IMAGING ASSESSMENT OF RHEUMATOID ARTHRITIS

EXPLORING THE ASSESSMENT OF INFLAMMATION AND EROSION IN THE METATARSOPHALANGEAL JOINTS OF PATIENTS WITH EARLY RHEUMATOID ARTHRITIS USING CLINICAL EXAMINATION, ULTRASONOGRAPHY AND MAGNETIC RESONANCE IMAGING

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LAY ABSTRACT

Current assessment of rheumatoid arthritis (RA) relies on physical examination for joint swelling and tenderness, but these methods often miss underlying inflammation. Ultrasonography (US) may help improve the diagnosis and monitoring of disease activity, but its effectiveness in imaging the feet is unclear. With MRI (another imaging technology) as the standard of reference, we compared the use of physical examination and US in assessing inflammation in the feet, and explored the potential of using US to see damage to bones. In 41 patients with early RA (<2 years of disease), US was able to detect inflammation in many joints that appeared normal, and was better at detecting decreased inflammation over 1 year than physical examination. Although US was limited at assessing early bone damage, it was able to see several large erosions. In conclusion, US can better visualize disease activity than clinical examination and can improve RA assessments.

ABSTRACT

Introduction

Disease monitoring in rheumatoid arthritis (RA) can be improved by incorporating imaging technologies. Clinical examination fails to detect subclinical inflammation in half of metatarsophalangeal joints (MTPJs), but the effectiveness of using ultrasonography (US) in MTPJs is unclear. We aimed to evaluate US assessment of disease activity in the MTPJs using MRI as the reference standard, in comparison to clinical examination.

Methods

Patients newly diagnosed with RA (ACR criteria) were recruited and assessed at baseline, 6 weeks, 3 months, 6 months, and 12 months. A rheumatologist assessed the MTPJs 2-5 bilaterally for swelling and tenderness (presence=1), and for erosion (presence=1), synovial thickening, and power Doppler (PD) by US. Synovial thickening and PD were graded semi-quantitatively (grade 0-3). The most clinically symptomatic foot was scanned using extremity MRI (1.0T) at the baseline and 12-month visits. MTPJs 2-5 were graded semi-quantitatively for synovitis, bone marrow edema (BME) (grade 0-3), and erosions (grade 0-10).

Results

Forty-one patients were recruited (mean (SD) age=51.9 (10.3) years, 81% female). Kappa agreement was moderate between PD and grade ≥2 synovitis (k=0.46) and BME (k=0.47), but poor agreement was found for clinical examination and synovial thickening. US was able to visualize subclinical inflammation in 41% of non-swollen joints. After 12 months, the average total score for synovial thickening, PD, and BME all significantly decreased, but not swollen or tender joint counts. US visualized few erosions (n=8) compared to MRI (n=101) in the most symptomatic foot. MRI observed erosion repairs in patients treated with DMARDs, and repairs appeared to be preferential for MTPJs that had low inflammation seen by US.

Conclusion

US appears to better visualize MTPJ inflammation than swollen and tender joint counts, and may be used in combination with clinical examination to improve routine disease monitoring in RA.

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LIST OF ABBREVIATIONS AND SYMBOLS

ACPA: anti-citrullinated peptide antibody
ACR: American College of Rheumatology
APC: antigen-presenting cell
BME: bone marrow edema
CDAI: Clinical Disease Activity Index
CRP: C-reactive protein
DAS: Disease Activity Score
DHFR: dihydrofolate reductase
DMARD: disease modifying anti-rheumatic drug
ESR: erythrocyte sedimentation rate
ETL: echo train length
EULAR: European League Against Rheumatism
FLS: fibroblast-like synoviocyte
FSE: fast spin-echo
GM-CSF: granulocyte monocyte-colony stimulating factor
HAQ: Health Assessment Questionnaire
HLA: human leukocyte antigen
IL-#: interleukin-#
LFIS: Leeds Foot Impact Scale
MCPJ: metacarpophalangeal joint
MHC: major histocompatibility complex
MMP: matrix metallo-proteinase
MRI: magnetic resonance imaging
MTPJ: metatarsophalangeal joint
MTX: methotrexate
NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells
NK cell: natural killer cell
NMR: nuclear magnetic resonance
NPV: negative predictive value
NSAID: non-steroidal anti-inflammatory drugs
OMERACT: Outcome Measures in Rheumatology Clinical Trials
OPG: osteoprotegerin
PABAK: prevalence-adjusted bias-adjusted kappa
PAD: peptidylarginine deiminase
PD: power Doppler
PIPJ: proximal interphalangeal joint
PTEN: phosphatase and tensin homolog
PPV: positive predictive value
RA: rheumatoid arthritis
RAMRIS: rheumatoid arthritis MRI scoring system
RANK: receptor activator of NF-κB
RANKL: receptor activator of NF-κB ligand
RF: rheumatoid factor
SD: standard deviation
SE: standard error
ST: synovial thickening
STAT3: signal transducer and activator of transcription 3
STIR: short tau inversion recovery
TE: echo time
TI: time of inversion
TR: repetition time
TNF: tumor necrosis factor
TSE: turbo spin-echo
US: ultrasonography
VAS: visual analog scale
VEGF: vascular endothelial growth factor

DECLARATION OF ACADEMIC ACHIEVEMENT

My supervisor, Dr. Maggie Larché, designed the research project conducted in this thesis. I assisted in designing a subsequent follow-up visit. I, Hanyan Zou, declare this thesis to be my own work. With the advice and guidance of Dr. Maggie Larché and Dr. Karen Beattie, I conducted literature reviews, gathered data, and conducted all data analyses. I wrote this manuscript with editorial advice from Dr. Maggie Larché, Dr. Karen Beattie and Dr. George Ioannidis. Parts of this research have been previously presented at scientific conferences as part of the project's development.

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CHAPTER 1: INTRODUCTION

1.1 Epidemiology

Rheumatoid arthritis (RA) is a chronic autoimmune disease that affects approximately 0.5-1% of the world population. Prevalence is highly variable depending on region. Chippewa Indians and Pima Indians have the highest incidence of RA (5.3-6.8%), whereas Chinese and Japanese have the lowest incidence (0.2-0.3%)[1]. Although RA can occur at any age, the incidence of RA increases with age and plateaus at around 60 years[2]. There is a higher incidence of RA in women than in men (4-5 times higher under age 50, and 2 times higher above age 60)[2]. In addition, women who actively take oral contraceptives were at a lower incidence of RA than women who were not taking oral contraceptives. The post-partum period after a first pregnancy appear to increase the risk of developing RA[1]. It is commonly perceived that RA in women tends to be more severe than in men, but this may be a false correlation as RA onset tends to be earlier in women. When patients were matched for RA duration, disease severity was similar between men and women[3]. Although health-related quality of life measures were generally worse in women than men at baseline, this may be affected by differences in patient perception, as the change over time appear to be similar between the sexes[4]. A recent meta-analysis reported that the risk of developing RA was 2 times higher for men and 1.3-times higher for women with a history of smoking than non-smokers[5].

The many direct and indirect costs for managing RA are accumulative. In a large longitudinal study following Canadian patients with RA, it was found that approximately 40% of patients' total annual direct health care costs were related to RA. Patients who responded well to a biologic therapy had the lowest direct annual health care costs, averaging $4800. The costs for patients using conventional disease modifying anti-rheumatic drugs (DMARDs) averaged $6600. The highest costs were observed in patients who needed to switch to another biologic agent, averaging $7300 annually. However, the costs for rehabilitation, physician, and outpatient clinics all decreased significantly after patients switched to a second biologic. Costs incurred by visits to the emergency room was almost twice as much in patients not taking tumor necrosis factor (TNF) inhibitors compared to those on drugs blocking TNF[6]. Health care costs also varied with patient-reported scores on the Health Assessment Questionnaire (HAQ). Patients with low HAQ scores averaged $4200 while patients with high HAQ scores averaged $14200, 42% of which was accounted by hospital costs[6]. It is difficult to quantify indirect costs as

a result of RA, as they accumulate through lost productivity due to RA (medical sick leave, early retirement, or ineffective presence at work) disability and premature death[7].

1.2 Pathophysiology

Although the exact causes of RA remain unknown, it is likely a manifestation of both environmental stressors and genetic factors, leading to the development of synovial inflammation and structural damage to bone and cartilage of various joints[8]. Joints involved in RA show symptoms of tenderness, swelling, stiffness, and loss of strength. The most commonly symptomatic joints are the small joints of the hands and feet, including the metacarpophalangeal joints (MCPJs), proximal interphalangeal joints (PIPJs), wrist joints, and the metatarsophalangeal joints (MTPJs). In addition, patients with RA commonly experience extra-articular symptoms like pain, fatigue, and morning stiffness. Progressive disease can result in loss of functionality and disability[8].

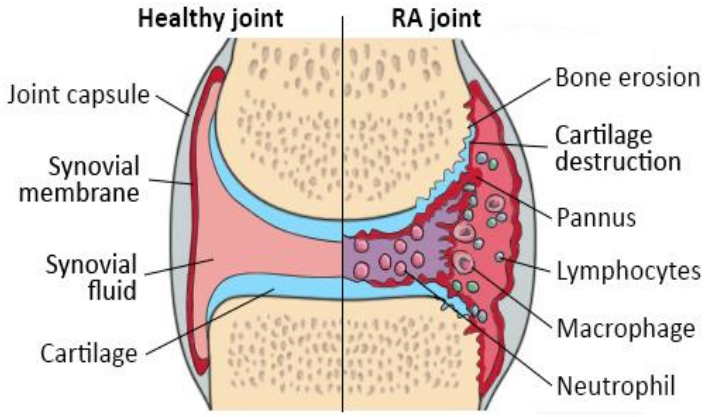

Figure 1: *Comparison of a healthy and RA joint, showing several immune cells involved in pannus formation.*

A complicated network of signalling pathways are involved in RA. Synovitis is the most notable sign of RA, and predates structural damage like bone erosion (Figure 1). The increased endothelial expression of adhesion molecules and chemokines results in leukocyte recruitment to the synovial compartment[10]. The leukocytes involved include monocytes, granulocytes, neutrophils, natural killer (NK) cells, B-cells and T-cells, all leading to the production of large amounts of pro-inflammatory cytokines[9,10]. Antigen-presenting cells (APCs) present RA-associated antigens to T-cells and activate them using cytokines like TNF-α, interleukin (IL)-12 and IL-6 for co-stimulation. B-cells function as

highly efficient APCs, and the presence of self-reactive B-cells can activate auto-reactive T-cells in RA. Once recruited to the synovial membrane, active CD4+ T-cells like Th17 cells further increase the production of inflammatory cytokines and chemokines, which creates a feedback loop to stimulate leukocyte activation[11].

Under these conditions, the synovial membrane proliferates and thickens to form fibrous tissue called pannus. Pannus consists of invasive fibroblast-like synoviocytes (FLS), macrophages and osteoclasts (Figure 1)[12]. As pannus invades the joint space, secretion of proteolytic enzymes and increased osteoclast activity lead to the development of bone erosions[12,13]. Hypervascularization of the synovial membrane provides increased blood supply to fuel the formation of invasive pannus[10,11]. Some key signalling molecules and effector cells implicated in RA are discussed in further detail.

Interleukin-6 (IL-6)

IL-6 is a glycopeptide produced by various cell types, like monocytes, B-cells and T-cells. In addition to activating cells through membrane-bound receptors like many other cytokines, IL-6 also participates in trans-signalling using soluble receptors (sIL-6R). Therefore, it is able to activate even cells that do not express membrane IL-6R, like endothelial cells[14,15].

Following IL-6 stimulation, neutrophils migrate to the synovium and secrete proteolytic enzymes and reactive oxygen intermediates which exacerbate inflammation and cause joint destruction[13,16]. Neutrophils at the site of inflammation release sIL-6R, which activates adjacent endothelial cells and recruits leukocytes that subsequently release chemokines[13]. In addition, IL-6 promotes the secretion of vascular endothelial growth factor (VEGF) by synovial fibroblasts and macrophages[15]. VEGF contributes to the formation of new blood vessels, which is a feature of the angiogenesis and hypervascularization processes crucial to pannus formation[17].

Developing the adaptive immune response is another important role of IL-6. It stimulates B-cell differentiation into plasma cells which then produce immunoglobulins. In RA, increased levels of IgM and IgG rheumatoid factors (RF) and anti-citrullinated peptide antibodies (ACPAs) have been observed, and are used as markers for RA diagnosis. In addition, IL-6 stimulates T-cell proliferation and differentiation into Th17 cells, which then produce IL-17, another pro-inflammatory cytokine[13].

IL-6 is also an important mediator of bone erosion[13]. In normal bone remodelling, osteoblast and osteoclast activity are balanced to maintain bone metabolism. Osteoclasts resorb trabeculae, while osteoblasts lay down bone matrix to form trabeculae[18]. This spongy bone comprises the heads and bases of bones that make up joints. IL-6 increases the resorptive activity of osteoclasts by regulating levels of receptor activator of NF-κB ligand (RANKL) and osteoprotegerin (OPG). RANKL is secreted by osteoblasts and fibroblast-like synoviocytes, and plays a role in inducing osteoclast differentiation by binding to receptor activator of NF-κB (RANK). OPG, also produced by osteoblasts, binds to RANKL and inhibits its interaction with RANK[19]. In neonatal mouse calvaria, it was observed that IL-6 was active after treatment with sIL-6R, which increased the expression of RANKL and decreased the expression of RANK, while OPG expression was also increased but less than that of RANKL. These new levels of RANKL, RANK and OPG caused a net increase in bone resorption[19].

Tumour Necrosis Factor-α (TNF-α) and Interleukin-1 (IL-1)

TNF-α is a cytokine with a broad spectrum of activities that is found in elevated levels in synovial fluid of patients with RA. It is produced mainly by macrophages, but also by B-cells, T-cells and fibroblasts. It acts as a paracrine stimulator of other pro-inflammatory cytokines, like IL-1, IL-6 and granulocyte monocyte-colony stimulating factor (GM-CSF). TNF-α increases the proliferation of macrophages and B-cells, and increases their cytokine production. Furthermore, TNF-α contributes to pannus formation by inducing proliferation of cells of the synovial membrane and GM-CSF production. TNF-α receptors are present throughout the body, on almost all nucleated cells. Specifically, the TNF-receptor 1 (TNF-R1) plays an important role in triggering defense and inflammatory responses[20].

IL-1 is an important mediator of synovial inflammation and formation of pannus. It induces cytokine production by monocytes and lymphocytes, increases matrix metallo-proteinase (MMP) production by fibroblasts and chondrocytes leading to cartilage destruction, and increases RANKL expression leading to bone erosion by osteoclasts[21]. The IL-1 family consists of IL-1α, IL-1ß and IL-1 receptor antagonist (IL-1Ra), which inhibits the activity of the other two. IL-1α is an autocrine messenger expressed usually on the cell surface. In contrast, IL-1ß is secreted to act on other cells, and it has been observed in increased serum concentrations in RA. Although IL-1Ra levels are also elevated in RA, this increase cannot sufficiently block the increase in IL-1ß activity[22]. Two major pathways leading to IL-1 production by macrophages have been proposed. In the

cytokine-dependent pathway, macrophages are stimulated by other cytokines like TNF-α, causing IL-1 release. In the cytokine-independent pathway, macrophages release IL-1 upon direct contact with activated T-cells, or contact with denatured proteins from the extracellular matrix[21].

There appears to be synergistic effects between TNF-α, IL-6 and IL-1 in mediating the pathophysiological processes in RA. In animal models, bone resorption and inflammation were most markedly reduced by combination therapy using both TNF-α and IL-1 inhibitors, compared to when either was used alone[23]. Furthermore, an in vitro study observed that TNF-α promotes IL-6 and IL-1ß production in monocytes, which subsequently increase signal transducer and activator of transcription 3 (STAT3) phosphorylation and induce CD4+ T-cells to differentiate into Th17 cells[24,25]. Conversely, monocytes without TNF-α treatment were unable to effectively promote Th17 cell differentiation[24].

Fibroblast-like synoviocytes (FLS)

FLS are essential in the formation of the inner synovial lining, and produce major components of synovial fluid. FLS can be activated by several stimuli, such as danger-associated molecular patterns (DAMPs), synovial citrullination, activated complement, or autoantibodies[26]. In RA, the thin (2-3 layers) inner lining proliferates into thick (10-20 layers) and invasive pannus-like structure. Once activated, FLS contribute to cartilage destruction by producing pro-inflammatory cytokines like IL-6, and proteases like MMPs[12]. Aggressive phenotypes of FLS have been identified in RA with features reminiscent of tumour cells. Most notably, FLS appear to be protected from apoptosis despite the highly genotoxic environment in RA synovium that would normally kill cells[12]. Although the exact mechanism of this phenomenon is unclear, limited expression of the tumour suppressor gene phosphatase and tensin homolog (PTEN) in the inner synovial lining has been hypothesized to be a factor in FLS survival[27]. In addition, *in vitro* incubation of FLS with T and B-cells prolonged T and B-cell resistance to apoptosis. This effect likely involves several cytokines produced by FLS, such as the chemokine receptor CXCR4, which inhibits T-cell apoptosis through the PI3K and MAPK pathways, and the B-cell survival factor BAFF[12].

Genetic variation

Over 100 genetic loci associated with RA have been identified. Most RA-associated polymorphisms or variations in gene expression are related to the major

histocompatibility complex (MHC) class II[28,29], which is responsible for presenting foreign peptides to the immune system to trigger immune responses. For example, human leukocyte antigen (HLA)-DRB1 alleles encode for amino-acids in the peptide binding groove of the ß-chain of the MHC class II complex. Over 80% of RA patients carry RA-associated HLA-DRB1 alleles[8,30], and it has been shown that people with HLA-DRB1*01 and *04 frequencies are more susceptible to developing RA[31]. These may play a role in the presentation of self-peptides to T-cells, and affecting the repertoire of T-cell receptors to become more self-reactive, thereby inducing an autoimmune response[32].

In addition, certain HLA-DRB1 genotypes contribute to the development of ACPA in RA. Citrullination, the deimination of arginine into citrulline, is a normal physiological process in apoptosis. When clearance of apoptotic products is inadequate, citrullinated proteins and peptidylarginine deiminase (PAD) can leak out of dying cells. PAD further deiminates extracellular proteins containing arginine, thus creating more citrullinated proteins that can be recognized by the immune system. This process generates ACPA in patients with susceptible HLA-DRB1 geonotyes[1].

Extra-articular manifestations

Approximately half of patients with RA report being affected by extra-articular manifestations like vasculitis, pericarditis and rheumatoid lung, and systemic co-morbidities like osteoporosis, depression and cardiovascular disease[33,34]. The increased risk of cardiovascular and pulmonary diseases is the leading cause for mortality in patients with RA[35,36].

1.3 Diagnosis and Disease Assessment

Patients with RA typically present with pain and stiffness in multiple joints, and these symptoms usually emerge over several weeks to months. “Early” RA is defined as disease duration of less than 2 years[37]. There is an average lag time of 18 weeks between symptoms onset and RA diagnosis[38]. Treating early RA is crucial, given that therapy may slow or prevent the development of structural damage within the first years of disease onset[37]. RA diagnosed in later stages tends to progress with greater severity and require more intensive therapy[39]. However, diagnosing early RA based on clinical features alone is difficult, as many inflammatory arthritides present with similar initial symptoms of pain and swelling in the joints[39].

Another consideration for diagnosis is the presence of serological autoantibodies like RF and ACPA, which are present in approximately 50-80% of patients with RA[40]. ACPA is a more specific disease marker than RF, which can be found in healthy individuals and in other diseases[40]. The presence of RF and ACPA also serve as predictors of worse prognosis, as they are both associated with more aggressive disease progression and structural deterioration[41]. Finally, C-reactive protein (CRP) levels and erythrocyte sedimentation rate (ESR) are measures of inflammatory activity, and are often elevated during active RA, but can be influenced by other factors[40]. Elevated levels of CRP may exacerbate RA progression, and has shown value as a predictor for erosive damage and comorbidities like cardiovascular disease[11].

2010 Rheumatoid Arthritis Classification Criteria

No single diagnostic test can definitely confirm an RA diagnosis. However, confirmation using multiple tests can increase diagnostic certainty. Several tools have been created in an attempt to standardize the definition of RA for clinical trials. A joint working group from the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) developed the 2010 Rheumatoid Arthritis Classification Criteria. A previous 1987 classification criteria was criticized for its lack of sensitivity in diagnosing RA in early disease. Therefore, radiologic bone erosion was removed from the 2010 criteria. Instead, the 2010 criteria uses a scoring system that combines a symptomatic joint count, serology, symptom duration and acute-phase response measure (ESR or CRP). Joints showing tenderness and swelling are considered 'involved', and can be small joints including the MCPJs, PIPJs, wrist joints and MTPJs, or large joints like the shoulders, elbows, hips, knees and ankles. A greater number of joints involved (especially of the small joints) increase the likelihood of an RA diagnosis[42].

Disease Activity Score (DAS)

The DAS includes several measures of disease activity: the Ritchie Articular Index which evaluates joint tenderness when firm pressure is applied, a 44-joint swollen joint count (including the MTPJs), and an ESR measurement. The DAS can also be used with a general health assessment score[43]. To expedite the clinical examination process, the DAS was simplified to include only 28 joints (DAS28), which examines the joints of the hands and wrists but excludes the feet. The Ritchie Articular Index is also replaced with a tender joint count of the 28 joints. Both DAS and DAS28 can be used in conjunction with ESR or CRP[44]. Studies have reported good test-retest reliability for DAS (r=0.80), and that

DAS was better able to discriminate low from high disease activity than some other indices[43].

Clinical Disease Activity Index (CDAI)

The CDAI is a simplified method of assessing disease activity, and is a composite score of sum of swollen joint count, tender joint count, patient global assessment and physician global assessment. The joints assessed include the MCPJs, PIPJs, shoulders, elbows, wrists and knees, but do not include the feet[45]. Patient global assessment asks the patients a single question "considering all the ways arthritis affects you, how well are you doing?", whereas the physician global assessment asks the physician a single question "considering all the ways arthritis affects the patient, how well are they doing?". They are both rated on a 0-10 scale, with 10 being "very poor". While the DAS requires complicated calculations for scoring and often involves online calculators, the CDAI can be immediately scored with simple calculations. Although researchers found a strong correlation between DAS-28 and CDAI assessments, CDAI appeared to be better at determining remission than DAS-28[46].

Health Assessment Questionnaire (HAQ)

HAQ is a widely used patient-report instrument that was designed to capture the long term influence of chronic illnesses. The full HAQ describes five patient-centred dimensions: disability, pain and discomfort, adverse treatment effects, treatment cost, and mortality. The more commonly used version is a shortened 2-page HAQ, which includes the HAQ Disability Index (HAQ-DI), the HAQ visual analog scale (VAS) for pain, fatigue, and patient global health. The HAQ-DI consists of 20 questions that assess the patient's functional ability and fine motor skills. Patients rate their ability to perform daily tasks (dressing, walking, eating, reach, and grip) on a scale of 0 (no difficulty) to 3 (with great difficulty). Additional questions capture the use of devices or help from another person in doing these activities, which increases the score of corresponding categories by 1. The sum of these scores is converted using a standard table to a scale of 0-3 with increments of 0.125, which represents the total HAQ score. A score of 0-1 is considered mild to moderate difficulty, 1-2 represent moderate to severe disability, and 2-3 represent severe to very severe disability[47].

The VAS (scored 0-10) is designed to assess the severity of pain and fatigue. Since pain and fatigue can vary from day-to-day, patients are asked to rate their pain and fatigue over the past week. In the full HAQ, information on drug toxicity is collected by

questions about the drugs that a patient takes, the dosage, and side effects. Direct sources of cost include physician visits, hospital stays, laboratory costs, imaging costs, and medication. Indirect costs stem from loss of productivity, and are captured by other sections of HAQ[47].

Many observational and clinical studies have assessed the validity of HAQ. HAQ demonstrated high reproducibility through test-retest correlation (r=0.87-0.96)[48]. Content validity was demonstrated by correlation with task performance tests (r=0.71-0.88)[49]. Furthermore, high construct validity and sensitivity to change of HAQ have also been found through observational and clinical studies[50].

Leeds Foot Impact Scale (LFIS)

There is a need to measure the impact of RA in the feet due to its frequent involvement in RA (approximately 70% of patients experience pain and swelling in the feet in early RA[63]). The LFIS is one of few patient-report questionnaires designed specifically for use in RA patients, and the only questionnaire that directly addresses the feet in this population. The LFIS captures both disease- and non-disease-related constructs that are relevant to patients with RA. Items on the LFIS were derived from qualitative interviews with RA patients and often retained the patients' own words. Items were discarded if they did not apply to all patients. Items were also checked for uni-dimensionality (not affected by factors like age and sex) by fitting into a Rasch model, which allows for linear parametric analysis. With The final LFIS asks 51 binary questions (yes=1/no=0) that are further separated into two subscales: 20 questions pertain to the domain of impairment/shoes, while 31 questions focus on activities/participation. A total score is obtained by adding scores from all questions. Test-retest analysis found high reproducibility (ICC=0.84-0.96), and the LFIS was able to discriminate between up to 4 groups of patients[51].

Remission

Approximately 10% of patients with early diagnosed RA enter natural remission without additional treatment[52]. An additional 75% of patients may achieve low disease activity with treatment. The definition of RA remission has evolved over time. The 1981 remission criteria approved by the ACR required that patients meet five out of six of the following items for two consecutive months: morning stiffness <15 minutes, no fatigue, no joint pain, no joint tenderness on motion, no swelling of soft tissue or tendon in joints, and normal ESR[53]. Due to the lack of effective RA treatments at the time, few

patients reached these stringent remission criteria[54]. Later, a DAS score <1.6 or a DAS28 score <2.6 indicated RA remission[55]. However, this use of DAS was criticized as patients deemed in-remission can still have active disease[56]. With the advent of more effective therapies, the definition of RA remission has become more stringent once again. In the 2011 ACR/EULAR remission criteria, a patient was in-remission if they satisfied all of the following: ≤1 tender joint, ≤1 swollen joint, CRP ≤1 mg/dl, and patient global assessment ≤1 out of 10[54]. Despite these stringent criteria, even in low disease activity assessed by conventional clinical methods, imaging modalities have observed subclinical synovitis and progressive joint damage[57].

1.4 Treatment

RA treatment aims to minimize pain and inflammation, prevent or control joint damage, and reduce systemic complications[58].

NSAIDs and Conventional DMARDs

Non-steroidal anti-inflammatory drugs (NSAIDs) are frequently used as an initial treatment to control joint pain and swelling. As NSAIDs do not alter the course of the disease, they are not used alone. Conventional DMARDs like plaquenil, methotrexate (MTX) and leflunomide are usually prescribed after an RA diagnosis. In patients with high disease activity, they may be prescribed in combination[58]. MTX is one of the most commonly prescribed DMARDs, but its precise mechanism of action is poorly understood. It is a modified folate that has greatly increased affinity for dihydrofolate reductase (DHFR). Although MTX depletes purine and pyrimidine, and leads to T-cell apoptosis in vitro, this hypothesis was not supported in clinical application. MTX prescriptions in RA are supplemented by folate to reduce the adverse effects of MTX therapy. A more validated hypothesis suggests that adenosine signalling may be a main mediator of T-cell depletion due to MTX therapy. Patients with RA overexpress adenosine receptors on immune cells, likely due to high levels of TNF. MTX increases extracellular adenosine levels, which have an anti-inflammatory effect by decreasing production of TNF and NF-κB. Other potential mechanisms involve the generation of reactive oxygen species and the regulation of adhesion-molecules[59]. However, conventional DMARDs do not appear to address the direct causes of RA inflammation, as a large proportion of patients on conventional DMARDs continue to experience active RA and progressive structural damage[60].

Biologic DMARDs

In more recent years, the development of biologics has markedly improved treatment outcomes and opened up new treatment options. "Biological" refers to substances created from a biological system and functions to target a specific biological molecule. Biologics are commonly used in combination with DMARDs. There are currently five TNF-α antagonists available: adalimumab, infliximab, etanercept, golimumab, and certolizumab[60]. By binding to and neutralizing TNF-α, they are able to inhibit TNF-α interaction with receptors and thereby limit its pro-inflammatory effects. Adalimumab is a humanized TNF-α antibody. Infliximab is a chimeric mouse-human monoclonal antibody. Etanercept is a fusion protein made from TNF-R2 fused with the Fc portion of human IgG1. Its dimeric structure is highly efficient at neutralizing TNF-α. Common adverse effects of TNF-α inhibitors are injection site reactions and infections, but usually mild or moderate. Lack of response to a TNF-α inhibitor does not predict ineffectiveness of other TNF-α inhibitors. Other marketed biologics neutralize other cytokines like IL-1, IL-6 or binds to surface receptors on B-cells and T-cells to prevent their activation. However, the use of biologics causes immunosuppression, which can lead to other complications like increased infections, reactivation of latent infections, and increased incidence of lymphoma[61].

1.5 Involvement of the Feet

The small joints of the hands and feet are the earliest to show signs of disease activity in RA[62,63]. Approximately 90% of patients complain of painful feet at some point during the course of disease[64]. In early RA, approximately 70% of patients experience pain and swelling in the MTPJs, and radiographic erosions have been observed in the MTPJs of 30% of patients[63,65]. Foot complaints severely impair patients' ability to perform daily activities and weight-bearing tasks, yet the feet receive little attention in RA research[66].

Routine clinical examinations and instruments often assess the hands but pay little attention to the feet. In fact, the DAS28 does not include the MTPJs at all[67,68]. Due to the extensive involvement of the MTPJs in RA, their exclusion from examinations leads to underrepresentation of RA disease activity. Van der Leeden *et al.* reported that in patients deemed "in-remission" by DAS-28, 40% still had at least one swollen or tender MTPJ[57]. Furthermore, synovitis and erosion on magnetic resonance imaging (MRI)

have been observed in the MTPJs of patients with clinically asymptomatic hands[69,70]. Therefore, overlooking the feet during assessments would risk continued, uncontrolled disease activity and potential functional disabilities.

The omission of the examination of the feet in routine visits is, in part, due to the poor inter-rater reliability of clinical examination in the MTPJs compared to the MCP joints[71]. Although swelling and tenderness are hallmark symptoms of joint inflammation, they can also be affected by many other factors, such as extra-articular fluids and non-inflammatory causes of pain[71]. Sewerin *et al.* reported several patients with markedly improved swollen and tender joint counts in the feet who actually had unchanged or worsened disease activity when the same joints were scanned by MRI[72]. Assessment of the MTPJs is very important in routine examinations. To increase the value of MTPJ assessments, a more reliable and accurate method than clinical examination for the MTPJs should be established.

1.6 Imaging Modalities

Currently, RA monitoring relies primarily on physical examination, which has been criticized for having low inter-rater reliability and low agreement with inflammation seen on imaging modalities[71,73,74]. Identifying swelling is very difficult in obese patients, and distinguishing between articular and extra-articular swelling is especially challenging in the MTPJs[75]. Furthermore, objective signs of swelling and tenderness may be suppressed after patients receive anti-inflammatory treatment, despite continued subclinical inflammation[76]. Swollen and tender joints counts are major components of many RA assessment tools such as the DAS[68], the ACR core data set for clinical trials[77], and the ACR remission criteria[67]. Imaging modalities like MRI and US are able to identify subclinical inflammation, especially in patients with early RA[78,79]. Incorporating these technologies in RA assessments may improve the accuracy of diagnosis and disease monitoring.

Magnetic resonance imaging (MRI)

MRI is a non-invasive imaging technique that uses a strong magnetic field to make use of the nuclear magnetic resonance (NMR) phenomenon. The magnet of the MRI is circular and contains electrons travelling in a loop, which creates a perpendicular magnetic field (B_o) (Figure 2A). The strength of the magnetic field is measured in Tesla

(T). The direction parallel to the magnetic field is the longitudinal direction (z direction), while the x and y directions are transverse (Figure 2B)[80].

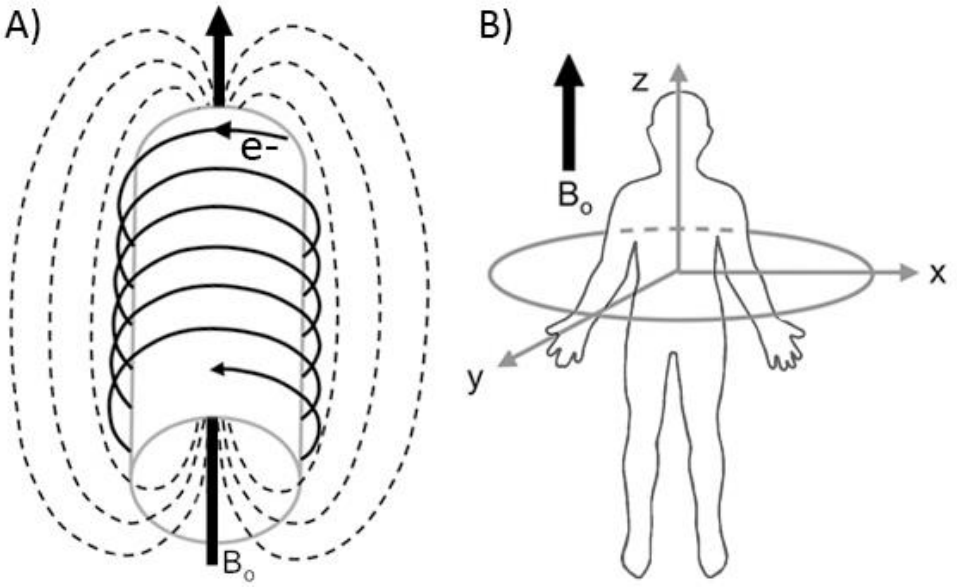

Figure 2: *A) Electrons travelling through a coil create a perpendicular magnetic field B_o. B) The direction parallel to the magnetic field is the longitudinal direction (z), while x and y are on the transverse plane. If a person were to lie in the supine position inside the MRI coil, x=medial-lateral direction, and y=anterior-posterior direction. Images modified from*[80].

Nuclei with an odd number of neutrons or protons can exhibit spin. In MRI, hydrogen is the most commonly used nuclei due to its high prevalence in the body, but other nuclei like oxygen, sodium and phosphorous can also be used[81]. The magnetic property of protons arises from its spin and charge. Without an external magnetic field, protons spin randomly and do not create net magnetization[80]. When a magnetic field is applied, protons act similar to magnets and align with the field. The inherent spin of the proton provides angular momentum (ω), which causes the proton to 'wobble' about the direction of the magnetic field. This 'wobbling' is termed 'precession'[81]. Although only a small proportion of protons align with the magnetic field, this slight imbalance produces a net magnetization (Figure 3)[80]. The frequency of precession for protons is highly important for MRI. It is the product of the strength of the magnetic field (B_o) and the gyromagnetic ratio (γ), which is a constant that varies for different nuclei ($f = \gamma \cdot B_o$). For the hydrogen proton, γ = 42.6 MHz/T[81].

A radiofrequency transmit coil transmits a radiofrequency pulse at the precessional frequency, which transfers energy from the radiofrequency coil to the protons. When protons absorb energy from the radiofrequency pulse, the net magnetization rotates depending on the strength and duration of the radiofrequency pulse. A 90^o radiofrequency pulse causes the net magnetization to rotate 90^o from the longitudinal plane to the transverse plane, while a 180^o pulse causes a 180^o rotation to the –z plane (Figure 4)[80]. This rotation is the basis behind T1- and T2-weighted MRI.

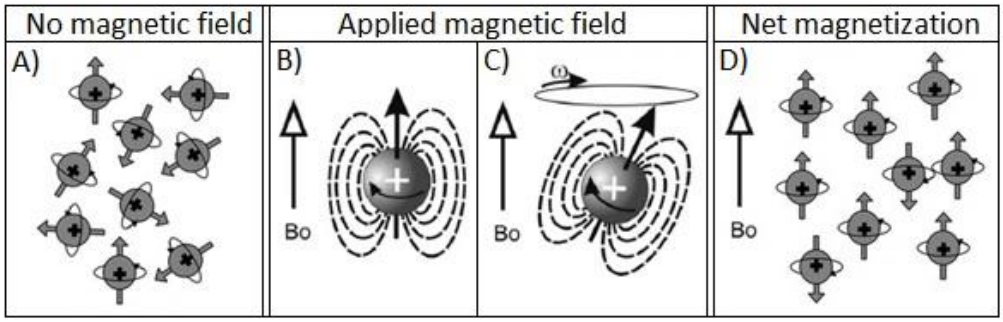

Figure 3: *A) In the absence of a magnetic field, proton spins are randomly distributed and do not create net magnetization. B) Proton aligns with applied magnetic field. C) Angular momentum (ω) caused by spin causes the proton to precess about the direction of the magnetic field. D) Protons can align in the same direction or the opposite direction as the magnetic field. A slight excess of protons aligning with the field and precessing in synchrony produces a net magnetization. Image adapted from*[80] *and*[81].

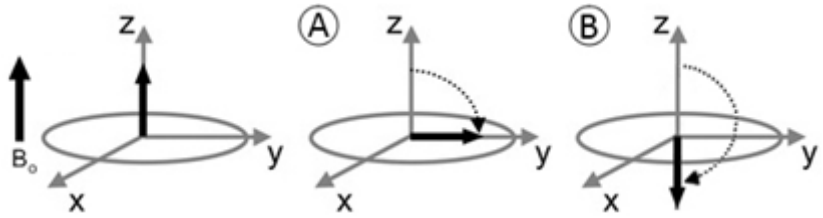

Figure 4: *A) A 90^o* radiofrequency *pulse rotates net magnetization to the transverse plane. B) A 180^o* radiofrequency *pulse rotates the net magnetization to the –z plane. Image adapted from*[80].

Tissues of varying densities have different T1 and T2 relaxation times, which allow them to be seen in different brightness intensities. After a 90^o radiofrequency is applied, the magnetic field rotates to the transverse direction and the longitudinal magnetization is 0. T1 relaxation occurs when the magnetization gradually returns to the

longitudinal direction, and T1 refers to the time it takes for longitudinal magnetization to reach 63%. The rate of relaxation is tissue dependent, which creates contrast in T1-weighted images. Relaxation is slower in fluids and faster in dense matter like fat[82]. In musculoskeletal MRI, synovial fluid has high T1 relaxation, and is presented as dark areas on images[80]. Although protons exist in bone, they have very fast T2 relaxation times due to high density of the bone, and these signals disappear too rapidly to be seen on MRI. Instead, MRI uses bone marrow as a surrogate to visualize porous trabecular bone[83]. Marrow has high fat concentration and slow T1 relaxation, and appears white on images. Protons in muscles have a moderate T1 relaxation time, and appear gray on images (Figure 5A)[80].

T2 relaxation, or T2 decay, occurs when protons in the transverse plane dephase following a 90° radiofrequency pulse, and T2 refers to the time it takes for transverse magnetization to decay to 37% of its original value (Figure 5B). Transverse magnetization can be measured with a receiver coil, which is a wire looped perpendicular to the transverse field. Similar to how a looped current creates a magnetic field, the transverse magnetization creates current in this coil, which is digitized and recorded[80].

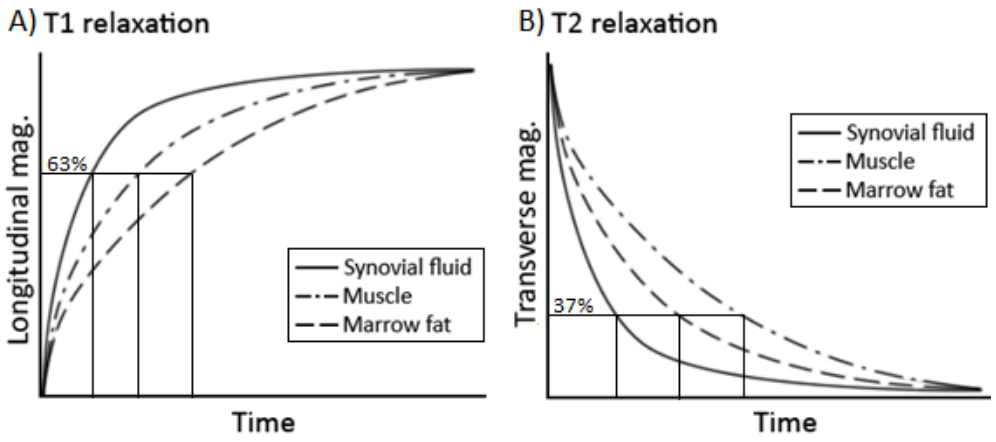

Figure 5: *Graphs showing A) longitudinal and B) transverse magnetization at varying times for synovial fluid, muscle and bone marrow, representing T1 and T2 relaxation times. Relaxation times for comparative reference only, not to scale. Images adapted from*[80].

Proton dephasing is mainly caused by spin-spin interactions between protons. The magnetic field acting on each proton varies slightly due to its interactions with the magnetic fields of surrounding protons. This causes protons to precess at slightly varying

frequencies. There are other causes of T2 relaxation, but they can be minimized using spin echo, whereby 180° radiofrequency pulses are applied after the original 90° pulse (Figure 6). This causes the spins to rotate to the opposite axis, rephase until they reach a maximum signal, and then dephase again (echo 1). This process repeats when another 180° pulse is applied (echo 2). The curve formed between the peaks of each echo forms a T2 decay that is only affected by spin-spin interactions. Time between peaks is the echo time (TE)[80].

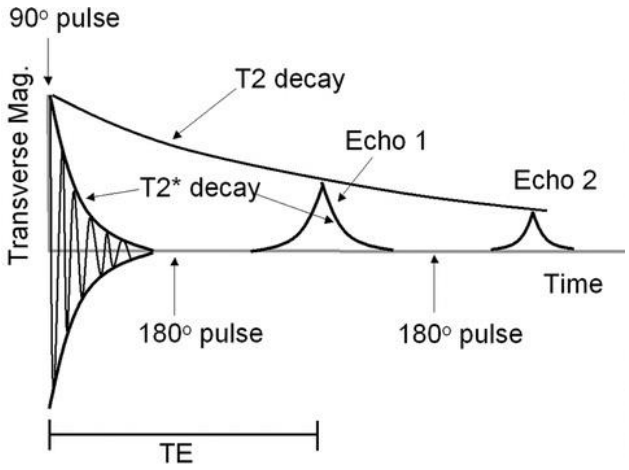

Figure 6: *When successive 180° radiofrequency pulses are applied after an initial 90° pulse, the curve joining their peaks represents T2 decay that is only caused by spin-spin interactions between protons. TE=echo time, the time between the 90° pulse peak and an 180° pulse peak. Image from*[80].

Spin echo is able to correct for all other causes of proton dephasing because they remain constant over time. For example, MRI coils do not produce a perfectly homogenous magnetic field, which causes protons to experience slightly different magnetic field strengths and to precess at slightly different frequencies. Since these inhomogeneities are constant, spin echo would cause a proton with a faster spin to spin slower by the same magnitude, thereby cancelling out its effects. However, spin-spin interactions are random, and therefore cannot be corrected by spin echo[80].

Repetition time (TR) is the time it takes to run through the pulse sequence one time. TE and TR can be used to control the amount of weighting effects in MRI. A T1-weighted image can be best produced when TR maximizes T1 while TE minimizes T2 (Figure 7)[80]. A short TR allows tissues with a short T1 relaxation time, like fat, to recover more magnetization between pulses and produce a more observable signal than tissue

with a long T1 time like fluids. T1-weighted images provide detailed anatomy and high contrast between fat and synovial fluid[83]. Conversely, a T2-weighted image can be produced with relatively long TR to reduce the T1-weighting (Figure 7)[80]. Both fat and fluids have high intensity on T2-weighted images, while muscles remain gray, and tendons and cartilage are dark[83].

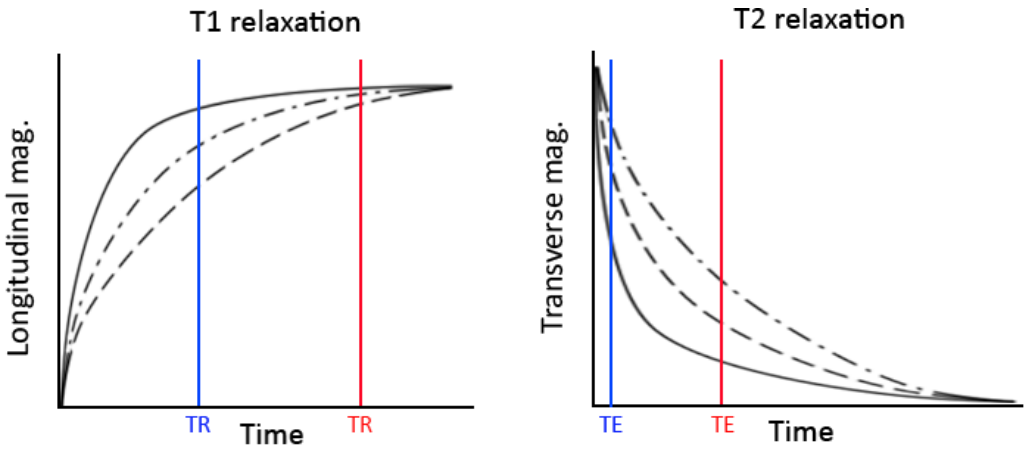

Figure 7: *T1-weighted images can be produced by maximizing TR and minimizing TE (blue), while T2-weighted images can be produced by minimizing TR and maximizing TE (red). Image adapted from*[80].

Fast spin-echo (FSE), or turbo spin-echo (TSE), uses multiple 180° radiofrequency pulses to create multiple echoes. The number of echoes formed is called the echo train length (ETL). Normally, one pulse sequence produce one row of data, and 256 rows of data would require 256 pulse sequences to be run. In FSE, with an ETL of 6, each pulse sequence produces 6 rows of data, thereby speeding up data acquisition by factor of 6[80]. An inversion recovery pulse sequence suppresses unwanted signals in MRI. In inversion recovery, a 180° radiofrequency pulse is applied before the 90° pulse. As the magnetization from the –z direction grows back to the +z direction, the 90° pulse is applied as the signal from the tissue to be suppressed reaches 0 (Figure 8). Since a 0 signal cannot be rotated to the transverse plane, this process removes the tissue of suppression from contributing to the final image. Time of inversion (TI) indicates the time from the initial 180° pulse to the 90° pulse[80]. Fat suppression helps distinguish fat from edema, which are both of high intensity. As lesions are generally accompanied by increase fluid content, this type of sequence is best used to demonstrate pathology[84]. The short tau inversion recovery (STIR) imaging uses the inversion recovery method to

suppress fat and better distinguish fluids. However, STIR also indiscriminately suppress signals from any tissue with T1 relaxation time shorter than fat[83].

Contrast agents can be used to change the relaxation times. Gadolinium, a common contrast agent, is a metal that shortens the T1 and T2 relaxation times, which causes contrast enhancement[83]. Although contrast enhancement is not widely used in musculoskeletal imaging, it has been shown to be beneficial for visualizing synovial proliferation in RA (Figure 9)[85].

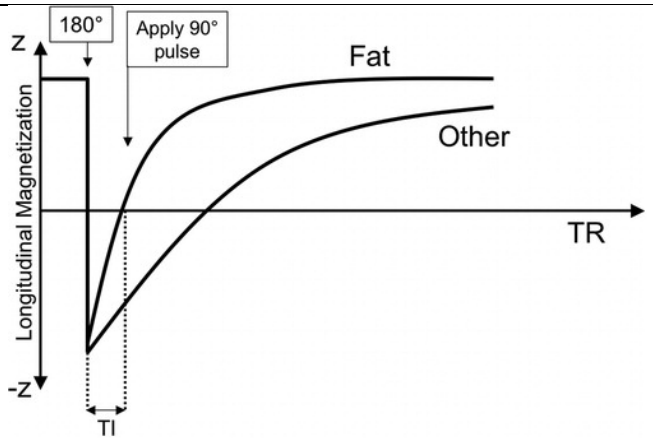

Figure 8: *Inversion recovery pulse sequence. A 180^o* radiofrequency *pulse causes magnetization recovery from –z to +z. When magnetization of the tissue of suppression reaches 0, a 90^o pulse rotates all other signals to the transverse plane*[80].

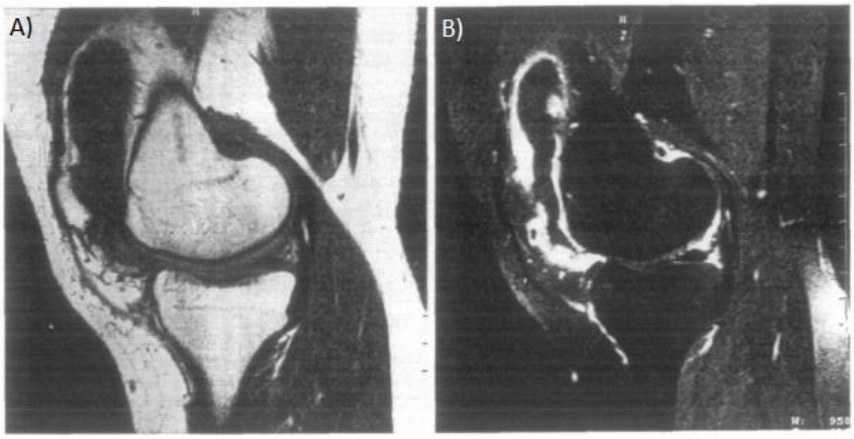

Figure 9: *MRI of the knee of a patient with RA. A) T1-weighted spin echo image showing increased joint fluid, but cannot demonstrate thickened synovium, which has similar intensity as the fluid. B) T1-weighted, gadolinium-enhanced, fat-suppressed spin echo image showing contrast enhanced synovium*[85].

MRI scoring in RA

The Outcome Measures in Rheumatology Clinical Trials (OMERACT) group developed a rheumatoid arthritis MRI scoring system (RAMRIS) for evaluating inflammation and joint destruction[69]. RAMRIS defined synovitis as a synovial compartment that shows greater thickness than the width of the normal synovium. Bone marrow edema (BME) is defined as a lesion within trabecular bone with signal indicating increased water content, and is evaluated based on the volume of edema. Although synovitis and BME are both measures of inflammation on MRI, they examine disease in different contexts. Studies have suggested that synovial inflammation propagates to bone marrow follicles located in superficial sites of the bone through erosions, leading to bone marrow inflammation and BME[86]. Synovitis and BME are scored as follows: 0 = no synovitis/edema, 1 = synovitis/edema in 1-33% of synovial compartment/bone, 2 = 34-66%, and 3 = 67-100%[69]. Bone erosion is defined as a sharp bone lesion visible in two planes, with a cortical break in at least one plane. It is graded on a scale of 0-10 based on the proportion of eroded bone compared to the volume of the bone being assessed: 0 = no erosion, 1 = 1-10% of bone eroded, 2 = 11-20%, etc.[69]

MRI is currently the gold standard for evaluating synovitis and bone erosions[87]. It can detect inflammatory markers like synovitis and BME that are often subclinical, and can visualize bone erosions earlier in the course of RA progression than conventional radiography[87]. Sewerin *et al.* reported observing patients with markedly improved swollen and tender joint counts on clinical examination, yet unchanged or worsened disease activity on MRI[72]. In addition, MRI allows for visualization of BME, which is predictive of progressive erosion[88]. However, MRI is impractical for routine use due to its high costs, time consuming scans, and limited availability and accessibility. Furthermore, the quality of MRI scans can be compromised by motion artifact which may be exacerbated by long scan times and patient discomfort[89,90]. As a result, only a few joints can be imaged per session, and obtaining a comprehensive view of all joints of interest is unlikely during routine visits.

Ultrasonography (US)

US is a non-invasive imaging technique that can be used to visualize musculoskeletal anatomy in RA. An US transducer transmits high frequency waves and detects the echoes when the wave is reflected from objects it hits. To do this,

transducers use piezoelectric elements, which transform applied electrical energy into mechanical vibrations and vice versa[91].

Tissues of the body have different densities, which influence the amount of waves reflected. The denser the material, the more waves are reflected and the brighter the tissue appears on the US image (Figure 10). The US machine calculates the distance from the boundaries to the probes, and display a two-dimensional image on the screen. The frequency of ultrasound waves can be adjusted to suit the purpose of the image. Waves with higher frequency yield images with higher resolution, but suffer from decreased depth of penetration. Conversely, lower frequency waves allow visualization of deeper structures, but at lower resolutions[91].

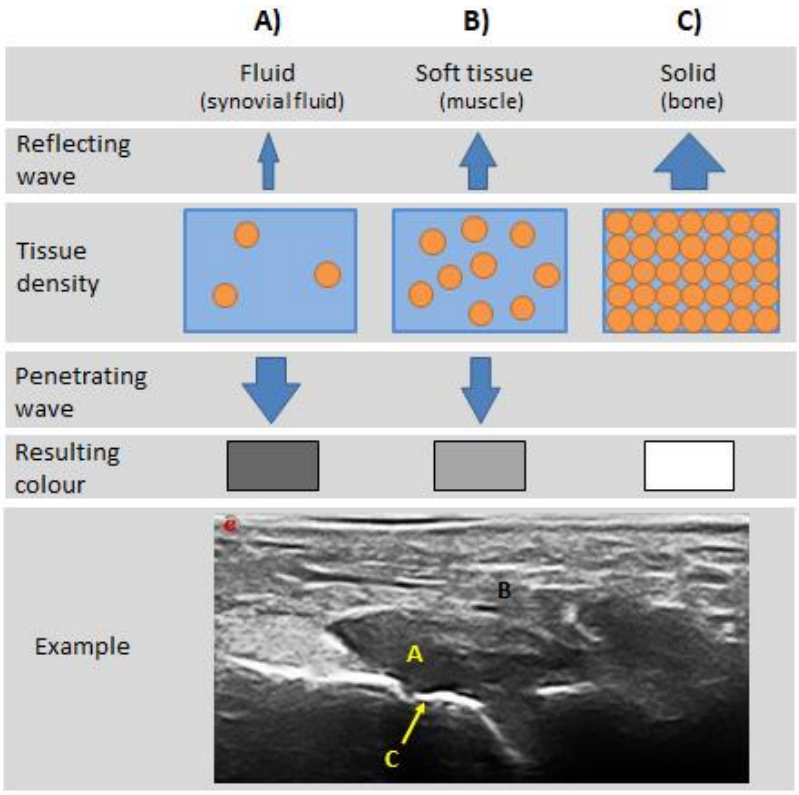

Figure 10: *US waves are reflected at different rates by different tissues depending on their density. A) Low density materials like synovial fluid transmit more waves, and appear dark. B) Moderately dense materials like muscle and fat reflect some waves, and appear grey. C) Dense materials like fibrous tissue and bone reflect most or all of the waves, and appear white with a dark acoustic shadow behind these structures.*

The US probe can be moved along the surface of the body and positioned to view different planes of the body. In RA assessments, the probe can be moved around certain joints to gather a more complete view. This is best obtained in the 1st and 5th joints in the hands and feet, as they allow the most movement of the probe[91].

In RA, US can be used to evaluate synovial thickening in Brightness mode (B mode) and hypervascularization in Power Doppler (PD) mode[92]. B mode provides black and white images showing the anatomical site. Synovial thickening is indicated by an enlarged hypoechoic area within the joint space. PD makes use of the Doppler Effect, where a wave reflected from a moving object will change in frequency. By detecting this change in frequency, PD is able to determine abnormal blood flow in tissue, indicating hypervascularization[93]. This is represented as coloured spots - the brighter and larger area covered, the greater the hypervascularization (Figure 11).

Szkudlarek et al. developed a 4-grade semi-quantitative scoring system for assessing synovial thickening, PD and bone erosions (Table 1). Synovial thickening is visualized as a non-compressible hypoechoic intracapsular area on grey-scale US, synovial flow was visualized on PD as coloured signals (Figure 3), and bone erosion was defined as changes in the bone surface adjacent to the joint[94].

Table 1: *Semi-quantitative definitions of synovial thickening, PD, and bone erosion by Szkudlarek et al.*[94]*.*

Grade	Synovial thickening	PD	Erosion
0	No thickening	No flow in the synovium	Regular bone surface
1	Minimal thickening filling the angle between the periarticular bones, without bulging over the line linking tops of the bones	Single vessel signals	Irregularity of the bone surface without formation of a defect seen in 2 planes
2	Synovial thickening bulging over the line linking tops of the periarticular bones but without extension along the diaphysis	Confluent vessel signals in <50% of the synovium	Formation of a defect in the surface of the bone seen in 2 planes
3	Synovial thickening bulging over the line linking tops of the periarticular bones and with extension to ≥1 of the diaphyses	Vessel signals in >50% of the synovium	Bone defect creating extensive bone destruction

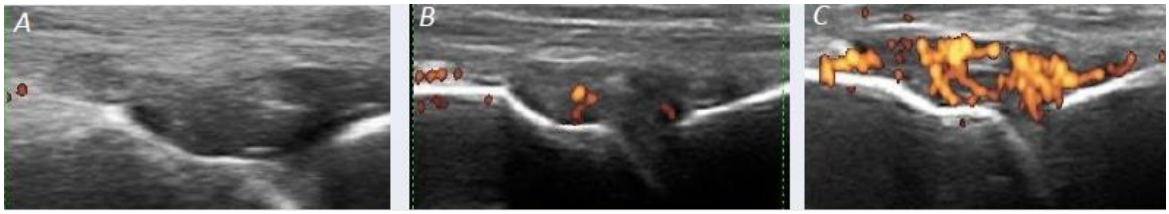

Figure 11: *Semi-quantitative grading of PD. A) grade 1=one or several vessels; grade 2=signal in <50% of joint space; C) grade 3=signal in >50% of joint space.*

Quantitative scoring systems have also been used. Synovial thickening can be quantified by measuring the vertical distance from the bone surface to the upper edge of the hypoechoic area[95], whereas PD can be quantified by measuring the number of coloured pixels[96].

In recent years, US has been sought after as a more feasible alternative to MRI. In addition to being a non-invasive, relatively inexpensive and accessible imaging modality, US has the advantage of allowing a clinician to observe joints in 'real-time' during patient visits. US is highly accessible to many rheumatology practices, and is less time-consuming than MRI to perform[87,97]. Both synovial thickening and PD have higher inter-observer reliability than clinical examinations in the MCP and MTPJs[71,98]. With MRI as standard of reference, US assessment of inflammation in the hands and wrists were consistently reported to be superior to that of clinical examination[71,79,99]. Studies have found that inflammation on US was predictive of erosion development seen on MRI[100,101]. In addition, US is able to visualize abnormalities on the cortical surface of bones, such as osteophytes and erosions. However, few studies to date have evaluated the use of US in the MTPJs, especially in early RA cohorts.

Although US has several advantages over clinical examination and MRI, it is limited in other ways. First, the US field-of-view is obstructed by adjacent joints, thus it is impossible to obtain a complete view of the outer perimeter of the small joints of the hands and feet. Second, ultrasonic waves are almost completely reflected upon contact with bone, which means that it cannot detect bony erosions that do not have a cortical break. Finally, while PD is very sensitive to detecting small vessels and low-velocity blood flow, nearby normal vessels can create PD signals and artefact[93]. Therefore, it takes an experienced US examiner to identify pathologic hypervascularization.

1.7 Objectives

This study aimed to evaluate the use of US to monitor disease activity and changes in disease activity in the MTPJs. We had several objectives:

1) Compare the use of clinical examination (swollen and tender joint counts) and US (synovial thickening and PD) to assess inflammation in the MTPJs of patients with early RA, using MRI (synovitis and BME) as reference.
2) Characterize erosions in early RA using US and MRI, and investigate the role of size and location of MRI erosions in their visualization by US.
3) Characterize changes in inflammation over 12 months, and compare the use of clinical examination and US to detect change in inflammation, using change in inflammation on MRI as reference; examine the relationship between changes in inflammation and changes in patient-reported outcomes.
4) Characterize changes in erosion over 12 months on US and MRI; examine the relationship between inflammation and changes in erosion.

CHAPTER 2: METHODS

2.1 Patient Recruitment

Treatment naïve patients with early RA (symptom duration <2 years) were recruited from an academic rheumatology clinic in Hamilton, Ontario, Canada. Diagnoses were made in accordance with the 2010 ACR/EULAR classification criteria[42]. Eligible patients were 18-85 years old who did not have other arthritic diseases (e.g., gout, inflammatory osteoarthritis), were not taking corticosteroids (within the last 3 months for intra-muscular or intra-venous injections and 2 months for oral pills), and had no contraindication to extremity MRI. Patients were treated as per standard of care, and returned at 6 weeks, 3 months, 6 months and 12 months after the initial visit.

This study was approved by the Hamilton Integrated Research Ethics Board and written informed consent was obtained from all participants.

2.2 Clinical Examination

At all visits, the 2nd-5th MTPJs were examined clinically for swelling and tenderness. The 1st MTPJ was excluded from examination as it is commonly involved in other arthritides like osteoarthritis and gout[102,103]. Patients also completed the shortened HAQ[50] and the LFIS[51]. RF and ACPA levels were measured at baseline. Standard blood work was performed as per standard of care, and results for CRP and ESR were recorded at all study visits.

2.3 Ultrasonography (US)

During all study visits, the same rheumatologist who performed clinical examinations also scanned the 2nd-5th MTPJs of both feet using US (Esaote MyLab70) with a 6-18 MHz linear array probe at 18 MHz. US images were graded semi-quantitatively for synovial thickening (assessed from the dorsal view) and synovial flow representing active inflammation on PD (dorsal view) as shown in Table 1[94]. Given that grade 1 synovial thickening has been observed in the small joints of healthy populations[104], we defined pathologic synovial thickening as grade ≥2.

Bone erosion (visualized in dorsal and plantar views of the 2nd-5th MTP, and lateral aspect of the 5th MTP) was defined as a break in the cortical surface on either the metatarsal head or the phalanx base, and must be visible in both longitudinal and transverse views. Twenty patients received an additional plantar scan at the baseline

visit, and all patients received plantar scans during follow-ups. The reason for the missing plantar scans at baseline was that these scans are not commonly conducted in routine US examinations[105], and were not part of the original protocol. For bone erosion, the presence or absence are reported for the dorsal surface of the 2nd-5th MTPJs and the lateral surface of the 5th MTPJ.

2.4 Magnetic Resonance Imaging (MRI)

The most clinically symptomatic foot determined at baseline was imaged using MRI at baseline and 12 months. If both feet were equally symptomatic, the dominant foot was chosen. MRIs were performed within a week of clinical and US examinations. Patients were seated on a reclining chair with knee bent, and one foot placed in the centre of the coil. The foot was placed such that the sole ran parallel along the side of the coil. Cushions were placed around the foot and ankle to minimize the potential for motion artefact. The other foot was placed on a foot stool to provide additional stability and to minimize torsion at the hip. Total MRI time was approximately 40 minutes.

All scans were acquired on an OrthOne (1.0 T) extremity scanner (GE Medical, formerly ONI Medical Systems). The recommended sequences were used based on the OMERACT-RAMRIS protocol (106). The forefoot was scanned using a T1-weighted spin echo sequence in the coronal plane (TR 667ms; acquisition matrix 320x192; 20 slices); and in the axial plane (TR 518ms; acquisition matrix 320x192; 22 slices). Forefoot scans used STIR FSE sequences in the coronal and axial planes (TR/TE 3929/30; acquisition matrix 300x192; ETL 6; 18 and 20 slices respectively). All sequences had a field of view of 100mm, slice thickness of 3mm and no slice gap.

MRI sequences were scored by a musculoskeletal-trained radiologist who was blinded to clinical and US data. The scans were assessed semi-quantitatively for synovitis (grade 0-3), BME (grade 0-3), and bone erosion (grade 0-10) in accordance with OMERACT recommendations for MTPJs[69]. Synovitis was scored for the entire joint, whereas BME and erosions were scored separately for the metatarsal head and phalanx base (max BME=24, max erosion=80). A joint was considered to be affected by BME or erosion if pathology was present on either the metatarsal head or phalanx base.

To better compare agreement between US and MRI on erosions, we further divided the MTPJ bones into dorsal, plantar, medial and lateral regions (Figure 12). The location of the erosions was recorded by the radiologist.

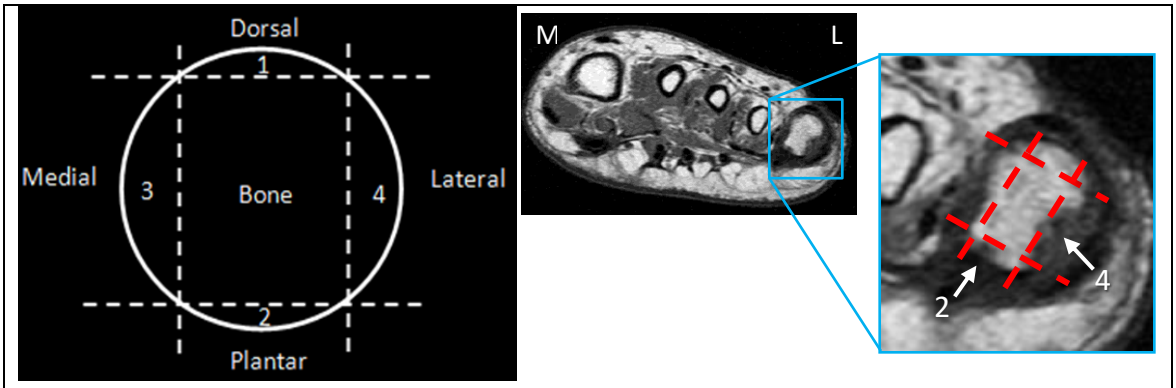

Figure 12: *The metatarsal head and phalanx base were divided into dorsal, plantar, medial and lateral regions as shown.*

2.5 Statistical Analysis

All descriptive statistics, continuous variables, means, standard deviations (SD), and frequencies were reported with 95% confidence intervals. Analyses were performed using the SPSS statistical software (IBM SPSS statistics version 20.0, Armonk, NY, USA). More detailed descriptions of statistical analyses are reported in chapter 4 to chapter 7.

The prevalence of clinically swollen and tender joints, and abnormalities identified on US and MRI were reported for each 2nd-5th MTPJ at each study visit. Comparisons were analyzed with only data from the most symptomatic foot since MRI was used as the reference standard.

Baseline cross-sectional analyses

With synovitis and BME on MRI as reference, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and agreement with MRI were analyzed for each measure of inflammation on clinical examination (swelling and tenderness) and US (synovial thickening and PD). Agreement was reached when two assessments both found a joint to be healthy or to show disease activity, and was analyzed using kappa statistic. Kappa agreement was interpreted as follows: poor $k<0.2$; fair $0.21<k<0.4$; moderate $0.41<k<0.6$; good $0.61<k<0.8$; and excellent $k>0.81$[107]. The magnitude of kappa can be affected by high prevalence (unequal distribution between true positive and true negative) or high bias (unequal distribution between false positive and false negative), whose effects would underestimate or overestimate kappa, respectively. To understand their influence, the prevalence-adjusted bias-adjusted kappa (PABAK) was reported[108].

Erosions detected by US and MRI were also analyzed using kappa statistic. Agreement was examined in two ways: 1) presence or absence of erosion in an MTPJ, and 2) presence or absence of erosion on MTPJ surfaces hypothesized to be accessible by the US probe (dorsal or plantar surfaces of all MTPJs, or lateral surface of the 5th MTPJ).

It has been previously reported that higher agreements were found when grade ≥2 MRI measures were referenced instead of grade ≥1[109]. Therefore, we evaluated clinical examination and US by comparing them with both MRI grade ≥1 and grade ≥2 as cut-offs to further investigate this relationship.

Longitudinal change analyses

A Friedman's test was used to determine the significance of changes in the total scores for clinical examination and US at different study visits. A Wilcoxon signed rank test was used to determine the significance of change in total synovitis and BME scores on MRI between baseline and 12 months. Spearman's rank order correlation was used to examine the associations between changes in different measures of inflammation, and their association with patient-reported outcomes.

CHAPTER 3: RESULTS

3.1 Cohort characteristics

In total, 41 adults with early RA were recruited. Patients were mostly women, with a mean age of 52, and a third of patients were seropositive for RF and ACPA. At baseline, both the mean CRP and ESR fall outside of normal ranges (normal CRP <6 mg/L and ESR 2-30 mm/hr). The patient-reported HAQ, VAS pain and LFIS scores all indicate moderate to severe functional disability at baseline (Table 2).

Patients received treatment as per standard of care. Most patients (90%) were taking single or combination DMARDs during the study period. These were often supplemented by NSAIDs. Four (10%) patients did not take any DMARDs over the 12-month span of the study. This may be due to the presentation of low disease activity that required no therapy or patient non-compliance to treatment. Three patients were on a biologic agent by the 6 month visit, and an additional 4 patients were on biologic by 12 months.

Table 2: *Characteristics of 41 patients at baseline.*

	(n=41)
Age in years, mean (SD)	51.9 (10.3)
Female sex, n (%)	33 (81%)
Symptom duration, mean (SD) months	12.2 (10.8)
CRP mg/L, mean (SD)	19.8 (31.2)
ESR mm/hr, mean (SD)	28.0 (22.2)
ACPA positive, n (%)	19 (46%)
RF positive, n (%)	16 (39%)
ACPA and RF positive, n (%)	14 (34%)
Morning stiffness, mean (SD) minutes	94 (109)
HAQ, mean (SD)	1.12 (0.69)
Pain, mean (SD)	5.6 (2.8)
LFIS, mean (SD)	23.4 (13.8)

SD: standard deviation; RF: rheumatoid factor; ACPA: anti-cyclic citrullinated protein antibody; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

3.2 Inter-rater reliability of US

Baseline synovial thickening, PD and bone erosions on US of all patients were scored independently by two blinded raters. Rater 1 was very experienced in

musculoskeletal US, and graded the US images as they were procured in real-time during patient visits. Rater 2 was less experienced (<1 year), who retrospectively graded the images procured by rater 1. Inter-rater reliability was excellent for both synovial thickening (k=0.81) and PD (k=0.87), and was good for erosion (k=0.65). Experience of the examiner did not appear to markedly affect US grading.

3.3 Cross-sectional comparison of clinical examination and US inflammation

At baseline, two patients had missing MRI data, therefore a total of 39 patients and 156 MTPJs (of the most symptomatic foot) were included in these comparisons. Tenderness appeared more prevalent than swelling in the MTPJs, and synovial thickening was more prevalent than PD on US. A similar number of joints showed synovitis and BME on MRI (Table 3). Forty-three MTPJs (28%) were both swollen and tender, and 22 (14%) joints showed both synovial thickening and PD signals on US. On MRI, most cases of synovitis or BME were grade 1, and few joints were grade ≥2. Synovitis and BME often occurred in the same joints.

Table 3: *Prevalence of disease activity in the MTPJs of the clinically most symptomatic foot.*

(156 MTPJs)	**n, (%)**
Swollen	31 (20)
Tender	91 (58)
US findings	
ST grade ≥2	76 (49)
PD grade ≥1	26 (17)
MRI findings	
Synovitis grade ≥1	58 (37)
Synovitis grade ≥2	17 (11)
BME grade ≥1	49 (31)
BME grade ≥2	12 (8)

ST: synovial thickening; PD: power Doppler; US: ultrasonography; MRI: magnetic resonance imaging; BME: bone marrow edema.

Greater sensitivity was observed when clinical examination and US assessments of inflammation were evaluated using grade ≥2 MRI (47-83%) as the reference standard than grade ≥1 MRI (28-71%), and without much decrease in specificity. Using grade ≥2 synovitis and BME on MRI as the reference, the highest sensitivity was achieved by

tender joint count (75-82%) and synovial thickening (82-83%) on US, but both had low specificity (43-55%). Their high sensitivities were likely due to low prevalence of disease activity identified on MRI, as both of their PPVs were low (10-18%). Of all measures of inflammation, PD had the highest combination of sensitivity (65-75%), specificity (88-89%), PPV (35-42%) and NPV (95-98%) (Table 4).

Although MRI is not a perfect gold standard, for ease of interpreting our results, we will assume that grade ≥2 synovitis and BME seen on MRI represent real inflammation. A high sensitivity of tender joint count and synovial thickening (75-83%) suggest that they can detect inflammation in most inflamed joints, but their low specificity (43-55%) suggest that they will be falsely positive for many non-inflamed MTPJs. This is clearly the case, as their PPVs were very low (10-18%), suggesting that 82-90% of MTPJs deemed to be 'inflamed' were actually non-inflamed. On the contrary, the high specificities of swollen joint count and PD (83-89%) suggests that MTPJs are rarely swollen or have PD signals if they are not inflamed. Therefore, swollen joint count and PD can help clinicians 'rule-in' inflammation.

Kappa agreement (Table 5) for swollen joint count, tender joint count and synovial thickening were poor to fair (k=0.05-0.31) regardless of whether MRI grade ≥1 or ≥2 were referenced, suggesting that their agreement with MRI were not dependent on the severity of inflammation on MRI. PD poorly agreed with both grade ≥1 synovitis and BME (k=0.20-0.23), but moderately agreed with grade ≥2 (k=0.46-0.47), suggesting that US can better detect hypervascularization in joints with more severe inflammation. Swollen joint count and PD were most affected by a high prevalence index (0.4-0.7), which led to an underestimation of kappa. On the other hand, kappa agreement for tender joint count and synovial thickening were not markedly skewed. The PABAK was calculated to allow comparisons between assessment methods without influence by prevalence or bias, and adjusted-kappa for PD remained higher than clinical examination and synovial thickening.

Table 4: *Sensitivity, specificity, PPV and NPV of clinical examination and US for assessing inflammation in MTPJs, with MRI synovitis and BME as reference standard.*

	MRI Synovitis				**MRI BME**			
	Sens. % (95%CI)	Spec. % (95%CI)	PPV % (95%CI)	NPV % (95%CI)	Sens. % (95%CI)	Spec. % (95%CI)	PPV % (95%CI)	NPV % (95%CI)
MRI grade ≥1								
Swollen	28 (17-41)	85 (76-91)	52 (36-67)	66 (62-70)	39 (25-54)	89 (81-94)	61 (46-75)	76 (72-80)
Tender	64 (50-76)	45 (35-55)	41 (34-47)	68 (58-76)	71 (57-83)	48 (38-58)	38 (33-45)	78 (69-86)
ST	60 (47-73)	58 (48-68)	46 (38-54)	71 (63-78)	61 (46-75)	57 (47-67)	39 (32-47)	76 (69-83)
PD	29 (18-43)	91 (83-96)	65 (47-80)	68 (65-72)	29 (17-43)	89 (81-94)	54 (37-70)	73 (69-77)
MRI grade ≥2								
Swollen	47 (23-72)	83 (76-89)	26 (16-39)	93 (89-95)	58 (28-85)	83 (76-89)	23 (14-35)	96 (92-98)
Tender	82 (57-96)	45 (36-53)	15 (12-19)	95 (88-98)	75 (43-95)	43 (35-52)	10 (7-14)	95 (88-98)
ST	82 (57-96)	55 (47-64)	18 (14-23)	96 (90-99)	83 (52-98)	54 (46-62)	13 (10-17)	98 (92-99)
PD	65 (38-86)	89 (83-94)	42 (29-57)	95 (92-98)	75 (43-95)	88 (82-93)	35 (23-48)	98 (94-99)

Table 5: *Kappa agreement of MRI compared to each of clinical examination and US assessments for inflammation. The un-adjusted kappa, prevalence-adjusted bias-adjusted kappa, and 95% confidence interval are shown.*

	Synovitis			**BME**		
	Kappa	**PABAK**	**95% CI**	**Kappa**	**PABAK**	**95% CI**
MRI grade ≥1						
Swollen	0.14	0.27	-0.01-0.29	0.31*	0.47	0.14-0.47
Tender	0.08	0.05	-0.06-0.22	0.16*	0.12	0.03-0.29
ST	0.17*	0.18	0.02-0.32	0.16*	0.18	0.01-0.31
PD	0.23*	0.39	0.09-0.37	0.20*	0.43	0.05-0.35
MRI grade ≥2						
Swollen	0.22*	0.59	0.04-0.40	0.25*	0.63	0.06-0.44
Tender	0.09	-0.03	0.01-0.17	0.05	-0.09	-0.02-0.12
ST	0.15*	0.17	0.05-0.25	0.11*	0.14	0.02-0.20
PD	0.47*	0.76	0.27-0.67	0.46*	0.78	0.25-0.67

**statistical significance at p<0.05. ST=synovial thickening, PD=power Doppler, PPV=positive predictive value, NPV=negative predictive value.*

US appeared to provide additional value by identifying patients and MTPJs with subclinical inflammation. In 61 MTPJs without any swelling or tenderness, synovial thickening was seen in 21 (34%) on US. Of these, 11 (52%) had grade ≥1 synovitis or BME on MRI (Figure 13A). PD served as a good tool to confirm inflammation: 73% of joints with both synovial thickening and PD were found to be inflamed on MRI (having either synovitis or BME on MRI), whereas 54% of joints showing synovial thickening but no PD signals were inflamed on MRI. Furthermore, all 7 patients who had clinically asymptomatic MTPJs had grade ≥2 synovial thickening on US (Figure 13B), which stresses the importance of using imaging to monitor disease activity in early RA.

Since most patients exhibited clinical tenderness in their MTPJs at baseline, we found it worthwhile to examine swelling and tenderness separately. Synovial thickening and PD on US were able to identify inflammation in 44% of non-swollen joints and 38% of non-tender joints (Figure 14). As previously discussed, since swollen joint count has high specificity for inflammation seen on MRI, it can be used to help rule-in disease when a joint is swollen. This was supported by Figure 14A, where 81% of swollen joints also had synovial thickening and PD on US, and 73% had grade ≥1 synovitis and BME on MRI. In addition, 40% of tender joints did not show disease activity on US, which is in accordance with our finding that tender joint count had low specificity.

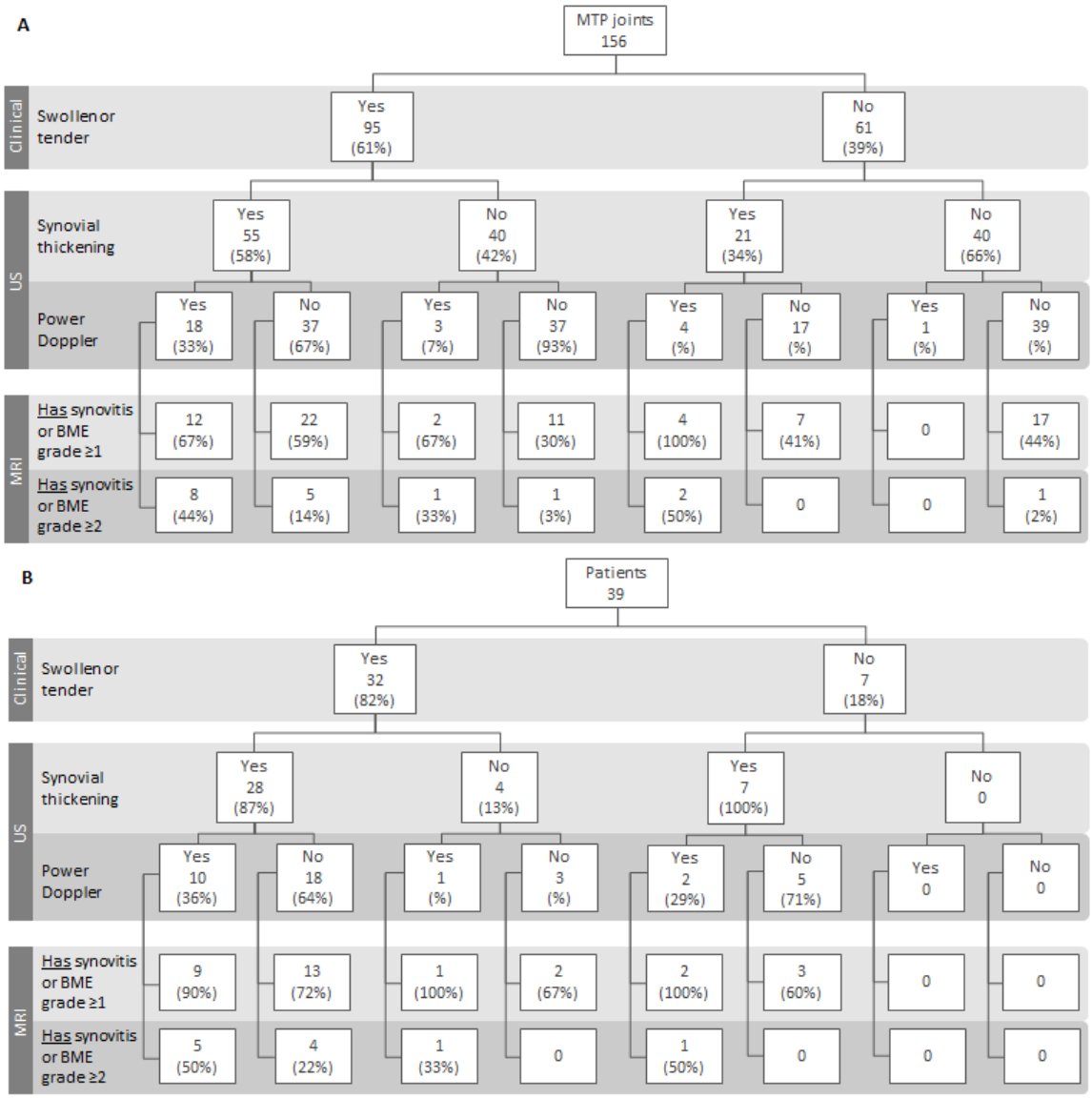

Figure 13: *The proportion of **A**) clinically symptomatic MTPJs and **B**) patients with clinically symptomatic MTPJs that also have synovial thickening on US, PD on US, and synovitis or BME on MRI.*

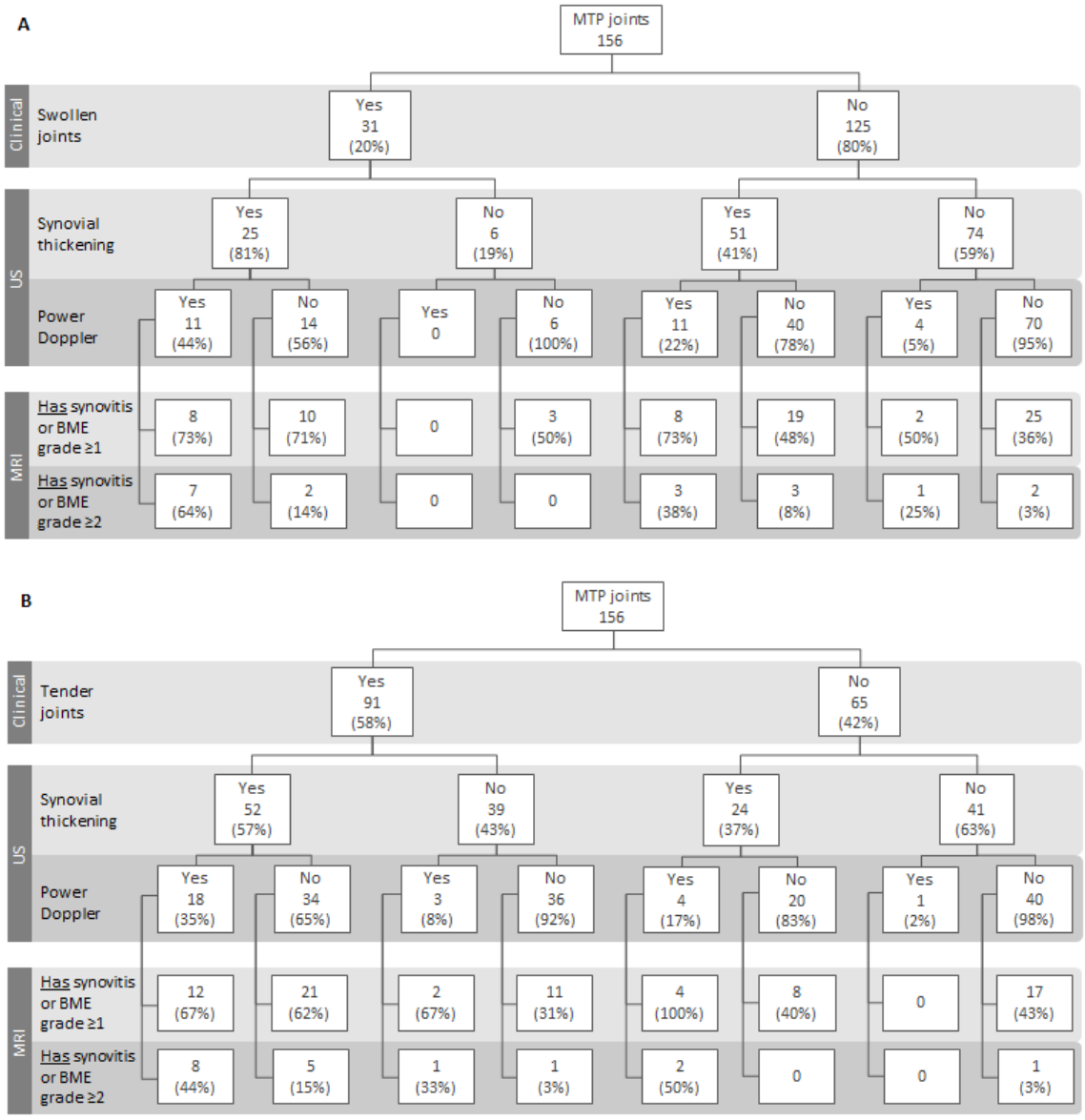

Figure 14: *The proportion of MTPJs with inflammation on US and MRI given that they showed A) clinical swelling, and B) clinical tenderness.*

3.4 Erosions on US compared to MRI

Nineteen erosions were visualized on US in this cohort at baseline. Erosions were most commonly seen on MTP 5, likely due to the US probe being able to access the lateral aspect of the bone. No erosions were seen on MTP 4. In the most symptomatic foot of 39 patients with baseline MRI data, US observed erosions in 7 patients and 8 MTPJs (Table 6). They were most commonly in MTP 5 (n=5), and often on the lateral aspect (n=4).

MRI visualized many more erosions than US. Grade ≥1 erosion on MRI was seen in 95% of patients and 65% of MTPJs. Very few grade ≥2 erosions were observed on MRI (7 patients and 15 MTPJs). MRI saw erosions more frequently seen on the metatarsal head than the phalangeal base, and more commonly on the plantar than dorsal aspect of the bones. This might be attributed to the higher biomechanical demands on the metatarsal heads and the plantar surface, as they are exposed to higher pressures. Erosions were least frequently seen on MTPJ 5 on MRI, however this may be because the MTPJ 5 was often not sufficiently captured to be graded (Table 6). The largest erosion recorded in this cohort was grade 5.

At first glance, US and MRI both detected erosions in two MTP 2 joints, one MTP 3 joint, and three MTP 5 joints. In addition, US detected erosions in two MTP 5 joints that appeared normal on MRI (Table 7). Using MRI as the standard for comparison, US found very poor kappa agreement (k=0.02, 95% CI = -0.03 to 0.07, p>0.05), low sensitivity (6%), but high specificity (96%). However, we see a different story when the location of erosions was also considered. The US probe can only access the dorsal and plantar surfaces of the 2^{nd}-5^{th} MTPJs, and the lateral aspect of the 5^{th} MTPJ, as adjacent joints block access to most medial and lateral surfaces of joints. All recorded US erosions were on the metatarsal heads, and most erosions on MRI were also seen on the metatarsal head (Table 6). Of 26 MRI erosions on the phalangeal base, only 4 were seen on the phalangeal base without an erosion on the corresponding metatarsal head, all of which were grade 1 erosions.

MRI and US detected erosions in similar numbers on dorsal metatarsal heads (5 and 4 respectively) and lateral 5^{th} metatarsal heads (3 and 4 respectively), but only agreed on one dorsal and one lateral erosion (Figure 15A). Five dorsal and one lateral-plantar US erosions were unseen on MRI (Figure 15B). Among 20 patients who received plantar US scans, US saw 2 plantar erosions, while MRI detected 47 erosions on plantar metatarsal heads. Furthermore, only 1 of these erosions was seen by both US and MRI.

Figure 15C shows an example of a grade 2 plantar erosion on MRI that was not seen on US. We hypothesized that only a small plantar surface represented by a yellow arc was visualized by US, as this region lies parallel to the plantar fat pad.

Table 6: *Description of US and MRI erosions in the most symptomatic foot.*

Total 156 joints in 39 patients	
US findings	
Patients with ≥1 US erosion, n (% of 39 patients)	7 (18%)
MTPJs with US erosion, n (% of 156 joints)	8 (5%)
2nd MTPJs with erosion, n (% of US erosions)	2 (25%)
3rd MTPJs with erosion, n (% of US erosions)	1 (13%)
4th MTPJs with erosion, n (% of US erosions)	0 (0%)
5th MTPJs with erosion, n (% of US erosions)	5 (63%)
MRI findings	
Patients with at least 1 **grade ≥1 MRI erosion**, n (% of 39 patients)	37 (95%)
MTPJs with grade ≥1 MRI erosion, n (% of 156 joints)	101 (65%)
Metatarsal head with MRI erosion, n (% of MRI erosions)	97 (96%)
Phalangeal base with MRI erosion, n (% of MRI erosions)	26 (26%)
2nd MTPJs with erosion, n (% of MRI erosions)	31 (31%)
3rd MTPJs with erosion, n (% of MRI erosions)	29 (29%)
4th MTPJs with erosion, n (% of MRI erosions)	26 (26%)
5th MTPJs with erosion, n (% of MRI erosions)	15 (15%)
Patients with at least 1 **grade ≥2 MRI erosion**, n (% of 39 patients)	7 (18%)
MTPJs with grade ≥2 MRI erosion, n (% of 156 joints)	15 (10%)
Metatarsal head with MRI erosion, n (% of MRI erosions)	14 (93%)
Phalangeal base with MRI erosion, n (% of MRI erosions)	2 (13%)

Table 7: *A 2x2 table showing number of joints with erosions on US and MRI.*

		MRI		
		Erosion	No erosion	Total
US	Erosion	6	2	8
	No erosion	95	53	148
	Total	101	55	156

Four out of six erosions previously thought to have been seen by both US and MRI were actually on different locations on the bone. With location considered, kappa found no agreement between US and MRI (k=-0.06, 95% CI = -0.12 to <0.01, p>0.05). Sensitivity was very low (2%) while specificity remained high (95%).

All grade ≥2 MRI erosions appeared to at least partially span surfaces hypothesized to be accessible to the US probe. The 2 erosions seen by both US and MRI were both larger in size relative to the average size of erosions seen in this early RA cohort (grade 3 and grade 5). Comparing US erosions to grade ≥2 MRI erosions still only achieved poor kappa agreement (k=0.13, 95% CI = -0.10 to 0.35, p>0.05). Compared to when grade ≥1 MRI erosions were referenced, sensitivity improved but was still very low (14%), while specificity remained high (96%).

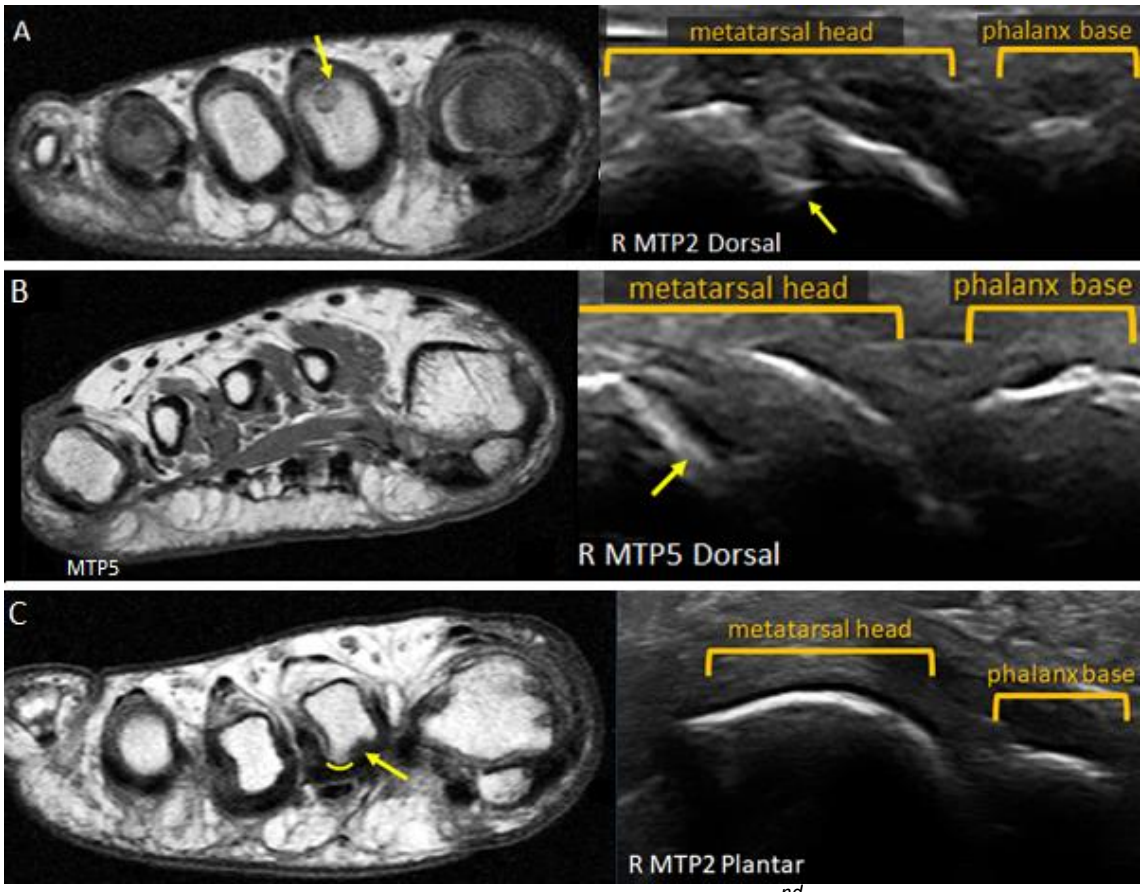

Figure 15: *A) MRI showing a grade 3 dorsal erosion on the 2nd metatarsal head (yellow arrow) and US image showing a dorsal view of the 2nd MTP with the corresponding erosion; B) MRI of the right foot with no erosion apparent on the 5th metatarsal head and US image showing an erosion on the dorsal surface of the same 5th metatarsal head; C) MRI showing a grade 2 plantar erosion on the 2nd metatarsal head (yellow arrow); B) US image showing plantar view of 2nd MTPJ in the same patient, erosion was not observed.*

3.5 Inflammatory changes over 12 months

There were no missing clinical examination or US data at baseline, and MRI was graded for 39 patients. At 12 months, clinical examination was missing for 1 patient, MRI was missing for 1 patient, and additional individual MTPJs were unable to be graded.

Characterizing inflammatory changes

Friedman tests compared the mean total disease activity scores over 5 patient visits, and found significant differences for swollen joint count ($X^2(4)=12.18$, $p<0.05$), synovial thickening ($X^2(4)=34.67$, $p<0.001$) and PD ($X^2(4)=18.26$, $p<0.05$), but not for tender joint count. Using the Wilcoxon Signed-Rank tests for post hoc analysis with Bonferroni adjustments, we identified significant differences between synovial thickening measured at the 3 month, 6 month and 12 month visits compared to synovial thickening at baseline (Figure 16). Two-to-five times as many patients had improved than worsened in swollen joint count, synovial thickening and PD, while a relatively larger proportion of patients had worsened in tender joint count (27%) (Table 8, for mean (SD) values see Appendix).

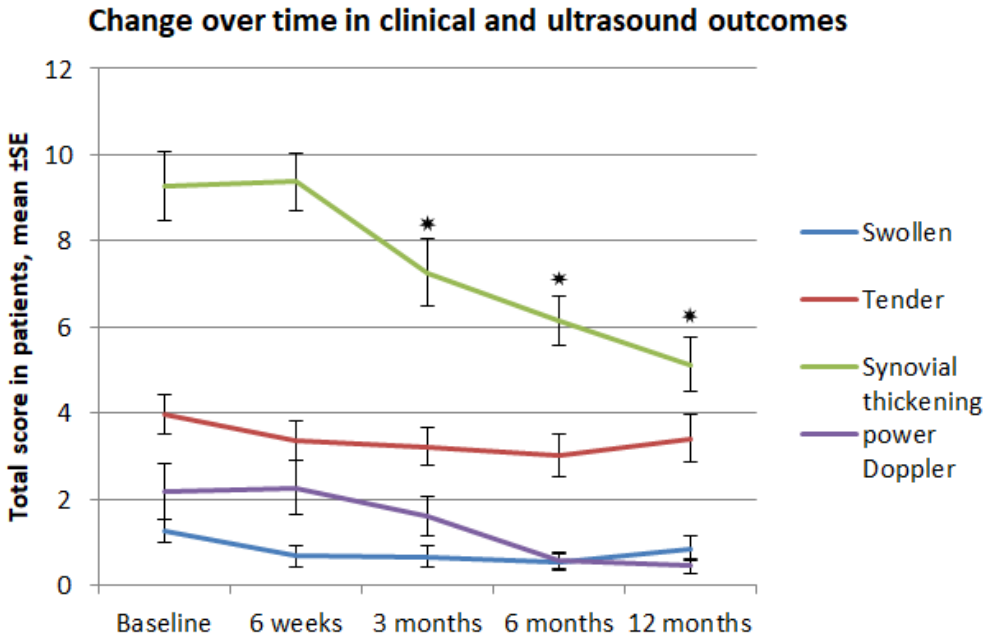

Figure 16: *Changes in swollen joint count, tender joint count, synovial thickening and PD measured at 5 visits over 12 months. *indicates significant difference ($p<0.05$) compared to baseline by ANOVA.*

Table 8: *Number of patients who had improved, unchanged or worsened score on swollen and tender joint counts, synovial thickening and PD over 12 months.*

	Number (%) of patients			
	Swollen joints	Tender joints	Synovial thickening	PD
Improved	15 (41%)	15 (41%)	26 (70%)	14 (38%)
Unchanged	16 (43%)	12 (32%)	6 (16%)	20 (54%)
Worsened	6 (16%)	10 (27%)	5 (14%)	3 (8%)

Many patients showed no PD signals at any visit (n=12), which contributed to the low mean of total PD. Individual patients greatly varied in total PD (highest observed = 18). While many patients at baseline had high total PD, all except 1 patient had total PD ≤ 3 by 6 months and 12 months (Figure 17).

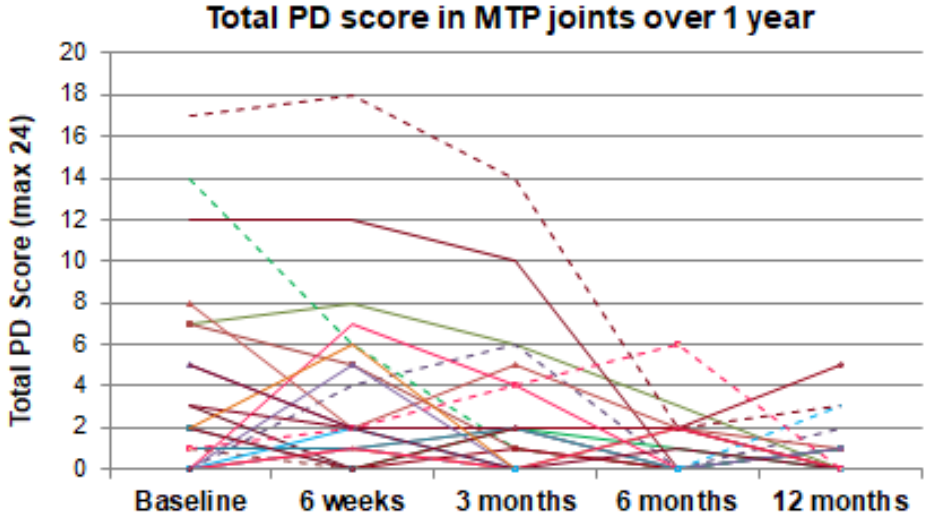

Figure 17: *Sum of PD from bilateral MTPJs 2-5 at each patient visit over 12 months. Patients with PD=0 at all times were omitted (n=12).*

MRI data were incomplete for 4 patients due to missing scans or because certain joints were not sufficiently captured. As a result, synovitis was graded for 156 MTPJs at baseline and 158 MTPJs at 12 months; BME was graded for 148 phalanx bases and 146 metatarsal heads at baseline, and 156 phalanx bases and 153 metatarsal heads at 12 months; erosion was graded for 147 phalanx bases and 152 metatarsal heads at baseline, and 154 phalanx bases and 154 metatarsal heads at 12 months.

A similar number of patients improved and worsened on synovitis (Table 9), and the mean of total synovitis did not change significantly from baseline to 12 months (Figure 18). Meanwhile, 6 times as many patients improved on BME than worsened (Table 9), and the mean of total BME was significantly lower at 12 months ($Z = -3.38$, $p<0.05$) (Figure 18, for mean (SD) values see Appendix). Seven patients had worsened in total synovitis by score≥2. No patients had worsened in total BME by score ≥2. In 7 (19%) patients, synovitis had worsened while BME improved, and 1 patient saw an improvement in synovitis but worsened BME (Table 9).

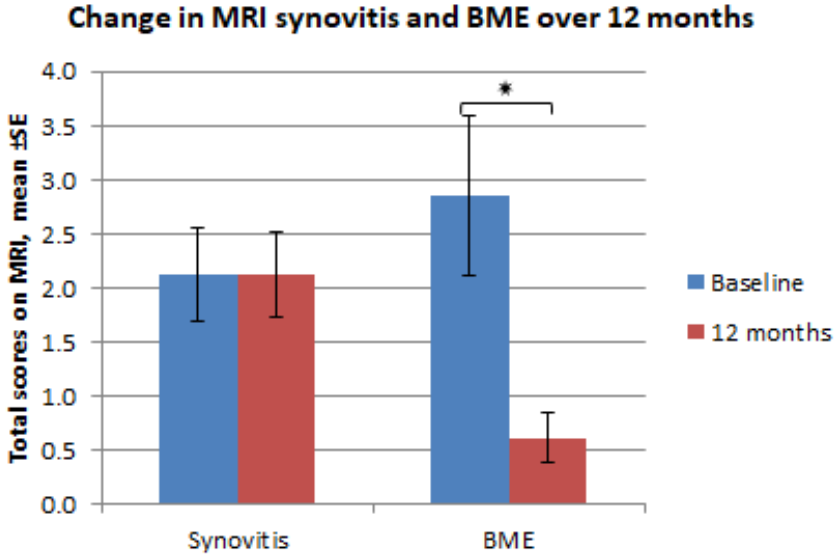

Figure 18: *Mean of total MRI scores for synovitis and BME at baseline and 12 month visits. *indicates t-test significance at p<0.05.*

Table 9: *Number of patients who had improved, unchanged or worsened synovitis and BME after 12 months.*

		Synovitis			
		Improved	**Unchanged**	**Worsened**	**Total**
BME	**Improved**	8	4	7	19
	Unchanged	2	8	5	15
	Worsened	1	1	1	3
	Total	11	13	13	37

In 11 patients who improved total synovitis score by ≥1, approximately the same number of patients improved on clinical examination (45-64%) and US (55-73%) (Table 10). In 4 patients who improved total synovitis score by ≥2, 2 patients improved on clinical examination while 3-4 improved on US.

Table 10: *Number of MTPJs that had improved, unchanged or worsened scores after 12 months for A) clinical examination compared to MRI and B) US compared to MRI synovitis or BME grade ≥1.*

A)		**MRI synovitis or BME**			
		Improved	**Unchanged**	**Worsened**	**Total**
Clinical exam	**Improved**	24	22	4	50
	Unchanged	11	32	13	56
	Worsened	6	10	3	13
	Total	41	64	20	119
B)		**MRI synovitis or BME**			
		Improved	**Unchanged**	**Worsened**	**Total**
US	**Improved**	22	23	9	54
	Unchanged	10	34	8	52
	Worsened	9	7	3	19
	Total	41	64	20	125

Association between inflammation and patient-reported outcomes

Significant Spearman correlations were found between changes in clinically tender and swollen joint counts per patient (r=0.36, 95% CI [0.06, 0.70], p=0.032), synovial thickening and PD on US (r=0.46, 95% CI [0.16, 0.77], p=0.004), but not between synovitis and BME on MRI. Significant correlations were observed between changes in tender joint count and total synovitis on MRI (r=0.36, 95% CI [0.04, 0.68], p=0.027), and between changes in total PD and BME (r=0.45, 95% CI [0.14, 0.79], p=0.006).

Spearman's rank correlations did not find any statistically significant associations between the change in clinical examination and patient-reported outcomes over 12 months. Although pain significantly correlated with both HAQ and LFIS (r=0.58 and r=0.47 respectively, $p<0.05$), tender joint count did not significantly associate with any patient-reported outcomes, including pain ratings. Significant positive associations were observed between changes in total PD score and HAQ (r=0.43, $p<0.01$), and LFIS (r=0.61, $p<0.001$) (Figure 19). No significant correlations between changes in synovial thickening

and patient-reported outcomes were observed. We found no association between changes in synovitis/BME and patient-reported outcomes.

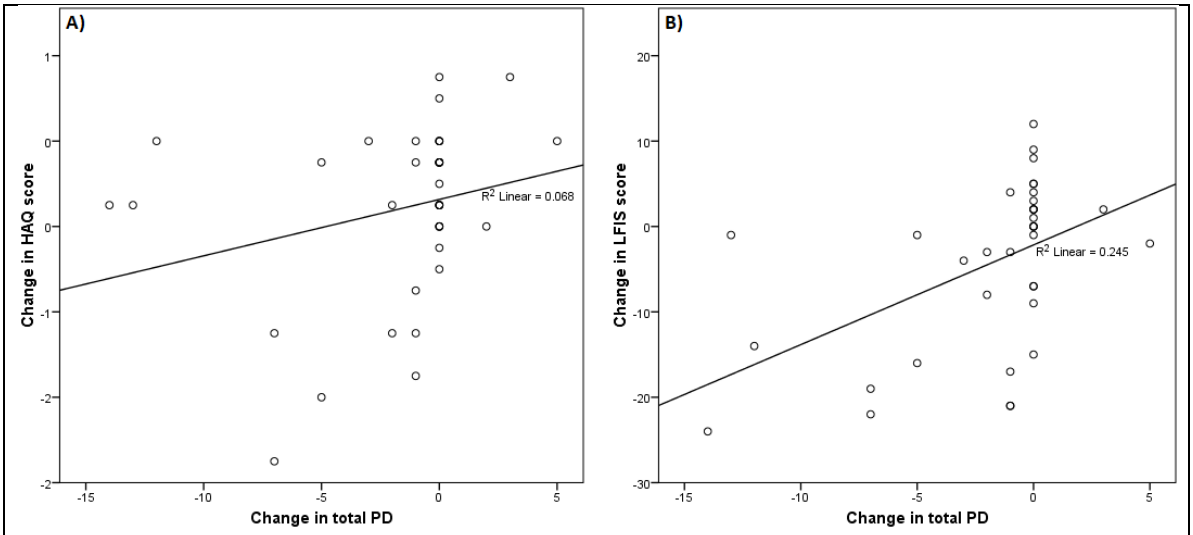

Figure 19: *Significant correlations were observed between changes in total PD of the most symptomatic foot over 12 months and changes in A) HAQ score (r=0.43, p<0.01) and B) LFIS score (r=0.61, p<0.001).*

3.6 Erosive changes over 12 months

Three patients did not have MRI data at the baseline or 12 month visits. A total of 152 MTPJs (304 metatarsal heads and phalangeal bases) in 38 patients were graded for erosion.

Characterizing change in erosion on MRI and US

At baseline, MRI erosions were observed in 119 (39%) bones in 96 (63%) MTPJs. Of these, 41 (34%) erosions improved and 33 (28%) worsened after 12 months. Most of baseline erosions on MRI [103 (87%)] were grade 1. After 12 months, 41 (40%) of these grade 1 erosions had resolved, 6 (6%) erosions had progressed to grade 2 or 3, and the rest stayed at grade 1. In addition, 25 new grade 1 erosions were identified. None of the 16 grade ≥2 erosions at baseline had progressed, and 6 had improved. A patient who had 3 grade ≥2 erosions had improved to only have grade 1 erosions at 12 months.

When both feet were examined, US observed more erosions at 12 months (29) than at baseline (15). Similar to baseline findings, erosions at 12 months were mostly seen on MTP 5 (24), especially on the lateral aspect (16). Ten erosions were seen at both

baseline and 12 month visits (Figure 20A), 5 erosions at baseline were not observed at 12 months (Figure 20B), and 19 new erosions were seen at 12 months (Figure 20C). MRI and US often disagreed on changes in erosion. Seven patients who had decreased (improved) erosion scores on MRI had increased numbers of erosions on US.

Patients who had experienced erosion repair were taking conventional DMARDs or biologics. Patients with the most erosion repair (erosion score decreased by 4) and the most erosion progression (erosion score increased by 4) were all taking conventional DMARDs. Patients who were taking biologics in this cohort tended to have relatively lower disease activity, and this was reflected in low erosion scores as well. As such, erosion repair or progression, if any, was represented by a change in score of 1. In addition, in 3 patients who were not taking any DMARDs, 1 had improved erosions on MRI while the other 2 maintained very low MRI erosion scores (total erosion score=1).

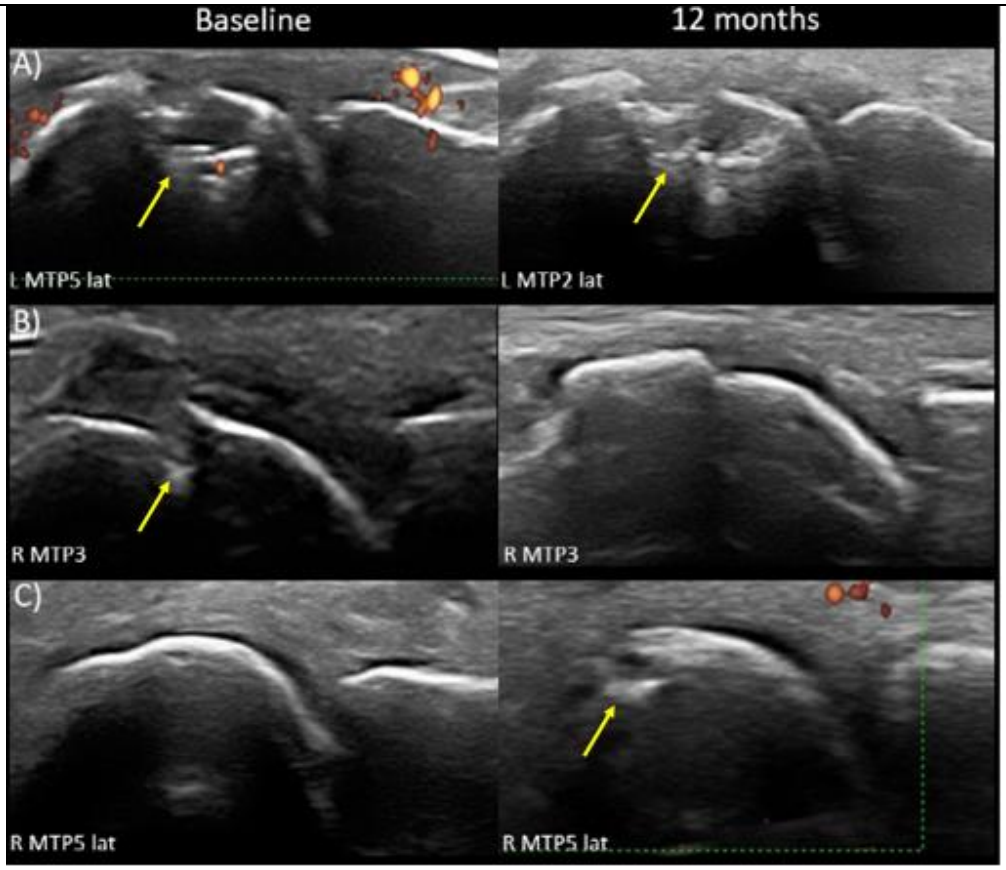

Figure 20: *US images showing the same 3 joints at baseline and 12 months, where A) an erosion was observed at both visits, corresponding to the MRI erosion that was grade 5 at baseline; B) an erosion was seen at baseline but not at 12 months; and C) an erosion was observed at 12 months but not at baseline.*

Relationship between erosion repair and inflammation

Our results suggest that a lack of prolonged inflammation may contribute to erosion improvement over 12 months. Most MTPJs that had erosion repair on MRI had either no clinical swelling or improved swelling over 12 months (29 (88%)), low or improved synovial thickening (28 (85%)) and PD (32 (97%)). One of the 2 patients who had apparent erosion repair on US had improved synovitis on MRI over 12 months, and the other patient had unchanged synovitis.

Although we expected to see high inflammation in patients whose erosions progressed, we did not find any such distinctive patterns. Of 17 patients whose total erosion score decreased (improved) after 12 months, total synovitis on MRI had decreased for 6 patients and increased for 4 patients. Of 15 patients who had an increased number of erosions seen on US after 12 months, only 5 patients also saw an increase in total synovitis score on MRI. An increase in total synovial thickening or PD scores was observed over 12 months in 4 patients who had more erosions on US at 12 months than at baseline. However, in 11 patients whose erosions progressed, US inflammation had improved.

CHAPTER 4: DISCUSSION

Much of the literature has focused on evaluating the use of clinical examination and US in the hands and wrists. The current study is one of very few to examine their use in the MTPJs, specifically in an early RA population, and using MRI as a reference standard. It is important to note that although MRI is considered the current gold standard for assessing RA, it is not a perfect representation of disease activity. For example, although BME is an associated marker for inflammation, it occurs inside the bones and is not synovial inflammation. Furthermore, it is difficult to distinguish between synovitis and other fluids without contrast-enhancement. In fact, it is possible that our comparator may better detect disease activity. For instance, US is able to distinguish synovium and effusion very well, and may out-perform MRI synovitis assessments without contrast enhancement. Therefore, although we used MRI as a reference standard, these considerations should be applied to all following interpretation of our results. In addition, due to most patients taking a combination of DMARDs or of biologics and DMARDs simultaneously, it is difficult to compare the effectiveness of different treatments.

4.1 Cross-sectional comparison of clinical examination and US inflammation

Current literature has reported that clinical examination demonstrated low sensitivity and poor agreement with MRI for assessing inflammation[110,111]. In addition, clinical examination has considerable inter-observer variability, especially in the MTPJs[71]. In concordance with previous research[78], we observed synovitis and BME in a large number of clinically asymptomatic joints. This may be due to a variety of reasons, such as an inherent difficulty in determining intra-articular swelling in the MTPJs, greater difficulty in persons with obesity, or perhaps early inflammation may not frequently cause noticeable swelling[71]. Studies have found that swollen joint counts in the MCPJs tend to have better inter-rater reliability than in the MTPJs, and this may be because the MTPJs are surrounded by more musculature and padding that can obstruct assessments of swelling[71]. Tenderness was often observed in joints without any signs of inflammation on US or MRI. Tenderness can be influenced by many other variables, such as injuries, wear, inflammation of extra-articular tissue, or have psychological origins[71]. As such, using joint tenderness as a marker of RA inflammatory activity may lead to over-treatment. These findings cast doubt on the validity of relying solely on clinical examinations to monitor RA disease activity.

We have previously reported that both clinical examination and US reached similarly poor agreement with MRI when assessing inflammation in the MTPJs[112]. However, Taniguchi et al. reported that in the MCPJs, US had higher sensitivity and specificity for detecting inflammation when MRI synovitis grade ≥2 was referenced instead of grade ≥1[109]. By also using grade ≥2 synovitis and BME on MRI for comparison in the current study, we found a similar pattern in the MTPJs: sensitivity was increased for clinical examination and US (most prominent for PD), while specificity was not markedly affected. This suggests that the severity of inflammation is an important factor in clinical presentation, and US appears to be better able to visualize more severe signs of inflammation.

The kappa agreement between PD on US and inflammation on MRI was quite high, given that they are not measuring the same signs, but different surrogate markers of inflammation. Therefore, we wouldn't expect a statistically high agreement, and finding moderate agreement between PD and BME actually suggests a clinically important relationship.

Clinical examination remains the fastest and least expensive assessment method for the joints. We found that swollen joint count alone would miss US inflammation in approximately half of MTPJs. However, the majority of swollen joints appeared to be inflamed on US. This suggests that in clinical practice, patients with swollen MTPJs should receive further treatment for inflammation without the need for additional imaging, whereas US would be most useful in detecting subclinical inflammation in patients without swollen MTPJs. Tender joint count did not appear to be a great indicator of disease activity, as all patients with no tenderness in the MTPJs still showed subclinical inflammation on US. However, the combination of tender joint count and US imaging would allow physicians to understand whether the pain is caused by inflammation or other causes.

4.2 Erosions on US compared to MRI

To date, very few studies have examined the use of US to detect erosions in patients with early RA, both in the MCPJs and MTPJs. In addition, few studies have evaluated this feature of US while considering the location of erosions as a factor[111,113]. In our cohort of early RA patients, erosions were detected by MRI in most patients and the majority of MTPJs, but far fewer erosions were seen on US.

Our study demonstrated the importance of considering the location of erosions on the MTPJ when evaluating the effectiveness of US at detecting erosions. When we compared the presence or absence of US and MRI erosions on the entire MTPJ (without considering their location on MTPJs), we found that US had moderate sensitivity for detecting erosions, similar to that previously reported in patients with established RA[98,111]. However, when the location of erosions on MTPJs was taken into account, we saw markedly decreased sensitivity as US and MRI often saw erosions in the same MTPJs but in different locations on the bones. Some possible explanations are that MRI uses bone marrow as surrogate markers for bone rather than examine the bone structure directly, or that some erosions may be missed due to the 3mm thickness of MRI slices (e.g. an erosion that is bisected by 2 slices and does not clearly appear on either slice).

Although MRI identified many plantar erosions, including several grade ≥2 erosions, US only detected two plantar erosions, both on the 5th MTPJ. When we re-examined the MR images of grade ≥2 plantar erosions that were missed by US, we found that they were located along the medial or lateral edges of the bone. Therefore, it appears that the US probe is able to access a smaller region than we had hypothesized, and its limited view is likely due to the plantar fat pad. In contrast, there is little obstruction to the lateral-plantar aspect of the 5th MTPJ, which may explain why the only plantar US erosions seen were on the 5th MTPJ.

We found that US erosion has poor kappa agreement with MRI and low sensitivity, but high specificity and NPV, which suggests that real structural damage likely exists if an erosion is seen on US. Another study using US in patients with established RA found a greater prevalence of plantar erosions[105]. This suggests that visualization of erosions on US may be dependent on disease duration, whereby early erosions may have small cortical breaks, or may develop in plantar regions not accessible by US. Future studies in patients with established RA should also aim to consider erosion location to avoid overestimating the ability of US to detect erosions. Furthermore, the clinical significance of grade 1 erosions on MRI remains unknown, and can affect how comparisons to MRI should be interpreted.

4.3 Inflammatory changes over 12 months

We observed an overall improvement in inflammatory activity in this early RA cohort after treatment with DMARDs and biologics over 12 months. Swollen and tender

joint counts decreased slightly, while total synovial thickening and PD scores were significantly lower at 12 months. In fact, all but 1 patient had total PD score ≤3 at the 6 and 12 month visits, indicating active inflammation was under control. In addition, while synovitis on MRI did not appear to change, BME had markedly decreased after 12 months. The lack of change in synovitis over 12 months and a lack of association between synovitis and BME may be because synovitis cannot be distinguished from effusion (fluid in or around the joint) without contrast-enhancement, as was the case with our MRI protocol. The decrease in total PD scores over12 months was significantly correlated with the decrease in total BME scores, whereas this was not found for clinical examination or synovial thickening. This suggests that PD is highly sensitive to change, and that PD should be used in US joint assessments. Our results contrasted findings from another study by Schmidt et al. on patients with early RA, which observed little change in inflammation over the first 12 months of RA disease course using US and MRI[98]. A possible reason for this disparity is that the majority of patients in the study by Schmidt et al. were already treated with at least one DMARD at baseline, therefore their inflammation may have already been under control.

We did not observe any association between the change in synovitis and BME on MRI and changes in patient-reported outcomes. Intuition would suggest that joint swelling and tenderness would play an important role in patient-perceived well-being and would hinder functionality. However, this did not appear to be the case in our cohort. This may be because swelling and tenderness were rated as 'yes or no', which failed to capture small improvements that may have impacted patient-perceived functionality. Change in total PD scores on US was the only measure of inflammation to have significantly correlated with changes in both the HAQ and LFIS over 12 months. This suggests that monitoring PD in the MTPJs provides a good representation of improvements in patient-important symptoms.

4.4 Erosive changes over 12 months

Studies that examine bone erosions in patients with RA often use radiographic imaging, and very few have used MRI to explore erosion repair. Considering that MRI can detect erosions at least 6-12 months before they can be detected by radiographs[87], we hoped that MRI would provide a sensitive assessment of how erosions in early RA progressed. In addition, we aimed to evaluate the sensitivity-to-change of US for monitoring erosions. Much of current research suggests that DMARDs, especially biologics, are capable of slowing or halting the progression of erosions in RA, but that

erosion reparations are rarely observed[114,115]. Previous studies observed MCP joint erosion repair in RA patients treated with conventional DMARDs, but this phenomenon was confined to a very small (<10%) proportion of patients[116].

The current study found erosion regression in early RA. Reparations were observed in patients taking either conventional DMARDs or biologics. This contrasts previous findings that suggested conventional DMARDs led to erosion progression while erosion regression was more prevalent in patients taking biologics[115]. Similar to findings by Ideguchi et al., we also observed erosion repair in a patient who was not taking any DMARDs, which supports the hypothesis of self-repair in patients with low disease activity[116]. Our early RA cohort had mostly grade 1 erosions at baseline, and the clinical significance of small regressions in these erosions is unclear. A grade 1 erosion on MRI involves ≤10% of the bone. Considering that the metatarsal heads and phalanx bases are very small, some erosions may be difficult to see due to their size, and confirmation from a second radiologist would be ideal. Therefore, validation studies are needed to evaluate the ability of MRI and MRI grading to recognize very small erosions. Since grade ≥2 erosions cover a larger bony area (≥10-20%), they are less likely affected by artefacts. Therefore, reparations of these erosions (n=5) may be more notable than erosions that started as grade 1 at baseline.

We did not observe any notable patterns between the progression of erosion in this early RA cohort and changes in inflammation. Over the 12-month follow-up period, many patients had improved MTPJ synovitis and BME on MRI or synovial thickening and PD on US. However, while some of these patients had improved erosions on either MRI or US, erosion progression was observed in others. Lukas et al. previously reported that erosion repair occurred preferentially in MCP and MTPJs that did not have clinical swelling, or that have improved in swelling over time[117]. We also found this to be the case for MTPJ erosions detected by MRI. In addition, erosion repair was preferential for MTPJs that did not exhibit, or had improved in synovial thickening and PD. This suggests that bone reparation in the MTPJs seems to occur when inflammation is under control.

It appeared that erosions in early RA were generally small, and many regressed by 12 months. However, MRI does not visualize the bone but rather bone marrow, thus discrepancies between erosive changes observed on US and MRI may be better explored by mapping the bones using computer tomography.

4.5 Limitations

There are several limitations to this study that should be considered when interpreting the results.

1. Our cohort characteristics are representative of the average RA population[2], however our patients were recruited from a single rheumatology clinic in Hamilton, Ontario, Canada, and may be subject to sampling bias.
2. All clinical examinations and US procedures were performed by the same rheumatologist during the same visits, which may result in bias in grading.
3. US: Inter-rater reliability may have been affected by the quality of images procured during the US process, since one observer had access to the full joints in real-time while the other could only grade what was captured. The image captured may not be representative of the pathology in the entire joint as seen by observer one. Furthermore, images in the transverse view were only taken when an erosion was suspected on the longitudinal view by observer one, which may affect the second observer's interpretation.
4. MRI: MRI was graded by one radiologist once at baseline and once at 12 months. Thus, we could not evaluate the intra- or inter-observer reliability. In addition, MTP 5 was not always sufficiently captured on MRI to be graded, due to the MRI protocol used to image the feet being adapted from a previous protocol for imaging the hands. Finally, OMERACT recommended that T1-weighted images be taken before and after intravenous administration of a contrast enhancement agent to best visualize synovitis[118]. However, our protocol excluded this procedure for several reasons: time constraints, the invasive intravenous injection, and reported mild to moderate side-effects of gadolinium agents which are still poorly understood.
5. This cohort of patients with early RA had low disease activity overall, and most had improved over 12 months. For example, the majority of participants (n=31) had a PDUS score of 1 or less out of a maximum score of 12. While this is good news for the patients, it posed problems for statistical analyses. This limitation will likely be unavoidable when examining patients with early RA.
6. Data was not complete for several patients due to non-compliance with follow-up visits. A few patients did not adhere to their treatment recommendations, and these patients generally had low or no symptoms.

4.6 Conclusion

Current RA assessments rely heavily on clinical examinations, but research has consistently shown that clinical examination lacks reliability, and that many patients experience subclinical disease activity. The present study demonstrated several advantages of including US imaging in routine RA assessments. First, US detected inflammation in many MTPJs that were not swollen or tender. Second, the PD on US appeared to be more sensitive to changes in inflammation than clinical examination, and was a good correlate of change in patient-perceived functionality. Third, US detected several bony erosions, which is impossible to see without using an imaging modality.

From a clinician's perspective, swollen and tender joint counts remain the fastest and most economical means of assessing patients, and they provide a level of patient contact and physical touch that can be lost through technology. Therefore, despite US providing a better assessment of inflammation in joints, it is still very important to address visible symptoms like swelling and tenderness. In fact, our results suggest that joint swelling is as specific as US in determining inflammation, and US assessment of swollen joints do not provide much additional benefit. We suggest that US can be best used as a secondary tool in patients who do not exhibit joint swelling. This would allow the clinician to detect subclinical inflammation and provide adequate treatment to prevent continued structural damage.

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APPENDIX

Mean (SD) values corresponding to Figures 16 & 18.

	Mean (SD)				
	BL	**6 weeks**	**3 months**	**6 months**	**12 months**
Swelling	1.32 (1.74)	0.70 (1.63)	0.66 (1.60)	0.57 (1.21)	0.84 (1.83)
Tenderness	4.24 (2.83)	3.54 (2.78)	3.45 (2.72)	3.24 (3.12)	3.68 (3.43)
Synovial thickening	9.29 (5.03)	9.43 (4.21)	7.11 (4.54)	6.11 (3.48)	5.00 (3.88)
PD	2.13 (4.14)	2.26 (3.97)	1.59 (3.04)	0.55 (1.22)	0.42 (1.08)
Synovitis	2.13 (2.66)	---	---	---	2.13 (2.43)
BME	2.86 (4.42)	---	---	---	0.61 (1.42)