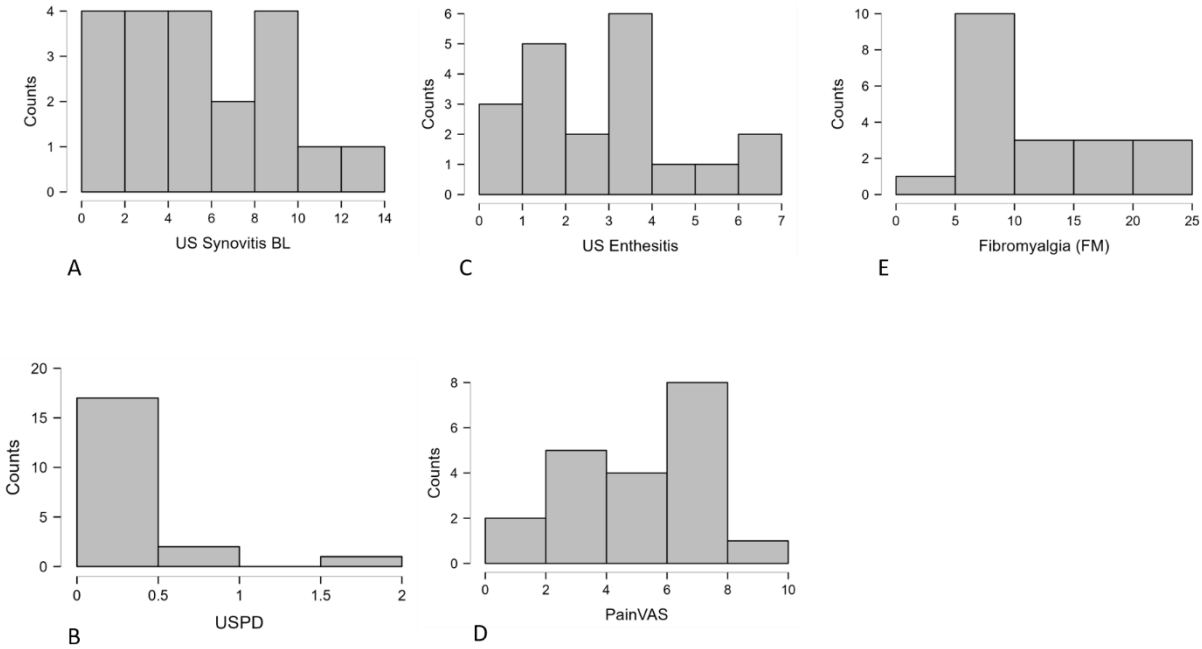

Figure 5.1: Histograms of MSUS metrics, pain VAS and FM at the baseline. The histogram of Pain VAS at baseline indicates a normal distribution.

The baseline distribution of pain intensity (VAS) was approximately normal, as observed in the histogram. In contrast, the distribution of FM scores was positively skewed, with most patients scoring between 5 and 10, and nine participants scoring above 10, indicating a subgroup with a positive diagnosis for FM (Figure 5.1).

The distribution of US enthesitis was also normal, with the majority of patients presenting with 1–4 affected sites. The distribution of USPD signals was notably skewed, as most patients showed no PD signal, while only three participants exhibited positive PD. Consequently, the data were categorised into (-) VE and (+) VE PD rather than being treated as a continuous variable. Non-parametric tests were employed due to the lack of proportionality among the categories.

Figure 5.2: Histograms of MSUS metrics, pain VAS and FM at the 6-month visit.

A uniform distribution of US synovitis was observed at the 6-month visit, with a range of 0 to 16 and a moderate spread. Additionally, the distribution of US enthesitis at the 6-month visit was right-skewed, with scores ranging from 2 to 7. Furthermore, the distribution of USPD at the 6-month visit was markedly skewed, with the majority of participants scoring zero (indicating negative PD signals) (Figure 5.2).

The histogram of pain VAS at the 6-month visit demonstrates an approximately normal distribution. In contrast, the distribution of FM at the same visit exhibits a bimodal distribution with two distinct peaks: one around 5-10 and another around 20.

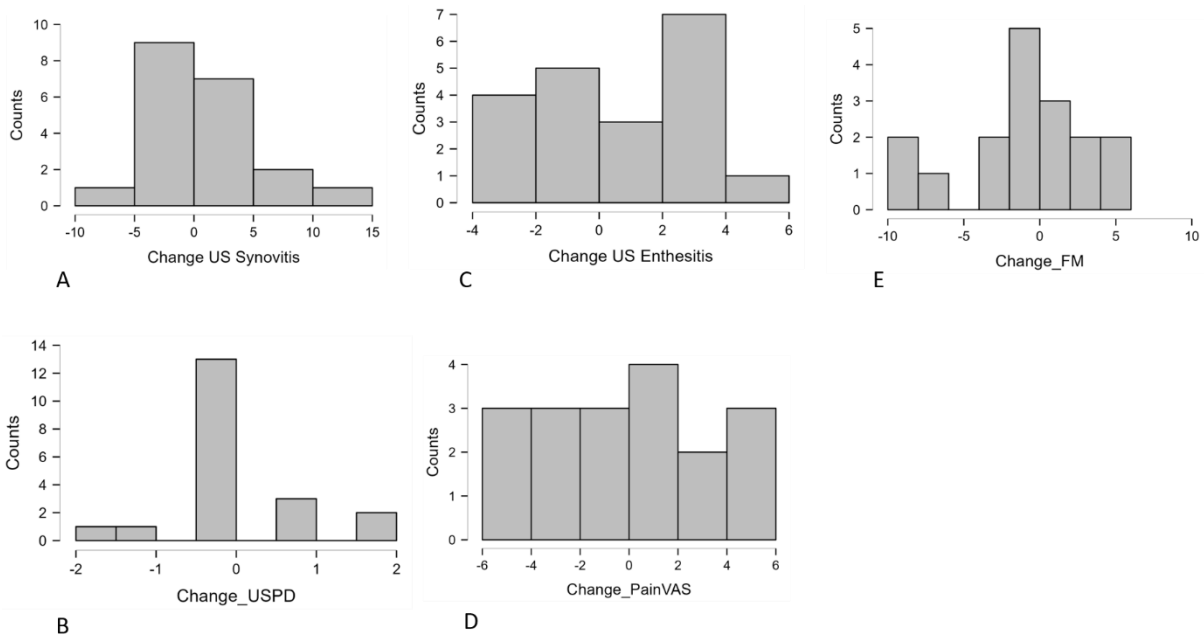

Figure 5.3: Histograms of the change of MSUS metrics, pain VAS and FM.

The distribution of changes in US synovitis scores exhibited a left skew, with the majority of participants showing a reduction in their scores. The most frequent scores fell between -5 and 0. In contrast, the distribution of changes in US enthesitis scores was right-skewed, ranging from -2 to 6 (Figure 5.3). Furthermore, the histogram for the change in USPD is skewed toward zero.

The histogram of the change in pain VAS indicates a balanced distribution centred around zero, reflecting a mix of both improvement and worsening scores in pain VAS. The histogram of the change in FM scores showed a slight right skew, indicating improvement, as most participants had reduced FM scores (Figure 5.3).

5.4.2 Univariate correlation between MSUS metric and pain VAS

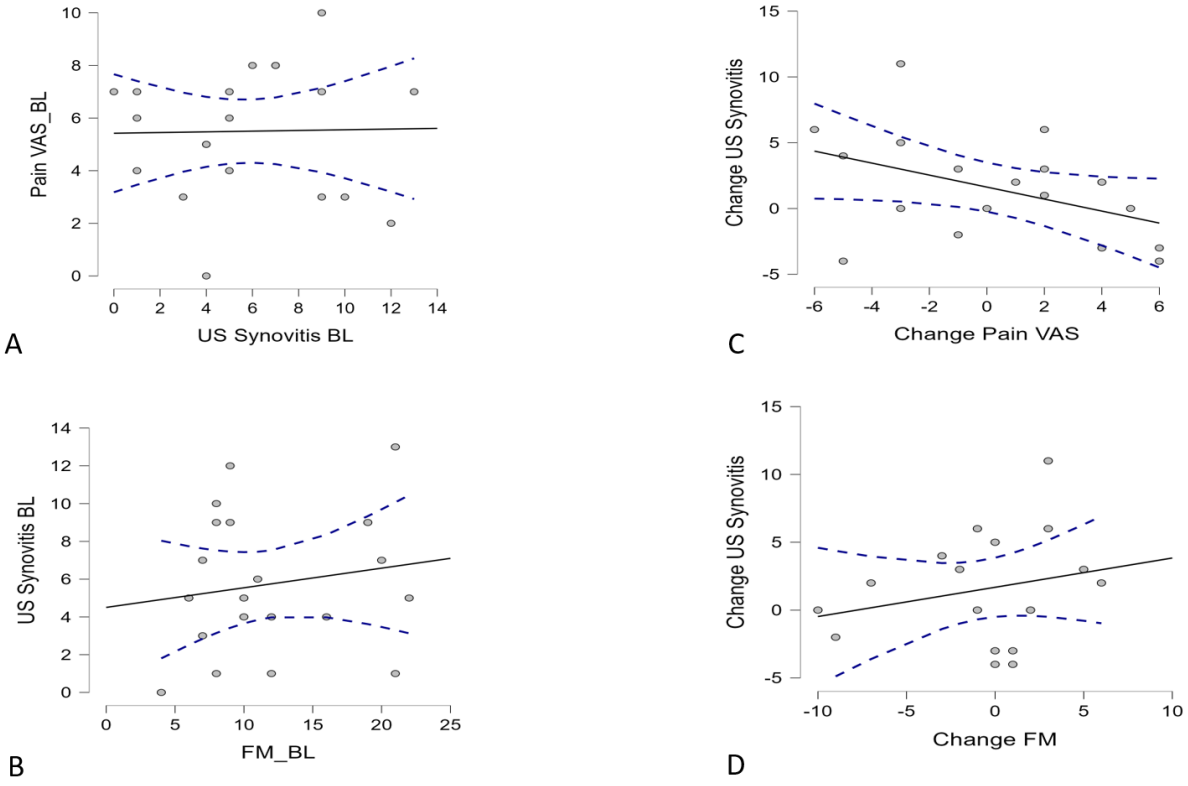

Figure 5.4: The correlation between US synovitis and pain VAS, and between US synovitis and FM at the baseline and follow-up visits.

A non-significant correlation was observed between FM scores and US synovitis scores at baseline ($r = 0.159$, $p = 0.5$). Additionally, there was no significant correlation between the pain VAS and US synovitis ($r = 0.020$, $p = 0.934$). However, a trend was noted regarding the change in US synovitis and the change in pain VAS ($r = -0.440$, $p = 0.068$). No significant correlation was observed in the change in US Synovitis and FM ($r = 0.234$, $p = 0.367$) (Figure 5.4).

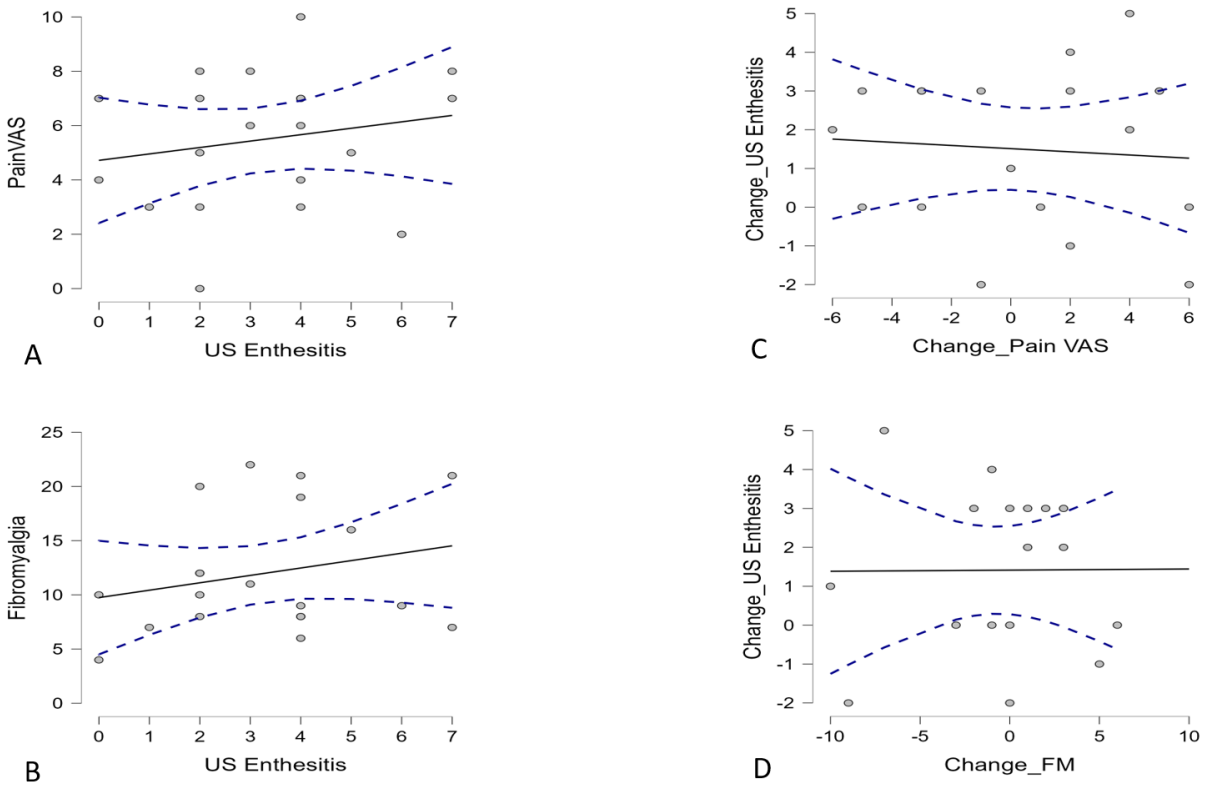

Figure 5.5: The correlation between US enthesitis and pain VAS, and between US enthesitis and FM at the baseline and follow-up visits.

The correlation analysis revealed a weak, insignificant positive correlation between the US enthesitis and pain VAS scores at baseline (r = 0.191, p value=0.31), and a similar weak, insignificant correlation between US enthesitis and FM scores (r = 0.240, p value=0.42). No significant correlation was observed between the change in US Enthesitis and the change in pain VAS (r = -0.077, p = 0.49) and between the change in US Enthesitis and the change in FM (r = 0.006, p = 0.98) (Figure 5.5).

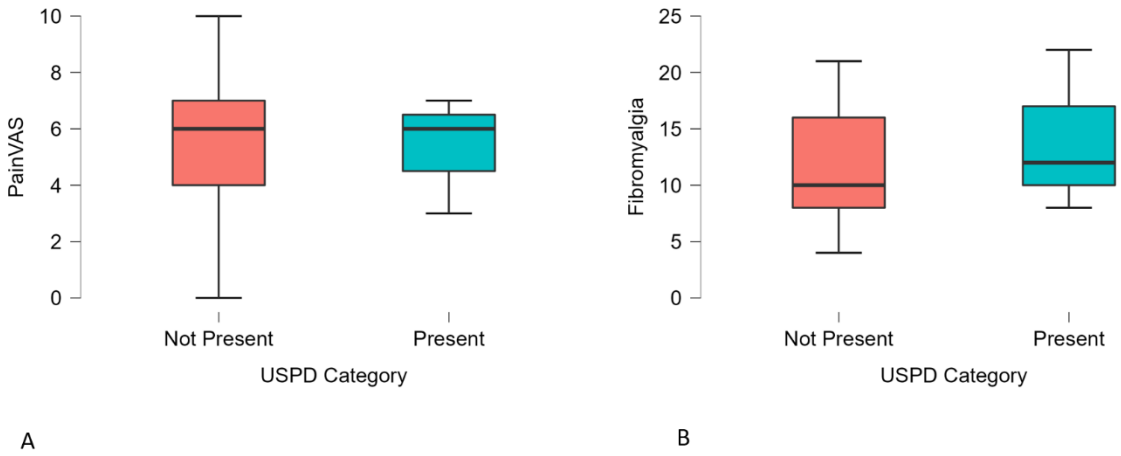

Figure 5.6: USPD Category groups with pain VAS and FM at the baseline.

Participants were categorised based on the presence or absence of USPD. Due to the relatively small number of participants exhibiting positive USPD, a grouping approach was employed to facilitate statistical comparison. Specifically, a dichotomous classification was adopted, where any participant with at least one site showing USPD activity was placed in the “USPD Present” group. In contrast, those with no Doppler signal at any site were categorised as “USPD Not Present”. This approach was necessary to address imbalances in group distributions in the baseline data.

Descriptive statistics revealed that the median Pain VAS scores were identical between the two groups, with a median of 6.0 in both the USPD “Present” (n = 3) and “Not Present” (n = 17) categories. As shown in the boxplots (Figure 5.6), the interquartile range (IQR) for Pain VAS was wider in the USPD “Not Present” group, indicating greater variability in pain perception among patients without detectable Power Doppler activity. In contrast, the USPD “Present” group exhibited a more compressed distribution of Pain VAS scores, suggesting more consistent, though not necessarily higher, pain levels.

Conversely, the analysis of fibromyalgia scores indicated that the median value was marginally higher in the USPD "Present" group (median = 12.0) compared to the "Not Present" group (median = 10.0). However, as illustrated in Figure 5.6, there is considerable overlap in the distribution of fibromyalgia scores between the two groups, and no distinct pattern emerged to suggest a significant correlation between the presence of USPD and the severity of fibromyalgia symptoms. Notably, greater dispersion was observed in the "Not Present" group. To evaluate the association between peripheral inflammatory activity, measured using ultrasound power Doppler (USPD), and the presence of fibromyalgia in patients with PsA, a chi-square test of independence was performed. A 2×2 contingency table categorised 20 participants by USPD signal and fibromyalgia criteria. Among them,

17 had no USPD signal (5 met fibromyalgia criteria), and 3 had detectable USPD (1 met criteria). The chi-square test indicated no significant association, with results showing $\chi^2(1, N = 20) = 0.019$, $p = 0.891$. Thus, no significant relationship was found between USPD presence and fibromyalgia criteria.

5.4.3 Univariate correlation between USPD and QST

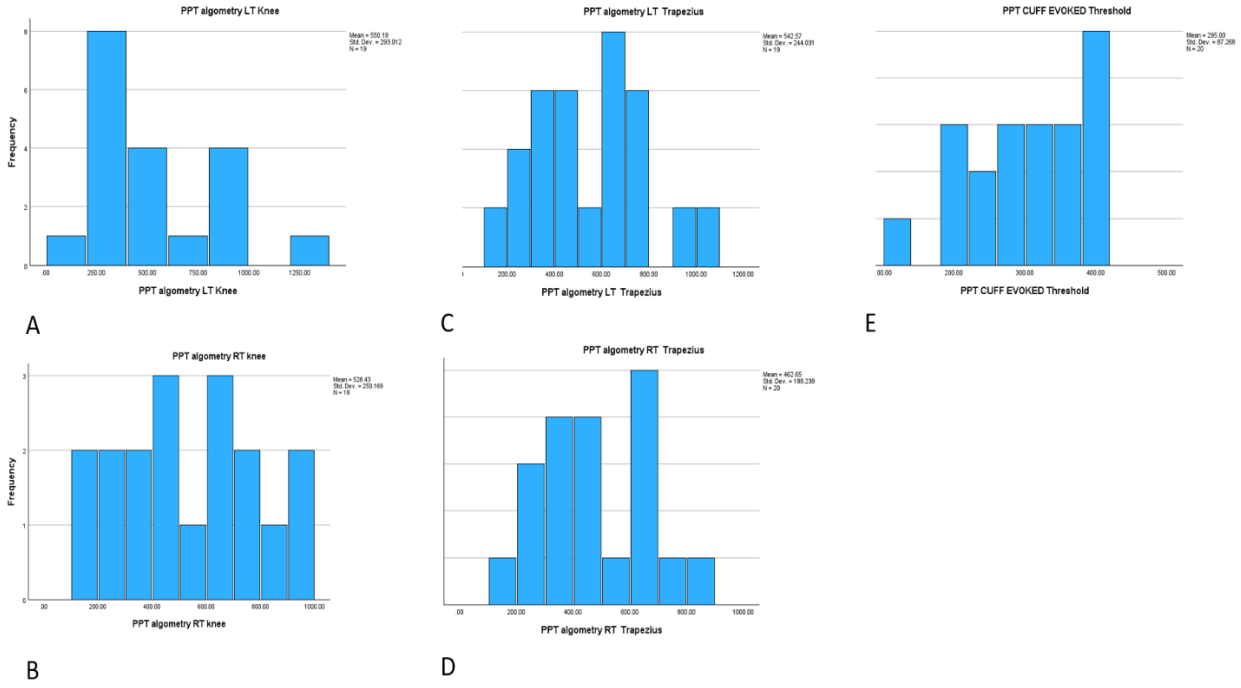

Figure 5.7: Histograms of the QST (PPT algometry for knees, trapezius, and cuff-evoked).

The distribution of PPT algometry at the left knee exhibits a positive skew, characterised by a higher frequency of lower threshold values, as illustrated in panel A of Figure 5.7. The histogram indicates that a significant number of participants reported lower pain thresholds. Additionally, the Shapiro-Wilk test suggested that the PPT algometry data at the left knee follow a normal distribution.

The distribution of PPT algometry at the right knee appears symmetric, which suggests a relatively normal distribution of the threshold, as illustrated in panel B of Figure 5.7. Additionally, the Shapiro-Wilk test indicated that the PPT algometry data at the right knee follow a normal distribution. The histogram suggests that a significant number of

participants reported lower pain thresholds. The histogram indicates that the mean PPT was higher in the left knee than in the right knee.

The distributions of PPT algometry for the right and left trapezius were positively skewed, as illustrated in panels C and D of Figure 5.7. The Shapiro-Wilk test indicated that the PPT algometry data for both the right and left trapezius follow a normal distribution.

The distribution of cuff-evoked pain thresholds is right-skewed, with the majority of values concentrated in the high range, as shown in panel D of Figure 5.7. The Shapiro-Wilk test indicated that the cuff-evoked pain threshold data follow a normal distribution.

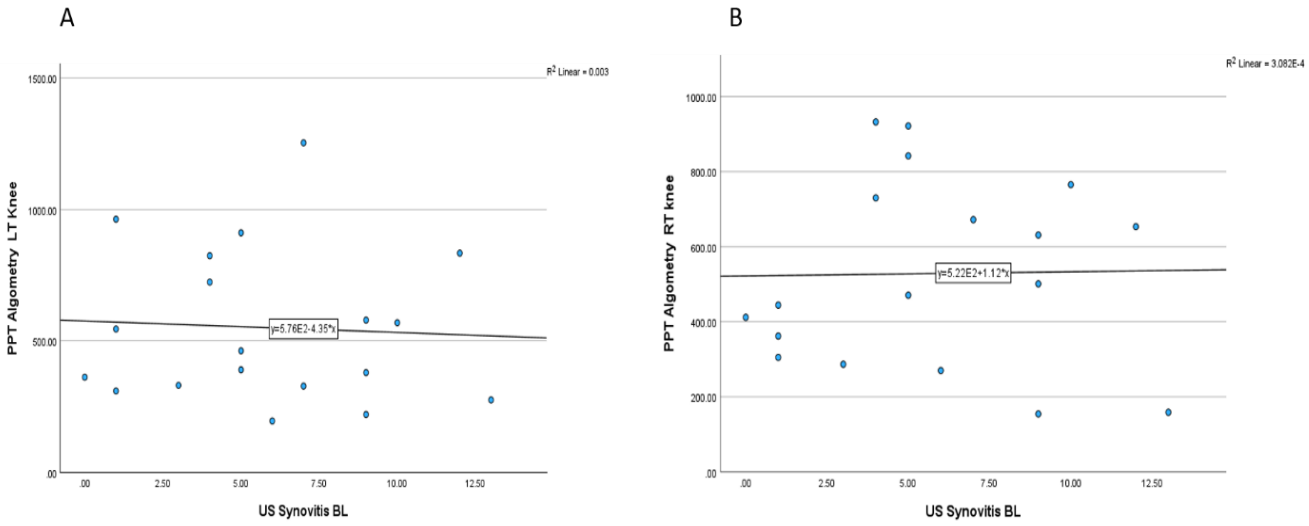

Figure 5.8: The correlation between US synovitis and PPT algometry for the knees.

There were no significant correlations between the US synovitis and PPT thresholds of the right knee (r = 0.05, p = 0.86) and the left knee (-0.06, p = 0.81), as shown in panels A and B of Figure 5.8.

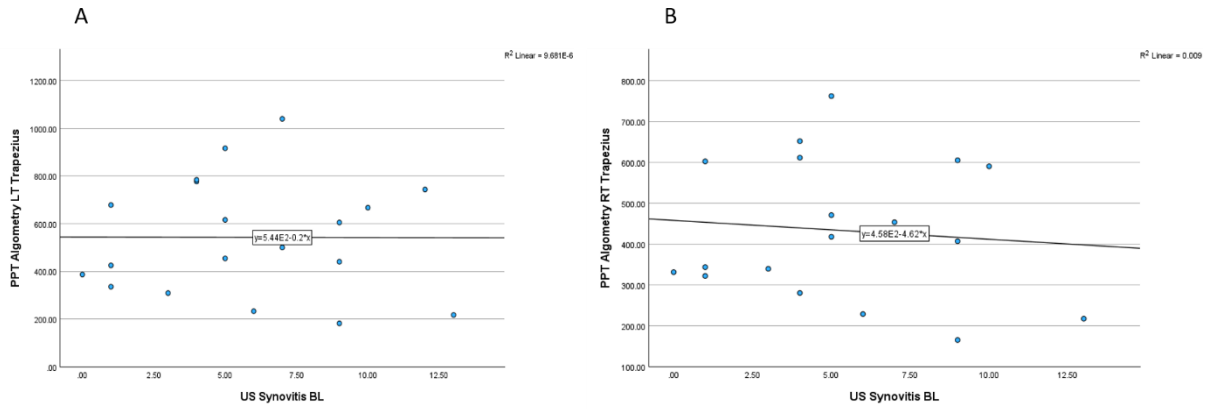

Figure 5.9 The correlation between US synovitis and PPT algometry for the trapezius.

There were no significant correlations between the US synovitis and PPT thresholds of the right trapezius (r = 0.09, p = 0.7) and the left trapezius (-0.003, p = 0.9), as shown in panels A and B of Figure 5.9.

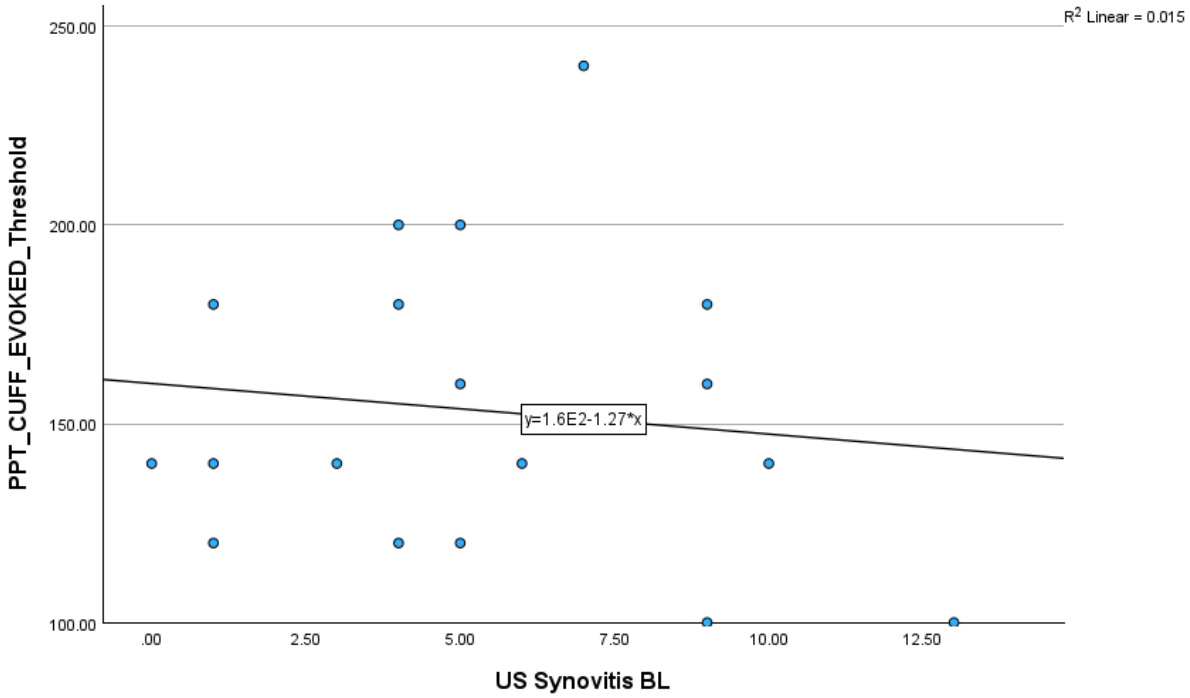

Figure 5.10: The correlation between US synovitis and PPT cuff evoked.

There was no significant correlation between US synovitis and PPT cuff-evoked responses (r = -0.08, p = 0.7), as shown in Figure 5.10.

Figure 5.11: The correlation between US enthesitis and PPT cuff-evoked responses was assessed using point biserial correlations (with binary enthesitis scores, where zero indicates absent and 1 indicates present).

Figure 5.11 illustrates the relationship between US enthesitis and PPT cuff-evoked values using point biserial correlation. It indicates that participants with US enthesitis display slightly higher PPT cuff-evoked values when compared to those without enthesitis. However, no significant correlation was found ($r = 0.08$, $p = 0.72$).

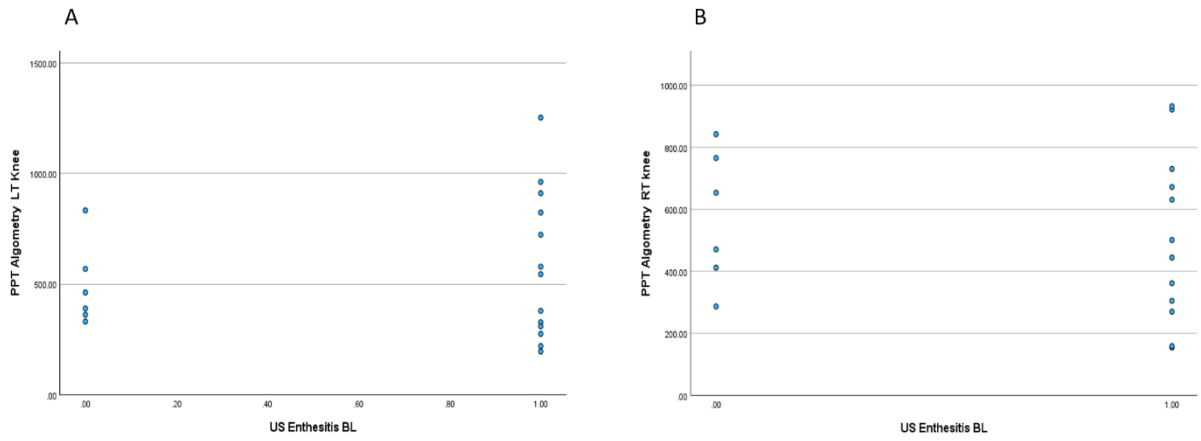

Figure 5.12 The correlation between US enthesitis and PPT algometry of the knees was examined using point-biserial correlations, with binary enthesitis scores indicating absence (0) or presence (1).

Panel A of Figure 5.12 illustrates the scatterplot for left knee PPT in relation to US enthesitis status. Although there is visual clustering of lower PPT values in the presence of enthesitis (value = 1), the spread of the data points suggests substantial within-group variability. While the negative association suggests that lower PPT values (indicative of greater pain sensitivity) are associated with US enthesitis, the observed correlations were weak. They did not achieve statistical significance (r = 0.14, p = 0.54).

A similar trend is evident for the right knee, with slightly lower PPT values among those with enthesitis, but again with overlapping distributions between groups (Panel B). However, the observed correlations were weak and did not achieve statistical significance (r = -0.1, p = 0.69).

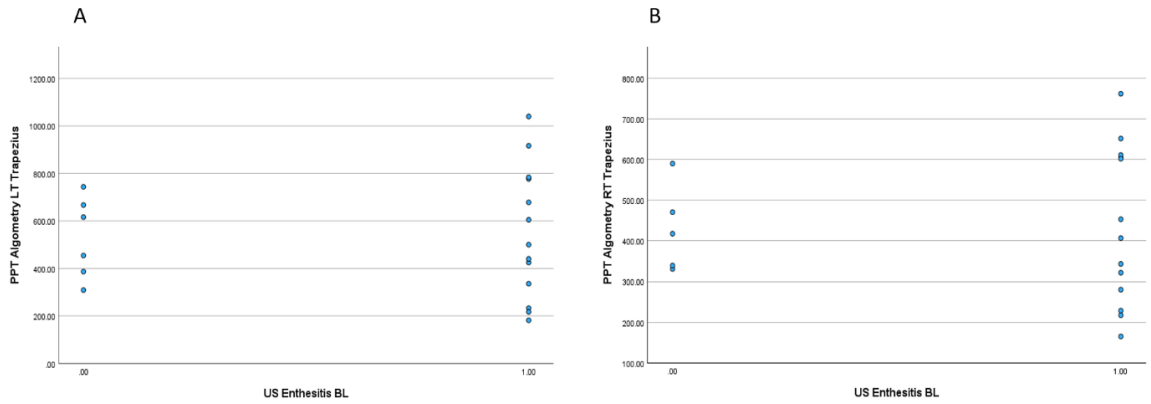

Figure 5.13 The correlation between US enthesitis and PPT algometry of the trapezius was examined using point-biserial correlations, with binary enthesitis scores (0 = absent, 1 = present).

Figure 5.13 presents the distribution of PPT values at the left trapezius according to enthesitis status. There is visual evidence of a broader spread in the enthesitis-negative group, while participants with enthesitis appear to cluster around lower PPT values, potentially indicating heightened central pain sensitivity. However, this correlation was not significant (r = 0.01, p = 0.96).

Similarly, lower PPT values were observed among participants with US enthesitis, as shown in panel B of Figure 5.13. However, no significant correlation was detected (r = 0.03, p = 0.87).

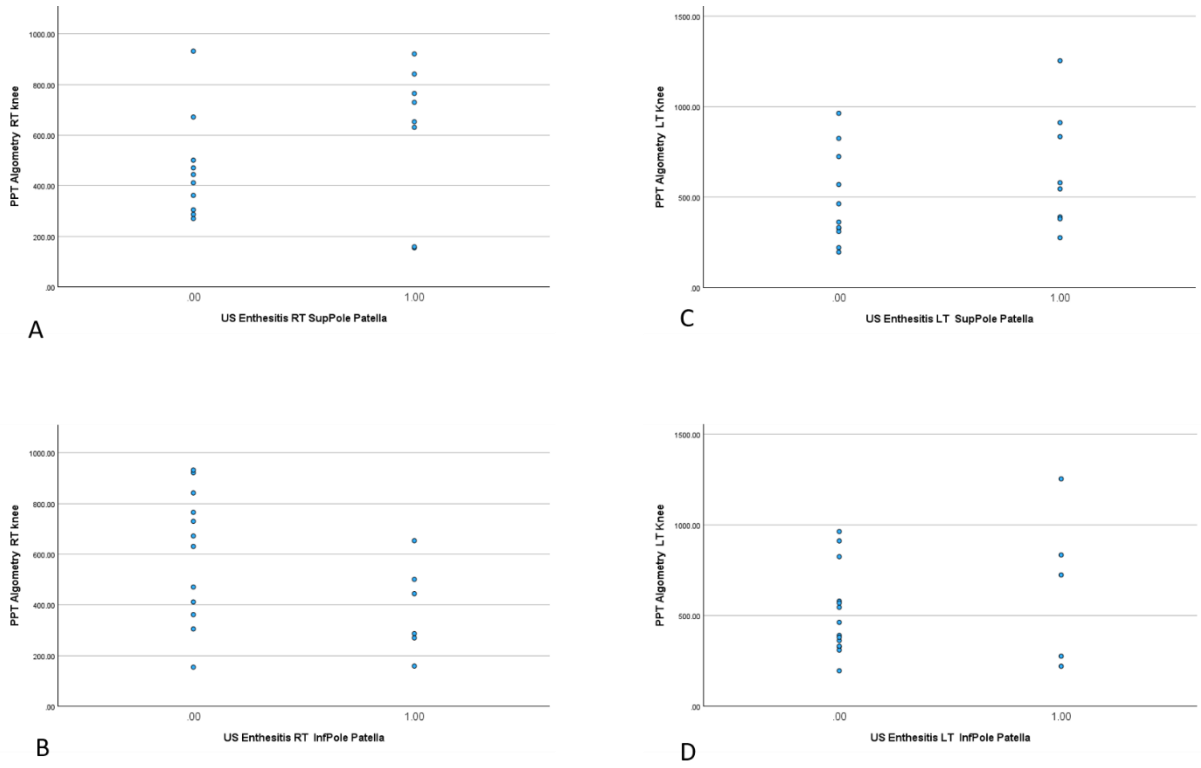

Figure 5.14: The correlation between US enthesitis at the patella and PPT algometry for the knees using point biserial correlations (with binary enthesitis scores, where zero indicates absent and 1 indicates present).

Panel A of Figure 5.14 demonstrates the relationship between right superior pole patellar enthesitis and PPT algometry in the right knee. The distribution suggests a tendency toward lower PPT values among participants with enthesitis, although data overlap exists between groups. Despite a negative correlation indicating that enthesitis may be associated with lower pressure pain thresholds (i.e., increased pain sensitivity), a suggested trend was observed ($r = -0.41$, $p = 0.087$).

In panel B of Figure 5.14, the relationship between right inferior pole patellar enthesitis and pressure pain threshold (PPT) algometry in the right knee is illustrated. The plot reveals only a slight differentiation between the groups, with a notable overlap in PPT values irrespective of enthesitis status. Furthermore, no significant correlation was observed between right inferior pole patellar enthesitis and PPT algometry in the right knee ($r = -0.29$, $p = 0.24$).

Panel C of Figure 5.14 exhibits left superior pole patellar enthesitis against PPT algometry in the LT knee. Similar to the right side, participants with enthesitis appear to exhibit slightly higher PPTs, though with variability within both groups. However, this association was not statistically significant ($r = 0.28$, $p = 0.23$).

Panel D of Figure 5.14 depicts the association between left inferior pole enthesitis and PPT algometry in the LT knee. The pattern reflects a mild trend toward reduced PPTs among those with enthesitis, but the scatter remains widely distributed. However, this correlation was not statistically significant (r = 0.23, p = 0.33).

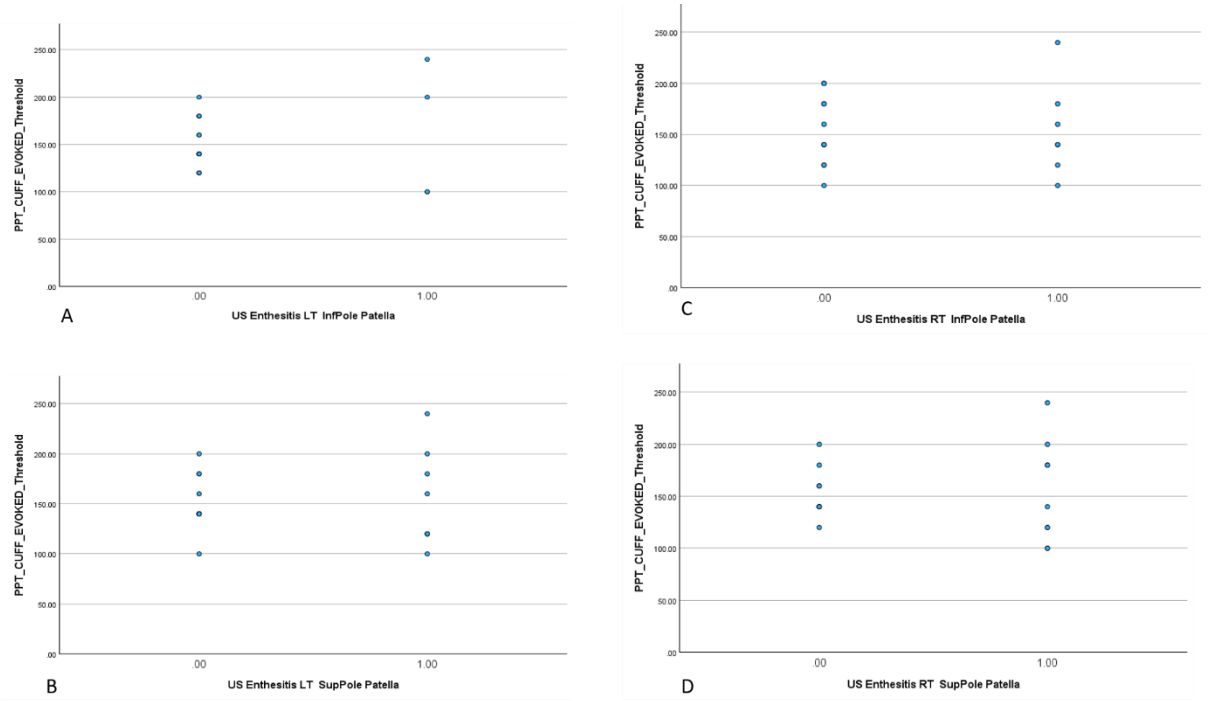

Figure 5.15: The correlation between US enthesitis at the patella and PPT cuff evoked threshold was examined using point biserial correlations, with binary enthesitis scores indicating absence (0) or presence (1).

Figure 5.15 (panel A) illustrates the relationship between enthesitis at the inferior pole of the left patella and pain evoked by cuff pressure testing. The data suggest that participants with enthesitis may exhibit slightly lower pain thresholds, which indicates increased central sensitivity; however, there is considerable overlap between groups. No significant correlation was found (r = 0.09, p = 0.7).

Similarly, panel B of Figure 5.15 explores the relationship at the superior pole of the left patella. The findings reveal no distinct separation between the groups, with cuff thresholds showing comparable distributions in both enthesitis-positive and enthesitis-negative participants. Again, no significant correlation was observed (r = 0.04, p = 0.87).
Panel C of Figure 5.15 presents a comparison of the right inferior pole, while panel D of Figure 5.15 depicts the right superior pole. In both figures, the distributions show considerable overlap, and no distinct trend related to enthesitis status emerges. However, no significant correlation was observed at the right superior pole of the patella (r = 0.0001, p = 0.99) or the right inferior pole of the patella (r = 0.02, p = 0.94).

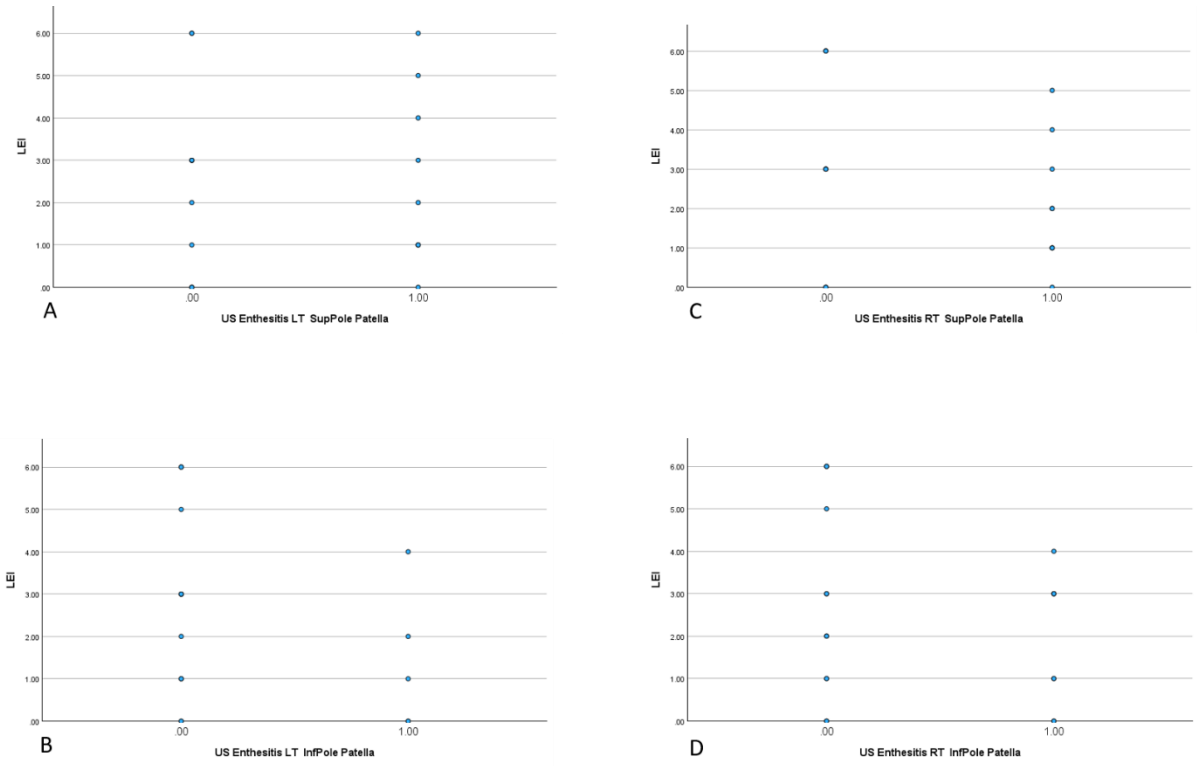

Figure 5.16: The correlation between US enthesitis at the patella and LEI using point biserial correlations (with binary enthesitis scores, where zero indicates absent and 1 indicates present).

In Figure 5.16 (panel A), the relationship between US Enthesitis at the left superior pole and LEI (clinical enthesitis) is presented. No distinct directional trend is evident. The LEI values show a wide distribution across both groups. Nonetheless, a weak but not significant negative correlation was observed (r = -0.02, p = 0.91).

Panel B of Figure 5.16 demonstrates the correlation between US Enthesitis at the left inferior pole and LEI. There was a slight concentration of higher LEI scores in enthesitis-positive cases, though overlap is substantial. However, a moderate but not significant negative correlation was observed (r = -0.31, p = 0.17).

Figure 5.16 (panel C) shows the correlation between US Enthesitis at the right superior pole and LEI. Similarly, participants with and without US enthesitis exhibit a wide range of LEI scores, with no clear distinction between the groups. However, a moderate but not significant negative correlation was observed (r = -0.24, p = 0.29).

Panel D of Figure 5.16 demonstrates the correlation between US Enthesitis at the right inferior pole and LEI. This figure shows a weak trend, with slightly higher LEI scores among those with no enthesitis. However, a moderate but not significant negative correlation was observed (r = -0.25, p = 0.28).

5.4.4 MSUS and QST among participants with psoriatic arthritis, comparing those with and without fibromyalgia (FM)

A total of 20 participants with PsA were included in the analysis, comprising 6 participants who met the FM criteria (positive FM) and 14 who did not (negative FM). The demographic characteristics showed no statistically significant differences between groups.

Around 30% of patients met the FM criteria and presented higher LEI scores and lower PPT-evoked threshold than FM-negative patients. Total FM scores significantly correlated with LEI scores ($r = 0.69$, $p < 0.001$) and calf PPTs ($r=-0.53$, $p=-0.014$), but not with knee and trapezius PPTs ($r=-0.49$, $p = 0.09$; $r=-0.30$, $p = 0.19$), or US enthesitis ($r=-0.04$, $p = 0.86$). The PPT measurements in the investigated areas did not demonstrate significant correlations with US enthesitis. Specifically, the PPT algometry at the left trapezius showed a correlation of $r = 0.21$ ($p = 0.35$). The PPT algometry at the left knee resulted in a correlation of $r = 0.23$ ($p = 0.33$), while a negative association was observed between LEI with calf PPT ($r=-0.51$, $p = 0.02$) and trapezius PPT ($r=-0.41$, $p = 0.06$). No significant correlation was demonstrated between LEI and left knee enthesitis ($r=-0.32$, $p = 0.17$) (Table 5.2).

Table 5.2 The correlation results of FM, QST, US enthesitis and LEI

	r	P value
FM vs PPT LT knee	-0.49	0.09
FM vs PPT LT trapezius	-0.30	0.19
FM vs PPT Cuff	0.53	0.014
FM vs LEI	0.69	< 0.001
FM vs MSUS Enthesitis at the LT knee	-0.04	0.86
US enthesitis VS. PPT LT trapezius	0.01	0.96
US enthesitis VS PPT LT knee	0.14	0.54
US enthesitis VS LEI	-0.32	0.17
LEI vs calf PPT	-0.51	0.02
LEI vs PPT LT trapezius	-0.41	0.06

FM= the total score of fibromyalgia, MSUS=musculoskeletal ultrasound, LEI=Leeds enthesitis index, PPT= pressure pain threshold.

5.5 Discussion

This chapter aims to explore the capability of ultrasound to identify pain in patients with PsA. The previous chapter (Naredo) emphasised the roles of ultrasound in detecting various pain mechanisms, including both directly nociceptive pain and indirectly nociplastic pain in patients with RA.

The results of this chapter indicate that USPD and US synovitis were not significantly correlated with pain VAS in patients with PsA. These findings are consistent with growing evidence that ultrasound findings in PsA may not fully reflect the patient's pain experience, particularly compared to RA. Merola and colleagues (2018) highlight that synovitis is more prevalent in RA compared to PsA, affecting approximately 90% of joints in RA and 60% of joints in PsA.

The lack of a correlation between USPD and the pain VAS in this population may have significant implications for our understanding of pain mechanisms in patients with PsA. However, due to the lack of detectable peripheral inflammation through USPD in PsA compared to RA, another ultrasound metric, specifically US synovitis, was assessed among these participants for a better understanding of the nature of pain.

The correlation between changes in US synovitis and pain VAS revealed a trend that may suggest an improvement in pain associated with inflammatory changes. In contrast, no such trend was observed between the changes in USPD and pain VAS. These results provide evidence that active US synovitis is prevalent in patients with PsA. These findings align with the study of Zuliani and colleagues (2019), who emphasise that active US synovitis is significantly more common in individuals with PsA. The active US synovitis appears to be better in explaining the pain mechanism in patients with PsA rather than USPD. However, the cross-sectional study and the limited number of participants limit the power of the ultrasound study, making it difficult to confirm this explanation strongly.

5.5.1 The ultrasound enthesitis and pain

In the present study, the assessment of US enthesitis was conducted with a protocol inspired by a study done by Balint (2018), which involved a bilateral evaluation of six entheseal sites: the superior and inferior poles of the patella, the calcaneal insertion of the Achilles tendon, and the lateral epicondyle of the elbow, as detailed in the methods section. This protocol incorporated both B-mode and PD ultrasound, with abnormal findings defined according to specific thickness thresholds and the presence of structural or

inflammatory features consistent with the OMERACT criteria. As clarified in the methods, enthesitis was identified based on one or more of the following characteristics: increased thickness, hypoechogenicity, calcifications, enthesophytes, erosions, or PD signal, all of which were measured within 2 mm of the cortical bone.

This protocol shares conceptual similarities with existing ultrasound enthesitis scoring systems, notably the Madrid Sonographic Enthesitis Index (MASEI), which integrates both structural and inflammatory components, including PD signal (De Miguel et al., 2009). In contrast, the Glasgow Ultrasound Enthesitis Scoring System (GUESS) focuses exclusively on grayscale findings and omits inflammatory markers, rendering it less sensitive to active disease (Balint et al., 2002). The main reason for not utilising these scoring systems was that they were specifically designed to assess the lower limbs. At the same time, the entheseal sites examined in this study included the lateral epicondyle of the elbow. The cut-off for enthesitis at these locations was established based on the work of Balint and colleagues (2002, 2018) and Toprak and colleagues (2012), as previously outlined in the Methods section. Compared to GUESS, the current protocol provides enhanced sensitivity to early inflammatory changes and disease activity, aligning more closely with the pathophysiological characteristics of PsA. Furthermore, adopting objective, site-specific thresholds for tendon thickness improves measurement reliability and supports consistency among assessors.

Thus, the ultrasound protocol and scoring system used in the current study represent a robust and clinically relevant approach for detecting both structural and active inflammatory changes at entheseal sites, thereby underscoring its utility in evaluating PsA-related enthesitis. However, the lack of a formal composite scoring system, such as MASEI or GUESS, may limit comparability with other studies and highlights the necessity for further standardisation in ultrasound enthesitis assessment.

MASEI and GUESS scores were significantly higher among patients with PsA (Agache et al., 2022). Both scores consider the presence or absence of PD signals (de Miguel et al., 2009). Eder and his colleagues (2014) observed that MASEI scores in patients with PsA were higher compared to those in healthy participants. Additionally, Polacek et al. (2017) demonstrated that the MASEI ultrasound score is correlated with radiological progression. The results demonstrated that the majority of participants exhibited US enthesitis at multiple entheseal sites, ranging from one to six locations at baseline. This is expected, as enthesitis represents a hallmark feature of PsA. These findings are consistent with Agache

et al. (2022), who similarly report a high prevalence of entheseal involvement in patients with PsA.

However, when examining the correlation between US enthesitis and patient-reported pain, as measured by the pain VAS, no significant relationship was identified. This lack of association suggests that ultrasound findings may not fully capture the pain experience in PsA.

In addition, the results of this research reveal no relationship between US synovitis and FM, or between US enthesitis and the presence of FM, either at baseline or over time (change) in the PsA population.

These results suggest that the presence of FM may not significantly impact ultrasound-detectable inflammatory features in PsA, particularly enthesitis. Additionally, it is not linked to changes in these features after intervention or during disease progression.

The relationship between FM and imaging findings in PsA has been a subject of increasing interest, particularly given the potential for FM to confound disease activity assessments. Several studies have reported that patients with concomitant PsA and FM tend to have higher pain VAS scores (Duffield et al., 2018).

5.5.2 The correlation between US metrics and QST

Assessment of QST metrics such as PPT is increasingly recognised as a non-invasive and objective method for evaluating pain sensitivity and central sensitisation in inflammatory rheumatic diseases, including PsA. In particular, cuff algometry allows the simultaneous activation of deep tissue nociceptors and has shown a strong correlation with generalised pain sensitisation (Arendt-Nielsen et al., 2017; Gervais-Hupé et al., 2018). The knee is a key site that could be used for evaluating both synovial and entheseal inflammation, while the trapezius serves as a remote, non-articular site useful for assessing widespread sensitisation independent of joint involvement (Kosek et al., 2016).

In the current research, the relationship between US metrics and QST was investigated. To my knowledge, this is the first study to examine these associations in a PsA population.

Given the complex nature of PsA, objective tools may help clarify the various factors contributing to pain and inflammation. Consequently, ultrasound assessments of synovitis and enthesitis were correlated with PPT algometry and PPT cuff-evoked measurements at various sites on both the right and left sides, including the trapezius and knees. This included separate evaluations of the superior and inferior poles of the patella. The results

indicated no significant correlations between PPT measurements and ultrasound metrics (synovitis and enthesitis), regardless of whether they were evaluated at the knee level or the trapezius sites.

These findings are consistent with the broader literature, which suggests a disconnect between inflammation detected by imaging and subjective or objective pain measures in PsA. For instance, Polachek et al. (2021) found poor concordance between ultrasound enthesitis scores and clinical tenderness, reinforcing the idea that peripheral inflammation may not fully account for pain in the PsA population. Although these findings indicate that significant pain in PsA may not stem from peripheral inflammation, as highlighted by Høegh (2022), it is essential to note that central sensitisation mechanisms in PsA may function independently of local inflammation. Further research is necessary to elucidate the pain mechanisms associated with PsA fully. Given that the PsA populations in this study were changing medication and are no longer in the early stages of the disease, when peripheral joint inflammation is typically active, additional investigation utilising functional MRI could yield valuable insights into these pain mechanisms.

The absence of significant correlations at both the right and left knees, as well as across the superior and inferior patellar poles, further supports the argument that pain sensitivity in PsA may be driven more by central mechanisms rather than by localised joint inflammation as observed in the PsA population in this study. These findings suggest that central mechanisms play a role in overall pain in PsA, a conclusion that will be further investigated using fMRI biomarkers in the next chapter.

The absence of correlation highlights a clinical challenge: although ultrasound provides reliable quantification of peripheral inflammation, it may not adequately capture the neurosensory changes that contribute to chronic pain in PsA. Additionally, the small sample size may limit the generalisability of the results, suggesting that a larger cohort could enhance the validity of the findings.

5.5.3 A comparison between the dominant and non-dominant sides

Handedness denotes the predisposition to utilise one hand with greater proficiency, speed, and precision than the other, classifying the preferred hand as dominant and the alternative as non-dominant (McManus, 2019).

Approximately 90% of the population is right-handed (Scharoun & Bryden, 2014). Left-handedness is more common in men, occurring in 5% to 25.9% of the population, depending on cultural factors (Gutwinski et al., 2011).

The impact of handedness on pain perception in humans remains inadequately clarified. Previous studies have indicated that handedness could be a significant factor influencing PPT (Pauli et al., 1999). One particular study found that for right-handed participants, the PPT was higher in the dominant hand compared to the non-dominant hand (Ozcan et al., 2004). In contrast, left-handed participants did not exhibit a significant difference in pain perception between their hands (Pud et al., 2009).

Moreover, the evidence suggests that the dominant side exhibits greater sensitivity, particularly in right-handed participants. In the current research, the PPT cuff was applied to the non-dominant side (left). When investigating the differences between FM and non-FM, PPT algometry was specifically selected for the trapezius and the knee on the non-dominant side (left). Utilising the non-dominant side enhanced the uniformity of the collected data and helped minimise potential biases related to differing levels of sensitivity (Ozawa et al., 2011).

In addition, using the non-dominant side offers several advantages. It is less frequently engaged in daily motor tasks, which may reduce mechanical stress and inflammation, providing a more "neutral" site for pain sensitivity assessment (Puta et al., 2013). Moreover, Hoegh et al. (2022) focused on contralateral (non-dominant) testing to analyse widespread pain patterns in inflammatory arthritis.

5.5.4 MSUS and QST among participants with psoriatic arthritis, comparing those with and without fibromyalgia (FM)

This study examined the intricate relationship between CS, specifically FM, and clinical and ultrasound assessments of enthesitis in patients with PsA. The findings highlight the challenges of accurately characterising pain mechanisms in PsA, particularly in distinguishing inflammatory enthesitis from pain driven by CS.

Approximately one-third of the current research cohort met the 2011 ACR criteria for FM, consistent with previous literature reporting FM prevalence rates of up to 30% among Patients with PsA (Molto et al., 2018). These FM-positive patients exhibited higher LEI scores and lower PPTs, indicating both increased self-reported tenderness and objective evidence of pain hypersensitivity. Notably, total FM scores demonstrated a significant positive correlation with LEI scores, suggesting that the LEI may, at least in part, reflect the presence of CS rather than purely inflammatory pathology.

The association between FM and reduced PPTs at the calf, a site not typically involved in PsA-related enthesitis, further supports the hypothesis of widespread sensitisation. Interestingly, while trends toward significance were noted between FM scores and knee and trapezius PPTs, these did not reach statistical significance. This may be due to sample size limitations or variability in PPT responses across anatomical locations.

Notably, no significant correlations were observed between US findings of enthesitis and either FM scores or PPT values. The findings of the current research align with those of Fiorenza et al. (2020), who investigated differences in enthesitis scores among US patients with PsA who also had FM compared with those without FM. Their findings revealed that clinical enthesitis scores were higher in patients with both PsA and FM; however, ultrasound scores, including both grayscale and power Doppler, showed no significant differences between the two groups. Moreover, the findings of this study align with those of Marchesoni and his colleagues (2021), who emphasise that patients with fibromyalgia experience widespread pain affecting entheses, resulting in significantly higher enthesitis scores, while showing no differences in inflammatory ultrasound assessments. This suggests that the presence of fibromyalgia may not influence the level of inflammatory activity that can be detected by ultrasound.

In addition, the current results are consistent with the results of Polachek et al. (2021), who investigated a cohort of 156 patients with PsA, some of whom also had FM. They found that while FM was associated with elevated clinical disease activity scores, ultrasound evaluations of synovitis and enthesitis were not significantly affected by FM. Di Matteo and colleagues (2022) note that clinical enthesitis is more prevalent in the FM group; however, the presence of USPD signals is rare, and total ultrasound scores, particularly for USPD, are significantly lower in FM patients.

Consequently, ultrasound findings of enthesitis and synovitis in the US are unable to identify the non-inflammatory characteristics of FM. Thus, the non-inflammatory pain reported by patients in the PsA population, as measured by pain VAS, may not reflect inflammatory changes at entheseal sites detectable by ultrasound.

Moreover, LEI scores did not correlate with US enthesitis at the non-dominant knee, further questioning the specificity of clinical enthesitis indices in differentiating inflammatory from non-inflammatory pain. These findings align with prior studies suggesting poor concordance between clinical and imaging-based assessments of enthesitis (Naredo et al., 2014). These findings contradict those of Kristensen and colleagues (2016), who report a moderate correlation between ultrasound elements of enthesitis and the LEI.

In contrast, ultrasound provides visual confirmation of structural and inflammatory changes and is less likely to be confounded by pain sensitisation.

A negative association between LEI and cuff-evoked PPT and trapezius PPTs suggests that higher clinical enthesitis scores may reflect widespread hyperalgesia, further supporting the influence of CS in symptom generation. The absence of a significant relationship between LEI and ultrasound enthesitis implies that reliance on clinical indices alone may risk misclassification, potentially leading to unwarranted treatment escalation.

These findings carry significant clinical implications. In patients with PsA, especially those who exhibit widespread pain or features of fibromyalgia, clinical enthesitis scores may inaccurately reflect the actual inflammatory burden. Thus, the integration of imaging techniques, namely ultrasound, is crucial for precise diagnosis and informed therapeutic decision-making. Additionally, employing QST, including PPTs, may provide valuable insights into the underlying pain mechanisms and help identify patients with predominant central sensitisation who may benefit from tailored non-immunosuppressive interventions.

5.5.5 Study limitations and future recommendations

Limitations of this study include the relatively small sample size, which may have reduced the statistical power to detect subtle or moderate associations between the measured variables. Although 50 participants were recruited, only 20 underwent ultrasound assessment. A potential reason for this low number is that ultrasound was optional rather than mandatory, which may have reduced participant uptake. Additionally, the limited availability of an ultrasound machine, due to the absence of a dedicated device for the study, further constrained data collection.

Small sample sizes also limit the generalisability of the findings, as the data may not adequately represent the broader population of individuals with PsA.

Furthermore, the COVID-19 pandemic negatively impacted ultrasound data collection due to the restrictions implemented during that period. As a result, multiple ultrasound operators were involved in collecting the MSUS data. This could have introduced inter-operator variability, potentially affecting the reliability and consistency of the ultrasound assessments. Ultrasound is inherently operator-dependent, and even minor differences in technique, probe positioning, applied pressure, or interpretation of findings (e.g., power Doppler signal or grading of synovitis and enthesitis) may lead to measurement variability.

Moreover, the establishment of a standardised ultrasound protocol was essential for delineating the specifics of the MSUS procedures. This included the development of standard operating procedures (SOPs), the definition of cut-off criteria, and the identification of target pathologies, all of which were established prior to the commencement of the study.

Future studies should be specifically designed to focus on ultrasound investigations in PsA or RA. This includes the provision of a detailed SOP outlining ultrasound protocols, measurement cut-offs, and standardised scoring systems. It is also recommended that a dedicated ultrasound machine be allocated for future research to ensure consistency in data collection and to minimise technical and logistical limitations.

Additionally, future studies using objective measures, such as functional magnetic resonance imaging (fMRI), will provide a clearer understanding of pain through more precise characterisation, as they do not rely exclusively on participants' self-reported data. Notably, fMRI can identify altered brain activation patterns associated with chronic pain processing, particularly changes in activation in areas such as the insula, the default mode network (DMN), and the prefrontal cortex. Meanwhile, MSUS reveals structural and inflammatory changes at joints and the entheseal sites. Examining the relationship between these modalities could help determine whether pain in conditions such as inflammatory arthritis is primarily caused by peripheral inflammation, central sensitisation, or a combination of both.

5.6 Conclusion

PsA is a chronic inflammatory arthritis associated with psoriasis, with persistent pain being a key clinical concern and a primary factor affecting patients' quality of life. Although the US remains an essential tool for detecting peripheral inflammatory changes such as synovitis and enthesitis, the current study found no significant correlations between US findings and pain intensity in patients with PsA. The absence of a clear association suggests that pain in PsA may be more influenced by central mechanisms rather than solely by peripheral inflammation. To explore this idea further, fMRI biomarkers will be utilised in the next chapter to gain a deeper understanding of the mechanisms behind pain.

QST, including PPT measured via cuff-evoked pain response and handheld algometry, is a semi-objective method for assessing CS. The results of the current study showed no significant correlation between US enthesitis and PPT responses at both the knee and trapezius sites. These findings further support the hypothesis that ultrasound, which

measures the inflammatory changes, does not fully explain the pain experienced by patients with PsA.

FM is a prototypical central pain condition that is frequently comorbid with PsA and can mimic enthesitis-related pain. While FM was associated with higher LEI scores in this cohort, LEI did not correlate with US findings. This raises concerns about the potential misinterpretation of CS-related pain as active enthesitis based on clinical indices alone. The observed association between FM and LEI, but not with US enthesitis, suggests that LEI may be more reflective of CS than of actual inflammatory pathology.

These findings highlight the limitations of relying solely on clinical examination for diagnosing enthesitis and emphasise the importance of incorporating ultrasound for a more accurate assessment of this condition. Using US alongside QST, especially PPT, can improve the differentiation between peripheral inflammation and central sensitisation, potentially preventing unnecessary treatment escalation and enhancing patient care.

5.7 Mapping the Neurobiological Mechanisms of Pain in Patients with Inflammatory Arthritis Using Musculoskeletal Ultrasound and Functional MRI

5.7.1 Abstract

Introduction

Pain is a critical and multifaceted symptom encountered by patients with inflammatory arthritis, particularly in conditions such as RA and PsA. The pain associated with inflammatory arthritis arises from various mechanisms, including nociceptive and nociplastic processes.

Despite notable advancements in DMARDs and biologics, effective pain management remains a significant challenge in these conditions. Many patients continue to report persistent pain, even when treatment successfully addresses peripheral inflammation. This highlights the need for a deeper understanding of pain mechanisms to improve the management of inflammatory arthritis.

The peripheral pain signals transmitted to the brain primarily involve the neospinothalamic tract, which is recognised as the classical pain pathway and includes several brain regions, such as the SMN-thalamus connectivity. Nociplastic pain, characterised by altered nociception without clear evidence of tissue damage, can lead to central pain sensitisation. This type of pain results in heightened pain responses to mild stimuli. Such changes generate sustained nerve impulses to the central nervous system, causing lasting alterations known as "central sensitisation." These alterations are associated with neurobiological changes in pain processing in the brain, including an increase in DMN-insula connectivity, which serves as a marker of nociplastic pain.

This research aims to bridge the gap between peripheral and central pain mechanisms in inflammatory arthritis by examining the relationship between MSUS metrics and advanced neuroimaging techniques, specifically fMRI. Since MSUS is a reliable method for assessing peripheral inflammatory changes, it is important to determine whether MSUS metrics correlate with functional connectivity between the thalamus and the SMN.

The mixed pain state observed in patients with FM and inflammatory arthritis, such as RA. The inflammation-driven nociceptive pain could contribute to overall pain in RA with FM. MSUS could detect this contribution. This research will investigate the correlation between MSUS metrics and the functional connectivity of the DMN and the insula to understand the pain mechanisms among patients with inflammatory arthritis and FM.

Methods

MSUS and fMRI data from the CENTAUR, SOAR, and TEMPO datasets were included in this research. Patients with RA about to start JAK inhibitors underwent fMRI in SOAR and TEMPO. Additionally, participants with PsA underwent fMRI in the CENTAUR study.

Preprocessing and subsequent image analysis were conducted using Statistical Parametric Mapping 12 (SPM12) alongside the functional connectivity CONN toolbox v19, within MATLAB R2019b. The preprocessing followed the standard Montreal Neurological Institute (MNI) pipeline provided by the CONN toolbox, which involved realignment, slice-timing correction, detection of motion outliers based on ART, co-registration, segmentation of functional and structural images, normalisation to the MNI template, and 8-mm smoothing (convolution with an 8 mm full-width at half maximum Gaussian kernel).

The traditional approach to estimating functional connectivity (FC) involves calculating Pearson correlation coefficients between two time series of BOLD signal fluctuations measured over time. These time series represent the low-frequency variations in the BOLD signal from a source (seed) to a target location. The analysis focused on the increased connectivity between the DMN and the left mid-insula, as well as the ROI-to-ROI functional connectivity between the SMN and thalamus. Additionally, a univariate correlation between the MSUS metric and the fMRI connectivity between the SMN-thalamus and DMN-insula was performed.

Results

A total of 18 participants underwent fMRI and ultrasound procedures in the CENTAUR study. Nineteen participants completed these procedures as part of the SOAR and TEMPO studies. In the CENTAUR dataset, a significant negative correlation was found between US enthesitis and SMN-thalamus connectivity ($r = -0.73$, $p < 0.001$). This negative correlation remains significant after adjusting for age and gender ($r = -0.8$, $p < 0.001$). There was no significant correlation between DMN-L mid-insula connectivity and US metrics, including US enthesitis and US synovitis.

In the SOAR and TEMPO datasets, a suggested trend was observed between USPD and DMN-L mid-insula ($r = 0.420$, $p = 0.07$). However, this correlation becomes significant after adjusting for age and gender ($r = 0.52$, $p = 0.03$). A significant correlation was identified between USBE and DMN-L mid-insula ($r = 0.6$, $p = 0.01$). This correlation remains significant after correction for age and gender ($r = 0.55$, $p = 0.01$). There was no

significant correlation between SMN-thalamus connectivity and US metrics in this population, either before or after correction for age and gender.

Conclusion

No ultrasound metrics, specifically US enthesitis and US synovitis, were found to be correlated with the biomarker of nociplastic pain (DMN-L mid Insula) in the CENTAUR dataset. Therefore, MSUS could identify the nociceptive contribution to the mixed pain among participants with PsA and FM. Additionally, MSUS is negatively correlated with SMN-thalamus connectivity. This could suggest a suppression of SMN-thalamus connectivity among participants with PsA and FM.

In the SOAR and TEMPO datasets, a significant correlation was observed between USPD and the DMN-L mid-insula, as well as between USJE and the DMN-L mid-insula. It is interesting to see a connection between peripheral measures, such as USPD and USBE, and a nociplastic biomarker like DMN-L in the mid-insula. This suggests that nociceptive pain may contribute to the mixed pain experienced by patients with RA and FM. This suggests that peripheral inflammation may influence nociplastic pain, i.e., this provides evidence for bottom-up nociplastic pain.

5.7.2 Introduction

This chapter builds upon previous discussions by exploring the relationship between MSUS metrics and neurobiological pain metrics as objective measures of pain.

In the concluding chapter, the relationship between pain and MSUS metrics was analysed, this time utilising objective pain measurement tools, specifically neuroimaging via fMRI, as objective indicators of pain signal processing. The capability of MSUS to detect nociceptive pain was evaluated by establishing correlations with the traditional pain pathway, specifically the sensorimotor network (SMN)-Thalamus connectivity. Furthermore, the effectiveness of MSUS in identifying inflammation that contributes to the mixed pain state was assessed by correlating MSUS metrics with the nociplastic pain marker, namely the Default Mode Network (DMN)-Insula.

The presence of nociplastic pain in inflammatory arthritis necessitates objective validation to deepen our understanding of the underlying pain mechanisms. Investigating the relationship between MSUS and fMRI will enhance the understanding of pain mechanisms in inflammatory arthritis and provide evidence for the role of peripheral pain in the overall pain experience.

5.7.2.1 Pain in inflammatory arthritis

Pain is a critical and multifaceted symptom experienced by individuals with inflammatory arthritis, particularly in conditions such as RA and PsA. These conditions not only compromise physical functionality but also significantly detract from the overall quality of life, leading to profound psychosocial implications. Despite substantial advancements in DMARDs and biologics, pain management in these diseases remains a significant challenge. Despite effective treatment of peripheral inflammation, a substantial number of patients report ongoing pain, revealing a pressing unmet need in the clinical management of inflammatory arthritis (Sluka and Clauw, 2016).

Historically, pain in RA has predominantly been attributed to peripheral inflammation and the resulting activation of nociceptors, signalling a straightforward somatic mechanism. However, emerging research underscores a more complex narrative that of "centralised pain," wherein changes in the central nervous system (CNS) contribute to the pain experience in these patients (Sluka and Clauw, 2016). Notably, studies indicate that up to 50% of Patients with RA continue experiencing pain despite the absence of measurable inflammatory markers (Taylor et al., 2010). Similarly, patients with PsA often grapple with

pain that extends beyond visible joint damage and inflammation, thus impacting their health-related quality of life, work capacity, and psychological well-being, even those undergoing therapy with TNF inhibitors (Conaghan et al., 2020).

As this investigation unfolds, it is essential to consider the multifactorial nature of pain, a phenomenon inherently shaped by biological, psychological, and social factors. By employing objective neurobiological measures, the aspiration is to contribute to a more holistic understanding of pain and its intricate relationship with MSUS findings. In doing so, the aim is to enhance diagnostic accuracy, develop more effective treatment strategies, and ultimately improve the quality of life for individuals suffering from chronic pain conditions.

Pain in inflammatory arthritis arises from multiple mechanisms: nociceptive, inflammation-associated, and nociplastic. Nociceptive pain reflects the classical pathway by which noxious stimuli are transmitted through the spinal cord to the thalamus, somatosensory cortices (S1/S2), and the insula. This pathway is often associated with active inflammation and tissue damage, which can be assessed via musculoskeletal ultrasound (MSUS).

The neospinothalamic tract, part of the three main spinal thalamic pathways shown in Figure 5.17, has a limited number of synapses and is recognised as the classical lateral spinothalamic tract (LST). First-order nociceptive neurons, situated in the dorsal root ganglion (DRG), establish synaptic connections with neurons in Rexed layer I (the marginal zone). The axons of these layer I neurons decussate in the anterior white commissure at approximately the same level at which they enter the spinal cord, subsequently ascending in the contralateral anterolateral quadrant. The majority of pain fibres from the lower body and extremities terminate in the ventroposterolateral (VPL) nucleus and the ventroposteroinferior (VPI) nucleus of the thalamus, which functions as a relay station to convey signals to the primary cortex. It is thought that the VPL primarily plays a role in discriminatory functions. The VPL then projects axons to the primary somatosensory cortex (SCI Brodmann areas 1 & 2). This pathway is key to the immediate perception of pain and the awareness of the exact location of the painful stimulus (Byrne and Dafny, 1997). The spinoreticulothalamic tract (SRT) represents another significant input pathway in the spinal cord. It is thought that the SRT conveys nociceptive information primarily to the medial thalamus via an additional synaptic relay in the brainstem known as the medullary reticular formation. The lateral and medial thalamus each connect to specific sets of cortical target areas: the lateral thalamus is associated with

the somatosensory cortex, while the medial thalamus innervates limbic structures, such as the anterior cingulate cortex and the insular cortex. These parallel spinothalamocortical pathways are referred to as the lateral and medial pathways, respectively (Groh et al., 2017).

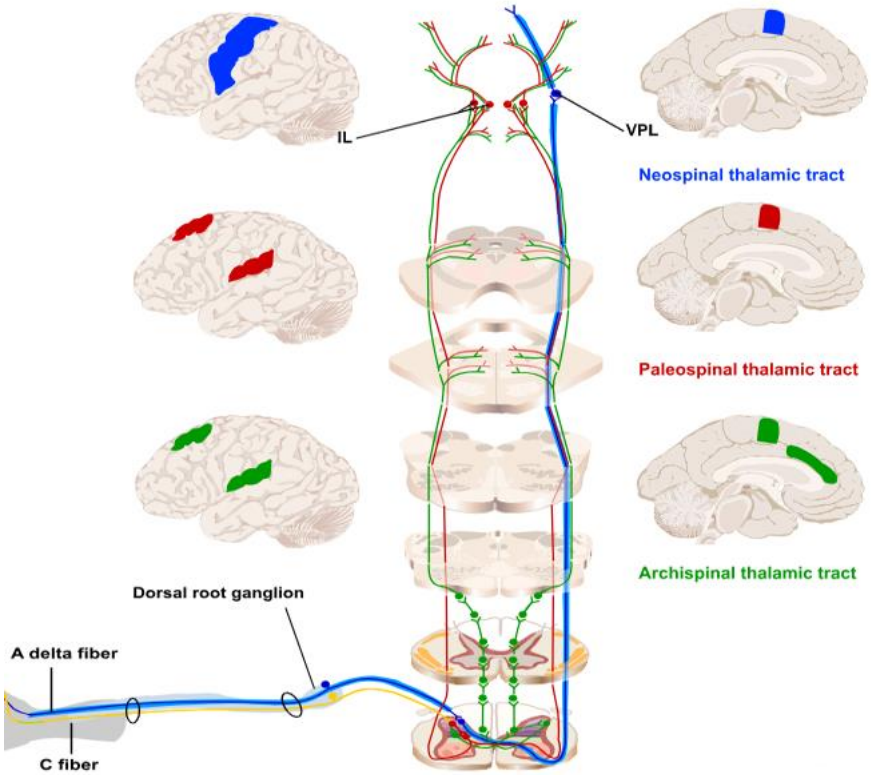

Figure 5.17: Three main spinal thalamic pathways include the neospinothalamic tract, responsible for the immediate awareness of a painful sensation and the precise location of the painful stimulus; the palaeospinothalamic tract, which activates brain stem nuclei to regulate noxious input at the spinal cord level; and the archispinothalamic tract, an older pathway that carries noxious information from an evolutionary perspective. Source: (Byrne and Dafny, 1997).

Nociplastic pain is defined as pain that results from changes in nociception without any clear evidence of tissue damage. This type of pain activates the peripheral nociceptor or the somatosensory system (Kosek et al., 2021). The pain process can lead to central pain sensitisation. This pain can elicit heightened sensitivity in the nervous system, leading to structural and chemical changes that serve to “prime the pain-processing pump”, i.e., sensitisation of the nervous system to amplify pain signals (Byrne and Dafny, 1997).

Sensitisation is a key mechanism underlying chronic pain. Prolonged exposure to harmful stimuli activates previously dormant nociceptive neurons, while biochemicals released at the injury site modify nociceptor functions, leading to spontaneous pain signals. This process, known as “peripheral sensitisation,” results in increased pain responses to mild stimuli. Such changes generate sustained nerve impulses to the central nervous system, causing enduring alterations referred to as “central sensitisation.”

Both forms of sensitisation can continue post-injury due to inflammatory mediators. Substances such as substance P and calcitonin gene-related peptide amplify pain signals from the injured area. At the same time, central sensitisation often involves excessive glutamate release onto dorsal horn neurons, engaging NMDA receptors and leading to hyperexcitability (Byrne and Dafny, 1997).

Nociplastic pain, which is characterised by central sensitisation and altered pain modulation, often occurs in the absence of inflammation. Neuroimaging studies such as fMRI have found that nociplastic has been associated with abnormal functional connectivity between the Default Mode Network (DMN) and the insula, a pattern observed in patients with fibromyalgia (Napadow et al., 2010), a subset of Patients with RA exhibiting "Fibromyalgianess" (Basu et al., 2018) and patients with PsA (Sunzini et al., 2025).

In RA, it is suggested that peripheral inflammatory pain signals may sensitise the CNS through pro-nociceptive pathways, contributing to the development of FM as a comorbidity (Harte et al., 2018).

Basu and his colleagues (2018) emphasise that Patients with RA with fibromyalgia exhibit coexisting central sensitisation alongside the more well-established peripheral inflammatory pain. They reported that high connectivity between the DMN and the insula is considered a key central marker of pain. They suggest that nociplastic pain in RA reflects a mixed pain mechanism characterised by significant central sensitisation, which plays a major role. In contrast, peripheral inflammation-driven nociceptive pain (classic RA) contributes less to the overall pain experience.

5.7.2.2 The role of MSUS in RA pain

MSUS, a non-ionising imaging technique, is commonly employed to assess musculoskeletal structures, especially in patients with RA, due to its effectiveness in revealing structural changes such as synovitis, enthesitis, and bone erosion.

Grayscale (B-mode) ultrasound depicts synovitis as hypoechoic thickening of the synovial tissue and is also capable of detecting soft tissue oedema and joint effusion. Power Doppler ultrasound (PD) is used to assess synovial vascularity, an indicator of active inflammation and a marker of disease activity in RA.

The MSUS is essential for diagnosing RA, as it assesses structural damage and evaluates disease activity. Furthermore, it contributes significantly to understanding the origins of pain by detecting peripheral changes associated with nociceptive pain. Moreover, MSUS provides crucial evidence for diagnosing nociceptive pain by assessing disease activity and excluding peripheral causes, while also playing a vital role in monitoring treatment responses and confirming remission in RA.

5.7.2.3 The Role of fMRI in RA Pain

Functional MRI (fMRI) is a powerful, non-invasive tool for measuring neural activity via blood-oxygen-level-dependent (BOLD) signals. The principles of MRI rely on the alignment of hydrogen nuclei in the body when exposed to a strong magnetic field created by a superconducting magnet, typically ranging from 1.5 to 7 Tesla. The hydrogen nuclei, consisting of a single proton with a magnetic moment, align their magnetic vectors in this field, generating longitudinal magnetisation. A radiofrequency (RF) then creates transversal magnetisation by aligning the phases of the protons and "bending" their magnetic moments. Once the RF is removed, longitudinal and transversal relaxation occur, releasing a detectable signal.

Time constant T1 indicates increasing longitudinal relaxation, while T2 measures the reduction of transversal magnetisation. Different body tissues have varying relaxation times, allowing for contrast differentiation based on RF frequency and signal detection timing. T1-weighted images provide high spatial resolution for solid tissues, whereas T2-weighted images emphasise fluid-rich tissues, such as cerebrospinal fluid (CSF) and blood vessels, offering valuable structural and morphological information.

The T2 star (T2*) acquisition technique integrates T2 properties with the effects of local molecules on transversal relaxation, making T2*-weighted sequences sensitive to tissue oxygenation. Haemoglobin displays different magnetic properties based on its oxygenation status, with oxygenated haemoglobin enhancing and deoxygenated haemoglobin reducing the T2* MRI signal. This allows for the investigation of oxygenation levels in the brain, reflecting metabolic demand and serving as a reliable indirect measure of neuronal activity.

The BOLD contrast is the most common approach in fMRI, which measures the ratio between oxygenated and deoxygenated haemoglobin. The use of BOLD fMRI has surged over the past two decades due to its high spatial and temporal resolution for studying brain activity, which enables the capture of metabolic activity in small brain volumes, or voxels, a three-dimensional cube of brain tissue, where the intensity value indicates the properties of that tissue, including signal strength, typically every 1-2 seconds.

To investigate the role of the brain in pain, fMRI data must first undergo several steps, typically including data acquisition, reconstruction, preprocessing, and analysis. Various parameters influence data acquisition, while reconstruction converts signals into images. Pre-processing reduces artefacts and standardises brain structures across subjects, enabling the comparison of neurobiological signals between individuals. Ultimately, the analysis phase employs statistical methods to address specific research questions, such as linking neurobiological signatures with objective or subjective measures of pain to identify its biomarkers.

One way to identify potential pain biomarkers is to extract functional connectivity from pre-processed fMRI data. Functional connectivity is inferred from BOLD signal correlations, indicating interactions between brain areas during tasks or at rest. It describes the temporal relationship between neuronal activity patterns in distinct brain regions and is typically measured using fMRI. By analysing the coactivation levels in functional MRI time-series data, researchers can infer patterns of communication between brain areas and explore how these relate to behaviour or disease. A high positive connectivity indicates synchronised activity (co-activation and co-deactivation), reflecting cooperation between regions. In contrast, negative connectivity (anticorrelation) suggests that the activity of one brain region decreases when the activity of another region increases, indicating functional competition (Martijn et al., 2010; Fox et al., 2005). Increased connectivity in an fMRI study, therefore, suggests improved communication and cooperation between these areas, while decreased connectivity indicates reduced synchrony (Hutchison et al., 2013).

Resting-state fMRI (rs-fMRI) has become a particularly valuable method for investigating chronic pain. Unlike task-based paradigms, it records spontaneous brain activity while participants are simply instructed to relax (Biswal et al., 1995). This technique avoids exposure to ionising radiation (Tu et al., 2020; Stefanov et al., 2023) and detects groups of brain regions with synchronised activity, which can offer unique insights into the intrinsic connectivity of pain-related networks without requiring external stimuli.

Among the most studied networks in the context of pain is the DMN, which supports self-reflection, autobiographical memory, and internally directed cognition (Raichle et al., 2001). DMN comprises various interconnected regions of the brain, including the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC), precuneus, inferior parietal lobule (IPL), hippocampal formation, as well as the lateral temporal and parietal cortices (Davey et al., 2016). Importantly, altered DMN connectivity has been linked to pain processing. For example, functional connectivity between the DMN and the insula correlates with fibromyalgia (FM) severity in patients with RA and PsA (Basu et al., 2018; Sunzini et al., 2025), suggesting that DMN–insula connectivity may serve as a consistent neural marker of nociplastic pain across different chronic conditions, including inflammatory arthritis. The insular cortex plays a central role in both acute and chronic pain, with the posterior insula encoding the intensity of pain and the anterior insula being involved in the emotional and cognitive dimensions of pain (Labrakakis, 2023).

While the DMN has been linked to nociplastic pain, the sensorimotor network (SMN) is central to nociceptive pain processing, which includes the primary and secondary somatosensory cortices, motor cortices, posterior insula, and basal ganglia (Bhatt et al., 2020). The thalamus plays a central role in processing bodily sensations and guiding appropriate motor responses. It acts as a major relay hub as it transmits nociceptive input from the periphery to cortical regions of the SMN (Yen et al., 2013). The thalamus relays sensory information and motor impulses through its connections with the somatosensory and motor cortices, playing a crucial role in pain perception and the persistence of chronic pain. Mao et al. (2024) identified altered SMN-thalamus connectivity in the lateral thalamus, indicating potential sensory discrimination issues in inflammatory arthritis, which highlight the role of the sensorimotor cortex-thalamus pathway. Thus, SMN-thalamus connectivity provides insights into the neural underpinnings of nociceptive and inflammation-related pain in inflammatory arthritis (Sunzini et al., 2025).

Studies have consistently demonstrated pain-related alterations in connectivity and morphology within the thalamus, insula, somatosensory cortices, prefrontal cortex, and cingulate regions (Sunzini et al., 2023; Smallwood et al., 2013).

5.7.3 Aims and Rationales

This chapter aims to bridge the gap between peripheral and central mechanisms of pain in RA by examining the relationship between MSUS metrics and advanced neuroimaging techniques, specifically fMRI. This research sought to provide new insights that could

transform pain assessment and management in these conditions. Previous chapters have laid a solid groundwork, focusing on subjective and semi-objective assessments of pain; however, there is a crucial need to shift towards an objective approach, utilising biomarkers that can elucidate the underlying mechanisms of pain.

Through the integration of fMRI and MSUS, this chapter endeavours to delineate the intricate interplay between structural changes observable via ultrasound and neurobiological biomarkers associated with pain processing in the brain. fMRI enables the tracking of functional connectivity between the DMN and insula, a central biomarker of pain. At the same time, MSUS is considered the gold standard for detecting peripheral synovial changes in RA. These approaches are objective tools that transcend subjective patient reports, enabling researchers to uncover how different pain stimuli are processed in the brain and how these processes may correlate with observable changes in joint structure and inflammation, as assessed by MSUS.

5.7.3.1 First aim

As described above, a classical pathway of pain exists, known as the neospinothalamic pathway. fMRI allows for the detection of nociceptor activation within this pathway, which occurs in response to active peripheral pain in RA. The neural regions of the thalamus and the SMN are part of the spinothalamic pathway and exhibit activation in response to stimuli originating from peripheral changes. Since MSUS is a reliable method for assessing peripheral inflammatory alterations, it is important to determine whether MSUS metrics correlate with functional connectivity between the thalamus and the SMN.

5.7.3.2 Second aim

Previous research highlights that Patients with RA with fibromyalgia experience mixed pain mechanisms characterised by significant central sensitisation in conjunction with peripheral inflammatory pain (Basu et al., 2018). fMRI can measure the neurobiomarker of nociplastic pain, specifically the connectivity between the DMN and the insula. This connectivity tends to increase in response to nociplastic pain experienced by patients with RA, PsA, and FM. This aspect represents one component of the mixed pain that may contribute significantly to overall pain levels in this population. In contrast, the inflammation-driven nociceptive pain is anticipated to make a smaller contribution to the overall pain experienced.

This research will investigate the correlation between MSUS metrics and the functional connectivity of the DMN and the insula, which serve as neurobiomarkers for nociplastic pain as measured by fMRI. It is not anticipated that any correlation will be found, given that the mechanisms of pain differ.

5.7.4 Hypothesis

In this study, it is hypothesised that MSUS metrics exhibit a statistically significant correlation with the neospinothalamic pathway, also known as the classical pain pathway, indicating the presence of nociceptive pain stemming from inflammatory joint changes in patients with active inflammatory arthritis.

Furthermore, it is also hypothesised that MSUS metrics will not demonstrate a statistically significant correlation with the connectivity of the DMN-insula, which serves as a biomarker for nociplastic pain in patients with RA and FM.

5.7.5 Methods

5.7.5.1 For the CENTAUR study

A single-centre observational study titled "Characterising Centralised Pain in Chronic Rheumatic Disease" (CENTAUR) aimed to investigate centralised pain in patients with PsA. The study has received ethical approval from the West of Scotland Research Ethics Committee. It employed various methods, including comprehensive questionnaires, QST, MSK and advanced neuroimaging techniques. These methods investigate the relationship between experienced pain and peripheral changes in the PsA population.

The inclusion and exclusion criteria were applied concurrently to assess the eligibility of participants. Initially, individuals diagnosed with PsA who met the CASPAR criteria and were experiencing active disease were targeted for recruitment, particularly those on the verge of initiating or changing a biologic treatment or DMARDs. Selecting participants with comparable high disease activity ensured a greater homogeneity within the study population. Notably, the level of disease activity is indicative of the extent of inflammation, which directly impacts the pain experienced. Moreover, the degree of active inflammation may correlate with sensitisation processes within the nervous system, both peripherally and centrally. Therefore, including individuals with active disease, as evidenced by the clinical need to commence a biologic or DMARD, was essential for this study. Additionally, assessing treatment response served as an indirect indicator of inflammation. However, it is crucial to recognise the influence of other variables that may affect pain mechanisms differently, including variations in disease duration and the initiation of different treatments, which are typically associated with cross-sectional studies.

In this investigation, participants aged 75 and older were systematically excluded from participation. The exclusion of this demographic from clinical trials is not universally applied and is influenced by various factors. Primarily, concerns regarding health and safety arise due to the complexities related to age-associated physiological changes, comorbid health conditions, and diverse pharmacological treatments. Furthermore, this age group is more prone to experiencing age-related structural changes, as well as alterations in vasculature and neurovascular coupling to the brain, which may complicate MRI analyses (Tsvetanov et al., 2015).

5.7.5.2 For the SOAR study

A single-centre, single-arm observational cohort study allowed us to investigate the analgesic mechanism of Olumiant in patients with RA. SOAR - Exploiting Leading Edge 7T MRI Brain Imaging to Decipher Olumiant's Mode of Analgesic Action in RA.

The inclusion criteria were as follows: Adults aged between 18 and 75 years. A clinical diagnosis of RA and selected to initiate treatment with Olumiant by their regular rheumatology clinical team, in line with local guidelines (having previously failed at least two DMARDs and exhibiting moderate to severe active disease). Also, participants were right-handed to reduce variability in neuroimaging results.

The exclusion criteria were as follows: participants unable to provide written informed consent, those with severe physical impairments (such as blindness, deafness, or paraplegia), pregnant or breastfeeding individuals, and those with contraindications to MRI (e.g., severe claustrophobia). Additionally, participants with significant confounding neurological diseases, including Multiple Sclerosis, Stroke, Traumatic Brain Injury, Parkinson's Disease, or Alzheimer's Disease, were excluded. Previous exposure to targeted synthetic DMARDs (such as Olumiant or tofacitinib) was also a factor. Furthermore, co-morbid medical conditions that could substantially impair physical functional status, as well as medical or psychiatric conditions that, in the judgment of the study personnel, would prevent participation in this study (e.g., malignancy, psychosis, or suicidal ideation), were considered exclusionary. Lastly, participants with a BMI greater than 40 or those who were unable to lie comfortably in the MRI scanner were also excluded.

5.7.5.3 For the TEMPO study

Exploiting leading-edge 7 Tesla MRI brain imaging to decipher Filgotinib's mode of analgesic action in RA (TEMPO).

A single-centre, observational test-retest study. Participants with moderate to severe active RA who have been prescribed Filgotinib according to standard care practices and meet the eligibility criteria. MRI scans and MSUS procedures were undertaken prior to treatment initiation.

Inclusion criteria specified that participants must be adults aged 18 to 75 years. Exclusion criteria included participants who were unable to provide written informed consent, those with severe physical impairments (such as blindness, deafness, or paraplegia), individuals

who were pregnant or breastfeeding, and participants with severe claustrophobia that would prevent them from undergoing an MRI. Additionally, individuals with contraindications to MRI and those with significant confounding neurological conditions, including multiple sclerosis, stroke, traumatic brain injury, or prior exposure to targeted synthetic DMARDs (e.g., baricitinib, tofacitinib), were also excluded from the study.

5.7.5.4 MSUS data collection

5.7.5.4.1 MSUS for CENTAUR study:

All participants involved in the ultrasound examinations provided written consent. The ultrasounds were performed at baseline and during follow-up visits at the 6-month mark. A single operator conducted the procedures using a portable ultrasound device (Voluson I, GE Healthcare) in conjunction with a 10–16 MHz linear array probe (SP 10–16RS, GE Healthcare). Power Doppler (USPD) assessments were executed with specific settings: high frequency, a pulse repetition frequency of 0.9 kHz, a low wall filter, and gain adjusted to a level below where Doppler artefacts became noticeable beneath the bone. The MSUS evaluation utilised a binary scale to assess synovial thickening and joint power Doppler findings in patients diagnosed with PsA.

The ultrasound assessment included forty joints per patient, encompassing bilateral metacarpophalangeal (MCP), proximal interphalangeal (PIP), distal interphalangeal (DIP), and metatarsophalangeal (MTP) joints. Both synovial hypertrophy on B-mode and Doppler activity were evaluated. Scoring was performed using a binary scale, where 0 indicated the absence of findings and 1 indicated their presence, based on previously published scoring criteria (Husic et al., 2014; Gutierrez et al., 2011). In this study, a joint was classified as having active synovitis only when both B-mode synovial thickening and/or PD signal were present (Dubash et al., 2020).

A bilateral assessment was conducted on six entheseal sites: the superior and inferior poles of the patella, the calcaneal insertion of the Achilles tendon, and the lateral condyle of the elbow. USPD signal is less common in PsA than in RA (Zabotti et al., 2017; Dumitrascu et al., 2022). Nevertheless, it remains a sensitive tool for detecting inflammation at entheseal sites adjacent to synovial joints in PsA (Dubash et al., 2020).

In B-mode evaluation of the enthesis, abnormal thickening was identified using site-specific thresholds established by Balint et al. (2002, 2018) and Toprak et al. (2012). The

cutoff threshold was determined as the mean value plus two standard deviations (2 SD), as described by Williams et al. (2022). The cutoff thresholds are as follows: ≥4.0 mm at both the superior and inferior patellar poles, ≥5.29 mm at the Achilles insertion (Balint et al., 2002), and >4.2 mm at the lateral epicondyle of the elbow (Toprak et al., 2012). Measurements were conducted within 2 mm above the bony cortex. The definition of MSUS enthesitis included the presence of one or more features, such as entheseal thickening, hypoechogenicity, calcifications, enthesophytes, erosions, and/or a positive PD signal, in line with OMERACT definitions.

5.7.5.4.2 MSUS for SOAR and TEMPO studies

Ultrasound imaging was performed using the GE Venue Fit R3 system equipped with a high-frequency linear transducer (3–20 MHz). USSH, USJE, USPD, and USBE were systematically assessed.

USPD imaging was uniformly applied to all joints using settings optimised for low-flow detection, including safe diagnostic power settings, minimised colour box size, a region of interest encompassing the intra-articular space and adjacent bone margins, pulse repetition frequency (PRF) set at 0.9 kHz to enhance sensitivity, high-frequency mode, low wall filter, and gain adjusted just below the threshold of Doppler noise artefacts. Standardised bilateral scanning included the wrists, metacarpophalangeal joints (MCPs), proximal interphalangeal joints (PIPs), knees, metatarsophalangeal joints (MTPs), and, where applicable, the two most symptomatic joints.

Inflammatory abnormalities were evaluated in accordance with internationally validated consensus-based definitions. Synovial hypertrophy was defined as abnormal hypoechoic intra-articular tissue that is non-displaceable and poorly compressible, while joint effusion was defined as abnormal anechoic or hypoechoic intra-articular fluid that is displaceable and compressible, without a Doppler signal, consistent with OMERACT criteria (Wakefield et al., 2005). USPD activity reflected intra-synovial vascularisation and was interpreted in line with EULAR–OMERACT recommendations (D'Agostino et al., 2017).

Although semi-quantitative grading systems are widely employed in inflammatory arthritis research, ultrasound findings in the SOAR and TEMPO studies were recorded using a binary scoring approach (0 = absence; 1 = presence). This strategy was adopted to enhance feasibility and optimise interobserver consistency in the context of comprehensive multi-joint assessment, consistent with methodologies reported in previous ultrasound studies (Husic et al., 2014; the et al., 2011).

Bone erosions were defined in accordance with OMERACT ultrasound criteria as intra-articular cortical discontinuities visible in two perpendicular planes (Wakefield et al., 2005). Structural damage was evaluated using the Ultrasound Structural Erosion Score (ScUSSe) system (Sommier et al., 2006). This system was selected on the basis of feasibility and practicality, as it enables structured categorisation of erosions according to predefined size thresholds without requiring direct measurement using callipers or rulers. Such an approach reduces operator dependency while maintaining systematic and reproducible assessment of structural abnormalities. A conservative interpretative approach was deliberately implemented. Isolated cortical surface irregularities were not automatically classified as erosions, as such appearances may reflect mechanical stress, degenerative change, or normal anatomical variation rather than inflammatory pathology (Wakefield et al., 2005; D'Agostino et al., 2017). Only unequivocal cortical discontinuities fulfilling consensus-based definitions were graded as erosions. This approach was adopted to enhance specificity, minimise misclassification, and avoid overestimation of inflammatory structural damage.

5.7.5.5 FMRI data collection

5.7.5.5.1 FMRI for CENTAUR study

Participants underwent scans using a 3 Tesla Siemens PRISMA (Siemens, Erlangen, Germany) located in Glasgow (UK), employing the body transmit and a receive-only head coil with 32 phased-array channels. These scans included a structural sequence: T1-weighted fast-field echo 3D structural image (TR = 2500 ms, TE = 2.88 ms, inversion time (TI) = 1070 ms, flip angle = 8°, FOV = 256 mm, consisting of 176 slices, with 1 mm iso-voxel). The functional images were acquired through a T2*-weighted multiband EPI sequence (TR = 800 ms, TE = 30 ms, flip angle = 52°, FOV = 216 mm, acceleration factor = 6, 60 slices, totalling 440 volumes at 2.4 mm iso-voxel). A 6-minute resting-state fMRI scan was conducted for the analysis, during which participants were instructed to lie on their backs in the scanner and keep their eyes open, concentrating on a fixation cross without participating in any particular task.

5.7.5.5.2 FMRI for SOAR and TEMPO studies

Participants underwent MRI scans using an ultra-high-resolution MRI scanner at The Imaging Centre of Excellence (ICE) in Glasgow. The scanner was a MAGNETOM Terra

7T scanner (Siemens Healthcare, Erlangen, Germany), equipped with a single-channel transmit and a 32-channel receive radiofrequency head coil (Nova Medical, Wilmington, MA).

A whole-brain T1-weighted structural image was collected utilising a twice magnetisation-prepared rapid gradient echo (MP2RAGE) sequence. The parameters for this sequence included: TR = 5000 ms, TE = 1.94 ms, TI1 = 700ms, TI2 = 2700ms, FA1 = 4, FA2 = 5, iso-voxel 1.5mm, 208 slices, FOV = 240mm.

A resting state BOLD-fMRI scan was performed. fMRI scans were performed while participants rested in the scanner. A duration of eight minutes of whole-brain resting state MRI data was gathered using a simultaneous multi-slice (SMS) echoplanar imaging (EPI) with the following parameters: TR = 1500ms, TE = 25ms, FA = 65, iso-voxel 1.5mm, 80 slices, 307 volumes, multiband acceleration factor = 4, FOV = 192mm.

5.7.5.6 Preprocessing of CENTAUR, SOAR, and TEMPO fMRI data

Preprocessing and subsequent image analysis were performed using SPM12 in conjunction with the functional connectivity CONN toolbox v19 (Nieto-Castanon, 2020), operating within MATLAB R2019b. The preprocessing followed the standard Montreal Neurological Institute (MNI) pipeline provided by the CONN toolbox, which included realignment, slice-timing correction, detection of motion outliers based on ART, co-registration, segmentation of functional and structural images, normalisation to the MNI template, and 8-mm smoothing (convolution with an 8 mm full-width at half maximum Gaussian Kernel). All scans underwent a visual inspection to check for artefacts. Individual volumes were excluded from analysis if they exhibited more than two millimetres of motion or a global BOLD signal exceeding nine standard deviations. A patient was deemed eligible for exclusion if over 20% of their functional volume was removed (88 volumes). Signals from white matter and cerebrospinal fluid were obtained using the CompCor method, and motion parameters were incorporated into the analysis as covariates of no interest through ordinary least squares regression. A bandpass filter (frequency range: 0.008–0.09 Hz) was utilised to eliminate linear drifts and high-frequency noise from the dataset.

5.7.5.7 Functional connectivity analysis pipelines

The traditional method for estimating functional connectivity (FC) involves calculating Pearson correlation coefficients between two time series of BOLD signal fluctuations measured over time. These time series consist of the low-frequency BOLD signal

variations from a source (seed) and a target location. Typically, the seed refers to a brain ROI, which includes a collection of voxels representing a specific anatomical area of the brain. The target could either be the time course of a single voxel (seed-to-voxel) or the time course averaged over all the voxels within another ROI (ROI-to-ROI). To determine if a participant experiencing nociplastic pain exhibits increased connectivity between the DMN and the left mid insula, the ROI-to-ROI functional connectivity between the DMN and the left mid insula was analysed.

Group independent component analysis was conducted to identify the DMN utilising the Group ICA of the fMRI Toolbox (GIFT) software (Egolf et al., 2004). Using the pre-processed functional data, the component estimates were validated 20 times with the Infomax ICA algorithm in the ICASSO software (Kaplan et al., 2019; Schrepf et al., 2018). In line with analyses performed in RA studies, 40 components were employed to pinpoint both cortical and subcortical components that relate to brain networks. Subject-specific spatial maps and time courses were derived using the GICA3 back reconstruction method. The DMN was validated through spatial correlation between the component maps and a published template map created by Beckmann et al. (2005), which examined intrinsic connectivity that significantly overlaps with networks derived from task-based connectivity (Smith et al., 2017). A spatial mask of the mean component map for the DMN was generated using the MarsBaR toolbox. The same pipeline was conducted to identify the sensorimotor network (SMN). Functional connectivity was extracted between the DMN and the left mid-insula region as a sphere with a diameter of 8 mm using coordinates from the findings of nociplastic pain in RA (Basu et al., 2018). The thalamus in the SMN-thalamus connectivity was based on the MNI-based brain Harvard-Oxford atlas (Whitfield-Gabrieli et al., 2012).

5.7.5.7.1 Statistical software

The analysis was conducted using JASP 0.16.2 (Jeffrey's Amazing Statistics Program). The statistical tests were considered significant if $p < 0.05$.

5.7.5.7.2 Descriptive analysis

Descriptive statistics were conducted on the MSUS metrics at baseline and fMRI connectivity between the SMN-thalamus and DMN-insula at the CENTAUR, SOAR, and TEMPO datasets at baseline. This involves calculating means, standard deviations (SD), medians, median absolute deviations (MAD), and frequency distributions, and performing normality tests using the Shapiro-Wilk test across various time points.

Finally, participants who met the FM criteria (WPI and SSS) were identified in CENTAUR, SOAR, and TEMPO. A participant was classified as having FM when the three conditions of the 2011 ACR FM criteria were fulfilled: 1) WPI ≥ 7 and SSS ≥ 5, or WPI between 3–6 and SSS ≥ 9 (Wolfe et al., 2011).

5.7.5.7.3 Univariate correlation between MSUS metric and fMRI connectivity between SMN-thalamus and DMN-insula

The relationship between MSUS metrics and fMRI connectivity between the SMN-thalamus and DMN-insula was investigated using univariate correlation, which assesses relationships between two variables, at the CENTAUR, SOAR, and TEMPO datasets. Pearson correlation was utilised for normally distributed continuous variables, while Spearman correlation was applied for ordinal or non-normally distributed variables. These methods provided insights into the strength and direction of variable relationships between MSUS metrics and fMRI connectivity between the SMN-thalamus and DMN-insula at the baseline in the CENTAUR, SOAR, and TEMPO datasets.

5.7.6 Results

5.7.6.1 The fMRI and MSUS results of the CENTAUR study

A total of 18 participants underwent fMRI and ultrasound procedures as part of the CENTAUR study. The table below presents the medians for DMN-Left mid Insula connectivity and SMN-thalamus connectivity, which are -0.176 and -0.017, respectively, as seen in Table 5.3. The negative values suggest a lack of synchronised activity between these regions, indicating that when one area is active, the other is not.

Table 5.3: Descriptive Results of fMRI and MSUS in the CENTAUR dataset.

	SMN-thalamus	DMN-Lmid Insula	Enthesitis	Synovitis
Count	18	18	18	18
Median	-0.01	-0.17	3.00	5.00
Mean	0.06	-0.18	3.11	5.22
Std. Deviation	0.26	0.21	1.99	3.50
MAD	0.13	0.15	1.00	2.00
IQR	0.33	0.29	2.00	3.75
Shapiro-Wilk	0.93	0.96	0.93	0.95
P-value of Shapiro-Wilk	0.19	0.72	0.21	0.56

Moreover, the strength of connectivity between the DMN-L mid Insula is greater than that of SMN-thalamus connectivity. This observation implies that nociplastic pain may be more prevalent in this population compared to nociceptive pain, warranting further investigation. Additionally, the mean absolute deviation (MAD) values for both DMN-L mid Insula and SMN-thalamus connectivity are large, indicating unstable variability around the median values. Figure 5.18 shows the distributions of MSUS metrics, SMN-thalamus connectivity, and DMN-insula connectivity.

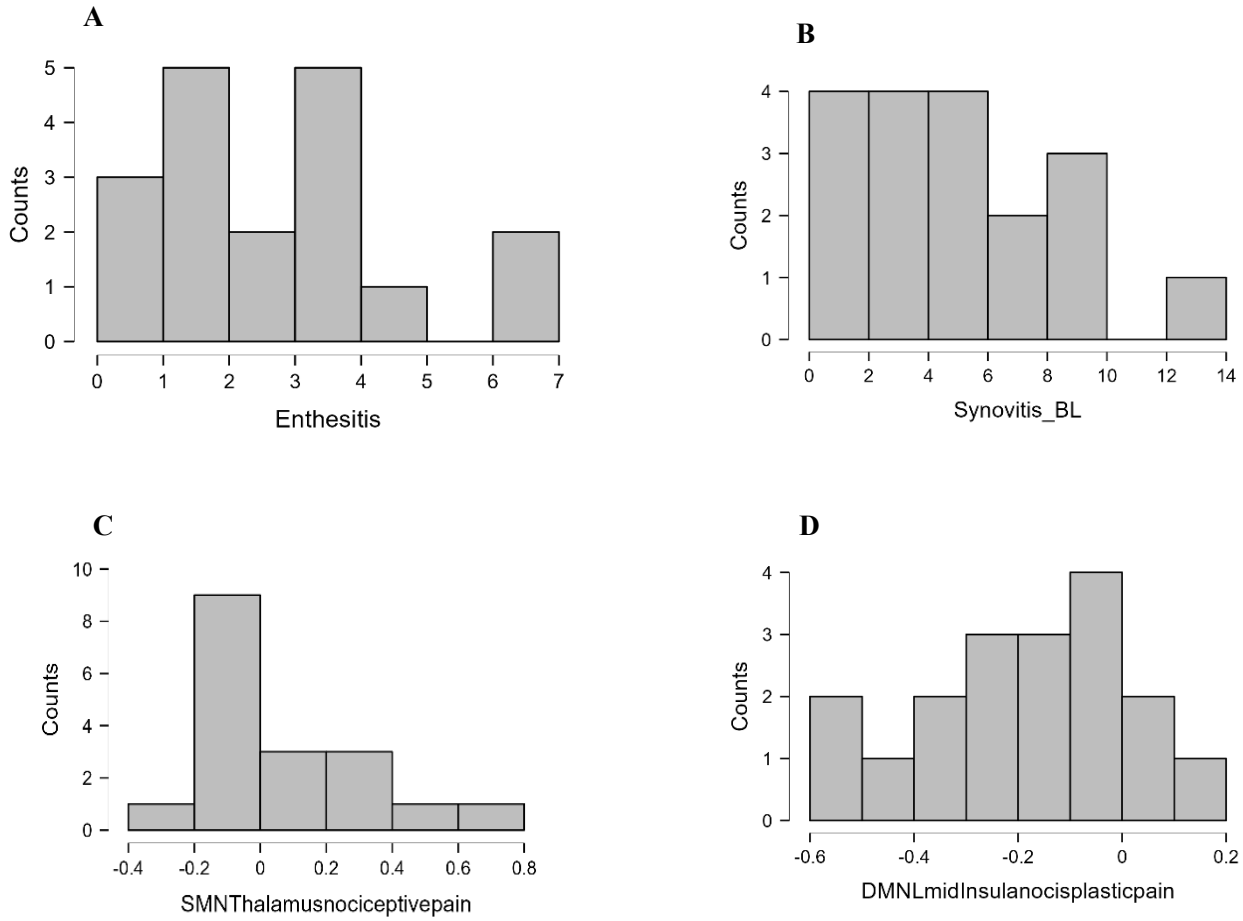

Figure 5.18: Distribution of US enthesitis score, US synovitis score, SMN-thalamus connectivity value, and DMN-Lt mid-Insula connectivity value at the baseline at the CENTAUR dataset. Histograms showing the distribution of (A) Enthesitis scores, (B) US synovitis show right-skewed distributions. In contrast, SMN–thalamus connectivity (C) and DMN–LT mid-insula connectivity (D) demonstrate broader distributions.

5.7.6.2 Univariate correlation

Univariate correlations were performed between US enthesitis and DMN-L mid Insula connectivity, US enthesitis and SMN-thalamus connectivity, US synovitis and DMN-L mid Insula connectivity, as well as US synovitis and SMN-thalamus connectivity, as seen in Table 5.4 and Figure 5.19.

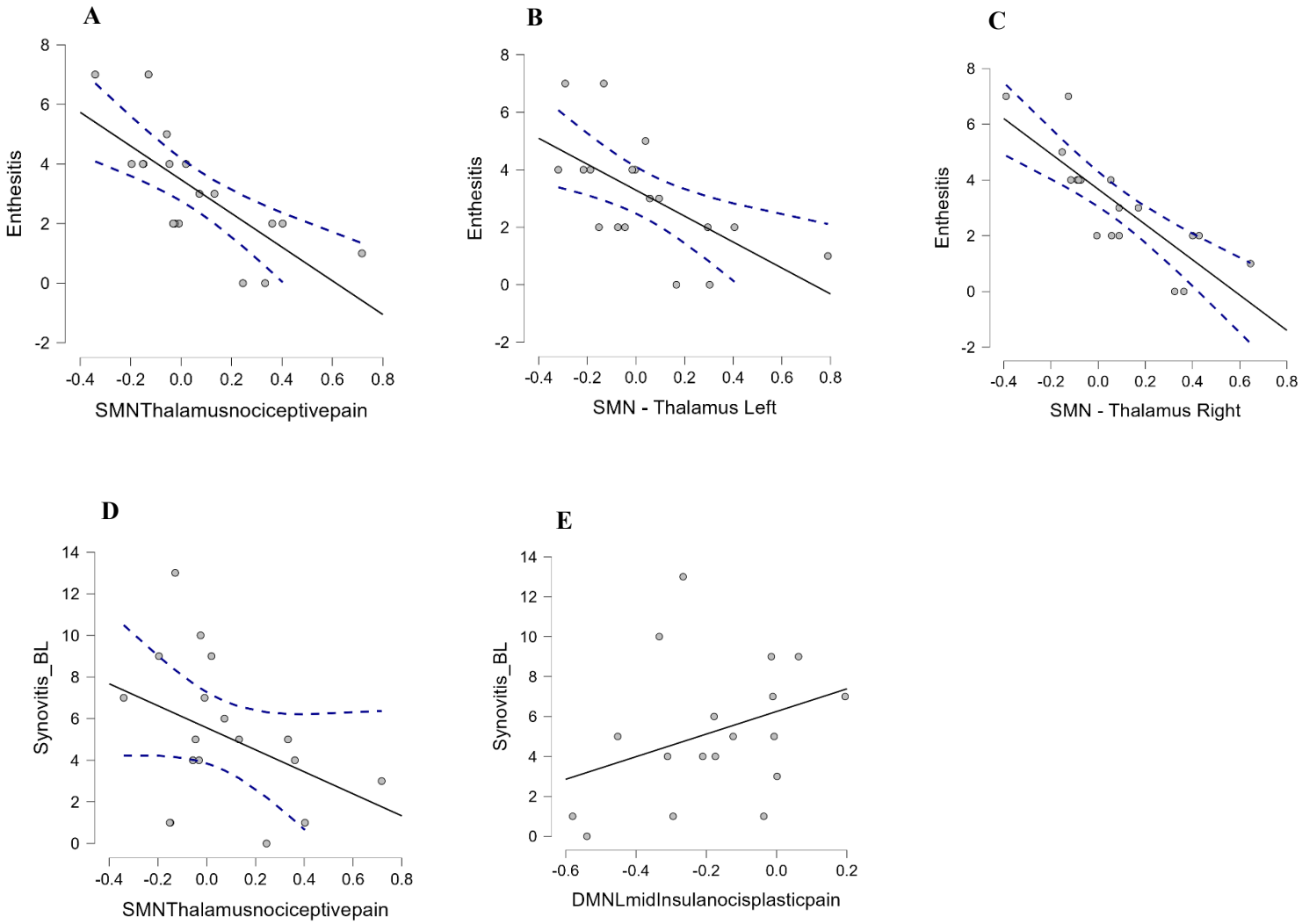

Figure 5.19: Correlations of US metrics vs. SMN-thalamus and DMN-LT mid insula at the baseline at the CENTAUR dataset. US enthesitis is significantly correlated with SMN-thalamus connectivity. No significant correlations were observed between US enthesitis and DMN-LT mid insula, nor between US synovitis and SMN-thalamus. Additionally, no significant correlation was found between US synovitis and DMN-LT mid-insula.

Table 5.4: The Correlation Results of fMRI and MSUS in the CENTAUR dataset

	Correlation (r)	P value
(SMN-Thalamus)-Enthesitis	-0.73	<0.001
(LT SMN-Thalamus)-Enthesitis	-0.62	0.006
(RT SMN-Thalamus)-Enthesitis	-0.87	<0.001
(SMN-Thalamus)-Synovitis	-0.39	0.10
(DMN-Lmid Insula)-Enthesitis	0.31	0.20
(DMN-Lmid Insula)-Synovitis	0.34	0.16

A significant negative correlation was observed between ultrasound (US)- enthesitis and SMN-thalamus connectivity ($r = -0.73$, $p < 0.001$). This negative correlation remains significant after correction for age and gender ($r = -0.8$, $p < 0.001$). Additionally, significant negative correlations were noted between US enthesitis and SMN-RT thalamus connectivity ($p < 0.001$), as well as between US enthesitis and SMN-LT thalamus connectivity ($p = 0.006$). No similar correlations were found between US synovitis and SMN-thalamus connectivity. However, a suggested trend was observed between US synovitis and SMN-thalamus connectivity after correction for age and gender ($r = -0.45$, $p < 0.07$). Moreover, there was no significant correlation between DMN-L mid-insula connectivity and US metrics (including both US enthesitis and US synovitis).

5.7.6.3 The fMRI and MSUS results of the SOAR and TEMPO studies

A total of 19 participants underwent fMRI and ultrasound procedures as part of the SOAR and TEMPO studies. Table 5.5 indicates that the medians for DMN-L mid Insula connectivity and SMN-thalamus connectivity are -0.02 and 0.162, respectively. The SMN-thalamus connectivity is higher than the DMN-L mid-insula connectivity in this population. The median of DMN-L mid-insula connectivity has a very low value, which may indicate low activity in this population.

The median absolute deviation (MAD) values for DMN-L mid Insula are large, indicating unstable variability around the median values, which suggests the presence of possible noise or an unstable connectivity pattern. In contrast, the MAD value of SMN-thalamus connectivity is large, indicating unstable variability around the median values.

Figure 5.20 shows the distributions of MSUS metrics, SMN-thalamus connectivity, and DMN-insula connectivity.

Table 5.5: The Descriptive Results of fMRI and MSUS in SOAR and TEMPO datasets.

	SMN-thalamus	DMN-Lmid Insula	USPD BL	USSH BL	USJE BL	USBE BL
Count	19	19	19	19	19	19
Median	0.16	0.002	5.00	21.00	7.00	19.00
Mean	0.11	-0.02	5.52	20.53	7.78	18.42
Std. Deviation	0.37	0.21	5.24	6.72	4.15	10.81
MAD	0.24	0.17	4.00	5.00	3.00	10.00
IQR	0.43	0.31	8.00	10.00	6.00	17.50
Shapiro-Wilk	0.95	0.96	0.88	0.97	0.96	0.94
P-value of Shapiro-Wilk	0.43	0.62	0.02	0.78	0.60	0.26

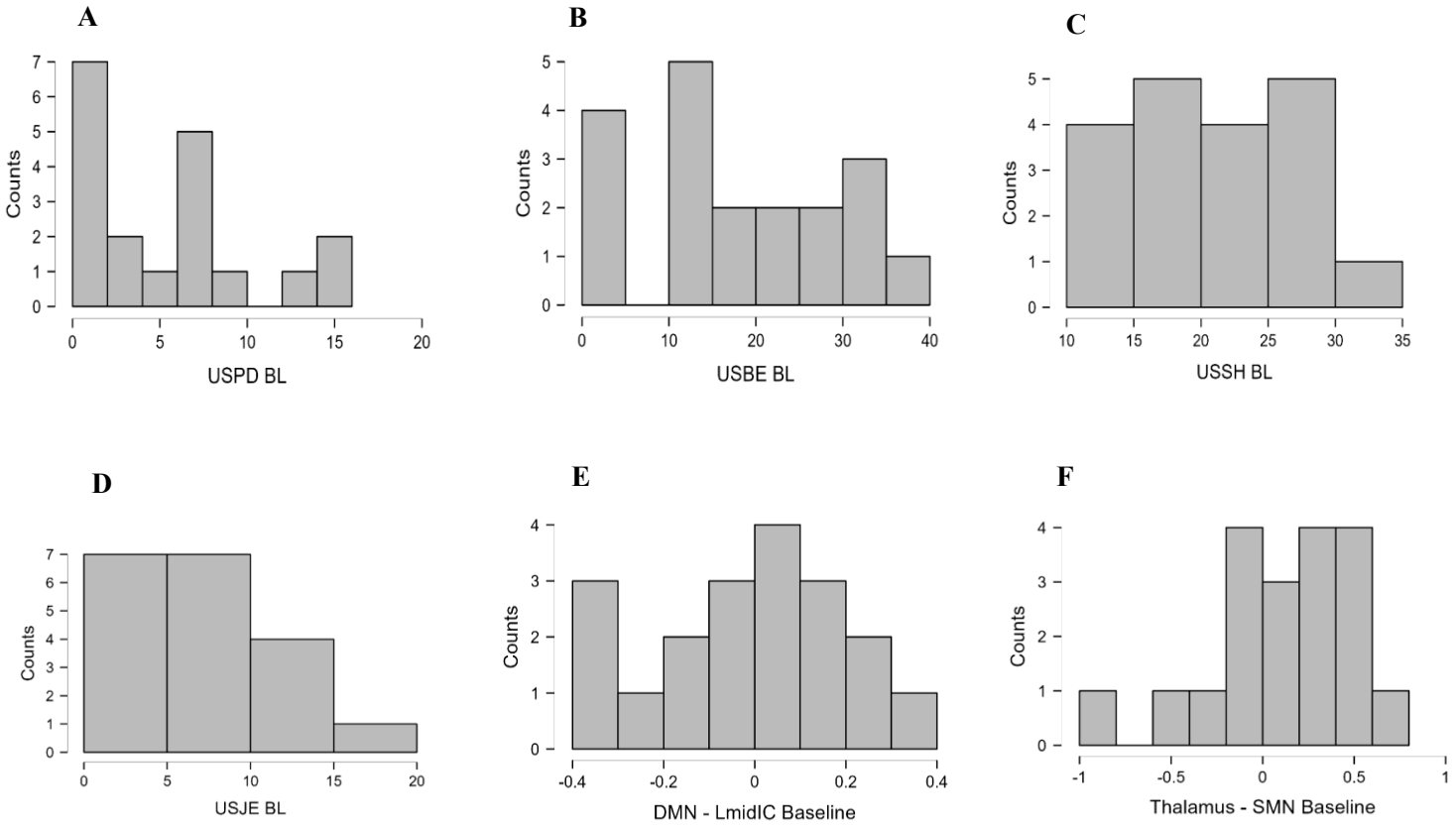

Figure 5.20: Distribution of ultrasound metrics, thalamus–SMN connectivity, and DMN-LT mid-insula connectivity at the baseline at SOAR and TEMPO datasets. Histograms showing the distribution of USPD (A), USBE (B), USSH (C), and USJE(D) are generally right-skewed. In contrast, DMN–LT mid insula connectivity (E), and thalamus–SMN connectivity (F) shifted toward positive values.

5.7.6.4 The results of FM criteria

The results showed that 8 participants (42%) in this population met the FM criteria, indicating a high prevalence of comorbid FM in the recruited population. Therefore, this could influence altered functional connectivity. As a result, brain regions and connectivity might become hyperactivated due to the presence of nociplastic pain (FM).

5.7.6.5 The results of the correlation analysis

A significant correlation was observed between USPD and DMN-L mid-insula ($r = 0.46$, $p = 0.04$). However, this correlation becomes significant after correction for age and gender ($r = 0.54$, $p = 0.02$), as shown in Figure 5.22, Tables 5.6 and 5.7. Additionally, a significant correlation was observed between USBE and DMN-L mid-insula ($r = 0.54$, $p = 0.01$) as seen in Figure 5.22. This correlation remains significant after correction for age and gender ($r = 0.6$, $p = 0.01$). No significant correlations were noted between the other US metrics (USSH and USJE) and DMN-L mid-insula connectivity. Furthermore, there was no significant correlation between SMN-thalamus connectivity and US metrics in this population, either before or after correction for age and gender, as seen in Figure 5.21.

Table 5.6: The Univariate Correlation Results of fMRI and MSUS in SOAR and TEMPO datasets.

	Correlation	**P value**
(SMN-thalamus)-USPD	-0.43	0.06
(SMN-thalamus)-USSH	0.11	0.65
(SMN-thalamus)-USJE	-0.03	0.89
(SMN-thalamus)-USBE	-0.31	0.19
DMN – LmidIC-USPD	0.46	0.04
DMN – LmidIC-USSH	0.13	0.58
DMN – LmidIC-USJE	0.02	0.94
DMN – LmidIC-USBE	0.54	0.01

Table 5.7: The Univariate Correlation Results (age and gender correction) of fMRI and MSUS in SOAR and TEMPO datasets.

After age and gender correction		
	Correlation	**P value**
(SMN-thalamus)-USPD	-0.006	0.981
(SMN-thalamus)-USSH	0.12	0.621
(SMN-thalamus)-USJE	0.23	0.374
(SMN-thalamus)-USBE	-0.23	0.372
DMN – LmidIC-USPD	0.54	0.02
DMN – LmidIC-USSH	0.23	0.363
DMN – LmidIC-USJE	-0.09	0.71
DMN – LmidIC-USBE	0.60	0.01

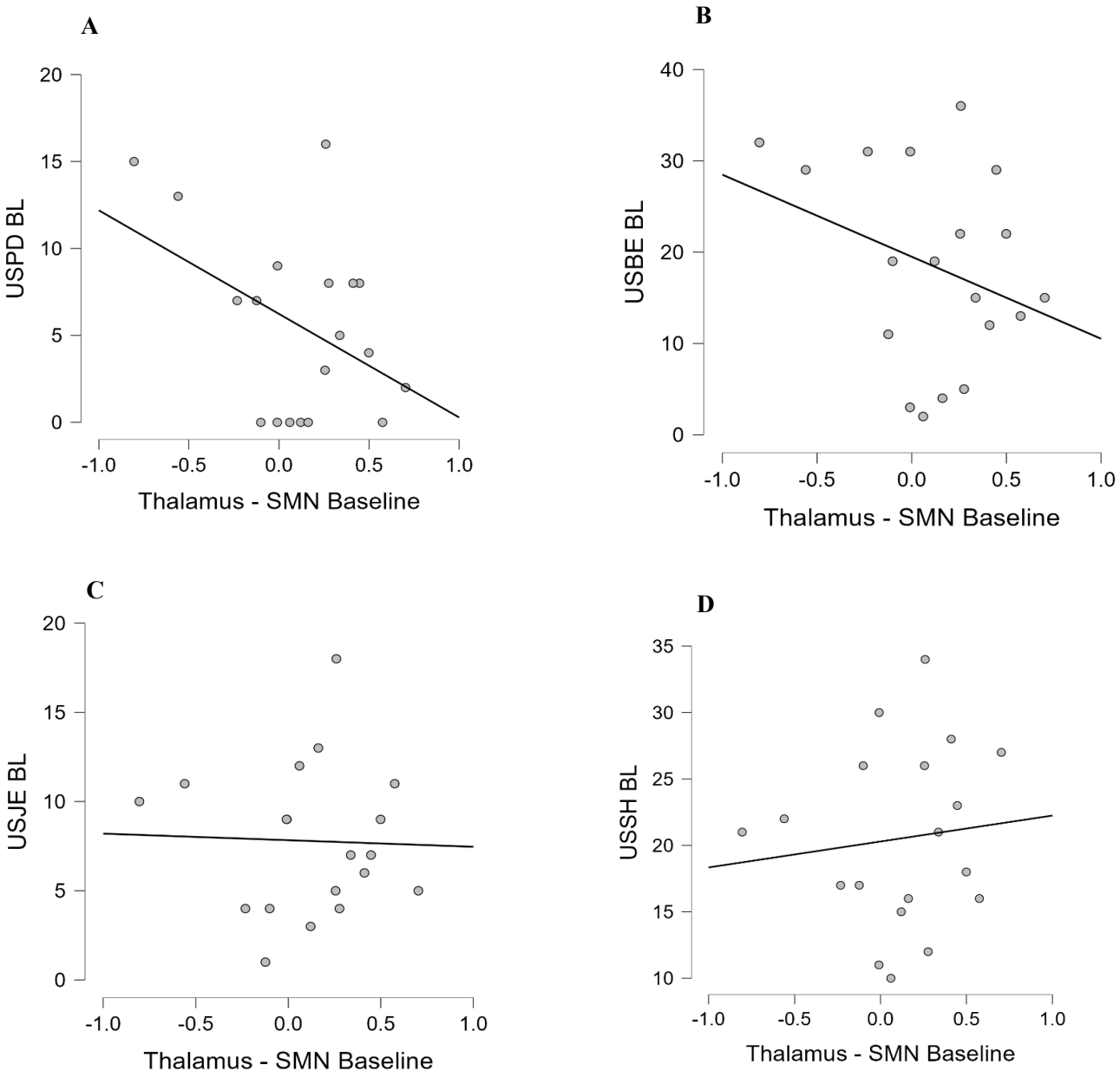

Figure 5.21: Correlations of US metrics vs SMN-thalamus connectivity at the baseline at SOAR and TEMPO datasets. No significant correlations were observed between US metrics and SMN-thalamus.

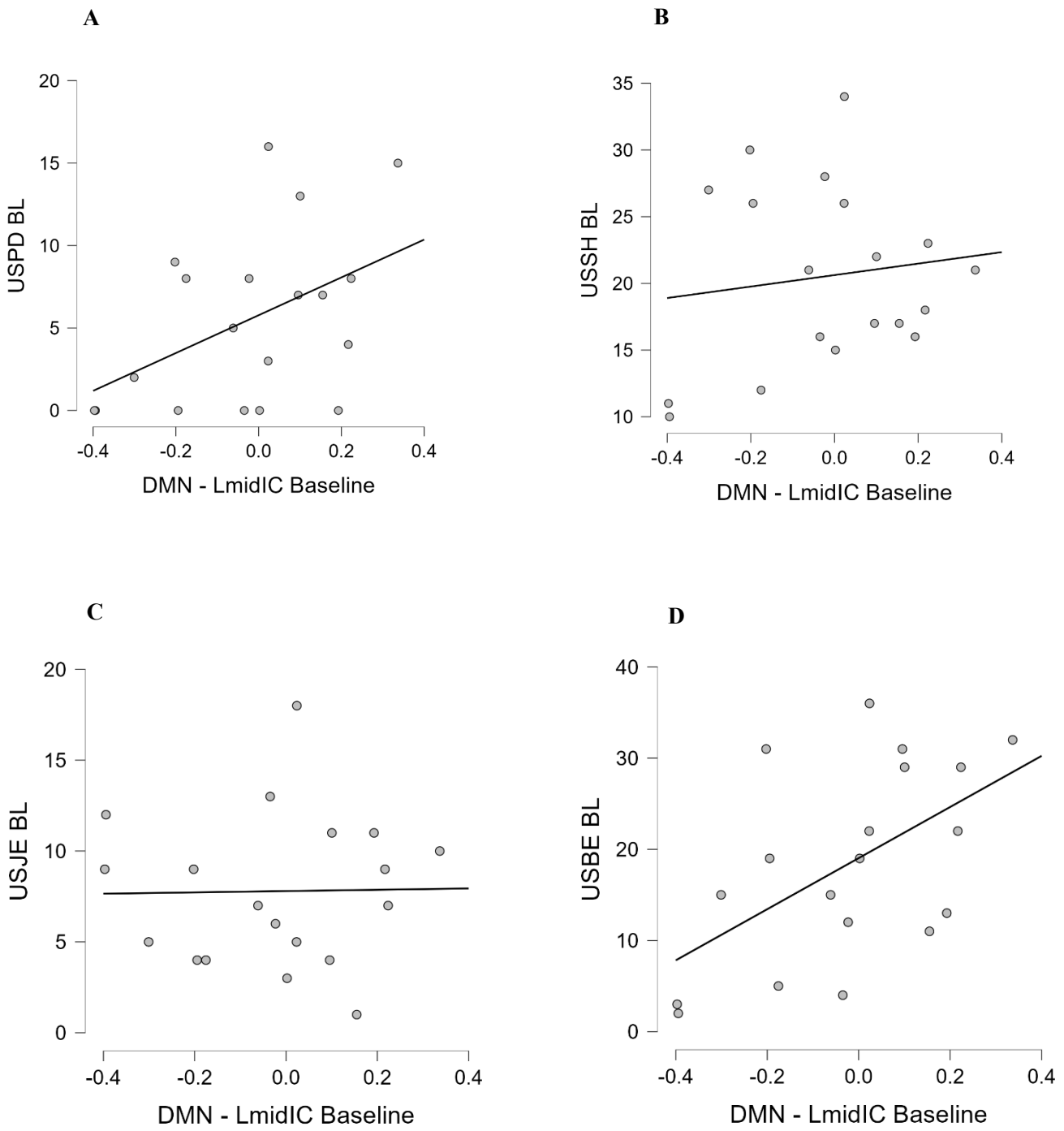

Figure 5.22: Correlations of US metrics vs. DMN-LT mid insula at the baseline at SOAR and TEMPO datasets. USBE and USPD are significantly correlated with DMN-LT mid-insula connectivity. No significant correlations were observed between USSH and USJE and DMN-LT mid insula.

5.7.7 Discussion

This is the first study to directly investigate the association between MSUS measures and neuroimaging measures, aiming to elucidate the mechanisms of pain in inflammatory arthritis. This novel approach was applied using three cohorts: CENTAUR, SOAR, and TEMPO studies. The population in the CENTAUR study consisted of participants with PsA, while the populations in SOAR and TEMPO included participants with RA.

Both diseases are autoimmune inflammatory disorders that affect joints, characterised by joint pain and swelling, and they also show significant systemic symptoms. RA is an autoimmune systemic inflammatory condition marked by joint inflammation, bone erosion, and cartilage damage. On the other hand, PsA is a heterogeneous autoimmune disorder characterised by a range of clinical and radiographic features (D'Agostino, 2018).

The lack of research exploring the link between functional connectivity and clinical and imaging pain measures, especially in inflammatory arthritis, emphasises the importance of this novel study.

5.7.7.1 Investigate the mechanism of pain in inflammatory arthritis using MSUS and fMRI within the CENTAUR study

No ultrasound metrics, specifically US enthesitis and US synovitis, were found to be correlated with the biomarker of nociplastic pain (DMN-L mid Insula), as anticipated. This is because ultrasound is recognised as the gold standard for detecting peripheral changes that may contribute to nociceptive pain. The Descriptive statistics revealed that DMN-L mid-Insula connectivity was greater than that of nociceptive pathways associated with pain signals in the brain, particularly the SMN-thalamus connectivity. The SMN-thalamus connectivity plays a crucial role in pain perception and the persistence of chronic pain (Groh et al., 2017; Mao et al., 2024). Alterations in SMN-thalamus connectivity in chronic pain have been reported in previous studies. For example, Mao et al. (2022) highlight the abnormal activation of SMN-thalamus connectivity in inflammatory back pain. In this research, a significant negative correlation was observed between SMN-thalamus connectivity and US enthesitis. The negative correlation between US enthesitis and SMN-thalamus connectivity appears clinically counterintuitive, as it is generally understood that pain intensifies with inflammatory changes at the entheseal sites. The alteration in SMN-thalamus connectivity due to chronic pain is characterised by increased activity between these regions, as the peripheral pain signal is amplified by persistent chronic pain.

Therefore, clinically, US enthesitis should be positively correlated with the SMN-thalamus connectivity. The mechanisms of negative connectivity in the context of network physiology are less understood and have been a subject of debate. The term "negative functional connectivity" refers to spontaneous BOLD signals between two brain regions that exhibit a negative Pearson cross-correlation coefficient; it is also called anticorrelation (Chen et al., 2011). However, the negative correlation involving the SMN-thalamus connectivity has been reported in previous studies. For example, Mao and colleagues (2024) indicate that central pain in patients with osteoarthritis leads to dysfunction in thalamus-SMN connectivity. This altered connectivity was negatively correlated with clinical measures, including pain intensity. Therefore, a possible dysfunction of the SMN-thalamus connectivity could occur in participants with RA and chronic pain. This alteration was negatively correlated with US enthesitis.

In addition, this negative relationship may stem from the SMN-thalamus connectivity, which exhibited a negative value in the descriptive statistics. Several studies demonstrate that negative connectivity may be an artefact caused by methodological factors, such as global signal regression procedures or related data preprocessing methods, such as bias correction (Giove et al., 2009; Murphy et al., 2009). Moreover, the small sample size might contribute to the negative association with US enthesitis, as this limitation has been shown to overestimate different relationships with functional connectivity. Despite the negative SMN-thalamus connectivity, a significant correlation between this connectivity and US enthesitis suggests that a peripheral inflammation marker, namely MSUS, can explain nociceptive pain, as it significantly correlates with the nociceptive pathways and SMN-thalamus connectivity involved in pain signalling within the brain.

Moreover, Sunzini and her colleagues (2025) investigated nociceptive biomarkers in PsA using the same fMRI data from their published study, which were also used in this study. The results indicated an increase in connectivity between the right anterior insula and DMN, as well as between the right mid insula and the DMN, both of which are associated with the nociplastic pain mechanism. Additionally, there was an increase in connectivity between the left posterior insula and the thalamus, which is linked to the nociceptive pain mechanism.

In this research, the observed correlation between SMN-thalamus connectivity and US enthesitis is linked to the spinothalamic tract; therefore, further investigation is required to understand this finding. It is important to determine whether participants in this population have experienced spontaneous pain that led to these findings, or whether central pain plays

a role in activating the spinothalamic tract. Additionally, investigating the relationship between SMN-thalamus connectivity and central pain measures, such as FM and QST, is needed.

5.7.7.2 Investigate the mechanism of pain in inflammatory arthritis using MSUS and fMRI within the SOAR and TEMPO studies

Surprisingly, no significant correlation was found between the US metrics and SMN-thalamus connectivity in this population. It was not anticipated that such a relationship would exist, given that the US metric measures peripheral changes at the joints. At the same time, SMN-thalamus connectivity is involved in the nociceptive pain pathway. Unlike the CENTAUR cohort, which consists of participants with PsA, there was no significant correlation between the MSUS metrics and SMN-thalamus connectivity in the RA cohorts.

Conversely, a significant correlation was observed between USPD and the DMN-L mid-insula, as well as between USBE and the DMN-L mid-insula. It is interesting to see a connection between peripheral measures, such as USPD and USBE, and a nociplastic biomarker like DMN-L in the mid-insula. This suggests that changes in peripheral joints may contribute to nociplastic pain or, at the very least, activate the nociplastic pain pathway. Similar findings were reported by Hemington and his colleagues (2016) as they highlight that there are associations between back pain severity and DMN connectivity with the salience network (of which the insula is a prominent component). Furthermore, connectivity between the DMN and insula has been shown to correlate positively with the severity of clinical pain in several studies (Napadow et al., 2010; Loggia et al., 2013; Baliki et al., 2014).

Moreover, these results are in line with Basu and colleagues (2018), who reported that the DMN-insula cortex (a nociplastic pain marker) was significantly correlated with DAS28 and concluded that inflammation contributes to central sensitisation. Therefore, the research findings support the role of inflammation in contributing to central sensitisation, as MSUS, a marker of peripheral changes, was significantly correlated with the DMN-insula cortex.

To explore this further, an additional analysis was carried out to assess the presence of FM, as it may influence functional connectivity (Fallon et al., 2016). FM could increase the connectivity to pro-nociceptive brain areas and suppress the connectivity to anti-nociceptive brain areas (Ichesco et al., 2014). Furthermore, Jensen and his colleagues

(2009) highlight that FM could suppress the brain activation of descending pain inhibition. This could cause amplification of pain signals in the spinothalamic pathway, leading to increased activity in regions such as the thalamus, SMN, and the spinal cord.

The findings revealed that 8 participants, which is 42% of this group, met the FM criteria, demonstrating changed functional connectivity. Therefore, the brain regions and connectivity could be hyperactivated due to the presence of nociplastic pain (FM). The peripheral nociceptors can become more sensitive after exposure to peripheral stimuli. When these receptors are subsequently activated, they lead to heightened neuronal firing and increased pain. While the evidence for this is currently indirect, it appears that peripheral pain mechanisms play a role in the pain experienced in FM (Staud, 2006). Thus, FM confirms the coexistence of central sensitisation with RA in this population.

The connectivity between the DMN-Insula is a marker for nociplastic pain; therefore, its major contribution is associated with non-inflammatory pain. However, the results indicate there was a strong and significant correlation between US metrics, especially USPD and USBE, and DMN-Insula connectivity. This strong relationship does not align with clinical reasoning. Thus, this may represent a spurious correlation, or confounding factors such as disease duration, medication type, or fatigue may be involved. An additional exploratory analysis was conducted to determine whether a robust correlation existed in both the SOAR and TEMPO datasets. The findings suggest that these observations were exclusively noted in the TEMPO dataset, prompting questions regarding the differences between the various datasets. Further investigation is necessary to examine factors such as disease duration, treatment type, or other elements that might contribute to a heightened correlation between DMN-insula connectivity and ultrasound metrics.

Future research will conduct an agnostic analysis using USPD and USBE with fMRI to determine which brain area correlates with these ultrasound metrics.

Bridging the gap between clinical pain measures, such as MSUS, and neurobiological evidence of nociplastic pain in inflammatory arthritis is crucial for a comprehensive understanding of the underlying pain mechanisms. This understanding could ultimately assist in the development of tailored pain management strategies to improve the well-being of individuals affected by inflammatory arthritis.

5.7.7.3 Limitations

Limitations of this study include the relatively small sample size, which may have reduced statistical power to detect subtle or moderate associations between the measured variables

and limited the ability to establish causal relationships. Longitudinal studies are essential for understanding temporal changes and potential causal relationships among nociplastic pain, brain connectivity, and MSUS metrics. The size of the study sample can influence how broadly the results can be applied, and having a larger group would improve the validity of the findings.

Although 50 participants were included in the CENTAUR dataset and around 35 in the SOAR and TEMPO datasets, a potential reason for this low number is that ultrasound was optional rather than mandatory, which may have reduced participant uptake.

Another limitation of this research is that it focused specifically on the connectivity of the DMN with the left mid-insula, without examining the connectivity between the DMN and other regions of the insula. Notably, Sunzini et al. (2025) found high connectivity between the DMN and the right anterior insula.

Furthermore, fMRI procedures in the CENTAUR dataset were performed using a 3 Tesla (3T) MRI scanner. In comparison, the fMRI procedures in the SOAR and TEMPO datasets were performed using a 7 Tesla (7T) MRI scanner. Ultrahigh-field MRI scanners (7T and above) offer a considerably higher signal-to-noise ratio (SNR) compared to 3T, enabling a 5- to 10-fold improvement in spatial resolution and nearly doubling BOLD contrast (Nemani and Lowe, 2021). This increased sensitivity enhances functional connectivity analyses, enabling more precise network mapping (Hale et al., 2010).

Using smaller voxels at 7T reduces artefacts from grey matter, white matter, and cerebrospinal fluid (CSF), resulting in sharper spatial features and improved localisation of networks (Yacoub et al., 2001; Newton et al., 2012).

Furthermore, physiological noise from cardiac and respiratory activities tends to be more noticeable at higher field strengths. However, studies comparing resting-state fMRI data from 3T and 7T indicate that ultrahigh-field imaging can improve both the sensitivity and specificity of functional connectivity results (An Thanh et al., 2017).

The following limitation is related to the fundamentals of functional connectivity analysis using fMRI. The BOLD fMRI signals serve as an indirect indication of neuronal activity, predicated on the assumption that increased neuronal activity corresponds to heightened metabolic activity and oxygen consumption. The temporal resolution is notably compromised, with delays of 4-6 seconds between neuronal activations and haemodynamic responses, which restricts the ability to detect events occurring over a short course of time. Furthermore, the magnitude of hemodynamic changes is relatively small in individual

cases; therefore, the inferences drawn from our fMRI analysis are based on population-level variations, which limits the generalisability of the findings due to intrinsic differences among participants. Additionally, local blood flow is influenced by various factors, including anatomical differences, vascular comorbidities, and haemodynamic responses that are independent of neuronal activity, such as anticipatory vasodilation and interactions between brain regions. Concerning the interpretation of brain connectivity and its links to nociplastic pain, I must emphasise that this analysis relies on correlations, which cannot infer causation. To uncover the underlying mechanisms, more robust experimental designs, such as pain management therapy studies and mediation analyses, are essential. Although BOLD-based fMRI encounters limitations in fully capturing the brain's complexity, the technique is validated and represents a reliable non-invasive method for investigating brain function.

5.7.7.4 Future study

Further research is needed to fully understand the correlation between SMN-thalamus connectivity and US enthesitis. Future research may help determine whether participants in this population have experienced spontaneous pain that led to the findings presented in this study, or whether central pain plays a role in activating the spinothalamic tract in this population.

Additionally, future research may investigate the relationship between SMN-thalamus connectivity and central pain measures such as FM and quantitative sensory testing (QST). If SMN-thalamus connectivity contributes to centralised pain, then the association of inflammation captured by MSUS to this connectivity could be used to indicate a nociceptive pain contribution in overall pain.

Moreover, SMN-thalamus connectivity is one established nociceptive pathway, and future studies could explore other brain pathways involved in classical nociceptive routes, such as spinoreticular and spinomesencephalic.

Furthermore, Sunzini et al. (2025) reported that L mid insula-DMN connectivity did not increase. This was the main area used in this analysis as a nociplastic pain marker. However, they reported high connectivity between DMN and other parts of the insula. Therefore, the future analysis is to correlate the connectivity that showed high in Sunzini et al. (2025) with the ultrasound metrics.

Furthermore**,** future research will conduct an agnostic analysis using USPD and USBE with fMRI to determine which brain area correlates with these ultrasound metrics.

5.7.8 Conclusion

This research is the first to correlate the MSUS metrics with fMRI connectivity of pain in patients with inflammatory arthritis. This investigation identified the contribution of nociceptive pain in the overall pain experienced by patients with inflammatory arthritis, with reported pain despite effective inflammation control (nociceptive pain). MSUS is an objective measure that detects inflammatory changes at joint sites, leading to nociceptive pain. At the same time, fMRI is an objective measure that identifies the activity changes at areas associated with pain signals in the brain. In this research, two brain connectivity, including SMN-thalamus and DMN-insula, were correlated with MSUS. SMN-thalamus is linked to the classical route of pain, while DMN-insula is a biomarker of nociplastic pain.

No MSUS metrics, specifically US enthesitis and US synovitis, were found to correlate with the biomarker of nociplastic pain (DMN-L mid Insula) in the CENTAUR dataset. Consequently, MSUS was able to identify the nociceptive contribution to the mixed pain experienced by participants with PsA and FM. Additionally, a negative correlation exists between MSUS findings and SMN-thalamus connectivity, suggesting a suppression of connectivity in this network among participants with PsA and FM.

In the SOAR and TEMPO datasets, a notable correlation was found between USPD and the DMN-LT mid-insula, as well as between USBE and the DMN-LT mid-insula. It is intriguing to observe a connection between peripheral measures, such as USPD and USBE, and a nociplastic biomarker, such as DMN-L, in the mid-insula. This finding suggests that nociceptive pain may play a role in the mixed pain experienced by patients with RA and FM.

Chapter 6 Summary

6.1 New knowledge

Pain is a hallmark of RA and a significant symptom that prompts patients to seek treatment. It is multifactorial because it can arise from different mechanisms. Acute pain in RA typically resolves once its cause is addressed. However, persistent pain can be found in some Patients with RA despite effective control of inflammation. This ongoing pain can impact patients' quality of life. Therefore, understanding the mechanisms of pain in RA could lead to improved pain management and a better quality of life for patients with RA.

This thesis investigated pain in RA through a series of progressive, interconnected steps aimed at understanding its mechanisms and nature. The research commenced with an examination of the prevalence of various pain mechanisms in RA, including persistent pain, and their impact on the quality of life of patients with early RA, utilising the SERA dataset (Chapter 2). Pain was measured using the Pain VAS in this chapter. The findings indicated that most patients reported elevated pain levels at baseline. Subsequently, pain levels improved after 12 months, attributable to anti-inflammatory treatment. Nonetheless, a subset of patients (35%) continued to report persistent pain. Overall, the quality of life, as measured by the EQ-5D, improved during the follow-up period, except in patients experiencing persistent pain. Clinical markers of inflammation were investigated within this cohort to determine whether inflammation was the underlying cause of persistent pain or whether alternative non-inflammatory factors might be responsible. The results suggest that a limited number of participants with persistent pain (12.8%) exhibited absent inflammatory markers at the follow-up visit, as evidenced by low ESR and negative SJC. These findings warrant validation through imaging modalities such as MSUS, which serves as a marker of peripheral inflammation.

In the subsequent chapter (Chapter 3), the nature of pain in RA was further examined utilising the same outcome measure (Pain VAS) and a different measure of inflammation, which is a reliable indicator for local inflammation, namely USPD in the TaSER dataset. This dataset encompassed only fifty-four participants who underwent MSUS. The pain VAS was used to assess the perceived pain in patients with early RA, while USPD served as a marker for peripheral inflammation changes. No significant correlation was found between USPD and pain VAS at the follow-up visit. Furthermore, in this chapter, participants were categorised into two groups to analyse variations in inflammatory markers among them (the Persistent Pain group and the Reduced Pain group). A similar analytical approach to that utilised in the preceding chapter was conducted to evaluate clinical inflammatory markers among early Patients with RA experiencing persistent pain.

The findings indicated that approximately 9% of participants reported persistent pain. The clinical inflammatory markers in patients with persistent pain were lower compared to those with reduced pain. USPD at two or more joints was detected in only one participant out of five, which may suggest a non-inflammatory origin of pain. Nonetheless, further research is required to substantiate these observations, considering the limited sample size of the TaSER dataset, the restricted number of joints examined via ultrasound, and the sole use of USPD as an ultrasound metric.

In Chapter 4, the investigation into pain assessment in patients with RA, using the pain VAS, was expanded by integrating MSUS metrics within the Spanish RA cohort (Naredo dataset). This dataset, characterised by a substantial sample size, encompasses a diverse range of MSUS parameters and includes a higher number of joints examined via MSUS, thereby serving as a valuable resource for validating the relationship between MSUS findings and pain in RA populations. Consequently, this facilitates more profound insights into the pathophysiology of pain in RA, particularly in patients experiencing persistent pain. Analyses examining the correlation between MSUS metrics, such as USPD, USJE, and USSH, and pain VAS demonstrated significant associations at both baseline and follow-up assessments. These findings suggest a linkage between these MSUS variables, patient-reported pain, and inflammatory activity as detected by MSUS at the examined joints. Further analysis into persistent pain within this cohort revealed that 76 Patients with RA (20.7%) reported ongoing pain, with 18% of this subgroup exhibiting negative USPD. This suggests that persistent pain may, in some cases, originate from non-inflammatory aetiologies. Additionally, the swollen-to-tender ratio (STR), used as an indicator of centralised pain, was calculated, revealing a higher prevalence of low STR in patients with persistent pain. These results may implicate the involvement of central sensitisation mechanisms in pain perception among this subgroup.

In the following chapter (Chapter 5), the extent to which previous RA findings are generalisable across the spectrum of inflammatory arthritis, such as PsA, was explored. Additionally, the pain mechanisms in patients with PsA are analysed through additional pain assessments, incorporating centralised pain metrics such as FM, alongside a semi-objective pain measure, specifically QST, in addition to the pain VAS. The current understanding indicates that there has been no previous research exploring the connection between MSUS and QST measures, whether specifically related to pain assessment or in broader contexts. To our knowledge, this study is the first to establish a link between QST and MSUS.

The results indicated that there was no significant association between pain VAS and MSUS findings. Additionally, no significant association was observed between MSUS metrics, such as US enthesitis and US synovitis, and QST measures, specifically PPT algometry. Furthermore, FM is a prototypical central pain condition that is often comorbid with PsA and can mimic enthesitis-related pain.

The findings demonstrated that FM was associated with higher LEI scores in this cohort, suggesting that LEI may reflect centralised pain. However, LEI did not correlate with MSUS findings, suggesting that LEI may not be able to capture inflammation. Therefore, in PsA and FM, clinical LEI alone is insufficient to confirm enthesitis; therefore, the use of MSUS is necessary to confirm inflammation accurately. Consequently, MSUS serves as a reliable tool for confirming enthesitis and providing valuable information for making informed treatment decisions.

The final section of this thesis aimed to elucidate the mechanisms of pain in RA through the application of MSUS and an objective pain measure, this time, specifically fMRI connectivity. To date, no studies have investigated the relationship between MSUS findings and fMRI connectivity, either within the context of pain or in a broader scope. In this study, two brain connectivity pathways, including the SMN-thalamus and the DMN-LT mid-insula pathways, were correlated with MSUS metrics. The SMN-thalamus pathway is associated with the traditional route of pain (nociceptive), while the DMN-LT mid-insula is considered a biomarker of nociplastic pain. The findings indicated that there was no association between MSUS metrics, specifically US enthesitis and US synovitis, and the DMN-LT mid-insula in the CENTAUR dataset. Additionally, a negative correlation was observed between MSUS findings and the SMN-thalamus connectivity, suggesting reduced connectivity in this network among participants with PsA and FM.

In the SOAR and TEMPO datasets, a significant correlation was observed between the USPD and the DMN-LT mid-insula, as well as between the USBE and the DMN-LT mid-insula. No such correlation was found between MSUS metrics and the SMN-thalamus connectivity. This finding suggests that nociceptive pain may contribute to the mixed pain experienced by patients with RA and FM. Therefore, peripheral inflammation may influence nociplastic pain, providing evidence for a bottom-up mechanism of nociplastic pain in RA.

The investigation into the relationship between MSUS and pain VAS scores reveals significant correlations within larger cohorts, such as the Spanish RA population. Conversely, a markedly different outcome was observed in smaller cohort studies,

exemplified by the TaSER cohort, where no such correlations were present. Notably, this association was established in the context of RA but was not replicated in other forms of inflammatory arthritis, including PsA.

Within the Spanish cohort, despite the statistically significant correlation between pain VAS scores and MSUS metrics, the strength of this correlation was found to be weak. This suggests that the peripheral changes identified through MSUS contribute minimally to the overall pain experienced by participants. The persistence of pain in this population indicates the potential for non-inflammatory factors to play a significant role in the pain experienced by participants with RA. To examine this hypothesis, various analyses were conducted throughout the thesis to elucidate the underlying mechanisms of pain in RA.

Participants were stratified into two distinct groups based on the presence or absence of USPD and persistent pain: the negative USPD group, characterised by the absence of USPD, and the positive USPD group, marked by the presence of USPD. Notably, in the TaSER study, only five out of fifty-four participants reported persistent pain, with a single participant displaying high USPD, indicating that four of the five participants with persistent pain were in the negative USPD group. Correspondingly, in the Spanish RA cohort, fourteen participants experienced persistent pain, also with negative USPD findings.

These observations lend weight to the proposition that the absence of inflammation suggests alternative, non-inflammatory sources of pain, which may be associated with nociplastic pain mechanisms. To further explore this, indirect measures of central sensitisation were employed, yielding correlations with MSUS metrics such as STR. Low STR values are indicative of centralised pain, whereas elevated STR levels are associated with peripheral pain in the context of RA. The positive correlation between MSUS and high STR implies that greater inflammation at the joints is associated with increased pain perception.

In the CENTAUR study, MSUS was also correlated with additional centralised pain markers, integrating both semi-objective and objective assessment modalities, including QST such as PPT algometry and fMRI. This establishes novel connections between peripheral imaging markers and central pain pathways. No significant correlation was observed between MSUS metrics and QST, such as PPT algometry. Significant correlations were found between the USPD and the DMN-LT mid-insula, as well as between the USBE and the DMN-LT mid-insula in SOAR and TEMPO studies. Collectively, these studies contribute to a comprehensive understanding of how MSUS can

elucidate both inflammatory and non-inflammatory pain mechanisms in RA, underscoring its significance in dissecting the interplay between peripheral and central pain processes and ultimately informing more precise pain management strategies in RA.

Furthermore, the Clinical LEI alone is insufficient to identify the presence of enthesitis; the use of MSUS is necessary to confirm the presence of inflammation accurately. FM, nociplastic pain, is commonly observed in patients with PsA and can mimic entheseal pain, as indicated by the strong correlation with LEI scores. In the CENTAUR study, LEI scores were not effective in capturing inflammatory enthesitis, as evidenced by their lack of association with MSUS findings. Furthermore, the link between objective measurements of clinical sensitivity, such as PPTs in the calf and trapezius, suggests that the LEI score may mainly reflect the presence of central sensitisation rather than actual inflammation. Consequently, relying solely on clinical detection of enthesitis could lead to inappropriate treatment escalation. In contrast, ultrasound proves to be a reliable tool for confirming the presence of enthesitis, providing valuable information for informed treatment decisions.

The thesis employs a range of pain assessment methodologies, with the pain VAS, widely regarded as the gold standard for pain measurement, being a prominent feature. Nonetheless, given its subjective nature, the limitations inherent in this approach are acknowledged. To augment this assessment, semi-objective (QST) and objective (fMRI) measures were integrated in Chapter 5, alongside the Pain VAS, to provide a more robust portrayal of pain experiences in RA.

6.2 Limitations

A key limitation of this thesis is the relatively small sample size in some cohorts, such as TaSER, CENTAUR, SOAR, and TEMPO, which may have reduced the statistical power to detect associations between MSUS metrics and pain measures and limited the generalisability of the findings. For example, 50 participants were recruited in the CENTAUR prospective study, but only 20 underwent ultrasound assessment, partly because the procedure was optional. Their main aim was not targeted ultrasound. This restriction was particularly evident in the subgroup with non-inflammatory pain, where the small number of participants makes it difficult to draw reliable conclusions about centralised pain mechanisms or sizes and also limits the generalisability of the findings to other populations. Moreover, in the SOAR and TEMPO research, ultrasound was also optional, resulting in missing data, especially at follow-up visits.

6.3 Future research

Future studies could explore whether an indirect measure of centralised pain, such as DAS28-PI, correlates with pain VAS in patients with negative MSUS findings. DAS28-PI is defined as the proportion of DAS28-ESR attributable to patient-reported components (TJC and VAS-GH). Previous studies have shown that DAS28-PI is associated with pain severity, predicts future pain in early RA, and is linked to heightened pain sensitivity as well as concurrent fibromyalgia in patients with RA. Therefore, this measure could be used to investigate centralised pain in RA by comparing DAS28-PI and pain VAS in the presence of USPD (positive USPD) and in its absence (negative USPD).

Moreover, future studies could explore the connection between MSUS and fMRI connectivity within the descending pain modulatory system in the archispinothalamic tract, particularly focusing on areas such as the periaqueductal grey (PAG) (Harper et al., 2018; Meeker et al., 2022). This region is involved in pain reduction; therefore, it is expected to show a negative correlation between PAG activity and MSUS metrics, meaning that higher levels of pain or joint damage are associated with decreased activity and functional connectivity in these regions.

In addition, the connectivity between the SMN and the thalamus is a well-recognised pathway for nociception. Future research could explore additional brain connectivity involved in nociceptive pain, such as thalamolimbic connectivity (Kowalsky et al., 2023). This connectivity appears to be altered following spinal cord injury, with a noted decrease in thalamolimbic connectivity corresponding to an increase in nociceptive activity (Kowalsky et al., 2023). It is anticipated that future studies will reveal a negative correlation between MSUS metrics and fMRI measures of thalamolimbic connectivity.

Furthermore, future studies could incorporate an objective MSUS metric, such as shear wave elasticity (SWE), to enhance the assessment of pain in RA. Recent research has demonstrated that SWE parameters, including the elastic modulus (in kPa) and mean synovial velocity, exhibit significant differences between patients with RA and healthy controls (Almolla et al., 2023). These ultrasound metrics can thus be used to explore elasticity in the inflamed joints of Patients with RA with varying levels of pain.

Contributions

CENTAUR (Chapter 5): Characterising the Centralised Pain Phenotype in Chronic Rheumatic Disease - A Stride Towards Personalised Analgesia: contributed to conducting clinical assessments, including BMI, joint evaluation, including BASDAI, Dactylitis score, DAPSA, ACR 66/68 joint assessment, and LEI, QST, questionnaires, including pain assessment, and MSUS.

Translate the Spanish dataset, which is chapter three of this thesis.

SOAR (chapter 5) Exploiting Leading Edge 7T MRI Brain Imaging to Decipher Olumiant's Mode of Analgesic Action in Rheumatoid Arthritis: contributed to conducting clinical measures, including BMI, joint assessment (CDAI, SDAI), DAS28, QST, questionnaires including pain assessment, and MSUS.

TEMPO (Chapter 5) Exploiting leading-edge 7 Tesla MRI brain imaging to decipher Filgotinib's mode of analgesic action in rheumatoid arthritis: contributed to conducting clinical assessments, including BMI, joint evaluation, such as CDAI, SDAI, CR66/68 joint assessment, DAS28, questionnaires, including pain assessment, and MSUS.

Cleaning and analysing all the datasets within this thesis, except for extracting the fMRI data.

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