Development of an Ultrasound Imaging Atlas to Grade the Severity of First Metatarsophalangeal Joint Osteoarthritis

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Abstract

Osteoarthritis (OA) is a prevalent, chronic, and disabling joint disease that imposes a significant global health burden. The foot is a target region for OA, but foot research is a novel and evolving discipline within the broader field of OA. The most commonly reported affected area in the foot is the first metatarsophalangeal joint (MTPJ). The current method of diagnosing OA using conventional radiography is reactive, detecting OA later in the disease process when irreversible structural damage has already occurred.

Ultrasound imaging (USI) represents an alternative for the diagnosis of OA with potentially inherent advantages, in its ability to detect tissue-specific morphological changes before pain and irreversible structural damage occur. USI can play a fundamental role in the early detection and assessment of foot OA. However, the role of USI for OA diagnosis in foot joints such as the first MTPJ is not clearly defined. The aim of the thesis was to (i) critically evaluate and summarise relevant studies that have used USI to examine foot OA, (ii) develop a USI acquisition procedure and grading system to examine OA features in the first MTPJ, and (iii) develop a USI atlas to grade the degree of osteoarthritic change in the first MTPJ and determine its reproducibility.

Chapter 1 provides an overview of the thesis with *Chapter 2* introducing the basic concepts of OA and C*hapter 3* introduces the role of imaging in the diagnosis of OA. *Chapter 4* reports a systematic review showing the wide degree of variation in which OA features were assessed, how features were defined, and what grading system was applied. *Chapter 5* reports a scoping review that showed limited implementation of consensus-based recommendations to guide the development and implementation of USI procedures to assess the first MTPJ. *Chapter 6* reports a bibliometric analysis that revealed that MRI, CT, and USI studies continue to evolve in research in this field. *Chapter 7* presents an international multispecialty Delphi study that identified 16 essential items that the USI acquisition procedure should encompass when examining the first MTPJ.

Chapter 8 describes the development of a USI acquisition procedure and grading system for examining OA features in the first MTPJ. The USI acquisition procedure and grading system were reliable in assessing first MTPJ OA features in participants with radiologically confirmed OA. *Chapter 9* describes the development of a semiquantitative USI atlas (called the AUTUSI atlas) to grade the extent of osteoarthritic change at the first MTPJ and assess the intra- and inter-examiner reproducibility of using the AUTUSI

atlas. The AUTUSI atlas demonstrated excellent intra- and inter-examiner reproducibility for evaluating first MTPJ joint effusion, synovial hypertrophy, synovitis, joint space narrowing, osteophytes, and cartilage thickness.

The research successfully developed a reliable procedure to assess both structural and inflammatory features specific to first MTPJ OA. The AUTUSI atlas offers the opportunity to identify prognostic inflammatory features earlier in the course of the disease, before potentially irreversible damage or disability occurs. The AUTUSI atlas may be the catalyst for the development of a USI classification criterion for defining and detecting early first MTPJ OA. Ultimately, the AUTUSI atlas will improve understanding of OA, provide capacity for earlier detection and standardisation of diagnosis, and provide a more sensitive method for classifying and grade the disease process.

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Attestation of Authorship

I hereby declare that this submission is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person (except where explicitly defined in the acknowledgements), nor material which to a substantial extent has been submitted for the award of any other degree or diploma of a university or other institution of higher learning.

Student Name: Prue Molyneux

Signature:

Date: 15/01/2024

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Ethics Approval

Ethical approval for the research presented in this thesis was granted by Southern Health and Disability Ethics Committee (HDEC 2022 FULL 12721) and Auckland University of Technology Ethics Committee (AUTEC 21/117). I extend my thanks to all the participants who generously gave their time, making this research possible.

Dissemination of Research

Parts of the research presented in this PhD thesis have been published (or submitted) and made available under the CC BY-NC-ND 4.0. deed.

Peer-reviewed Papers from the Research

Candidate contribution to co-authored publications	
Chapter 4. **Molyneux P**, Bowen C, Ellis R, Rome K, Frecklington M, & Carroll M. Evaluation of osteoarthritic features in peripheral joints by ultrasound imaging: A systematic review. *Osteoarthritis and Cartilage Open.* 2021; 3(3), 100194. https://doi.org/10.1016/j.ocarto.2021.100194	Molyneux P, (80%) Bowen C, (2.5%) Ellis R, (2.5%) Rome K, (2.5%) Frecklington M, (2.5%) Carroll M, (10%)
Chapter 5. **Molyneux P**, Bowen C, Ellis R, Rome, K, Jackson A, & Carroll M. Ultrasound imaging acquisition procedures for evaluating the first metatarsophalangeal joint: A scoping review. *Ultrasound in Medicine and Biology*. 2021; 48(3), 397-405. https://doi.org/10.1016/j.ultrasmedbio.2021.11.009	Molyneux P, (80%) Bowen C, (2.5%) Ellis R, (2.5%) Rome K, (2.5%) Jackson A, (2.5%) Carroll M, (10%)
Chapter 6. **Molyneux P**, Stewart S, Bowen C, Ellis R, Rome K, & Carroll M. A bibliometric analysis of published research employing musculoskeletal imaging modalities to evaluate foot osteoarthritis. *Journal of Foot and Ankle Research.* 2022; 15(1), https://doi.org/10.1186/s13047-022-00549-0	Molyneux P, (80%) Stewart S, (10%) Bowen C, (2.5%) Ellis R, (2.5%) Rome K, (2.5%) Carroll M, (2.5%)
Chapter 7. **Molyneux P**, Bowen C, Ellis R, Rome K, & Carroll M. International multispecialty consensus on how to image, define, and grade ultrasound imaging features of first metatarsophalangeal joint osteoarthritis, a Delphi consensus study. *Osteoarthritis and Cartilage Open*. 2023; 5(1), 100336. https://doi.org/10.1016/j.ocarto.2023.100336	Molyneux P, (85%) Bowen C, (2.5%) Ellis R, (2.5%) Rome K, (2.5%) Carroll M, (7.5%)
Chapter 8. **Molyneux P**, Bowen C, Ellis R, Rome K, Fitzgerald K, Clark P, & Carroll M. Reliability of an ultrasound imaging acquisition procedure for examining osteoarthritis in the first metatarsophalangeal joint. *Journal of Foot and Ankle Research. 2024*;17(1):e12002. https://doi.org/10.1002/jfa2.12002	Molyneux P, (85%) Bowen C, (2.5%) Ellis R, (2.5%) Rome K, (2.5%) Fitzgerald K, (1%) Clark P, (1%) Carroll M, (5.5%)

We the undersigned, herby agree to the percentages of participation identified to the chapters above.

Catherine Bowen		Aaron Jackson	
Keith Rome		Sarah Stewart	
Richard Ellis		Kate Fitzgerald	
Matthew Carroll		Philip Clark	
Mike Frecklington			

Presentations of Work Arising from the Thesis

Research stemming from in this thesis has been presented at the following conferences.

International Conference Presentations

1. **Molyneux P**, Bowen C, Ellis R, Rome K, Fitzgerald K, Clark P, & Carroll M. Reliability of an ultrasound imaging acquisition procedure for examining osteoarthritis in the first metatarsophalangeal joint. Paper presented at: Royal College of Podiatry Conference: November 23-25, 2023; Liverpool, UK.
2. **Molyneux P**, Bowen C, Ellis R, Rome K, & Carroll M. International multispecialty Delphi on how to examine ultrasound imaging features of first metatarsophalangeal joint osteoarthritis. Paper presented at: Royal College of Podiatry Conference November 23-25, 2023; Liverpool, UK.
3. **Molyneux P**, Stewart S, Bowen C, Ellis R, Rome K, & Carroll M. A bibliometric analysis of published research employing musculoskeletal imaging modalities to evaluate foot osteoarthritis. Paper presented at: Royal College of Podiatry Conference November 23-25, 2023; Liverpool, UK.
4. **Molyneux P**, Bowen C, Ellis R, Rome K, Fitzgerald K, Clark P, & Carroll M. Reliability of an ultrasound imaging acquisition procedure for examining osteoarthritis in the first metatarsophalangeal joint. Paper presented at: Australian Podiatry Conference 22-24, June 2023; Brisbane, Australia.
5. **Molyneux P**, Bowen C, Ellis R, Rome K, & Carroll M. International multispecialty Delphi on how to examine ultrasound imaging features of first metatarsophalangeal joint osteoarthritis. Paper presented at: Australian Podiatry Conference June 22-24, 2023; Brisbane, Australia.
6. **Molyneux P**, Stewart S, Bowen C, Ellis R, Rome K, & Carroll M. A bibliometric analysis of published research employing musculoskeletal imaging modalities to evaluate foot osteoarthritis. Paper presented at: Australian Podiatry Conference June 22-24, 2023; Brisbane, Australia.
7. **Molyneux P**, Bowen C, Ellis R, Rome K, Frecklington M, & Carroll M. Evaluation of osteoarthritic features in peripheral joints by ultrasound imaging: A systematic review. Paper presented at: Australian Podiatry Conference June 22-24, 2023; Brisbane, Australia.

Published Conference Proceedings

8. **Molyneux P**, Bowen C, Ellis R, Rome K, & Carroll M. International multispecialty Delphi on how to examine ultrasound imaging features of first metatarsophalangeal joint osteoarthritis. Paper presented at: Osteoarthritis Research International Congress March 17-20, 2023; Denver, USA. https://doi.org/10.1016/j.joca.2023.01.289
9. **Molyneux P**, Stewart S, Bowen C, Ellis R, Rome K, & Carroll M. A bibliometric analysis of published research employing musculoskeletal imaging modalities to evaluate foot osteoarthritis. Paper presented at: Osteoarthritis Research International Congress March 17-20, 2023; Denver, USA. https://doi.org/10.1016/j.joca.2023.01.288
10. **Molyneux P**, Bowen C, Ellis R, Rome K, Frecklington M, & Carroll M. Evaluation of osteoarthritic features in peripheral joints by ultrasound imaging: A systematic review. Paper presented at: Osteoarthritis Research International Congress March 17-20, 2023; Denver, USA. https://doi.org/10.1016/j.joca.2023.01.287

National Conference Presentations

1. **Molyneux P**, Bowen C, Ellis R, Rome K, Fitzgerald K, Clark P, & Carroll M. Reliability of an ultrasound imaging acquisition procedure for examining osteoarthritis in the first metatarsophalangeal joint. Paper presented at: Te Anga Kaikōiwi o Aotearoa New Zealand Osteoarthritis Research Network Conference November 2-4, 2023; Dunedin, New Zealand.
2. **Molyneux P**, Stewart S, Bowen C, Ellis R, Rome K, & Carroll M. A bibliometric analysis of published research employing musculoskeletal imaging modalities to evaluate foot osteoarthritis. Paper presented at: Te Anga Kaikōiwi o Aotearoa New Zealand Osteoarthritis Research Network Conference November 2-4, 2023; Dunedin, New Zealand.
3. **Molyneux P**, Bowen C, Ellis R, Rome K, & Carroll M. International multispecialty consensus on how to image, define, and grade ultrasound imaging features of first metatarsophalangeal joint osteoarthritis, a Delphi consensus study. Paper presented at: Te Anga Kaikōiwi o Aotearoa New Zealand Osteoarthritis Research Network Conference November 2-4, 2023; Dunedin, New Zealand.
4. **Molyneux P**, Bowen C, Ellis R, Rome K, & Carroll M. Capacity of ultrasound imaging for New Zealand podiatrists. Presented at: Podiatry New Zealand Conference October 13-14, 2023; Christchurch, New Zealand.

5. **Molyneux P**, Stewart S, Bowen C, Ellis R, Rome K, & Carroll M. A bibliometric analysis of published research employing musculoskeletal imaging modalities to evaluate foot osteoarthritis. Paper presented at: Rangahau Aranga: AUT Graduate Review November 17, 2022; Auckland, New Zealand.
6. **Molyneux P**, Bowen C, Ellis R, Rome K, Frecklington M, & Carroll, M. Evaluation of osteoarthritic features in peripheral joints by ultrasound imaging: A systematic review. Paper presented at: Rangahau Aranga: AUT Graduate Review November 17, 2022; Auckland, New Zealand.
7. **Molyneux P**, Bowen C, Ellis R, Rome K, & Carroll M. International multispecialty consensus on how to image, define, and grade ultrasound imaging features of first metatarsophalangeal joint osteoarthritis, a Delphi consensus study. Paper presented at: Rangahau Aranga: AUT Graduate Review November 17, 2022; Auckland, New Zealand.
8. **Molyneux P**, Bowen C, Ellis R, Rome K, & Carroll, M. Development of an ultrasound atlas to grade osteoarthritic change in the first metatarsophalangeal joint. Paper presented at: Te Anga Kaikōiwi o Aotearoa New Zealand Osteoarthritis Research Network Conference November 18-19, 2022; Wellington, New Zealand.
9. **Molyneux P**, Bowen C, Ellis R, Rome K, & Carroll M. International multispecialty Delphi consensus on how to examine ultrasound imaging features of first metatarsophalangeal joint osteoarthritis. Paper presented at: Te Anga Kaikōiwi o Aotearoa New Zealand Osteoarthritis Research Network Conference November 18-19, 2022; Wellington, New Zealand.
10. **Molyneux P**, Bowen C, Ellis R, Rome K, Frecklington M, & Carroll, M. Evaluation of osteoarthritic features in peripheral joints by ultrasound imaging: A systematic review. Paper presented at: Taupuni Hao Huatau Kaikōiwi Osteoarthritis Basecamp July 24, 2021; Auckland, New Zealand.

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Chapter 1

Thesis Overview

Rationale

The global impact of osteoarthritis (OA) constitutes a major worldwide challenge for individuals affected, health systems, and society as a whole (1, 2). In 2019 OA was the 15th highest cause worldwide of years lived with disability (3). By 2030, OA is predicted to be the single greatest cause of disability globally, with an estimated 35% prevalence (4). Foot OA results in functional limitations and significant impairments in balance, strength and locomotor ability, and impacts work ability negatively (5). The most commonly reported affected foot site is the first metatarsophalangeal joint (MTPJ) (6). However, the feet are often overlooked as a site of involvement relative to other joints commonly affected by OA (7), in spite of the fact that foot OA prevalence is comparable to more commonly spotlighted areas such as the knee and hip. Consequently, knowledge of foot OA and the evidence to guide assessment, diagnosis and therapeutic management of OA occurring in the feet is limited, particularly when compared to the hip and knee.

One way to mitigate the epidemic of OA is to modify both its structural progression and symptomatic consequences. OA diagnosis, treatments, management and research have not made comparable progress with other chronic non-communicable and musculoskeletal diseases (8). The structural failure of the joint is known as the *disease,* while symptoms and disability at the level of the individual comprise the *illness* (9). OA does not feature in global strategic plans for non-communicable diseases, yet OA commonly coexists with diabetes, heart disease and mental health problems, and can worsen the morbidity and mortality associated with these conditions (8, 10). Knowing when to provide the right treatment throughout the pathophysiological destructive processes that lead to OA has potential to substantially improve health outcomes before using unnecessary medications, procedures and hospitalisations (9, 11). Even more important is knowing when to intervene before the destructive process has even started, specifically after significant injury/trauma, as post-traumatic OA can be anticipated long before the destruction has begun. The International Foot and Ankle Osteoarthritis Consortium global community of investigators in the field of foot and ankle OA came together in 2021 to address the limited attention foot OA has received, providing a comprehensive agenda to guide future research (12).

To advance treatment capacity and mitigate disease impact, there is a need to change the current model of studying end-stage irreversible disease, necessitating improved detection and monitoring of the whole disease process. Current methods of diagnosing OA by conventional radiographs remains reactive and captures OA later in the disease process once the condition is significantly advanced and irreversible structural damage has already occurred (13, 14). Plain radiographs underestimate joint tissue involvement in OA, as radiography only visualises a component of the condition including joint space narrowing and osteophyte formation (15) Diagnostic omission necessitates a new model of care for OA that is proactive and preventative.

The increasing importance of imaging in OA for diagnosis, prognostication and follow-up is well recognised by clinicians and researchers (16). Recommendations published in 2017 by the European League Against Rheumatism (EULAR) highlighted the need for further imaging research into less commonly studied sites of OA, such as the foot (17). Mathiessen et al. (18) highlighted the importance of ultrasound imaging (USI) to obtain an early diagnosis in hand OA, demonstrating that USI could detect extensive synovial inflammation five years earlier than what could be seen radiographically. The findings of that study are pivotal to the present research and underpin the supposition that inflammatory USI features precede radiographically evident structural damage.

The purpose of the present research was to develop a USI atlas (picture-based classification system) to grade the degree of osteoarthritic change in the first MTPJ. The motivation to include USI for defining OA was to detect prognostic inflammatory features associated with structural disease progression, and to overcome the limitations of traditional and conventional methods such as relying on radiographs (18). The development of a USI atlas will provide capacity for earlier detection and standardisation of diagnosis, and provide a more sensitive method to classify and grade the disease stages. Currently, no foot specific classification criteria based on USI exist to grade foot OA. This research aimed to lay the foundation for a USI-based diagnostic and classification criteria, specific for first MTPJ OA. The USI atlas will be the first step in a longitudinal analysis to determine the predictive value of USI features in people with MTPJ OA. From here, the field can move forward and determine the role of USI for diagnosis and management of foot OA.

Benefits of the Research

The USI atlas developed through the present research has extensive capability to make a meaningful difference to how OA is diagnosed and managed in clinical practice and in future research. The USI atlas will advance understanding of the pathological process of first MTPJ OA and subsequently improve comparability of defining first MTPJ OA across studies, investigators and clinicians. This research aimed to demonstrate the role of USI in foot OA and be the catalyst in developing a classification criterion, specific for first MTPJ OA, which could be utilised both clinically and in future research. The translation and implementation of the USI into clinical practice will create a paradigm shift, reshaping the model of care for first MTPJ OA. The clinical application of the USI atlas has potential to advance clinical decision making, increasing the workforce capabilities of a wide range of healthcare professionals, improving healthcare provision, access and outcomes with early disease detection. The application of the USI atlas in future research may mitigate current limitations of investigating interventions targeted for end-stage disease. The atlas holds significant promise for future research in identifying the disease early in its course, to enhance responsiveness to interventions. Consequently, the USI atlas will broaden eligibility of people to participate in OA research, enabling the investigation of targeted interventions at different stages along the disease process. The output of this thesis is the potential wave of change needed to modify the historical story of OA detection, monitoring and management.

Thesis Aim and Objectives

The aim of this thesis was to develop an USI atlas to grade OA in the first MTPJ. The atlas was developed by addressing three objectives.

Objective One:

To critically evaluate and summarise relevant studies that have used USI to examine foot OA.

Objective Two:

To develop an USI acquisition procedure and grading system to examine OA features in the first MTPJ.

Objective Three:

To develop an USI atlas to grade the degree of osteoarthritic change in the first MTPJ and determine its reproducibility.

Research Questions

Objective one was investigated through the following research questions:

1. What USI structural and inflammatory features are indicative of first MTPJ OA and how are they graded?
2. What USI acquisition procedures and guidelines are used to assess the first MTPJ?
3. What are the temporal and global changes in research utilising imaging to assess foot OA?

Objective two was investigated through the following research questions:

4. What are the most valuable sonographic features to diagnose first MTPJ OA?
5. How should severity for each sonographic feature of first MTPJ OA be graded?
6. What USI acquisition protocol should be used to evaluate first MTPJ OA?
7. Is the USI acquisition procedure and grading system reliable for the assessment of structural and inflammatory features of first MTPJ OA?

Objective three was investigated through the following research question:

8. Is the USI atlas reproducible between sessions and between examiners for evaluating first MTPJ OA?

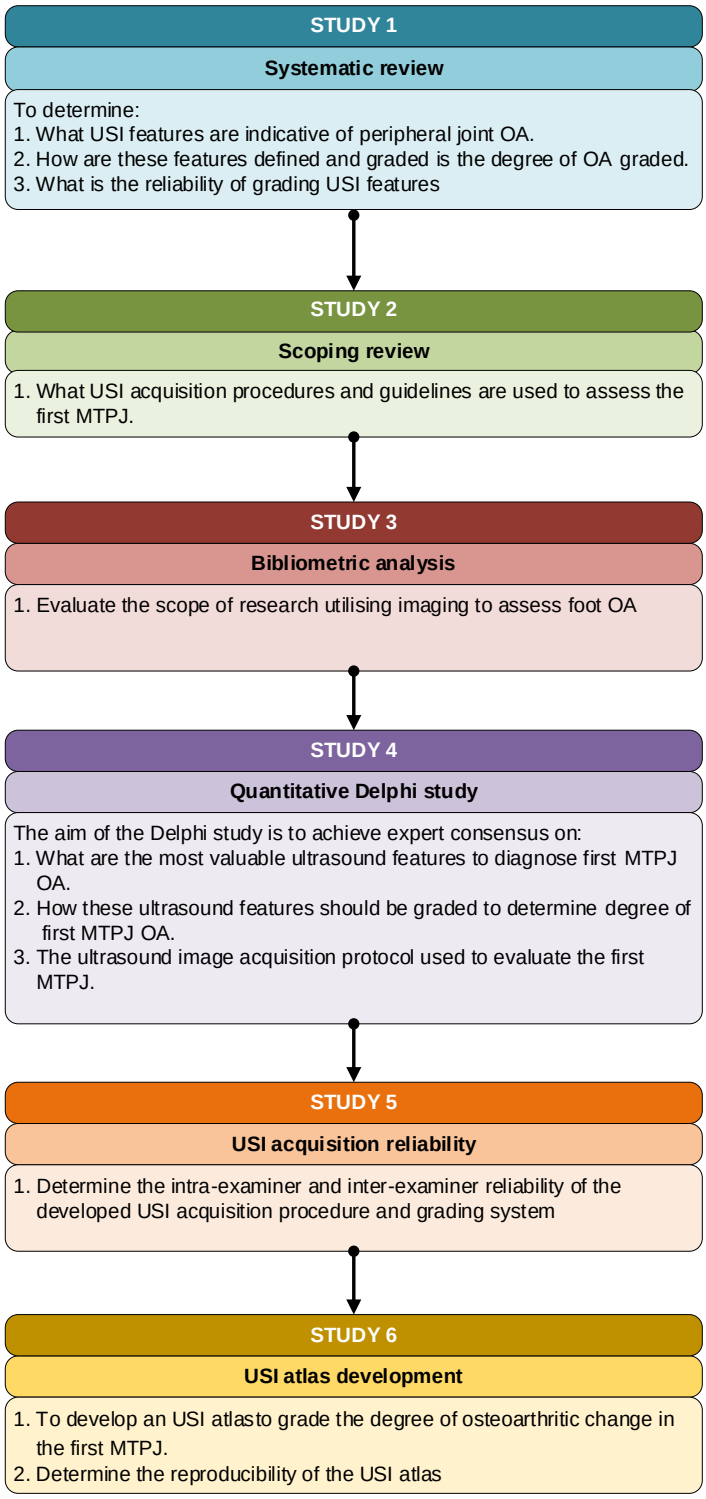
Thesis Outline

The thesis comprises 10 chapters, including six interconnected studies that have been completed in series. **Table 1** presents an overview of the chapters with alignment to the research objectives and research questions. **Figure 1** provides a graphical overview of the thesis.

Table 1. Overview of thesis chapters

	Alignment of chapter to research objectives and questions	
Chapter 2 Provides an overview of OA, including disease burden, epidemiology, risk factors and pathophysiology, and introduces foot and first MTPJ OA.		
Chapter 3 Provides an overview of the different imaging techniques used for the evaluation of OA.		
Chapter 4 Presents study one, which involved undertaking a systematic review to critically evaluate and summarise relevant studies that have used USI to evaluate OA features in peripheral joints of the hands and feet.	Research Objective 1	Research Question 1
Chapter 5 Presents study two, which utilised a scoping review to investigate USI acquisition procedures and guidelines used to assess the first MTPJ.	Research Objective 1	Research Question 2
Chapter 6 Presents study three, which involved a bibliometric analysis of published literature to evaluate the scope of research utilising imaging to assess foot OA, including global and temporal trends, and performance-based metrics.	Research Objective 1	Research Question 3
Chapter 7 Presents study four, which utilised a quantitative Delphi study technique to achieve expert consensus concerning USI of the first MTPJ.	Research Objective 2	Research Questions 4, 5 & 6
Chapter 8 Presents study five, which determined the reliability of the USI acquisition procedure and grading system for evaluating first MTPJ OA.	Research Objective 2	Research Question 7
Chapter 9 Presents study six which outlined the development of the USI atlas for evaluating first MTPJ OA and its intra-examiner and inter-examiner reproducibility.	Research Objective 3	Research Question 8
Chapter 10 Includes the thesis discussion, presenting an overview of the main findings, future directions, clinical implications, and the strengths and limitations of the thesis, followed by the thesis conclusion.		

Figure 1. Graphical overview of the thesis



Methodological Approach

The Gluud and Gluud framework was used to inform the methodological approach for the development of the first MTPJ OA USI atlas (**Table 2**) (19). The Gluud and Gluud framework proposes an architecture for diagnostic research that is applicable to diagnostic imaging (19). The framework is divided into four phases, where the first phase focuses on establishing the normal range. The second phase focuses on establishing sensitivity and specificity, and other measures of diagnostic accuracy. The third phase requires randomised trials to determine whether patients benefit from testing. The final phase involves large continuous surveillance studies to identify the consequences of testing in clinical practice (19). Applying this approach will extend the validity of the USI atlas and lay the foundation for longitudinal analysis. The four temporal phases provided a logical, stepwise procedure for the novel expert-derived USI atlas to reliably detect and grade first MTPJ OA. As the aim of the thesis was the development of diagnostic imaging technology, only Phases I, IIa and IIb of the Gluud and Gluud framework (19) were addressed in the study. Phases IIc, III and IV are proposed to be incorporated into postdoctoral studies.

Table 2. Four phases in architecture of diagnostic research (19)

Phase	Aim	Design
I	Determining the normal range of values for a diagnostic test	Observational studies on healthy subjects. Examine the potential influence of participant characteristics. May find abnormal results in an apparently healthy person.
II	Evaluation of the diagnostic accuracy of a test	Case-control studies; (i) Phase IIa: compare test results in participants with disease diagnosed by a standard method with those in healthy participants (from diagnosis to test result). (ii) Phase IIb: examine whether test results are related to the severity of a disease. (iii) Phase IIc: examine the predictive value of a test among people with suspected disease (from test results to diagnosis).
III	Determining the clinical consequences of introducing a diagnostic test	RCT; randomisation to determine whether a subject receives the diagnostic test or not
IV	Determination of the long-term consequences of introducing a new diagnostic test into clinical practice	Cohort studies of consecutive participants to evaluate if the diagnostic accuracy of a test in practice corresponds to predictions from systematic reviews of phase III trials

Study 1 and Study 4 of the research determined what USI features are indicative of first MTPJ OA (Phase I). Additionally, Phase I of the framework allows for investigation of USI features which can be considered to manifest sub-clinically (i.e. in the absence of symptoms). The findings from this phase are pivotal to future explorations of the causal

relationship between sub-clinical first MTPJ OA sonographic changes and clinically assessed structure and function of the joint. USI may provide a method to detect first MTPJ OA before irreversible structural changes occur. Phase IIa of the framework was addressed by Study 5 and 6 of the research, which examined USI features in participants with and without radiographically confirmed first MTPJ OA. To further test the diagnostic accuracy of the atlas and address Phase IIb of the framework, all acquired ultrasound images were graded according to OA severity.

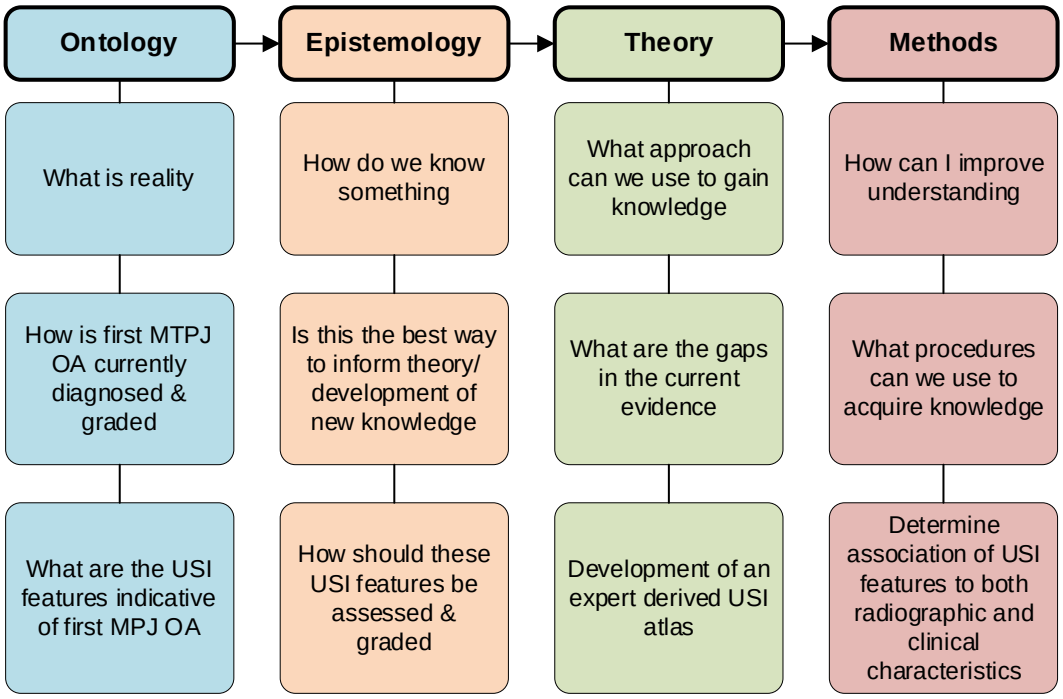
The research methodology was based on the philosophy of post-positivistic observational research. This approach encapsulates the use of quantifiable observed phenomena using scientific methods of enquiry that lend themselves to statistical analysis. The post-positivist paradigm seeks the 'truth' by understanding the world through observation and measurement (20). The concept of understanding the 'truth' may allow researchers to predict and/or control outcomes in the future (21). To achieve this, researchers develop hypotheses to test by applying reasoning and theory (20). A post-positivist belief system understands that the 'truth' can be understood by following specific procedures to observe consistency, change and accuracy (21).

The present research challenged my own perceptions on what I had considered OA to comprise. The process of completing this portfolio of studies refined my personal philosophical approach and understanding of OA pathophysiology, diagnosis, management, and the contemporary debate and evidence. The research was primarily designed to determine which USI features are indicative of first MTPJ OA. To achieve this, one critical step was applying a Delphi method to address research objective two. The Delphi technique is one methodology that utilises participant's opinions and beliefs to gain consensus. Therefore, elements of critical realism shaped some of the methodology to address the research objectives. A critical realist believes that in order to understand the reality uncovered by science, there is a need to look at the subject from all angles, with an openness about the way in which data is collected and analysed (22). Like the post-positivist paradigm, a critical realist seeks to understand the 'truth' but also appreciates there may be bias and/or error in achieving this (22).

The research paradigms of ontology, epistemology, theory and methodology were also used to inform the development of the atlas. Ontology refers to the concept of existence and belief about what constitutes reality (23). This paradigm questioned how first MTPJ OA is currently diagnosed and graded. Epistemology is the theory of understanding human knowledge and justification of choosing methods to further develop theory. Epistemology also considers the distinction between justified belief and opinion (23).

Epistemology requires questioning the current state of OA knowledge and whether it limits the potential for new knowledge. Epistemology led me to question the current model for diagnosis and care of foot OA. Is the current model the best way to inform theory and the development of new knowledge? Furthermore, is the current method valid and reliable? Ontology and epistemology create a holistic view of how knowledge is viewed and inform the development of new knowledge (23). The development and application of this knowledge to a problem is sometimes referred to as a theory. A theory is a system of ideas intended to explain a problem or subject. The thesis introduces a novel theory, the USI atlas, by initially identifying gaps in the existing evidence. It outlines a fresh approach that aligns with contemporary understanding and the evolving emphasis on early disease detection and prevention. **Figure 2** summarises the sequential theory process.

Figure 2. Visual representation of how the research paradigms link in this thesis



Chapter 2

Overview of Osteoarthritis

Introduction

OA is a prevalent, chronic, progressive and disabling joint disease that imposes a significant global health burden, with notable implications for the individuals affected, healthcare systems and wider socioeconomic costs (24, 25). The impact of OA continues to grow due to the ageing population, the rising prevalence of obesity, and the lack of definitive treatments to prevent or halt the progress of the disease (26). OA is a leading cause of chronic pain, joint stiffness, functional limitation and disability among older adults (24, 27-29). OA is the most common form of arthritis and possesses marked variability in disease expression (30, 31). Although most patients present with joint pain and functional limitations, the age of disease onset, sequence of joint involvement and disease progression vary from person to person. OA ranges from an asymptomatic, incidental finding on clinical or radiologic examination to a progressive disabling disorder eventually culminating in 'joint failure' (32).

The pathophysiology of OA has long been thought to be cartilage-driven (33). That paradigm was mainly based on the observation that chondrocytes have very low metabolic activity with no ability to repair cartilage (33). Moreover, articular cartilage, once damaged, cannot respond by a usual inflammatory response because it is non-vascularised and non-innervated (33). For that reason, there can be a long period of silent deterioration that does not produce clinical signs unless innervated tissues become involved. This imperfect concordance between the disease and the illness is one reason for the late diagnosis of OA and may explain the unclear correlation between radiographic OA and patient reports of pain (34). The contemporary concept of OA emphasises the complex pathogenesis of the disease, as a disorder of the joint as a whole organ, which involves not only hyaline cartilage, but an additional and integrated role of bone and synovial tissue (35).

This fundamental shift in our understanding of OA, from a cartilage-only disease to a whole organ disease, recognises the heterogeneous involvement of multiple joint tissues, including cartilage damage, subchondral bone remodelling, synovial inflammation, and osteophyte development (29, 36-38). The traditional view of OA as a degenerative disorder of articular cartilage, resulting from normal bodily wear and tear is obsolete (35, 39, 40). Archaic terms such as 'wear and tear' and 'degenerative' are now

considered both pejorative and inaccurate (41). OA is now generally appreciated as a multifactorial disease of the whole joint, due to abnormal remodelling of the joint tissues driven by a host of inflammatory mediators (29, 40, 42-47). Attention has now turned to the prognostic value and role of inflammatory markers (29, 35, 46), with several studies reporting an association between active synovitis and structural OA progression (33, 48-50). It is now known that synovial inflammation is pivotal in the pathogenesis of OA and that the 'itis' in osteoarthritis is entirely appropriate (40).

Disease Burden

OA is an impactful disease, with more than 500 million people affected globally (8). Women, lower education levels and the socially disadvantaged are disproportionally affected by the condition (3, 51). OA is the most prevalent arthritis globally; the consequent disability and socioeconomic impact are enormous. Analyses conducted in the United States, Australia and Spain suggest that the medical costs associated with OA make up approximately 0.25%–2.5% of the respective national gross domestic product (52-54). The rapid increase in prevalence of OA will lead to major challenges for healthcare systems (9, 55, 56). The ageing global population and the epidemic of obesity are likely to compound this impact (8, 39, 57). Compared to age- and sex-matched peers, OA patients incur higher personal health-related expenditures and substantial costs due to lost productivity (9). The disease burden of OA is typically measured in: direct costs such as pharmacological treatments, surgery, and long-term care; indirect costs such as absenteeism (days off work), presenteeism (reduced self-reported productivity at work), reduced employment, and premature mortality; and in less well-defined intangible costs such as pain, activity limitation, fatigue, reduced social participation, and reduced quality of life. In a 2016 systematic review examining the economic impact of knee and hip OA, per-patient costs ranged from 0.7 to 12 k€, with direct costs ranging from 0.5 to 10.9 k€ and indirect costs from 0.2 to 12.3 k€ (52). The estimated annual economic burden of OA is approximately US$45 billion in the United States (58). Among United States adults with OA compared to those without, annual total healthcare costs were US$1,778 and US$189 per person, respectively (58). The primary cost contributors were hospitalisation expenses related to joint replacement surgery (59). Total joint replacement is one of the most significant burdens of OA and is associated with elevated healthcare costs. With an ageing global population and obesity rates on the rise, the anticipated surge in total joint replacement utilisation suggests a continuing increase in the average cost of OA management (60, 61), emphasising the importance of prevention, early disease detection, and earlier interventions.

Despite the significant burden of OA, it is now becoming apparent that OA research efforts and attention do not necessarily match disease prevalence or disability. In the early 2000s it was predicted that OA population prevalence would increase by 50% over the next 20 years, with the caveat that past projections have underestimated the future burden (62-64). In fact, from 1990 to 2019 the number of people affected globally increased by 48%, the sharpest upward trajectory across all musculoskeletal conditions (65). The World Health Organization has designated the 2020-2030 decade as the "Decade of Healthy Ageing," which highlights the need to address chronic diseases with no cure, such as OA, that have a substantial impact on health-related quality of life (66, 67). There is substantial morbidity associated with OA, which presents major barriers to healthy ageing, including pain, disability, fatigue, loss of mobility, depressed or anxious mood, and reduced quality of life (51). Furthermore, it is anticipated that restricted healthcare access associated with the COVID-19 pandemic and its residual impacts will magnify the burden of OA over time (68).

It is important to reflect that the OA burden is not distributed equally. Social determinants, the built environment and access to healthcare all have impacts on the disparate disease burden of OA, particularly in lower-income and middle-income countries (8, 69). Within the New Zealand (NZ) context, data from the 2018 Arthritis NZ economic report indicated that Māori men are more likely to have arthritis than non-Māori males (70). While there are no significant differences in arthritis prevalence between Māori and non-Māori in the older age cohorts, arthritis is more prevalent among young Māori compared to non-Māori. Consequently, Māori are living with the burden of this disease for longer than non-Māori. Māori who undergo joint replacement surgery for OA are younger, have poorer general and mental health, have greater pre-operative co-morbidities and have poorer post-operative functional outcomes than non-Māori (71, 72).

Epidemiology

Defining OA

“OA is a disorder involving movable joints characterised by cell stress and extracellular matrix degradation initiated by micro- and macro-injury that activates maladaptive repair responses including proinflammatory pathways of innate immunity. The disease manifests first as a molecular derangement (abnormal joint tissue metabolism) followed by anatomical, and/or physiological derangements (characterised by cartilage degradation, bone remodelling, osteophyte formation, joint inflammation, and loss of normal joint function), that can culminate in illness” (73).

OA is characterised as a progressive disease of synovial joints that represents failed repair of joint damage resulting from stresses that may be initiated by an abnormality in any of the synovial joint tissues, including articular cartilage, subchondral bone (74-76), ligaments, menisci (when present) (77, 78), periarticular muscles (79), peripheral nerves, or synovium (80, 81). Abnormal intra-articular stress and failure of repair may arise as a result of biomechanical (82), biochemical (83) and/or genetic factors (84). This process may be localised to a single joint or a few joints, or generalised, and the factors that initiate OA likely vary depending on the joint site.

The complexity and variability of OA aetiology suggests the need for patient-specific, aetiology-based treatment. Additionally, a large proportion of people with radiographic evidence of OA have no symptoms or disability (34, 85). Consequently, it is unclear whether such people should be considered as having OA (86). These difficulties have led to the existence of several definitions of OA (27, 87, 88), which may partly explain the variance in OA estimates (89-91). How OA populations are defined is often determined by the focus of the investigation and varies depending on whether the diagnosis is based on clinical findings, such as restrictions in joint motion, the presence of pain and/or joint deformity, or by radiographic findings (27, 87, 88). The prevalence of OA defined by radiographic confirmation is distinctly higher (92). Defining joint abnormality in OA by plain radiography evaluation alone does not provide a complete description of the disease; changes to soft tissues in the joint cannot be visualised by plain radiography. Therefore, alterative imaging modalities are needed to characterise and define the onset and early progression of OA, when intervention may be more likely to achieve joint preservation.

Prevalence of OA

OA is a major global public health problem, with a worldwide prevalence of 23.9% (92). The prevalence of OA has been assessed in studies spanning several decades. The prevalence of OA varies across studies according to the clinical or radiographic definition used, the specific joint(s) under investigation, and the characteristics of the study population (93, 94). Radiographic OA, symptomatic OA and self-reported OA are the most commonly used case definitions (95-99). Radiographic OA has long been considered the reference standard for defining the presence and severity of OA (100). The most common method for radiographic definition is the Kellgren and Lawrence (KL) radiographic grading system – an atlas which has been in use for over four decades (101).

The Johnston County OA Project and the Framingham OA study are population-based cohort and community-based studies which have further documented the prevalence of OA at different joints (102, 103). Hand OA estimates derived from the Framingham OA Study were approximately 34% to 35% for any hand joint for both sexes (103). The age-standardised prevalence of radiographic hand OA was 44.2% in females and 37.7% in males (103), and symptomatic hand OA was 14.4% and 6.9% in females and males, respectively (103), which increased to 26.2% and 13.4%, respectively, among those aged 71 and older in an older Framingham cohort (102). In the Framingham OA study, females had a slightly higher prevalence of radiographic knee OA compared with males (34.4% versus 30.9%). Symptomatic knee OA was substantially more common in females than males, with 11.4% versus 6.8% respectively (104). There has also been an increase in prevalence of symptomatic knee OA among females and males, over the past 20 years by 4.1% and 6% respectively. in the Framingham cohort (105). From the Johnston County OA Project, both radiographic hip and knee OA had a prevalence of 28% (106, 107). The prevalence of symptomatic knee and hip OA was 17% and 10% respectively from the Johnston County cohort (106, 107).

The presence of OA in multiple joints is an often-overlooked component of the burden of OA, with varying definitions within the literature making it difficult to enable a global estimate (108). Population-based data from Korea suggested that almost 23% of females and 11% of males had more than two joints involved (109). Among a Swedish population, almost 27% of OA cases reported OA in multiple joints (110). One study attempted to define multiple-joint OA and apply the definitions to the Johnston County dataset, finding that 52% reported symptomatic hip or knee OA with one other site (spine, ankle, or foot) (111).

Incidence of OA

The incidence of OA increases with age, and females have a higher incidence than males, especially after age 50 (112). One estimate of the lifetime risk of developing symptomatic knee OA was approximately 40% in males and 47% in females, with higher risk among those who are obese (113). From the Framingham OA Study, the incidence of symptomatic hand OA was 4% for men and 9.7% for females over a 9-year period (103). Age- and sex-standardised incidence rates for symptomatic knee, hip and hand OA have been estimated to be 240, 100 and 88 cases per 100,000 person-years, respectively, with incidence rising sharply after age 50 (112). The increasing trend of OA incidence continues until age 80, after which there is a levelling off or decline in the incidence rates for all joints (112).

Risk Factors

OA has a multifactorial aetiology and is the result of a complex interplay between mechanical, cellular and biochemical factors leading to common end-stage pathology (114). The risk of developing OA is determined by both systemic and local risk factors (93, 94). Several systemic factors have been identified; these may act by increasing the susceptibility of joints to injury, by direct damage to joint tissues, or by impairing the process of repair in damaged joint tissue. Local factors are most commonly biomechanical in nature and adversely affect the forces applied to the joint (94, 101, 115). The most common risk factors for OA include age, sex, prior joint injury, obesity, ethnicity, genetic predisposition, and mechanical factors, including malalignment and abnormal joint shape (99, 116, 117).

Age

Age is one of the strongest risk factors for OA (116), with both incidence and prevalence of OA increasing with age (118). Increased risk is particularly pronounced in the commonly affected/reported joints, such as the knee, hip and hand, especially after the age of 50 years (30, 93, 94, 119). The exact mechanism behind this increased risk with increasing age is poorly understood. Rather than being one and the same, ageing of joint tissues and the development of OA are distinct processes. While ageing is not viewed as the initiating factor for the development of OA, age-related changes within the chondrocytes (i.e. cellular senescence), age-related sarcopenia, increased body mass index (BMI) and increased bone turnover are likely contributing factors (93). Therefore, ageing changes are most likely make the joint more susceptible to the development of OA

and promote progression, with age being a proxy for the accumulation of a sufficient set of risk factors over the years (30, 94).

Sex

Females have a higher prevalence and greater severity of OA than men, particularly following menopause (85, 93). The increase in prevalence and incidence of OA at the time of menopause has led to hypotheses regarding the role of oestrogen in OA. Loss of oestrogen may unmask the symptoms of OA by enhancing pain sensitivity (94). However, results from observational studies and clinical trials have been conflicting (120, 121). A large meta-analysis demonstrated a greater risk in females compared with males for prevalence and incidence of knee and hand OA as well as hip OA incidence (85). Sex disparities may also be caused by differences in alignment, bone strength, neuromuscular strength, ligament laxity, and pregnancy (93).

Obesity

Obesity represents one of the most important risk factors for both the incidence and progression of OA (93, 122, 123). Being overweight not only predisposes the development of OA but also increases the risk of radiographic progression (116). With the rising epidemic of obesity, it is likely that more individuals will be affected by OA in the future. Obesity increases the risk of developing knee OA and its progression, regardless of knee alignment (93, 94, 117, 124, 125). The Framingham Study showed that weight reduction by 5 kg provided a decreased risk for the development of knee OA by 50% (126, 127). Excess weight will produce increased load on the joint, but there is growing evidence for a metabolic contribution to OA (94). Obesity is also associated with radiographic and symptomatic hand OA incidence (93, 94, 128, 129), conferring the possibility that obesity may also provide some metabolic and inflammatory systemic effects (130). Adipose tissue is known to be metabolically active, secreting adipokines such as adiponectin, leptin and resistin, but the role of these adipokines in OA is not yet clear (131, 132). The cytokines associated with obesity may promote a low-grade, systemic, proinflammatory state that could increase joint susceptibility and contribute to the development of OA, while leptin has been proposed to have direct effects on joint tissues that promote the development of OA (133, 134).

Ethnicity

OA has a similar risk factor profile to many chronic diseases that disproportionately affect indigenous peoples (135). Racial/ethnic differences in the prevalence of OA and specific patterns of joint involvement have been noted. In the Johnston County OA Project,

African-American males had a higher prevalence of radiographic hip OA than Caucasian males (32.2% vs 23.8%), whereas there was no difference between African-American and Caucasian females (40.3% vs 39.4%) (107). In the Beijing OA Study, hand and hip OA were less prevalent among Chinese than Caucasians (age-standardised prevalence 44.5%–47% vs 75.2%–85% and 0.8% vs 3.8–4.5%, respectively), but knee OA was more prevalent among Chinese females than among Caucasian females (46.6% vs 34.8%) (136-138). Within NZ, OA affects an estimated 37,000 (7.4%) Māori adults (139). Rates of OA are slightly higher among Māori females (7.7%) than males (7.2%) (139). However, prevalence rates for OA is highest in non-Māori females (13.5%) (70).

Genetics

Twin and family studies suggest that the influence of genetic factors are approximately 40% for knee OA, 60% for hip OA, 65% for hand OA, and approximately 70% for OA of the spine, independent of known environmental or demographic confounding factors (140-143). Genetics appear to account for approximately half the variability of susceptibility to OA in women (140, 141, 144-147) and men (146, 147). While genetics play a significant role, no single gene is involved in the development of OA. Heterogeneity across published studies, including participants' age, ethnicity, sex, and phenotype distribution, and the range of different clinical, biological and radiographic outcome measures collected alongside the genetic material, make it difficult to compare across studies (93, 142, 148).

Joint Injury

Traumatic joint injury is associated with the development of OA and is commonly referred to as post-traumatic OA. The knee is most often investigated and reported as one of the most frequently injured joints (149). Knee injury at a young age (mean age of 27 years) is an independent risk factor for the development of knee OA at middle age (mean age of 39 years) (150, 151). Further, following anterior cruciate ligament (ACL) injury individuals have four times higher odds of developing knee OA, and this rate increases to six times higher odds when combined with meniscal injury (152). The pathological changes are often evident within 10 years after injury (153-155). Interestingly, the risk of developing OA after an ACL tear is the same whether the ligament is repaired or not (156). This finding suggests that either the mechanics of the joint are not completely restored following reconstruction, or that the acute inflammation that occurs with the tear initiates the OA process, which is not stopped by reconstruction of the ACL (157). The latter is supported by studies demonstrating a host of inflammatory mediators are present shortly after injury (158), and markers of collagen and proteoglycan degradation are

sustained over time (157). Approximately 1% of the global population is estimated to have OA of the ankle joint, with prior joint trauma the most common cause, accounting for between 20% and 78% of all cases of ankle OA (159, 160). There are no known investigations for post-traumatic foot/first MTPJ OA.

Anatomical Factors

Joint shape can influence the development of OA. The relationship of anatomical factors to OA is best explained by altered joint mechanics as the initiating cause for OA. Altered mechanics that place excessive and abnormal loads on joint tissue cells activate mechanotransduction pathways that result in increased production of inflammatory mediators and proteolytic enzymes (161). An important anatomical factor related to knee OA progression is lower-extremity alignment (162-164). Individuals who have a varus alignment (bow-legged) are at increased risk of medial tibial-femoral OA, while those with a valgus alignment (knock-kneed) are at risk for lateral tibial-femoral OA (165). Hip joint shape alterations such as femoroacetabular impingement and acetabular dysplasia have been associated with increased risk of early-onset and progression of hip OA (166). Hallux valgus (malalignment and medial enlargement of the first MTPJ) has been linked with OA in the first MTPJ (167).

Occupation and Physical Activity

Repetitive joint use has been associated with an increased risk of OA. Studies have reported occupations that require excessive lower extremity joint loading (squatting or kneeling) are associated with increased risk for knee and hip OA (93, 94), in particular, those who are overweight or whose jobs required heavy lifting (168, 169). Occupations that require increased manual dexterity have been associated with features of hand OA (170).

Physical activity may potentially be detrimental if it places undue load on the joint, despite the observed benefits of strengthening periarticular muscles to help stabilise the joint. There is inconclusive evidence regarding high-volume running and OA development (171), suggesting that, in the absence of joint injury, the risk of OA development due to running and exercise is minimal. Conversely, there does appear to be an association between OA and elite-level athletes involved in highly repetitive, intense and high-impact sports such as tennis and squash (172). However, it is unclear whether this association is a result of injury or solely due to sports participation. However, the nature of the sport is very important to the degree of risk (172). Sports that involve more intense impact and

torsional loading, such as basketball, tennis and football, have greater evidence for post-traumatic OA (173).

Pathophysiology of OA

At the molecular level, OA is characterised by the presence of a host of proinflammatory mediators, including cytokines and chemokines, that are part of an innate immune response to joint injury (174). Proinflammatory factors appear to be driving the production of the proteolytic enzymes responsible for the degradation of the extracellular matrix that results in joint tissue destruction (175). Although destruction and loss of the articular cartilage is a central component of OA, the pathologic process affects multiple structures, including degradation of the articular cartilage, thickening of the subchondral bone, osteophyte formation, variable degrees of synovial inflammation, and hypertrophy of the joint capsule (29, 176). The pathological changes detected in all the joint tissues provides reasoning for considering OA as a disease of the joint as an organ resulting in “joint failure” (29).

Mechanical factors certainly play a key role in OA. Rather than simply causing joint tissue damage by wear and tear, excessive or abnormal joint loading also stimulates joint tissue cells to produce proinflammatory factors and proteases that mediate joint tissue destruction (29). Cartilage and subchondral bone are susceptible to abnormal external mechanical stress and internal biochemical or morphological changes, thus losing the function of absorbing biomechanical forces (177). Notably, the synovium in OA can exhibit inflammatory responses, which further damage surrounding tissues through the release of proinflammatory mediators into the synovial fluid (178). This interdependence among tissues underpins the multifactorial nature of the disease, with the loss of normal function in one tissue directly influencing another. Thus, OA rarely has a single cause and often presents as a variety of pathological features and symptoms.

The exact sequence of events that trigger the onset of the disease is widely debated. One hypothesis suggests that secretion of proinflammatory cytokines into the synovial joint induces matrix metalloproteinases which cause the fragmentation and degradation of cartilage extracellular matrix, leading to bone remodelling and synovitis (179, 180). Contrary to this theory, some studies suggest that synovitis and subchondral bone remodelling precede articular degeneration in the early stages of OA (179, 181, 182). In the later stages of OA, subchondral sclerosis, subchondral cysts and osteophytes occur as a direct result of bone remodelling, cartilage degradation and synovitis (183-185).

Articular Cartilage

OA has long been characterised by a breakdown of the repair process of damaged cartilage as a result of biomechanical changes in the joint (39, 186). Cartilage has limited capacity to repair, and once collagen is degraded and lost, it is not replaced to a measurable degree (187). Cartilage architecture and biochemical composition are strictly regulated by chondrocytes (188). In normal adult cartilage, chondrocytes are quiescent cells and there is very little turnover of the cartilage matrix (29). In OA, the chondrocytes become “activated”. characterised by cell proliferation, cluster formation, and increased production of both matrix proteins and matrix-degrading enzymes (29, 189). The chondrocytes within the joint fail to synthesise a resistant and elastic matrix and therefore cannot maintain the balance between cartilage synthesis and degradation (188, 190, 191). Inflammatory mediators such as interleukin (IL)-1 and mechanical stress then drive chondrocytes to produce less functional collagen, smaller proteoglycans, more degradative enzymes, and multiple mediators of inflammation (192). This reaction causes a vicious cycle in which breakdown exceeds synthesis of the extracellular matrix (39), leading to loss of articular cartilage (193). As articular cartilage is aneural, these changes do not produce clinical signs unless innervated tissues become involved (39). However, recent evidence shows an additional and integrated role of bone and synovial tissue (35), indicating that inflammation has a critical role in its pathogenesis of OA (46, 47). Chondrocytes could first be activated by inflammatory signals originating from other joint structures such as synovium or subchondral bone (35).

Subchondral Bone

There is growing evidence that subchondral bone plays an important role in the pathogenesis of OA. Subchondral bone is responsible for shock absorption and supplies nutrients to cartilage (194). In early OA, an increased rate of bone remodelling is observed, associated with a transient loss of bone, increased porosity in the subchondral region, and reduced density, leading to a decrease in the subchondral plate thickness (39, 184). This potentially makes the subchondral plate less able to absorb and dissipate energy (26). These changes lead to increases in forces transmitted throughout the joint (26). The causes of increased bone remodelling in early OA are unknown, but several different mechanisms are suspected – cellular signalling, vascular invasion, and bone-cartilage crosstalk (184, 195, 196). As the disease progresses, the remodelling rate decreases (184, 197). This process increases bone volume and can be associated with subchondral sclerosis and the development of osteophytes at joint margins (184, 192). However, it remains unclear whether changes in the subchondral bone precede cartilage degeneration or result from it (198, 199).

Synovial Inflammation

The synovial membrane plays a key role in normal joint function, as it nourishes chondrocytes through the synovial fluid and eliminates metabolites and matrix degradation products (35). Synovitis is a common feature of OA, associated with clinical symptoms such as joint swelling and pain, and reflects joint degradation in OA (200-202). Synovial macrophages produce catabolic and proinflammatory mediators which alter the balance of cartilage matrix degradation and repair (203, 204), leading to excess production of the proteolytic enzymes responsible for cartilage breakdown (205). Cartilage alteration in turn amplifies synovial inflammation, creating a vicious cycle (35). Thus, OA synovitis perpetuates the cartilage degradation (33). Consequently, synovial fluid loses its viscoelastic properties, rendering the joint susceptible to further mechanical wear (190). As a result of joint synovitis, sensory nerves within the synovial membrane may also be activated, resulting in pain and neurogenic symptoms (206). Despite synovial inflammation being a key factor in OA pathophysiology, OA is still considered a non-inflammatory disorder, as the leukocyte count is below the threshold that defines inflammatory disorders (207). Synovitis contributes to pain and predicts the development of symptoms and disease progression (29, 174, 200, 208, 209). Therefore, synovitis may be an indicator of early-stage joint disease and provides a rational target for intervention.

Foot OA

The foot is a target region for OA (210), yet foot research is a relatively nascent and evolving discipline within the broader field of OA (12, 17). Radiographic foot OA affects 16.7%-22% of people (6, 211), as such making it is as prevalent as knee OA. The most commonly reported affected foot site is the first metatarsophalangeal (MTPJ) (6). Foot OA is an important contributor to the burden of OA, with a significant negative impact on physical mobility and health-related quality of life (6, 212, 213). The adverse effects on health, physical function and quality of life from foot OA can impact on working ability (5, 214). The foot was included in early descriptions of generalised OA (215), but subsequent OA research has often overlooked the foot as a site of involvement (7, 216). Consequently, knowledge of foot OA substantially lags behind that of other joint sites, such as the knee, hip and hand, where research evidence is more advanced (119, 217-219). Accordingly, foot OA is identified as a research priority (219-222).

A key barrier to progress with foot OA research has been the absence of a standardised case definition. Definitions for OA of the knee, hip and hand are well established and

based on decades of research (223-225). In contrast, defining foot OA is under-researched. Definitions for other joints may not necessarily be generalisable to the foot, which is anatomically complex and fundamentally different from the knee, hip, and hand. A consideration unique to the foot is whether separate definitions are needed to delineate different phenotypes of foot OA that require distinct management approaches (219, 226). Despite the high prevalence and disabling nature of foot OA, no accepted classification criteria for foot OA exist, and development has been limited by unclear signs and symptoms and the need for a radiographic examination for clinical confirmation (7, 227, 228). The most universal tool for the classification of hip, hand and knee OA are the American College of Rheumatology (ACR) criteria (223-225, 229), but no ACR criteria for classifying foot OA have been developed. There is no consensus as to which outcome measures should be used to diagnose, grade the degree of foot OA, and assess treatment effectiveness.

Definitions and a classification criteria are needed for use in future longitudinal studies, to better understand the disease pathogenesis, risk factors, clinical presentations and prognoses, and develop target interventions (226, 230, 231). In the current decade dedicated to promoting 'healthy ageing', defining a complex and heterogenous condition such as foot OA has implications variously for clinical decision-making, research design, healthcare resource allocation, and policy decision making.

Prevalence and Incidence of Foot OA

Historically, the knee has been considered the most commonly affected weight bearing region, with a global OA prevalence of 14.3–17.8% (232). However, investigators have reported the population prevalence of symptomatic radiographic foot OA as 16.7% (233), suggesting it may be as common as knee OA. The first MTPJ is the most commonly affected foot joint, and a distinct phenotype of foot OA (226, 234), with a prevalence rate slightly higher than hip OA (7.8% vs. 5.0–7.4%) (6, 92, 212). By age 60 years, radiographic first MTPJ OA is present in approximately 46% of women and 32% of men (235). Midfoot joints are also commonly affected, including the second cuneiform-metatarsal joint (6.8%), talo-navicular joint (5.8%), naviculo-cunieform joint (5.2%), and first cuneiform-metatarsal joint (3.9%) (6).

Population-based epidemiological studies have reported a high prevalence of OA in the feet. In the Johnston County OA Study, the prevalence of radiographic foot OA was 22% (211) and the prevalence of symptomatic radiographic foot OA was 5% (211, 236); in the Clinical Assessment Study of the Foot, it was 17% in adults aged ≥50 years (237). First MTPJ radiographic OA prevalence was 10% in the Johnston County OA Study (236), 8%

in the Clearwater OA Study (238), and ranged from <4% in the 20-24 age group to approximately one half of over-80s in the Zoetermeer study (235). In the Clinical Assessment Study of the Foot, symptomatic radiographic first MTPJ OA affected 8% (6). The prevalence of radiographic first MTPJ OA ranged from 6.3% in rural African women aged 40 years and over (239) to 39% in women aged 35-64 years resident in Wensleydale, UK (240). Over seven years, in the Clearwater OA Study, approximately one quarter developed radiographic first MTPJ OA (241). In the Chingford study, 13.5% developed radiographic OA in the right first MTPJ and 8.3% in the left over 19 years (242). First MTPJ OA has also been shown to worsen symptoms at other joints, and to increase the risk of developing OA in joints proximal to the foot (5, 233).

Radiographic OA at other sites within the foot appears to occur less frequently than at the first MTPJ. In the Zoetermeer study, tarsometatarsal radiographic OA prevalence ranged from <1% in people aged 20-24 years to >7% in the over 80s (235). Applying the La Trobe Foot Atlas (LFA), the second cuneometarsal joint is the most commonly affected of the four midfoot joints (6, 243). The base of the second metatarsal occupies a recessed position relative to the first and third metatarsals, potentially making it more susceptible to excess loading and development of OA (244). The prevalence of radiographic OA at the first cuneometatarsal, second cuneometatarsal, navicular-first cuneiform, and talonavicular joints was 3%, 7%, 5%, and 6% respectively in the Johnston County OA Study (236), but substantially higher (22.9%, 65.4%, 39.5% and 35.6%, respectively) in older adults (mean age 76 years) in Australia (245). In the Clinical Assessment Study of the Foot, the prevalence of symptomatic radiographic midfoot OA was 12% overall, and 3.9%, 6.8%, 5.2%, and 5.8% respectively at the same individual joints (6, 212). Much higher prevalence was reported for midfoot OA in a population of retirement village residents in Australia, with first cuneometatarsal joint at 23%, second cuneometatarsal joint 60%, navicular-first cuneiform joint 39%, and talonavicular joint 33% (243). Over 3-4 years in the Johnston County OA Study, 4% of participants developed incident foot radiographic OA (246).

First MTPJ OA

First MTPJ OA is characterised by localised joint pain and stiffness, and has a significant negative impact on physical mobility and health-related quality of life (6, 213, 226, 230, 247, 248). First MTPJ OA is highly debilitating, with most afflicted individuals (72%) describing the pain as “disabling” (6). Reduced range of motion of first MTPJ dorsiflexion is a cardinal clinical feature of first MTPJ OA and is associated with pain and increasing radiographic severity (167, 249, 250). The first MTPJ plays a crucial role in stabilising

the foot and ensuring efficient transfer of the body's centre of mass over the foot during the propulsive phase of gait (251-253). Reduced first MTPJ dorsiflexion from the effects of OA can inhibit efficient forward transfer of body weight and lead to altered foot function and load distribution (247, 254-256). Consequently, individuals with first MTPJ OA adopt pain-avoidance gait patterns (249, 257, 258). These may contribute to the development of secondary calluses or interphalangeal joint hyperextension (167, 254, 259), and increase the risk of developing other foot pathologies or OA in joints proximal to the foot (5, 233).

Clinical Characteristics of First MTPJ OA

Few agreed guidelines exist for the clinical diagnosis of first MTPJ OA. Zammit and colleagues developed a diagnostic rule for the identification of radiographic first MTPJ OA in 181 participants presenting with first MTPJ pain, based on five reported symptoms and clinical observations (230). In people with first MTPJ pain for longer than 25 months, the presence of a dorsal exostosis, hard-end feel, crepitus and less than 64° of first MTPJ dorsiflexion were significantly associated with radiographic OA (230). Since the correlation between radiographic OA and patient-reported pain is unclear (34), the diagnostic rule proposed by Zammit and colleagues is limited by the exclusion of patients without pain. People with asymptomatic OA may go undiagnosed until symptoms manifest.

More recently, a consensus study involving 214 podiatrists and physiotherapists developed five recommended assessment components for first MTPJ OA, to inform the management of people with a clinical and/or radiographic diagnosis of first MTPJ OA (260). Paterson and colleagues developed five recommend clinical assessments, which included: pain on walking over the past week; first MTPJ and ankle joint range of motion; foot posture; resting calcaneal stance position; and palpation to determine pain location (260). **Table 3** outlines five clinical observations developed as a diagnostic rule to identify the presence of radiographic first MTPJ OA in symptomatic patients (230) and the five recommended assessments for first MTPJ OA from a consensus study (260).

Table 3. Clinical characteristics and assessments

Clinical characteristics	Outcome measure
Foot pain and function (230, 260)	National Health and Nutrition Examination Survey (NHANES)–based query about foot pain (261)
Dorsal exostosis (230)	Absent/present
Palpation of pain to determine location (260)	Record pain around the first MTPJ as medial, lateral, dorsal, plantar, distal or proximal.
Activity limitation scale (260)	The Health Assessment Questionnaire - Disability Index (HAQ-DI) (262).
Hard end-feel (230)	A positive test result was concluded if a hard osseous end-feel was determined as opposed to a gradual end-feel of joint motion (263).
Crepitus present (230)	A positive test result concluded if a grating or cracking sensation occurred during at least three of the test trials (264).
First MTPJ ROM (230, 260)	Procedure described by Hopson, McPoil (265) as the maximum angle at which the hallux cannot be passively moved into further extension in a non-weightbearing position.
Ankle joint ROM (260)	Ankle joint dorsiflexion will be measured using the weight bearing lunge test, with the knee flexed (266) and extended (267).
Foot posture index (260)	Foot type will be determined by the use of the six-criterion scoring system (268).
Resting calcaneal stance position (260)	Inverted/ perpendicular/ everted (degrees) (269).

CHAPTER 3

Imaging in Osteoarthritis

Imaging modalities have expanded knowledge of OA pathogenesis, showing that all structures of the joint might be involved (270). The importance of imaging in evaluating OA has been recognised (271). Musculoskeletal imaging has an essential role in the diagnosis of OA, grading of OA severity, monitoring the effect of therapeutic management, and predicting the course of OA (18, 49, 272-274). Significant technological advances have been made in the field of imaging, allowing higher resolution and increased portability of devices (275), and enabling a more accurate evaluation of both bone and soft tissue abnormalities (17). The increasing importance of imaging in OA for diagnosis, prognostication and follow-up is well recognised by clinicians and researchers (16). Recommendations published in 2017 by the European League Against Rheumatism (EULAR) highlighted the need for further imaging research into less commonly studied sites of OA, such as the foot (17).

A significant barrier to the study of foot OA has been the lack of a foot-specific imaging-based grading system to classify the degree of pathological change in joint tissues (231). Plain radiography has traditionally been regarded as the leading modality for the assessment of osseous changes in foot OA (13), and considerable research has been undertaken to assess the diagnostic sensitivity of radiography and its association with clinical symptoms for foot disorders (226, 243, 276). The limitation of a radiographic-based classification system is the focus solely on bone changes. However, the advent of more advanced techniques, including magnetic resonance imaging (MRI), computed tomography (CT), and ultrasound imaging (USI), has gained increasing recognition of their fundamental role in understanding the pathophysiology of OA, due to their ability to observe subclinical osseous and soft tissue changes (277-280). The advantages and disadvantages of different imaging modalities are outlined in **Table 4**. Ongoing research is crucial in determining the capacity of modern imaging modalities to detect early inflammatory changes that precede osseous involvement, informing more timely management approaches to prevent or slow further structural progression (48-50).

Table 4. Advantages and disadvantages of imaging modalities

Imaging Modality	Advantages	Disadvantages
Plain radiograph	Low cost Widely available Reference technique Short testing time Screening or baseline Assess osteophytes and joint space narrowing	Radiation Limitations in imaging soft tissue and subchondral structures Poor sensitivity Poor indicator of clinical symptoms Limited sensitivity to change
MRI	Sensitive Evaluation of all articular and periarticular structures Non-invasive technique No radiation 3D sectional imaging technique High spatial resolution Excellent soft tissue contrast High accuracy and reliability	High cost and low availability Scanning time can be prolonged Not dynamic Contraindicated in some patients (e.g. cardiac pacemaker)
USI	Safety non-invasiveness No radiation Low cost Absence of contraindications Does not require intravenous contrast for assessment of active synovitis High temporal resolution Repeatability over time Wide equipment availability Bedside procedure Optimal patient acceptance Real-time imaging with a short acquisition time Ability to detect active synovitis using power of colour Doppler imaging US-guided procedures	Limited number and width of acoustic windows Low contrast and strong boundary effects Operator dependency Long learning curve Lack of standardised definitions and scoring systems for findings Unable to assess deep articular structures

Plain Radiography

Plain radiography represents the current reference standard imaging modality for the visualisation of bony change and the diagnosis of radiographic OA (13, 14). Although plain radiography can detect joint space narrowing and bony alterations (15), shortcomings include insensitivity to change, non-specificity, and poor indication of clinical symptoms (281). Radiographic imaging cannot directly visualise articular cartilage or detail the soft tissue changes in and around joints (282). Radiographic findings are also poorly associated with clinical symptoms (96, 283). At the point where a ‘bone-on-bone’ change is seen on a plain radiograph, the OA pathological processes may have progressed beyond repair and joint structure and function may be significantly impaired. Once the joint has reached this point, it is possibly too late to intervene effectively with non-surgical interventions, so patient outcomes and management are limited.

Two radiographic systems are commonly utilisd for the diagnosis and classification of foot OA – the Kellgren and Lawrence (KL) system (14), and the LFA (13). A systematic review (7) of the radiographic prevalence of foot OA from 27 studies found that most

(70%) applied the KL grading system to define first MTPJ OA (14). The KL system was developed in 1957 and an accompanying atlas was published in 1963 (14). The KL system is a generic, composite measure reflecting osteophyte presence and joint space narrowing (14). Although widely adopted, the major disadvantage of the KL grading system is that it does not include specific atlas images for the first MTPJ. Therefore, grading first MTPJ OA must be interpreted from other joints. Under the KL system, OA is considered present when radiographic structural evidence of disease is graded as 2, 3, or 4, as defined in **Table 5** (238). The KL system has been criticised for placing too much emphasis on the presence of osteophytes to classify joint OA, and that the system is insensitive to change (13, 284). The system is non-specific to the foot and does not incorporate observations specific to individual joints provided by other atlases (285). There have also been several inconsistencies in the interpretation of classifying and grading OA which have resulted in large scoring variations, making comparison across studies problematic (15, 286). There were significant developments of radiographic atlases in other joints in the late 1980s. However, the foot was still not included when the Osteoarthritis Research Society International (OARSI) (287) revised the radiographic atlases for the hand, hip and knee.

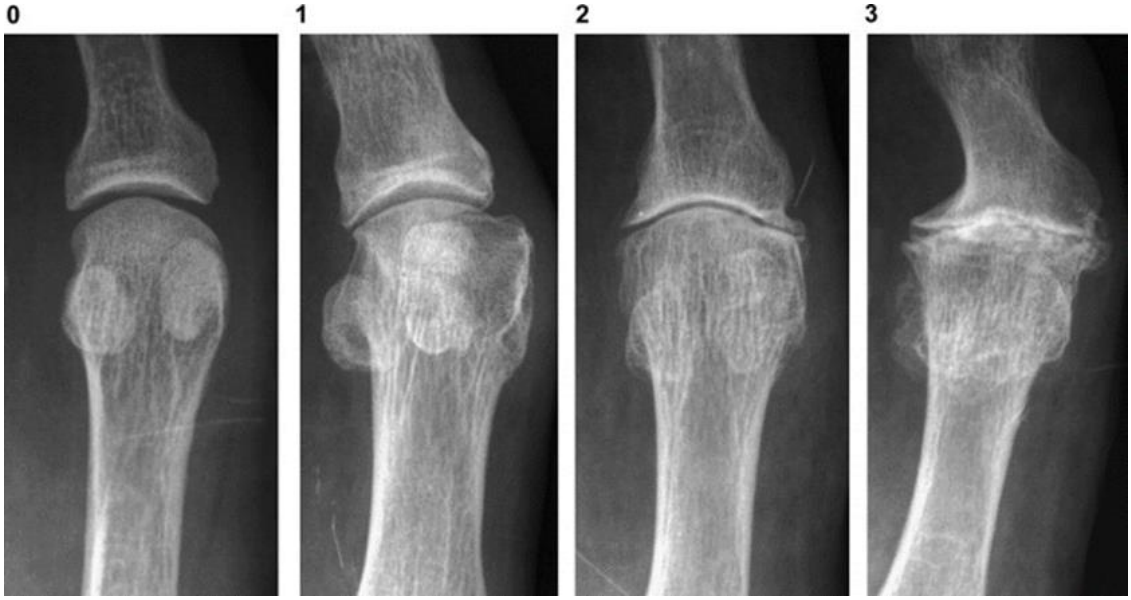
Table 5. The Kellgren and Lawrence grading system

Grade	Radiographic finding
0	No Radiographic features of osteoarthritis
1	Presence of equivocal osteophyte
2	presence of definite osteophyte without joint space narrowing;
3	presence of joint space narrowing
4	complete loss of joint space, “bone on bone” appearance

To address the limitations of the KL grading system, Menz and colleagues (13) developed the LFA to standardise the documentation and interpretation of OA in commonly affected joints of the foot. To date, the development of the LFA in 2007 is one of the most notable imaging advancements specific to foot OA (13). This atlas has led to significant improvements in the ability to consistently estimate prevalence of foot OA (167), as well as understand different patterns of foot joint involvement (226). The LFA consists of standardised dorso-plantar and lateral radiographs of five joints in the foot – the first MTPJ, the first cuneo-metatarsal joint, the second cuneo-metatarsal, the navicular-first cuneiform joint, and the talonavicular joint. Atlas images for first MTPJ joint space narrowing (dorsal projection) are shown in **Figure 3**. The LFA grading system incorporates both osteophytes and joint space narrowing to provide a quantitative means of assessing foot OA. The case definition of radiographic OA is defined if a score of 2 or

above is documented for either osteophytes or joint space narrowing, from either the dorso-plantar or lateral view. The scoring of the LFA grading system is displayed in **Table 6.** The inclusion of region-specific radiographic features of OA avoids many of the problems associated with generic tools such as the KL system (14). The LFA is more sensitive than the KL system to radiographic foot OA (248). Menz et al. (13) reported good intra-rater reliability (percentage agreement from 86.0 to 99.0% and weighted κ from 0.45 to 0.95), of the LFA and construct validity relative to foot symptoms (13, 243).

Figure 3. Example atlas images for joint space narrowing of the first MTPJ from the dorso-plantar view of the LFA.



Note: 0, grade 0; 1, grade 1; 2, grade 2; 3, grade 3.
Reprinted with permission from Menz et al. (13).

Table 6. The La Trobe Foot Atlas grading system

Osteophytes	
0	Absent
1	Small
2	Moderate
3	Severe
Joint space narrowing	
0	None
1	Definite
2	Severe
3	Joint fusion at one point

Radiographic evaluation has formed the cornerstone of imaging for first MTPJ OA and demonstrated that osteophytes and joint space narrowing (a surrogate measure for

articular cartilage loss) are characteristic features of this condition (13). However, the heterogeneous damage of the joint and associated soft tissues, which are known to contribute to pain and symptoms, cannot be visualised by radiography (288, 289). Modern imaging techniques such as USI and MRI offer new opportunities to provide further insights, as they allow for the assessment of pathology of multiple joint structures, including articular cartilage, perichondral and subchondral bone, and the joint capsule (290, 291). Although more advanced modalities, including MRI and USI, are emerging as more accurate evaluators of both bone and soft tissue abnormalities in foot OA (210, 292), it is likely that plain radiography will remain the gold standard until validity of these more advanced techniques is determined.

Magnetic Resonance Imaging

MRI has played a principal role in changing understanding of OA in recent decades when evaluating OA as a whole organ disease (29, 293). MRI has become the most widely utilised imaging tool in research to evaluate OA risk factors, identify predictors of disease progression, and assess treatment change (294). Within the foot, Halstead et al. (295) developed a preliminary Foot Osteoarthritis Magnetic Resonance Imaging Score (FOAMRIS) to evaluate OA features in the hindfoot, midfoot and first MTPJ. The preliminary FOAMRIS demonstrated good intra-reader reliability and fair inter-reader reliability when assessing the total feature scores. More recently, Munteanu and colleagues developed a MRI atlas for the assessment of first MTPJ OA (292). The atlas demonstrated excellent intra-rater and inter-rater reproducibility (292, 296). An advancement of the Munteanu et al. (292) atlas was the inclusion of pictorial representation of each MRI feature for each scoring item. Supporting images which clearly depict the grade of each feature ensured correct interpretation and enhanced reproducibility across sessions and examiners. In contrast, the preliminary FOAMRIS relied purely on text descriptions (295). Although MRI is useful in detecting the whole joint structure, its shortcomings include high costs, prolonged duration of image acquisition, and limited availability in community care, and it is contraindicated in certain conditions such as metal implants (297, 298).

Ultrasound Imaging

USI presents an alternative to plain radiography in the diagnosis of OA due to its ability to detect features present during disease progression related to both inflammation and structural damage (17, 18, 299-306). USI has gained recognition in the assessment of rheumatic diseases such as gout, rheumatoid arthritis and OA, due to its high sensitivity and ability to detect subclinical (absence of clinical symptoms)

inflammatory joint pathology (36, 307-311) and reliably quantify both bone and soft tissue abnormalities (17, 302-304, 312). USI provides the ability for real-time, dynamic and multiplanar assessment of joint pathology, allowing the examiner a unique advantage of immediate and direct correlations between the clinical picture and sonographic findings (279, 280).

USI has proved to be a reliable and valid imaging technique to assess OA features when compared with MRI (313, 314). Oo et al. (2022) demonstrated that the correlations between quantitative knee OA USI features and corresponding MRI findings were strong (ICC range = 0.85–0.98) (315). The same group assessed 89 people with knee OA to establish if USI findings were associated with radiographic and MRI findings (316). All USI scores (excluding power Doppler) were significantly correlated with KL grade. Moreover, USI findings (excluding cartilage damage) demonstrated at least moderate correlation with their MRI counterparts (316), with USI synovitis having the greatest correlation.

USI can be readily used chairside, presents a lower cost, is widely available, is not contraindicated for some patients, has no radiation exposure, and does not require intravenous contrast for assessment of active synovitis (282, 301, 317-319). The advantage is the ability of USI to depict tissue-specific morphological changes before the onset of pain and before the point of irreversible structural damage, such that USI may play a fundamental role in the earlier detection and assessment of first MTPJ OA (320). Earlier detection would provide capacity to broaden the scope and capabilities of targeted interventions to alter the progression of the disease and improve quality of life.

The use of USI to categorise OA-based change is limited by the lack of consensus of how USI can determine the degree of foot OA. A classification criterion is crucial to improve diagnostic confidence and understand the progression of first MTPJ.

USI is a rapidly evolving field and has been increasingly incorporated into clinical practice as a valuable diagnostic and monitoring tool (321-323). Although the depth of tissue penetration by ultrasound waves is limited compared to other imaging modalities, developments in USI software and transducers have advanced the resolution to better identify superficial structures, such as the first MTPJ, allowing more detailed assessment of associated pathology (17, 279, 280, 304, 312-314, 321, 324). In some instances, USI resolution is comparable to (if not better than) MRI and CT scanning (313). High resolution USI with power Doppler capability has further enhanced the diagnostic capabilities of USI by allowing quantification of inflammatory joint activity (308).

Chapter 4

Evaluation of Osteoarthritic Features in Peripheral Joints by Ultrasound Imaging: A Systematic Review

Reference

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Molyneux P, Bowen C, Ellis R, Rome K, Frecklington M, Carroll M. Evaluation of osteoarthritic features in peripheral joints by ultrasound imaging: A systematic review. *Osteoarthritis and Cartilage Open*. 2021; 3(3):100194.
https://doi.org/10.1016/j.ocarto.2021.100194

Preface

The foot is a target region for OA (210), but OA research has often overlooked the foot as a site of involvement (7, 216). Consequently, knowledge of foot OA is approximately 30 years behind that of other joints for which the research evidence is more advanced. Radiographic foot OA affects 16.7%-22% of people (6, 211), making it is as prevalent as knee OA. Despite the high prevalence and disabling nature of foot OA, no accepted classification criteria for foot OA exists. The development of a classification criteria has been limited by unclear signs and symptoms and the need for a radiographic examination for clinical confirmation (7, 227, 228). Accordingly, foot OA has been highlighted as an under-researched problem and identified as a research priority (219-222).

A significant barrier to the study of foot OA has been the lack of a foot-specific imaging-based grading system to classify the degree of pathological change in joint tissues (231). Furthermore, EULAR has highlighted the need for further imaging research into less commonly studied sites of OA, such as the foot (17). Despite significant limitations, conventional radiography has remained the preferred method for the assessment of foot OA (13). The limitation of a radiographic based classification system is the focus solely on bone changes. However, the advent of more advanced imaging techniques, including USI, has gained notable recognition in the assessment of rheumatic diseases such as gout, rheumatoid arthritis and OA, due to its high sensitivity and ability to detect subclinical inflammatory joint pathology (36, 307-311) and reliably quantify both bone and soft tissue abnormalities (17, 302-304, 312). Ongoing research in this area is crucial

in determining the capacity of USI to detect early inflammatory changes that precede osseous involvement, therefore informing more timely management approaches that aim to prevent or slow further structural progression (48-50).

With no established classification criteria for foot OA, irrespective of imaging modality, the present research needed to search for evidence to determine those commonly reported USI features for the initial foundations of an atlas and classification. This chapter reviews the current literature to determine how structural and inflammatory OA features in peripheral joints are assessed by USI. This review served as the basis of the present research and establishes which USI features are associated with OA in peripheral joints, how the features are defined, and which grading systems have been used for examining OA.

Abstract

Objective

To determine how structural and inflammatory osteoarthritis (OA) features in peripheral joints are assessed, defined, and graded by ultrasound imaging (USI).

Design

MEDLINE, CINAHL, Cochrane and SPORTDiscus were systematically searched in March 2021. To be eligible, studies needed to (1) include participants with peripheral joint OA, and (2) used grey scale USI or power Doppler (PD) to assess one or more USI features in peripheral joints of the hands and feet. Methodological quality of all included studies was assessed using the Critical Appraisal Skills Program (CASP) tool.

Results

A total of 159 citations were identified for screening. Thirty-two articles were included for final analysis and were of good methodological quality. Thirty articles evaluated USI features of hand OA and two assessed USI OA features in the foot. There were inconsistencies between studies in terms of what USI features were assessed, how these features were defined and what grading system was applied to determine degree of osteoarthritic change.

Conclusion

The review found inconsistencies in the definition of synovial pathology. Consequently, it is unclear whether synovial pathology is best represented as separate entities or combined as a single domain, termed “synovitis”. How OA USI features were defined and graded has largely been extrapolated from recommendations originally constructed for populations with rheumatoid arthritis (RA). Given the prognostic value of synovitis for OA progression and the reduced degree of inflammation experienced in OA compared to RA, the validity of applying definitions, grading systems and atlases originally developed for inflammatory arthritis needs consideration.

Introduction

Osteoarthritis (OA) is a global health burden and leading cause of chronic pain, joint stiffness, functional limitation, and disability among older adults (24, 27). OA is a degenerative joint disease and affects multiple structures; including the perichondral and subchondral bone and associated joint capsular structures (36, 37, 290, 299). Our knowledge of foot and hand OA substantially lags behind that of other joint sites, such as the knee and hip (119, 217-219), for which the research evidence is more advanced. However, foot and hand OA are also important contributors to the burden of OA and have a significant negative impact on physical mobility and health-related quality of life (6, 212, 213).

Plain radiography represents the gold standard imaging modality for the visualisation of bony change and the diagnosis of radiographic OA (13, 14). Although radiographic imaging can detect joint space narrowing and bony alterations (15), it has numerous shortcomings in diagnosing OA. At the point where structural damage is evident radiographically, joint structure and function may be significantly impaired. Once the joint has reached this point, patient outcomes and management are limited. Radiographic imaging cannot directly visualise articular cartilage or detail the soft tissue changes in and around joints (282). Radiographic findings are also poorly associated with clinical symptoms (96, 283).

Significant advances have been made in the field of imaging, allowing a more accurate evaluation of both bone and soft tissue abnormalities (17). Ultrasound imaging (USI) presents an alternative to plain radiography in the diagnosis of OA due to its ability to detect features present during disease progression, related both to inflammation and structural damage (18, 299-301, 305). USI has proved to be a reliable and valid imaging technique to assess OA features when compared with MRI (313, 314). USI can be readily used chairside, presents a lower cost, is widely available, is not contraindicated for some patients, and does not require intravenous contrast for assessment of active synovitis. USI has been shown to have high sensitivity to detect subclinical (absence of clinical symptoms) inflammatory joint pathology (36, 307) and provides excellent resolution of superficial tissues/structures (313, 314, 324). Given the ability of USI to depict tissue-specific morphological changes before the onset of pain and before the point of irreversible structural damage, USI may play a fundamental role in the earlier detection and assessment of peripheral joint OA (320). Earlier detection would provide the capacity to alter the progression of the disease and improve quality of life.

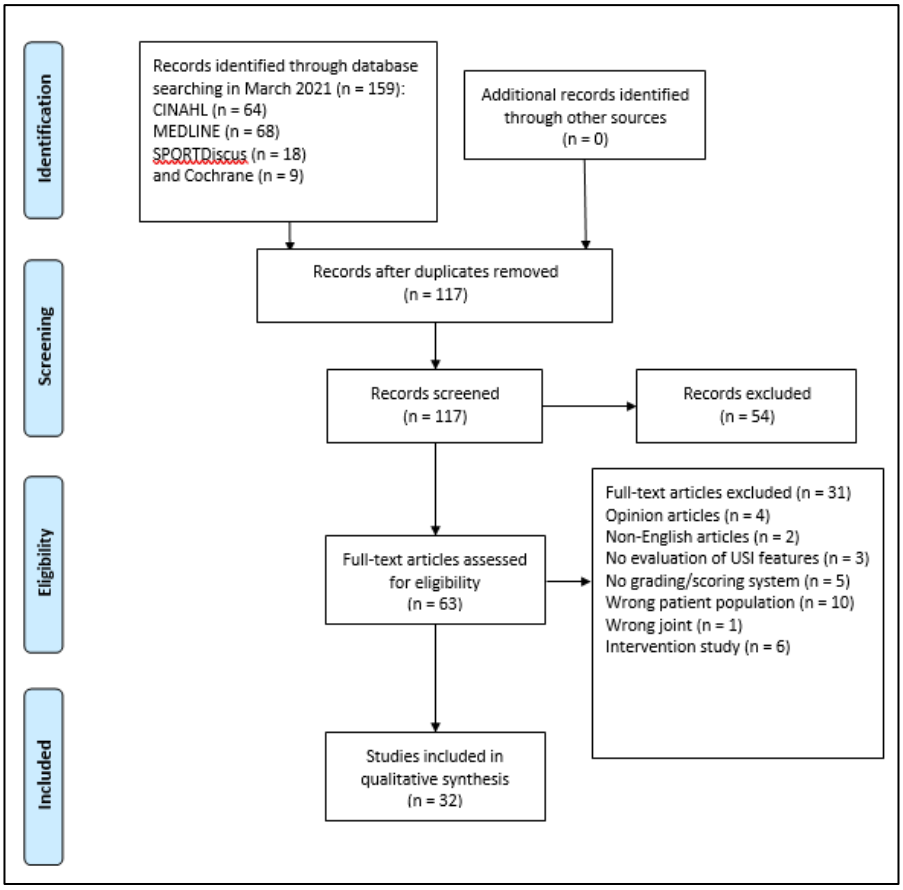
The application of USI has enhanced the understanding of the complex, multi-tissue processes underpinning the OA phenotype (325). However, the role of USI for OA diagnosis in peripheral joints has not been clearly defined. To further understand this role, the aims of this study were to critically evaluate and summarise relevant studies that have used USI to evaluate OA features in peripheral joints of the hands and feet. The primary questions investigated in the review were: What USI features are associated with OA in peripheral joints? How are USI features in peripheral joints defined and graded? What is the reliability of grading the USI features?

Methods

Search Strategy

This systematic review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (326) **(Figure 4)**.

Figure 4. PRISMA flow diagram



The identification of articles for the systematic review was completed with a comprehensive search of titles and abstracts from key electronic databases and additional records **(Table 7)**. The search was conducted between July 2020 and March

2021. The electronic databases MEDLINE, CINAHL, Cochrane and SPORTDiscus were systematically searched from their earliest record (1997) to 2021. Broad-ranging search terms were agreed on by the authors (P.M and M.C). A secondary search was performed to address publication bias by searching the Open Grey literature (to search for unpublished literature and ongoing trials) and Google Scholar (327). All titles and abstracts identified from the search were downloaded into EndNote version X9 (Thomson Reuters, Philadelphia, PA USA).

Table 7. Search strategy

MEDLINE, CINAHL, Cochrane and SPORTDiscus		
1	Subject term	Osteoarthritis
2	Keywords	Foot or feet or hand
3	Subject term	Ultrasonography
4	Keywords	Ultrasonograph* or Sonograph* or Ultrasound or US or MSUS or Doppler or power Doppler or PDUS or Colour Doppler or Elastograph*
5	Keywords	Features or Characteristics or Osteophyte or Synovitis or Cartilage or Effusion or synovial hypertrophy or Erosion or Vascularisation or Neovascularisation
6	Keywords	Atlas or Grad* or Scor*or severity or assess* or evaluat*
7	Combine	1 and 2
8	Combine	3 and 4
9	Combine	5 and 6
10	Combine	7 and 8 and 9

Inclusion and Exclusion Criteria

The studies were cross-referenced with duplicates removed. The retrieved articles were imported into Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia (328). In the first stage of selection the titles and abstracts were independently screened by P.M and M.C. Subsequently, the full texts of the selected articles were retrieved and judged against the inclusion and exclusion criteria **(Table 8)**. The selected studies were discussed between authors until consensus for inclusion was achieved. In cases of non-consensus, a third author's opinion was planned for consultation; however, this was not required. The eligibility criteria were initially applied to all titles and abstracts, and later to full-text articles if more detail was required. All studies that met the inclusion, had their reference lists hand searched for further included articles. When the included studies referred to a previous paper for methodology or reliability, that paper was accessed, and appraised for inclusion against the selection criteria. This systematic review was registered with the international database of prospectively registered systematic reviews in health and social care (PROSPERO), registration number CRD42021199396.

Table 8. Eligibility criteria

Inclusion criteria:
• participants were over 18 years old • participants (cases) with osteoarthritis, defined by either radiographically confirmed osteoarthritis, patient reported osteoarthritis, or clinical diagnosis • they used grey scale ultrasound imaging or power Doppler to assess one or more ultrasound imaging features in peripheral joints of the hand and feet
Exclusion criteria:
• were unpublished; non-peer-reviewed; do not involve humans; are in vitro studies; opinion articles; letters to the editor; non-English articles and abstracts • included participants with inflammatory arthritis or a neurological, endocrine or metabolic disorder. • only evaluated ultrasound imaging features evaluated in other joints, aside from those of the hands and feet • studies that utilised ultrasonography only for guiding injections and did not report any USI feature data or findings of the ultrasonography examination

Methodological Quality Assessment

The methodological quality of included articles was appraised independently by two reviewers (PM, MF) using the Critical Appraisal Skills Program (CASP) case control and cohort checklists (329). The CASP tools are succinct and effectively cover the areas needed for critical appraisal of evidence (330). The cohort and case control checklists comprise a series of 12 and 11 questions, respectively. Completion of the checklists provides a systematic and comprehensive way of appraising studies to determine whether their findings are valid, accurate and meaningful at a local level. Each criterion was weighted by applying a three-point scale; No = criterion not met (0 points); Yes = criterion totally met (1 point); Can't tell = criterion partially met (C/T). A total score was generated out of 14 points for cohort studies and a total of 12 points for case control studies. A consensus meeting was held to resolve any disagreement between the reviewers. Following methodological assessment, articles were grouped and discussed according to USI feature, definition, and applied grading system.

Data Extraction

The following information was extracted from all included studies: study characteristics; author's name, year of publication, study design and aim(s), and outcome measure(s) reported. Participant characteristics including sample size, gender, mean age (years), mean BMI ($kg.m^{-2}$), and symptom duration were also extracted **(Appendix 1).** Additionally, the following USI measurement techniques were extracted: what OA features were imaged, how the USI features were graded (dichotomous or on a

semiquantitative scale), if an USI atlas was used, the sonographer(s) involved in the assessment, and all reliability data that were recorded **(Appendix 2**).

Results

Selection and Characteristics of Studies

A total of 159 citations were identified for screening with 32 articles included for final analysis. Thirty articles evaluated USI features of hand OA (18, 48-50, 313, 331-355) and two assessed USI OA features in the foot (210, 356). Twenty-seven hand OA studies assessed the proximal and distal interphalangeal joints (18, 48-50, 313, 331, 332, 335-347, 349-355), 22 studies assessed the metacarpophalangeal and carpometacarpal joints (18, 49, 50, 313, 332-336, 340-343, 346-352, 354, 355), and four studies assessed the first interphalangeal joint (49, 336, 340, 341). With regards to the two-foot studies, both assessed USI OA features in the first metatarsophalangeal joint (MTPJ) and the midfoot (210, 356). One study evaluated and graded the midfoot joints as a single joint complex (210) and one evaluated and graded each joint at the midfoot and forefoot level (356).

A total of 3069 participants were reported (654 male, 2330 female) of which 2952 were diagnosed with peripheral joint OA. Sex was not reported in two studies, involving eighty-five participants (336, 350). The mean age of participants ranged from 51.1 to 74.5 years old. Mean BMI was reported in 16 studies and ranged from 24.9 kg/m^2 to 28.4 kg/m^2. Eleven studies reported disease duration (range, 3.2 to 18.5 years). Ethnicity of the study population was reported by one study(337). Five studies delineated separate OA sub-groups as erosive and non-erosive hand OA (48, 338, 345, 346, 349). All included studies were observational studies published after 2008, 26 were cohort and six were case-control studies. The aims, participant characteristics and how peripheral joint OA was defined of all included studies are presented in **Appendix 1**. Meta-analyses were not deemed appropriate based on the variation in features imaged, specific joints that were imaged and how USI features were defined and graded.

Quality Assessment of Studies

The quality scores for the included cohort studies ranged from 4 to 14/14 on the CASP quality checklist. The quality scores for the included case control studies ranged from 5 to 8/12 on the CASP quality checklist. The quality of all included studies was summarised in a table format **(Appendix 3).** Due to the exclusion of intervention studies, questions related to treatment effect were not applicable.

USI Features Associated with OA

There was wide variation across all studies in relation to what USI features were assessed. The following inflammatory USI features were investigated by the included studies: synovitis, synovial hypertrophy, joint effusion, tenosynovitis, and power Doppler (PD) signal. PD signal was the most reported USI feature across all studies (n=24) (18, 48, 49, 210, 331-334, 337-341, 343-345, 347, 349, 350, 352-356). There were also inconsistencies between the different entities of synovial pathology, making comparison between studies difficult. Of the 32 studies included in the review, 16 assessed synovitis (18, 331-333, 335, 338, 340, 344, 346, 347, 349, 350, 352-355), of which eight studies combined joint effusion and synovial hypertrophy as a single domain, termed “synovitis” (18, 333, 340, 342, 344, 349, 350, 352), whereas five studies assessed synovitis and joint effusion as separate entities (340, 346, 347, 353, 354). Furthermore, several studies clearly differentiated between synovial hypertrophy and joint effusion; with 14 studies having assessed joint effusion (48, 49, 210, 334, 339-341, 343, 345-347, 354, 356) and 12 studies assessed synovial hypertrophy (48, 49, 210, 334, 337, 339-341, 343, 345, 353, 354, 356) as separate entities (USI features). Tenosynovitis was reported by two studies (346, 347). OA features indicative of structural damage included osteophytes, which were reported in 18 studies (50, 210, 313, 332, 333, 336, 341, 342, 344-347, 350-352, 354-356) joint erosions, reported in seven studies (48, 332, 333, 344, 346, 347, 354), cartilage breakdown, reported in five studies (50, 210, 344, 348, 349), and joint space narrowing reported in three studies (344, 350, 351).

Defining USI Features Associated with OA

Definitions of USI features for all included studies are presented in **Table 9**. There was no consistent use of USI definitions used to define each USI feature associated with OA. Common inconsistencies were evident between individual studies interpretation of the different entities of synovial pathology. How individual studies differentiated synovitis, joint effusion and synovial hypertrophy as either a single or combined entity determined how that feature was defined. Definitions of the imaging appearance of the USI features were provided in 23 studies (18, 48, 50, 210, 313, 332, 338, 340, 342-351, 353-357). Only 16 of those studies included a definition for each USI feature evaluated, of which four studies referred to a previous study for definition of pathology (48, 332, 340, 354) **(Appendix 2).** Eight studies did not define any of the USI features evaluated (49, 331, 334-337, 339, 341).

Table 9. Defining and of grading of OA features using USI

USI features	Definition	Grading system		
		Semiquantitative	Dichotomous (present or absent)	Continuous (mm)
Osteophytes	Cortical protrusion >1 mm at the end of the normal bone contour or at the margin of the joint (50, 313, 333, 342, 344, 346, 347, 350, 351, 355, 356)	(50, 210, 313, 333, 336, 341, 345, 350, 352)	(332, 342, 344, 346, 347, 350, 354, 355)	NR
Erosions	Irregularity of the hyperechoic cortical bone, evident in two perpendicular planes (48, 333, 347, 354)	NR	(332, 346, 347, 354)	NR
Articular cartilage damage	Loss of the normal sharpness of cartilage interfaces, irregularities/ thinning of the margins and/or increased echogenicity of the cartilage (210, 344, 348)	(50)	(210, 344, 348)	(349)
Synovitis	Distension of the joint capsule ≥1.5 mm in its anteroposterior diameter with compressible material (338, 344). A composite of effusion and synovial thickening (18, 333, 340, 349-351)	(18, 331-333, 338, 340, 350-352, 354)	(335, 344, 346, 347, 349, 350)	NR
Synovial hypertrophy	Abnormal hypoechoic intraarticular tissue or thickening of the synovial membrane that is non-displaceable and poorly compressible and is often associated with increased vascularity (333, 340, 343)	(49, 334, 337, 339-341, 343, 345)	(48, 210, 354, 356)	NR
Joint effusion	Abnormal hypoechoic or anechoic intra-articular material that is displaceable and compressible but does not exhibit power Doppler signal (48, 333, 340, 345-347, 353, 356)	(18, 49, 334, 340, 341, 343, 345, 353)	(48, 210, 346, 347, 354, 356)	NR
Power Doppler activity	A pulsating colour spot found within the synovial structure, which represented presence of vascularisation (18, 48, 333, 338, 340, 343, 344, 350, 351, 353, 354)	(18, 49, 50, 210, 331, 332, 334, 337, 338, 340, 341, 343, 345, 350-354)	(48, 331, 333, 344, 347, 349, 356)	NR
Joint space narrowing	Decrease in the space between the cortical margins (344, 350, 351)	NR	(344, 350, 351)	NR
Tenosynovitis	A hypoechoic rim around tendon with or without PD signal (346, 347)	NR	(346, 347)	NR

NR, Not reported

Grading USI Features Associated with OA

A summary of how each USI feature was graded in the 32 reviewed studies is presented in **Table 9**. There was also no consistent way in which each USI feature was graded to classify the degree of pathological change in joint tissue. The variation between studies made comparison difficult and leaves grading of USI features open to interpretation. The grading systems applied were either dichotomous, semiquantitative, or continuous. The majority of studies applied a previously developed grading system to evaluate each USI OA feature. **Table 10** outlines studies that cited a previously developed grading system.

Table 10. Origin of grading system applied to evaluate USI OA features

Sonographic feature	**Origin of grading system** (number of studies which applied a grading system)				
	Semiquantitative		Dichotomous (present or absent)		Continuous (mm)
	Grading system referenced	Studies that referenced system	Grading system referenced	Studies that referenced system	
Osteophytes	4x Mathiessen (313) 2x Keen (350) 1x Kortekaas (340) 1x Hammer (358)	(50, 210, 333, 336) (313, 352) (341) (313)	1x Keen (350)	(355)	NR
Erosions	NR	NR	1x Wakefield (319)	(354)	NR
Articular cartilage damage	NR	NR	1x Iagnocco (348)	(210)	NR
Synovitis	5x Keen (350) 2x Hammer (358) 1x Terslev (359) 1x Mandl (360) 1x Mathiessen (313)	(331, 333, 340, 351, 352) (18, 338) (332) (354) (18)	1x Hammer (358) 1x Keen (350) 1x Wakefield (319)	(335) (349) (350)	NR
Synovial hypertrophy	5x Kortekaas (340) 2x Szkudlarek (361) 2x Keen (2008) (350) 1x D'Agostino (362) 1x Mandl [89]	(49, 334, 339, 341, 343) (337, 345) (333, 340) (210) (354)	1x Terslev (359) 1x Wakefield (319)	(210) (48)	NR
Joint effusion	5x Kortekaas (340) 2x Szkudlarek (361) 1x Mandl [89] 1x Keen (350)	(49, 334, 339, 341, 343) (345, 353) (354) (340)	1x Terslev (359) 1x Wakefield (319)	(210) (48)	NR
Power Doppler activity	5x Kortekaas (340) 4x Keen (350) 2x Hammer (358) 1x Terslev (359) 1x Mandl (360) 1x Szkudlarek (361) 1x D'Agostino (362)	(49, 334, 339, 341, 343) (331, 340, 351, 352) (336, 338) (332) (354) (337) (210)	2x Wakefield (319) 1x Keen (350)	(48, 333) (350)	NR
Joint space narrowing	NR	NR	NR	NR	NR
Tenosynovitis	NR	NR	NR	NR	NR

Use of an USI Atlas

Of the 32 studies included, six reported using an USI atlas to assist with grading of USI features (18, 50, 313, 333, 335, 338). Across the six studies, six different USI features were assessed. An USI atlas was only used as a reference to evaluate synovitis, PD activity, cartilage damage and osteophytes. Three studies (18, 335, 338), applied the same USI atlas that was originally developed to assess synovitis in RA (358). One study developed an original USI atlas to grade osteophytes in finger joints (313), which was later used by two studies to grade severity of finger joint osteophytes (50, 333). The later study also developed a new USI atlas to grade cartilage (50). Hammer et al. (50) was the only included study that used multiple USI atlases to assist grading of all features evaluated. Neither foot study used an USI atlas to assist grading.

Reliability of Grading USI Features

Twenty studies evaluated reliability of grading USI features (18, 48-50, 210, 313, 331, 333, 337, 340-342, 345-351, 355). The reliability of grading PD signal and osteophytes were the most commonly evaluated features. Seventeen studies assessed intra-rater reliability of grading USI features (18, 48-50, 210, 313, 333, 337, 340, 341, 345, 347-351, 355) and nine assessed inter-rater reliability of grading USI features (18, 50, 210, 313, 331, 337, 342, 348, 350). Data was predominantly assessed by Kappa statistics and four studies assessed data by intra-class correlation coefficients (ICC) (49, 340, 341, 345). One study assessed agreement between USI and magnetic resonance imaging (MRI) (346). **Appendix 4** outlines which studies assessed reliability for each USI feature, which grading system was applied to each feature, what type of reliability was evaluated, and the sonographer(s) involved in the assessment.

Discussion

This review investigated what USI features were associated with OA in peripheral joints, how these features were defined and graded, and the reliability of assessing USI features. There were inconsistencies between studies in terms of what USI features were assessed (synovitis, synovial hypertrophy, joint effusion, tenosynovitis, PD signal, osteophytes, joint erosions, cartilage breakdown, and joint space narrowing), how these features were defined and what type of grading system (dichotomous, semiquantitative, or continuous) was applied to determine degree of osteoarthritic change. The methodological quality of the included studies as assessed by the CASP tool, demonstrated that only three of the 32 studies met all the checklist criteria, with eight studies scored at 50% or less of the criteria.

OA is characterised by both structural damage and inflammatory abnormalities (290, 356). USI enables evaluation of articular cartilage, bone, and soft tissue (17, 302-304, 363). The traditional view of OA as a cartilage-only disease is obsolete and attention has now turned to the prognostic value and role of synovitis (35). Several studies have demonstrated an association between active synovitis and structural OA progression (18, 48, 49, 339). This association indicates that USI could identify those patients, or those joints at greatest risk for progression and provide capacity for earlier detection and assessment of OA-related change in peripheral joints. Mathiessen et al. (18) highlighted the importance of USI to obtain an early diagnosis showing that USI could detect inflammatory changes five years earlier than what could be seen radiographically. Kortekaas et al. (49) presented similar findings in hand OA, where osteophytes and joint space narrowing progression were often preceded by PD activity and synovitis. The synovial inflammation exhibited in early OA suggests a window of opportunity may exist for interventions targeting the inflammatory processes (364), thus providing the ability to intervene before irreversible structural damage occurs (208, 209, 365). However, the use of USI to categorise OA-based change is limited by inconsistencies and the lack of consensus as to which USI features should specifically be evaluated to diagnose and grade peripheral joint OA.

Defining USI features also remains inconsistent as there are no universally accepted definitions for USI features in OA. The OMERACT ultrasound working group have recommended provisional definitions of USI features considered to represent inflammatory arthritis (319). Despite the fact that OA is considered a non-inflammatory disorder, as the leukocyte count is below the threshold that defines inflammatory disorders (207), OMERACT ultrasound definitions were applied to OA in some studies (48, 313, 333, 345, 349, 350, 353-356), but not consistently. In terms of defining OA USI features the key inconsistency identified in the review was between the different entities of synovial pathology indicative of inflammation. There were discrepancies across studies in terms of how synovitis, synovial hypertrophy and joint effusion were defined and categorised as USI features. Consequently, it is unclear whether synovial pathology is best represented as separate entities (joint effusion and synovial hypertrophy) or combined as a single domain, termed “synovitis”. The OMERACT ultrasound group recently proposed a new definition of synovitis detected by USI, which encompasses the whole concept of synovitis, “presence of a hypoechoic synovial hypertrophy regardless of the presence of effusion or any grade of Doppler signal” (366). Due to the recent publication of this study, none of the studies included in this review applied the revised OMERACT definition.

No study reported following an international consensus-based standard for grading OA features. There was no clear consensus as to which type of grading system (dichotomous or semiquantitative) should be applied for specific USI features of peripheral joint OA. While dichotomous scoring may be viewed as a simpler method to distinguish between the absence or presence of a feature, it presents no mechanism to determine the progression of peripheral joint OA. Alternatively, semiquantitative systems do enable quantification of disease progression and provide further insight into the degree of osteoarthritic change. However, semiquantitative grading systems applied to OA were adopted from those originally designed and validated to quantify inflammatory change in rheumatoid arthritis (RA). This assumes that inflammatory pathology is only quantitatively but not qualitatively different between RA and OA (357, 367). Issues related to the subjectivity of semiquantitative systems have also been highlighted, with studies reporting challenges in interpretation and differentiation between grades (331). In particular, the low frequency of inflammatory pathology that is graded as severe on a semiquantitative system, may be reflective of the reduced degree of inflammation experienced in OA compared to RA (49, 331). This reinforces the need for OA-specific grading systems that truly depict the disease progression of peripheral joint OA.

An USI atlas permits the sonographer to have a direct comparison between the detected USI features and examples of defined graded images in the atlas, reducing the degree of subjectivity related to grading (50). Previously published studies have emphasised the need for the development of an USI atlas to accompany protocols (368), due to variability in image interpretation (357, 369). This review demonstrated that the use of a USI atlas to aid grading of USI features in peripheral joints was limited. Significantly, an USI atlas which depicts and quantifies the degree of structural and inflammatory change for multiple peripheral joint OA features has not been developed. The review also found that atlas use is limited by two factors. First, despite most studies assessing multiple USI features, no study included an atlas that graded more than one USI feature. Second, USI atlases used to grade OA have been extrapolated from atlases originally developed to grade USI features in RA.

The variation in intra-rater and inter-rater reliability from poor to excellent across all studies is attributable to several factors including what USI features were evaluated, variation in how each USI feature was defined, variation in the type of grading system applied, whether an USI atlas was utilised, the use of multiple sonographers involved in the assessment, and the academic background and/or experience of the sonographers. There is a general opinion that USI is heavily operator dependent for image acquisition

and interpretation (370). However, USI has previously demonstrated a strong correlation with MRI in principal OA features (357). USI has been shown to be as reliable as other imaging modalities when a standardised USI acquisition protocol and grading systems is used (370).

This systematic review is not without limitations. Potential sources of heterogeneity include differences in diagnostic criteria, populations, and case definitions, this variation limited the ability to perform meta-analysis. All relevant studies were included in this systematic review, regardless of methodological quality. We restricted the search to studies published in English. Inclusion of data from non-English language studies may alter the outcomes. We excluded studies that included participants with inflammatory arthritis even as a comparator group. Inclusion of participants with RA as a comparator group may have provided more insight or enabled a stronger comparison between grades of inflammation and allowed the direct comparison between definitions and grading systems applied.

Future USI studies of peripheral joints will be improved by including more ethnic and age diverse populations, and assessment of changes in asymptomatic healthy controls as well as those who are symptomatic or have radiographic change. The prevalence and burden of OA is not uniform across demographic groups. However, there is a dearth of research examining ethnic differences in peripheral joint OA. Minority populations, especially African American, Hispanic, Māori and Pasifika experience poorer health outcomes (such as pain and disability). Future research should proactively recruit an ethnic diverse population to ensure there is adequate data to undertake an ethnic specific analysis and examine what factors are contributing to these disparities. Future studies should include 3D USI to provide further diagnostic information and allow quantification of osteoarthritic change. 3D USI provides numerous advantages including visualisation of the coronal plane, image reconstruction, reduced scanning time and limits the influence the sonographers experience has on image acquisition. This would be of particular interest for the determination of the extent of peripheral joint synovitis. Standardisation is also required regarding imaging acquisition protocols, definitions, grading systems, and USI atlases. These items align with the recently developed EULAR USI recommendation checklist to ensure transparent and comprehensive reporting of USI research in rheumatic and musculoskeletal diseases (371). Addressing these inconsistencies in USI research will considerably improve the interpretability, reproducibility and generalisability of the study results (371). USI holds significant promise as a diagnostic tool in OA, providing prognostic information as well as advancing clinical decision making to reduce the burden of peripheral joint OA. As indicated by the

review there is a dearth of USI research related to foot OA, consequently more foot specific USI research is required to understand the progression of foot OA.

Conclusion

USI presents an alternative to plain radiography for the imaging-based diagnosis of peripheral joint OA. However, no standardised USI grading system exists to classify and grade the disease process. This review has demonstrated the large degree of variation in what OA features were assessed, how features were defined, and what graded system was applied. The key inconsistency identified was between the different entities of synovial pathology indicative of inflammation. Consequently, it is unclear whether synovial pathology is best represented as separate entities or combined as a single domain, termed “synovitis”. How OA features were defined and graded has largely been extrapolated from recommendations originally constructed for populations with RA. Given the prognostic value of synovitis for OA progression and the reduced degree of inflammation experienced in OA compared to RA, the validity of applying definitions, grading systems and atlases originally developed for inflammatory arthritis needs consideration. This review strengthens the case for further refinement and validation of OA definitions, grading systems and USI atlases specific to peripheral joints.

Brief Update Since Publication

Since publication of this systematic review, up to the 6th of November 2023, six studies have been published that met the inclusion criteria. All used USI to evaluate OA features in the joints of the hands. Since the review, no new foot studies that used USI to evaluate OA have been published. Extracted USI characteristics are presented in **Table 11**. The additional six studies demonstrated inconsistencies in the USI features assessed, the definition of these features, and the type of grading system used to determine degree of osteoarthritic change.

Table 11. Defining and grading sonographic features of OA

Author	Joint	US feature	Definition	Atlas included	Grading system	US acquisition protocol	Sonographer
Eymard (2022) (372)	Hand: PIPs 2-5 DIPs 2-5	Synovitis	According to US OMERACT criteria (319)	NR	Semiquantitative (0-3) (319)	Dorsal surface, longitudinal and transverse views	Two rheumatologist with >10 years' experience
		Effusion					
		Osteophytes					
		Erosions	Intraarticular discontinuity of the bone surface that was visible in two perpendicular planes		Present or absent		
Gasperi (2022) (373)	Hand: CMC 1 MCP 1-5 DIP 2-5 PIP 1-5	Erosions	Referenced previous definitions (374)	NR	0 = no change 1 = horizontal cortical break of 0-1mm 2 = horizontal cortical break of 1.1-2mm 3 = horizontal cortical break >2mm	Dorsal surface, longitudinal and transverse views	Two rheumatologist with 5-8 years' experience
		Osteophytes			0 = none 1 = minor 2 = moderate 3 = major (313)		
		GS synovitis			0 = none, 1 = mild, 2 = moderate, 3 = severe (50)		
Steen Pettersen (2022) (375)	Hand: CMC 1 MCP 1-5 DIP 2-5 PIP 1-5	GS synovitis	NR	NR	Semiquantitative (0-3) (350)	Dorsal surface in the longitudinal plane. Transverse scanning was carried out when presence of pathology was uncertain	Trained medical student
		PD activity					
Mathiessen (2021) (376)	Hand: CMC 1 MCP 1-5 DIP 2-5 PIP 1-5	Joint effusion	Abnormal hypoechoic or anechoic intraarticular material that is displaceable and compressible, but does not exhibit Doppler signal (1)	Developed their own USI atlas for hand OA	0–3, scored relative to the maximal size of effusion 0 = none, 1 = minimal, 2 = moderate, 3 = severe	Dorsal and palmer surface, longitudinal and transverse views	Six sonographers
		Synovial hypertrophy	Abnormal hypoechoic intraarticular tissue that is nondisplaceable and poorly compressible and which may exhibit Doppler signal (1)		0 = none 1 = minimal (up to the level of the horizontal line connecting bone surfaces of the joint) 2 = moderate (extending beyond joint line but with upper surface concave or flat) 3 = severe (extending beyond joint line but with upper surface convex)		
		PD Signal	Flow signal in the synovium; must be detected within synovial hypertrophy to be considered as a sign of synovitis (374)		0 = no flow in the synovium 1 = minor (single vessel signals ≥1) 2 = moderate (confluent vessel signals in less than half of the area of the synovium)		

					3 = major (vessel signals in more than half of the area of the synovium)		
		Osteophytes	A clear, step-up cortical prominence at the bony margin that is visible in 2 perpendicular planes (366)		0–3, severity scored relative to largest osteophyte is scored: 0 = none, 1 = minor, 2 = moderate, 3 = major		
		Cartilage damage	Normal cartilage has a sharp interphase (white band) on its margins perpendicular to the probe; loss of sharpness occurs when cartilage interphase is not visible; complete loss when cartilage cannot be visualized		0 = normal cartilage 1 = focal or complete thinning of cartilage, or loss of sharpness of at least 1 cartilage margin 2 = focal or complete loss of cartilage		
Mattap (2021) (377)	Hand: CMC 1 MCP 1-5 DIP 2-5 PIP 1-5	Osteophytes	Cortical protrusions seen in both the longitudinal and transverse plane (350)	NR	0 = no pathology 1 = mild pathology 2 = moderate pathology 3 = severe pathology (350)	Dorsal surface, longitudinal and transverse views	Experienced sonographer
		GS Synovitis	A composite of both effusion and synovial hypertrophy (350)				
		PD Synovitis	Power Doppler signal identified within the synovium of the area of grey scale synovitis (350)		0 = no PDI signal within the synovium adjacent to the joint 1 = minimal PDI signal 2 = moderate signal 3 = marked evidence of PDI signal (350)		
Shi (2021)	Hand: CMC 1	Effusion	presence of hypoechoic or anechoic fully compressible materials, and synovial hypertrophy was defined as the presence of echogenic or hypoechoic slightly compressible or non-compressible intra-articular tissues (358)	NR	present/absent	Dorsal and palmer surface, longitudinal and transverse views	Sonographer with 6 years of experience
		Synovitis	The presence of synovial hypertrophy and effusion was considered together as “synovitis” (350)		0-3 scale (absent, mild, moderate and severe)		
		PD Signal	Pulsating color spot within the synovial structure (319)		present/absent		
		Osteophytes	Cortical protrusions at the joint margin seen in two planes (319)	Atlas reported by Mathiessen et al (313)	Semiquantitative (0-3)		

US, Ultrasound; OA, Osteoarthritis; MTPJ, metatarsophalangeal joint; PIP, Proximal interphalangeal joint; DIP, Distal interphalangeal joint; CMC, Carpometacarpal joint; MCP, metacarpophalangeal joint; MSK, Musculoskeletal; PD, power Doppler; OMERACT, Outcome Measures in Rheumatology; NR, Not reported; NA, Not applicable.

Chapter 5

Ultrasound Imaging Acquisition Procedures for Evaluating the First Metatarsophalangeal Joint: A Scoping Review

Reference

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Preface

No standardised USI procedure has been reported for examining OA in any body region, including the foot. Within the foot, the first MTPJ is the most commonly reported affected foot joint, providing a logical joint to commence USI investigation and procedure development. The review in Chapter 4 provided the foundation work to establish which USI may be indicative of first MTPJ OA. However, the systematic review also identified large variation in the different USI features reported, their definition and how they are identified. Furthermore, much of what is reported has been extrapolated largely from recommendations originally constructed from other forms of arthritis. USI features aside from those focussed on articular cartilage also appear critical, for example synovial inflammation.

The successful reproducibility and validity of USI studies evaluating pathologies affecting the first MTPJ require a standardised acquisition procedure that is comprehensively reported. A criticism of USI is that image acquisition and interpretation are operator-dependent and consequently create variation across studies. That variation has been attributed to several factors, including which USI features were evaluated, how each USI feature was defined, what type of grading system applied, whether a USI atlas was used, that multiple sonographers were involved in the assessment, and the academic background and/or experience of the sonographers. Despite these variations, USI has been shown to be as reliable as other imaging modalities for detecting OA features when

a standardised USI acquisition procedure is used. To ensure a standardised procedure, numerous variables must be considered as part of the USI acquisition procedure (e.g., patient positioning, transducer orientation, and surfaces scanned). The number of components involved in image acquisition raises the need to review USI acquisition procedures and guidelines used for examining the first MTPJ. The article reproduced in Chapter 5 analyses components of the USI acquisition procedures used to assess the first MTPJ, determine if published guidelines were reported to inform procedures, and ascertain if guidelines were adhered to.

Abstract

The aim of this scoping review was to investigate ultrasound imaging (USI) acquisition procedures and guidelines used to assess the first metatarsophalangeal joint (MTPJ). MEDLINE, CINAHL, AMED and SPORTDiscus were systematically searched in May 2021. Studies were included if they used grey scale USI or power Doppler and reported an USI procedure to assess the first MTPJ. Screening and data extraction were performed by two independent assessors. The scoping review was reported in accordance with the PRISMA (ScR) extension for scoping reviews. A total of 403 citations were identified for screening, with 36 articles included in the final analysis. There was wide variation in USI acquisition procedures used to evaluate the first MTPJ. Inconsistencies in reporting may be attributable to the number of elements the USI acquisition procedure encompasses, which include the model of the USI device, the type of transducer, USI modalities and settings, patient position, transducer orientation, surfaces scanned, and the scanning technique used. The review found inconsistencies against international guidelines and limited implementation of consensus-based recommendations to guide image acquisition. Current guidelines require further refinement of anatomical reference points to establish a standardised USI acquisition procedure; subsequently improving interpretability and reproducibility between USI studies that evaluate the first MTPJ.

Introduction

Foot pain is one of the most common presenting complaints in adults (378-382), with a prevalence estimated between 13% and 36% across several international population-based cohorts (261). Foot pain adversely affects physical function and quality of life, and places a significant burden on both individuals and healthcare systems (383, 384). Within the foot, the prevalence of degenerative disease in the first metatarsophalangeal joint (MTPJ) is second to that of knee osteoarthritis (OA) (385, 386). The first MTPJ is the most commonly affected joint in the foot in people with gout and OA (226, 387), and epidemiological data suggest that its incidence is increasing (70, 388, 389). People with gout and first MTPJ OA exhibit localised joint pain, structural and functional changes, and experience a significant negative impact on physical mobility and health-related quality of life (6, 213, 390).

Musculoskeletal ultrasound imaging (USI) has gained notable recognition in the assessment of rheumatic diseases such as gout, rheumatoid arthritis, and OA due to its ability to detect subclinical (absence of clinical symptoms) inflammatory joint pathology (307-310), and reliably quantify both bone and soft tissue abnormalities (17, 302-304, 312). USI provides the ability for real-time, dynamic and multiplanar assessment of joint pathology, allowing the examiner a unique advantage of immediate and direct correlations between the clinical picture and sonographic findings (279, 280).

USI is a rapidly evolving field and has been increasingly incorporated into clinical practice as a valuable diagnostic and monitoring tool (321-323). Developments in USI software and transducers have advanced the resolution to better identify structures, such as the first MTPJ, allowing more detailed assessment of pathology (17, 279, 280, 304, 312, 321). High resolution USI with power Doppler capability has further enhanced the diagnostic capabilities of USI by allowing quantification of inflammatory joint activity (308). However, there are numerous variables that need to be considered as part of the USI acquisition procedure, these include: the brand and model of the USI device (including transducer/s), USI modalities and settings, patient positioning, transducer orientation, surfaces scanned, and scanning technique. The number of components involved in image acquisition raise the need for evidence-based guidelines to outline a standardised USI acquisition procedure to evaluate the first MTPJ. A standardised procedure will increase reliability, validity and enable comparison amongst studies (391).

The European League Against Rheumatism (EULAR) task force of world leading rheumatologists, experts in musculoskeletal USI, developed the first guidelines for the

use of USI in rheumatology in 2001. The EULAR guidelines included vague instructions on body position, transducer orientation and surfaces of the first MTPJ to scan (324). These guidelines set the technical standards for the use of USI. The widespread uptake of USI, technological advancements, and need for evidence-based imaging, necessitated an update of these guidelines. Consequently, in 2017 a new EULAR-endorsed task force revised the standardised procedures for USI in rheumatology (279). The updated EULAR guidelines for performing USI of the first MTPJ address transducer orientation and position (starting point), surfaces scanned and scanning technique (279). Despite this enhancement, the revised guidelines still lack sufficient detail outlining specific anatomical reference points to ensure a standardised USI acquisition procedure. Further refinement of anatomical landmarks to guide probe positioning is still required to improve interpretability and reproducibility between studies. Current guidelines have overlooked how the USI acquisition procedure may need to be adapted to accommodate severe structural changes often associated with rheumatic diseases.

The successful reproducibility and validity of USI studies evaluating pathologies affecting the first MTPJ requires a standardised acquisition procedure that is comprehensively reported. Despite the well-recognised susceptibility and burden of first MTPJ pathologies, a published synthesis of an USI acquisition procedure has yet to be undertaken. The aims of this review were to analyse components of USI acquisition procedures used to assess the first MTPJ, determine if published guidelines were reported to inform procedures and ascertain if guidelines were adhered to.

Methods

The framework proposed by Arksey and O'Malley (392) was used to guide the scoping review methodology. This method involves five stages: identifying the research question, identifying relevant studies, selecting studies, charting the data, and collating, summarising, and reporting the results (392). To ensure methodological quality and transparent reporting, this scoping review has been reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for scoping reviews (PRISMA-ScR) (**Appendix 5)** (393).

Search Strategy

The identification of articles for the scoping review was completed with a comprehensive search of titles and abstracts of key electronic databases **(Table 12)**. The search was conducted between 14th April and 10th May 2021. The electronic databases MEDLINE, CINAHL, AMED and SPORTDiscus were systematically searched from their earliest

record (1955) to 2021. Broad-ranging search terms were agreed on by two of the authors (P.M and M.C). All titles and abstracts identified from the search were downloaded into EndNote version X8 (Thomson Reuters, Philadelphia, PA USA). The articles were cross-referenced with duplicates removed.

Table 12. Search strategy

MEDLINE, CINAHL, Cochrane and SPORTDiscus		
1	Subject term	Ultrasonography
2	Keywords	Ultrasonograph* or Sonograph* or Ultrasound or US or MSUS or Doppler or Power Doppler or PDUS or Colour Doppler or Elastograph*
3	Subject term	'Metatarsophalangeal joint'
4	Keywords	'Metatarsophalangeal joint' OR MTP* OR Hallux OR Toe
5	Keywords	Protocol OR acquisition OR procedure OR process OR exam* OR Position OR Scanning OR technique* OR guideline* OR Recommendation* OR approach
6	Combine	1 OR 2
7	Combine	3 OR 4
8	Combine	5 AND 6
9	Combine	6 AND 7 AND 8

Selection Criteria

Original articles that included USI of the first MTPJ that detailed the acquisition procedure were included. In the first stage of selection, the titles and abstracts were independently screened by two of the authors (PM and AJ). The full texts of the selected articles were retrieved and assessed against the eligibility criteria. Articles were included if they: used grey scale USI or power Doppler to assess the first MTPJ; reported the USI procedure used to acquire images of the first MTPJ; and participants were over 18 years old. Articles were excluded if they were not published in English, opinion articles, commentary letters, review articles or non-human studies. Case reports and case series were also excluded due to potential issues with selection bias. Relevant articles were assessed according to the selection criteria with conflicts discussed between two authors (P.M and A.J) until consensus was achieved. In cases of non-consensus, a third author's opinion was planned for consultation (M.C); however, this was not required. All articles that met the inclusion criteria had their reference lists hand searched for further potentially relevant articles. When the included articles referred to a previous paper for methodology or reliability, that article was accessed, and appraised for inclusion against the eligibility criteria.

Data Extraction

The following information was extracted from all included articles: study characteristics, author's name, year of publication, study design and aim(s). Participant characteristics

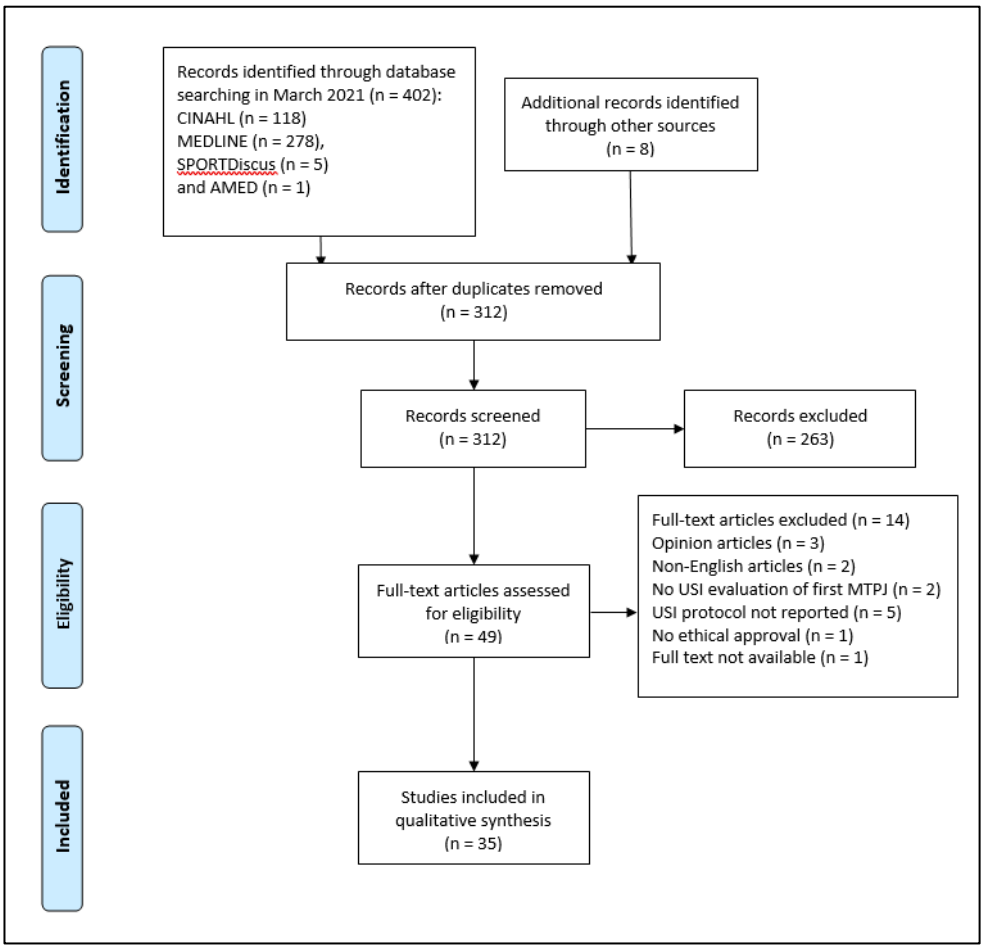
including sample size, gender, mean age (years), mean BMI ($kg.m^{-2}$), ethnicity, and pathology were also extracted **(Appendix 6)**. Additionally, the following components of the USI acquisition procedure were extracted: anatomical region, patient position, USI mode and settings, transducer orientation, surfaces scanned, and the scanning technique **(Appendix 7)**.

Results

Selection and Characteristics of Studies

The study aims, participant characteristics and the pathology examined of all included studies are presented in **Appendix 6**. A total of 402 citations were identified for screening with 36 articles included for final analysis **(Figure 5).** All 36 studies used USI to evaluate the first MTPJ. The combined sample size from the included studies was 3,921 (2,736 male, 1,182 female). The mean age was 55.5 years and mean BMI was 28.5 kg/m^2. Ethnicity of the study population was reported by four studies (394-397). Ethnicities that were reported included White American, African American, Hispanic, Asian, European, Māori, Pasifika and Chinese.

Figure 5. PRISMA flow diagram



USI Guidelines

This review found three USI acquisition guidelines were reported to assess the first MTPJ. In terms of application, ten studies (28%) reported their USI acquisition procedure was in accordance with the 2001 EULAR guidelines (36, 309, 356, 397-403). No studies applied the updated 2017 EULAR guidelines (279). Zhang, Jin (398) reported their scanning procedure was in accordance with the European Society of Musculoskeletal Radiology (ESSR) guidelines, although these guidelines do not include the first MTPJ (404).

USI Acquisition Procedure for Evaluating the First MTPJ

Patient Positioning

Descriptions of the various procedures that report evaluation of the first MTPJ include how the body and lower limb joints were positioned. The position the patient was placed in during the scanning procedure was reported by 17 (47%) studies. Details of body and joint position reported by each study are outlined in **Appendix 7**. Components of patient positioning included how the body was positioned (e.g. supine or prone) and how each lower limb joint was positioned (e.g. first MTPJ dorsiflexed, ankle neutral and/or knee extended) for the imaging procedure. Body positioning was reported by seven studies, all of which reported supine positioning (36, 309, 356, 395, 405, 406). When assessing the first MTPJ there was no standardisation across studies as to which lower limb joints were included as part of the USI acquisition procedure description. Of the studies that included the same joint in their procedure description, there was considerable variation as to how that joint was positioned (e.g. variation in knee flexion angle or extended). It was unclear from all included studies if body and/or joint position changed during the USI acquisition procedure depending on the surface of the first MTPJ scanned. Of the ten studies which reported their USI acquisition procedure was in accordance with the 2001 EULAR guidelines, only three studies positioning descriptions aligned with the 2001 guidelines (supine position for the dorsal scans and prone position for the plantar scans) (36, 309, 356).

USI Modalities and Machine Settings

All included studies detailed the brand and model of the USI device, type and model of the transducer, and the USI modalities used. Details of USI mode and settings reported by each study are outlined in **Appendix 7**. The USI technique, grey scale mode (B-mode) was reported by all 36 studies. Doppler (colour, power, and pulse) were reported by 18 studies (36, 308, 309, 356, 395-397, 399-401, 407-414). Most studies specified a linear

array transducer with a multi-frequency ranging between 8-18 MHz. Nine studies reported a set transducer frequency between 10-18 MHz (36, 356, 394, 395, 399, 403, 415, 416). A hockey stick probe with a multi-frequency of 7-15 MHz was employed by one study (408). One study performed volumetric PD acquisitions using three-dimensional (3D) USI (410). USI settings that were reported included dynamic range, which ranged between 40-70 dB and grey scale gain, which ranged between 17 dB to 60 dB. Of the 18 studies that reported using power Doppler, the pulse repetition frequency ranged from 400-1000 Hz and Doppler frequency ranged between 5-10 MHz. Additional settings reported by several studies included a low to medium wall filter with the Doppler gain adjusted to a level just below the disappearance of the colour signs within the bony cortex.

Transducer Orientation and Surfaces Scanned

Details of the transducer orientation and surfaces scanned for the included studies are outlined in **Appendix 7.** Studies varied in terms of transducer orientation (e.g. transverse or longitudinal) and which surface(s) of the first MTPJ were scanned (e.g. dorsal, plantar, lateral or medial). Of the ten studies that reported their USI acquisition procedure was in accordance with the 2001 EULAR guidelines, only Elsaman, Muhammad (402) description of transducer orientation and surfaces scanned clearly adhered to the guidelines. Naredo, Acebes (410) applied 3D volumetric USI technique, which allows examination in the longitudinal, transverse, and coronal plane by producing a 3D reconstruction of the anatomic area. The different descriptions of transducer orientation and surfaces scanned of the first MTPJ led to 12 different variations in reported procedures across studies. Le Boedec, Jousse-Joulin (414) and Pineda, Amezcua-Guerra (309) described a multiplanar technique with no further clarification of what their scanning procedure entailed. Only one study did not delineate their specific scanning method (412).

Scanning Technique

Details of the scanning techniques used by included studies are outlined in **Appendix 7**. The scanning technique (static or dynamic) was not commonly reported. A dynamic procedure is when the transducer is moved along the anatomical region (first MTPJ); or the anatomical region is moved during the USI examination (371). Three studies reported their scanning procedure involved a dynamic technique in which the probe was manoeuvred to investigate the first MTPJ (395, 411, 412). Dynamic examination involving flexion-extension of the first MTPJ was reported by one study (309). Roddy, Menon (399) and Terslev, Gutierrez (417) reported dynamic manoeuvres but failed to

report if it was the transducer or the first MTPJ that was dynamic during the USI examination. In regards to 3D USI, the acquisition of the USI volume consists of an automatic sweeping scan movement of the piezoelectric crystals located inside the transducer, not a sweep of the transducer over the joint surface (410). Naredo, Acebes (410) reported the volumetric probe was placed over the central part of the joint and a volumetric sweeping on the longitudinal plane was performed.

Discussion

This review found a wide variation in USI acquisition procedures used to evaluate the first MTPJ. The variation between studies may be attributable to the number of elements the USI acquisition procedure encompasses. Technological developments coupled with the expansion of USI research has led to the development of consensus-based guidelines (279). However, as it stands only two consensus-based guidelines exist to inform the USI acquisition procedure to assess the first MTPJ (279, 324). As most studies in this review were published prior to publication of the revised EULAR guidelines (279), no study included in this review had applied the updated EULAR guidelines.

The reporting of rheumatic and musculoskeletal USI research has also been enhanced by the recent publication of the EULAR recommendation checklist (371). The checklist encompasses 23 items, four of which specifically relate to the USI acquisition procedure. The checklist was developed to ensure transparent and comprehensive reporting of USI research and procedures. It has been suggested that the global uptake of this checklist may considerably improve interpretability, reproducibility and generalisability of study results (371). Therefore, two mechanisms need to be considered by USI research, the acquisition guidelines and the reporting of USI studies.

Numerous studies referred to adhering with the 2001 EULAR guidelines, despite their description of patient and joint positioning not aligning with the standardised procedure (supine position for the dorsal scans and prone position for the plantar scans) (324). Of the 12 studies which stated they examined both the dorsal and plantar aspect of the first MTPJ, no study indicated they modified patient position based on the surfaces scanned. The USI procedure description for assessing the first MTPJ often included how the body, knee, ankle, and foot were positioned in conjunction with the positioning of the first MTPJ. However, there was inconsistent reporting of which lower limb joints should be included as part of the USI acquisition procedure. Of the studies that included the same joint in their procedure description, there was wide variation as to how that joint was positioned. Previous USI researchers have confirmed the importance of a standardised joint position

for the reliability and generalisability of the results (418-423). Data from previous studies has demonstrated variations in joint position can influence USI outcomes, irrespective of the anatomical site under investigation (418-423). The updated 2017 EULAR guidelines for performing USI of the first MTPJ address both joint and patient positioning (279). To comply with the recently developed EULAR recommendation checklist for reporting USI (371), both patient position (item 9a) and the anatomical region position (item 9b) are recommended to be implemented in future studies. A further enhancement of the updated EULAR guidelines is the accompaniment of an electronic illustrated manual (i.e., app) which clearly depicts the USI technique and procedures. The downloadable EULAR USI scanning app (http://ultrasound.eular.org/#/home) contains images detailing foot positioning and transducer orientation (longitudinal and transverse) for examining the first MTPJ. No study included images demonstrating how they acquired the ultrasound image to support their protocol description. Given the number of studies that inadequately described or failed to report patient and/or joint position, supporting images would ensure correct interpretation and allow subsequent studies to correctly replicate their procedure. Consequently, the inclusion of images may have revealed similarities between studies or adherence with cited guidelines that were unclear based on the descriptions of patient position alone.

The reporting of the USI device, type and model of the transducer, whether the software was changed during the study, and the USI mode and settings varied between studies. Technical characteristics of the imaging device such as USI modalities and settings used may affect the reliability and generalisability of the results (424-426). One study employed 3D USI, enabling automatic image acquisition. 3D USI has been shown to reduce the operator dependence in assessing synovitis and bone erosions compared with conventional 2D USI (427, 428). Costantino, Carmona (371) reported that the type of USI device may influence both power Doppler and grey scale USI results. Advanced technology, such as 3D imaging, may illustrate more in-depth information of joint pathology.

In keeping with the updated EULAR recommended procedures (279), grey scale USI should be performed with high-resolution linear transducers with frequencies greater or equal to 15 MHz for superficial areas. Higher frequencies produce better resolution of superficial structures such as the first MTPJ (429). However, 21 of the included studies used a transducer with an operating frequency lower than 15 MHz. The machine setting for grey scale and Doppler mode (e.g. focal zone, frequency, gain, dynamic range, depth for B-mode; focal zone, colour box, frequency, gain, pulse repetition frequency and wall filter) were rarely reported by the included studies. Additionally, whether these settings

were adjusted prior to and during the examination to optimise the USI acquisition procedure was uncertain. Optimal settings will depend on the individual machines; however, it is difficult to compare settings between studies due to the limited data reported. For the reporting of equipment items (15 and 16) of the EULAR checklist, future studies should detail the brand and model of the USI device, type and model of the transducer and whether the USI device was changed during the study (item 15). To comply with item 16, the USI modalities and settings should be reported.

In reference to patient and joint position, the orientation and positioning of the transducer is open to interpretation without images to ensure clarification of location. The position of the transducer has previously been shown to influence the reliability and accuracy of USI results in knee inflammation (420-422). Included studies that have used phrases like “multiplanar examination” or “examined circumferentially” leaves the reader open to interpretation as to whether all surfaces of the joint were examined and in what plane they were imaged. It is unclear if the number of procedure variations reported were a result of missing information from the procedure description, or if studies intended to only view a certain aspect of the first MTPJ. Subsequently, it is possible that the reported descriptions were not a true reflection of what was conducted, and acquisition procedures might be more alike between studies than they appear.

Numerous studies referred to adhering with the 2001 EULAR guidelines, despite their description of transducer orientation and surfaces scanned not adhering with the standardised procedure (324). Discrepancies from the guidelines included the absence of an imaging plane (e.g. transverse) or alteration in surfaces scanned such as including the medial aspect of the first MTPJ. Individual study interpretation of the lateral and medial aspect of the first MTPJ relative to the midline of the foot may explain the deviation from cited guidelines. This component of the original EULAR imaging procedure has since been amended to the medial aspect of the first MTPJ by the 2017 EULAR guidelines (279). For that reason, it is unclear if medial and lateral can be used interchangeably when comparing acquisition procedures between studies.

The updated EULAR guidelines for performing USI of the first MTPJ address transducer orientation and position (starting point), surfaces scanned and scanning technique (279). The probe placement starting point includes a longitudinal and transverse examination of the dorsal and plantar aspects of the forefoot, parallel to the metatarsal bones. Despite this addition, the current guidelines lack sufficient detail required to ensure a standardised USI acquisition procedure. Given the general opinion that USI is heavily operator dependent for image acquisition further refinement and detail of anatomical

reference points used to guide probe positioning is required. The scanning technique involves longitudinal and transverse sweeping. A sweeping scanning technique, involves slight movements of the probe from side-to-side, back-to-front or rotation to allow the best visualisation of the first MTPJ (279). In addition, the medial aspect of the first MTPJ is also scanned (279). However, it is difficult to make strong consensus-based recommendations, as the implementation of the revised technique lacks clear repeatable evidence to support this. It is problematic that one study reported to apply the 2010 ESSR guidelines, despite these guidelines not including a procedure to scan the first MTPJ (404). To fulfil the EULAR checklist items for acquisition procedures (371), studies should detail the surfaces scanned (item 9c), transducer orientation/location (item 9d) and whether the examination was dynamic (item 9e).

This scoping review is not without limitations. All relevant articles were included in this scoping review, regardless of methodological quality. We restricted the search to articles published in English. Inclusion of data from non-English language articles may alter the outcomes. Assessing the reliability between USI acquisition procedures and between sonographers was not an objective of this review. However, extraction of reliability data may have provided more insight into the reliability of different USI acquisition procedures, given the inconsistencies reported. Particularly between sonographers who possess different academic backgrounds and levels of USI experience.

Future studies should aim to accurately implement the updated EULAR guidelines. However, further refinement of anatomical reference points used to guide probe positioning is required to ensure a standardised USI acquisition procedure is used for evaluating the first MTPJ. Given the ambiguity in procedure descriptions, future research should adopt the EULAR recommendation checklist for reporting USI research of rheumatic and musculoskeletal diseases. A standardised procedure supplemented with a checklist for reporting the USI procedure of the first MTPJ will improve interpretability, reproducibility, and generalisability of study results. Current guidelines have overlooked how the USI acquisition procedure may need to be adapted to accommodate severe structural changes. The degree of joint deformity often associated with rheumatic diseases poses a challenge when acquiring an optimal image. Consequently, future research should aim to provide guidance on how to image the first MTPJ that has significant deformity. Finally, there is also great value in developing guidelines that investigate volumetric probes to enable 3D reconstruction of the anatomical area and automatic image acquisition, as this will reduce operator dependence in examining the first MTPJ.

Conclusion

The review found inconsistency in the application of the EULAR guidelines and limited implementation of consensus-based recommendations to guide image acquisition of the first MTPJ. There was wide variation in what items were reported as part of the USI acquisition procedure to evaluate the first MTPJ. Additionally, there were discrepancies between the level of detail reported for each item the imaging procedure encompasses. The key inconsistencies identified were between patient position, USI mode and settings, transducer orientation, and surfaces scanned. The review emphasises the need for further refinement to ensure a standardised USI acquisition procedure is used to evaluate the first MTPJ. A standardised procedure supplemented with a checklist for reporting the components the USI acquisition procedure encompasses will improve interpretability and reproducibility between studies.

Brief Update Since Publication

Since publication of the scoping review up to the 6th of November 2023, one study has been published that met the inclusion criteria. Zhao et al. (430) investigated the relationship between specific ultrasonic manifestations of lower limb joints and impaired kidney function in gout. The following components of the USI acquisition procedure were extracted and are presented in **Table 13**: anatomical region, patient position, USI mode and settings, probe orientation, surfaces scanned, and the scanning technique. In addition to reporting the USI acquisition procedure used to assess the first MTPJ, the study also examined the knee and ankle joints. Unfortunately, the authors did not differentiate the USI device and machine settings for specific joints. The probe and patient position were reported but lacked anatomic detail in the procedure description. As with studies included in the present scoping review, Zhao et al.'s study did not include images demonstrating how they acquired the ultrasound images to support the protocol description; nor did it report if they adhered to any guidelines to inform the USI procedure.

Table 13. Reported USI acquisition procedures evaluating the first MTPJ

Author	Anatomical region	Patient position	US mode and settings	Probe position/orientation and surfaces scanned	Scanning procedure
Zhao (2023) (430)	First MTPJ	Sole of the foot placed flat on the examination table	Linear array probes, including Philips IU22, Siemens Acuson S3000, and Toshiba Aplio500, were used for scanning at frequencies of 8–14 MHz, with the musculoskeletal mode selected	Scanning the dorsal and lateral aspects in both longitudinal and transverse planes	NR

MTPJ, Metatarsophalangeal joint; US, Ultrasound; NR, not reported

Chapter 6

A Bibliometric Analysis of Published Research Employing Musculoskeletal Imaging Modalities to Evaluate Foot Osteoarthritis

Reference

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Molyneux P, Stewart S, Bowen C, Ellis R, Rome K, & Carroll M. A bibliometric analysis of published research employing musculoskeletal imaging modalities to evaluate foot osteoarthritis. *Journal of Foot and Ankle Research*. 2022; 15(1): 39. https://doi.org/10.1186/s13047-022-00549-0

Preface

The reviews in Chapters 4 and 5 illustrate the infancy in understanding of the role of imaging for examining foot OA. The findings from those reviews provided justification for exploring other imaging technologies for the assessment and grading of first MTPJ OA to overcome the limitations of traditional methods. Whilst the justification for questioning traditional imaging methods (i.e. radiography) may appear anecdotal and formed on opinion, identifying alternative imaging modalities (i.e. USI) that may be of greater utility is critical. The global status of research employing various imaging modalities to assess OA in the foot was unknown. In order to evaluate the scope of research utilising imaging to assess foot OA, a bibliometric analysis was required. Bibliometric analyses summarise information to uncover emerging trends in article and journal performance, collaboration patterns, and research constituents, thus providing a means to monitor the productivity and impact, or influence, of published information. Published research is central in providing information and improving knowledge. In using novel methodologies such as bibliometric analysis, performance-based metrics of published research which has examined alternative imaging modalities for foot OA can validate anecdotal evidence, to strive towards more contemporary methods of assessment and grading.

The article reproduced in Chapter 6 presents a bibliometric analysis of published literature to evaluate the scope of research utilising imaging to assess foot OA, including global and temporal trends, and performance-based metrics. Given the technological

advancements made in modern imaging, this analysis provides insight into the application and adaption of different imaging modalities in research over time.

Abstract

Objectives

Temporal and global changes in research utilising imaging to assess foot osteoarthritis is currently unknown. This study aimed to undertake a bibliometric analysis of published research to: (1) identify the imaging modalities that have been used to evaluate foot osteoarthritis; (2) explore the temporal changes and global differences in the use of these imaging modalities; and (3) to evaluate performance related to publication- and citation-based metrics.

Methods

A literature search was conducted using Scopus to identify studies which had used imaging to assess foot osteoarthritis. Extracted data included publication year, imaging modality, citations, affiliations, and author collaboration networks. Temporal trends in the use of each imaging modality were analysed. Performance analysis and science mapping were used to analyse citations and collaboration networks.

Results

158 studies were identified between 1980 and 2021. Plain radiography was the most widely used modality, followed by computed tomography, magnetic resonance imaging (MRI) and ultrasound imaging (USI), respectively. The number of published studies increased over time for each imaging modality (all $P \geq 0.018$). The most productive country was the United States of America (USA), followed by the United Kingdom and Australia. International authorship collaboration was evident in 57 (36.1%) studies. The average citation rate was 23.4 per study, with an average annual citation rate of 2.1.

Conclusions

Published research employing imaging to assess foot osteoarthritis has increased substantially over the past four decades. Although plain radiography remains the gold standard modality, the emergence of MRI and USI in the past two decades continues to advance knowledge and progress research in this field.

Background

Osteoarthritis is a progressive joint disease involving degradation of articular cartilage, subchondral bone and surrounding soft tissue structures, leading to symptoms of pain and stiffness (40). Small joints of the feet are often overlooked as a site of involvement relative to other joints commonly affected by osteoarthritis (7, 216). Population-based epidemiological studies have reported a high prevalence of radiographic osteoarthritis in the feet, with up to 39% of older adults having first metatarsophalangeal joint involvement (7).

Musculoskeletal imaging has an essential role in the diagnosis and assessment of osteoarthritis (18, 49, 272-274). Plain radiography has traditionally been regarded as the leading modality for the assessment of osseous changes in foot osteoarthritis (13), and there is emerging evidence that assesses the diagnostic sensitivity of radiography and its association to clinical symptoms for foot disorders (73, 226, 243). However, the advent of more advanced techniques, including magnetic resonance imaging (MRI), computed tomography (CT), and ultrasound imaging (USI) have gained increasing recognition for their fundamental role in understanding the pathophysiology of osteoarthritis due to their ability to observe subclinical osseous and soft tissue changes (210, 277-280, 295).

Recommendations published in 2017 by the European League Against Rheumatism (EULAR) highlighted the need for further imaging research into less commonly studied sites of osteoarthritis, such as the foot (17). However, the global status of collaboration and temporal trends of research employing various imaging modalities to assess osteoarthritis in the foot is currently unknown. Published research is central in providing information and improving knowledge, and publication and citation-based metrics provide a means to monitor the productivity and impact, or influence, of published information (431).

In order to evaluate the scope of research utilising imaging to assess foot osteoarthritis, including global and temporal trends, and performance-based metrics, a bibliometric analysis is required. Bibliometric analyses summarise information to uncover emerging trends in article and journal performance, collaboration patterns, and research constituents (431, 432). The objectives of this study were to conduct a bibliometric analysis of published literature used to evaluate foot osteoarthritis to: (1) identify the imaging modalities that have been used; (2) explore the temporal changes and global differences in the use of these imaging modalities; and (3) evaluate performance related to publication- and citation-based metrics.

Methods

The procedure and best practice guidelines proposed by Donthu et al. (431) were used to frame the bibliometric analysis methodology. The techniques for bibliometric analysis manifest across two categories: (1) performance analysis and (2) science mapping (431). In essence, performance analysis examines the contributions of research constitutes, which is descriptive in nature. Whereas science mapping focuses on the relationships between research constitutes (431, 433-435). Both techniques were used to address the study objectives. Performance analysis was used to examine publication-related metrics and recognises the influence of various constituents (authors, institutions/affiliations, countries, and journals) on publication performance which is measured using a range of metrics (total publications, number of contributing authors, co-authored publications, number of active years of publication, total citations, average citations and annual citation rate). Science mapping was used to examine the relationships between research constituents (433-435). Two science mapping techniques were used; (1) citation analysis, to identify the most influential publications in the field and (2) co-authorship analysis, to examine the social interactions or relations among authors and their affiliations and equivalent impacts on the development of the research field (431).

Search Strategy

The search strategy required for a bibliometric analysis is similar to that of a systematic review. However, it must identify a large enough volume of articles to warrant bibliometric analysis and fulfil the requirements of the analysis techniques, yet also be focused enough to remain in the dedicated research field (431). An electronic search was designed and conducted by two authors (P.M and S.S) in August 2021 using the search terms displayed in **Table 14**. The two most commonly utilised databases are Scopus®, and Web of Science®. Therefore, it is accepted practice when using metadata for bibliometric analysis to use either Scopus® or Web of Science® (431). It is recommended to select one appropriate database to mitigate the need for consolidation of data, minimising unnecessary action items can help to mitigate potential human errors (431). The Scopus® database (Elsevier, Amsterdam, Netherlands) was selected as it has the largest abstract and citation database of research literature (436). As of January 2020, Scopus® had in excess of 25,100 active titles and over 550 articles in press (437). Additionally Scopus® includes a more expanded spectrum of journals than PubMed and Web of Science® (438). There were no restrictions on date, allowing a search for studies published from the database's earliest record (1963) through to August 2021. The electronic search was supplemented with hand-searching of references lists from included studies and review articles to identify additional eligible papers.

Study Selection

The titles and abstracts of all identified studies were downloaded from the Scopus® database and exported into Rayyan (http://rayyan.qcri.org), an online literature review application (439), suitable for bibliometric analysis. In the first stage of selection the titles and abstracts were independently screened by two authors (P.M and S.S). Studies were included if they used imaging to assess the foot in patients with foot osteoarthritis (inclusive of post-traumatic foot osteoarthritis), for the purpose of recruitment or as a research outcome, reported original research findings, and were published in English. Studies were excluded if they did not report original research findings, including reviews, case reports, commentaries, letters, non-human studies, conference proceedings, or editorials, or did not report which imaging modality was used to assess the foot. Studies that evaluated ankle osteoarthritis but did not also include the assessment of foot osteoarthritis were excluded. To determine the final articles for inclusion, the full texts of all articles included at the title/abstract screening stage were retrieved and reassessed against the criteria. Conflicts were discussed between the two authors (PM and SS) until consensus was achieved.

Table 14. Search strategy

Scopus		
1	Subject term	Imaging
2	Keywords	“diagnostic imaging” OR radiograph* OR x-ray* OR roentogram OR roentgenogram OR ultrasonograph* OR ultrasound OR sonograph* OR “power doppler” OR doppler OR tomograph* OR “x-ray computed” OR “computed tomograph*” OR ct OR mri OR “magnetic resonance imaging” OR “SPECT-CT” OR “single photon-emission computed tomography"
3	Combine	1 OR 2
4	Keywords	osteoarthrosis OR osteoarthriti* OR oa
5	Keywords	foot OR feet OR podiatr*
6	Combine	3 AND 4 AND 5

Data Extraction

All studies were imported into Biblioshiny (based on R version 3.6.1, Bibliometrix package version 2.2.1; University of Naples Federico II, Naples, Italy, 2016) (440) for data extraction. The following bibliometric indicators were extracted from each study: year of publication, journal name, journal impact factor (IF) (in prior year, 2020 using the Web of Science Journal Citation Reports™ tool (Clarivate Analytics, Philadelphia, Pennsylvania, USA), number of citations (determined the Scopus® database (Elsevier)), author names, total authors per manuscript, and institutional affiliation of each author.

The extent of collaboration for each study was also determined based on four categories: (1) “international collaboration” in which studies involved collaboration with international authors; (2) “bi-national collaboration” in which studies originated from authors affiliated to only two institutions/affiliations from the same country; (3) “multi-national collaboration” in which studies were authored by researchers from three or more institutions/affiliations from the same country; and (4) “no collaboration” in which all authors were affiliated with the same institution (441, 442).

Additional data from each included study were also extracted into a standardised Microsoft Excel spreadsheet (Version 2016, Microsoft Corp., Redmond, Washington, USA), including: the imaging modality/modalities used (plain radiography, CT, MRI or USI), the specific joints in the foot that were assessed, the reason for assessment (outcome measure vs. recruitment screening tool) and the study design. Finally, study design was classified using the Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of Evidence (443), in which randomised controlled trials are classified as Level 2, cohort/longitudinal studies as Level 3, and case-series and case-control studies as Level 4 (note: systematic reviews (Level 1) and studies involving mechanism-based reasoning (Level 5) were not eligible for inclusion in the current analysis).

Data Analysis

Descriptive statistics were used to summarise the study characteristics and data related to each imaging modality. Bibliometric data were analysed separately for each imaging modality using the bibliometrix package, Biblioshiny. Studies utilising more than one imaging modality to assess osteoarthritis in the foot were included in analyses for each imaging modality used. As described above, the bibliometric analysis included both a performance analysis (to determine the total publications, number of contributing authors, co-authored publications, number of active years of publication (number of years from publication to 2021), total citations, average citations and annual citation rate); and science mapping (to undertake a citation analysis and co-authorship analysis). The citation analysis included evaluating the difference in publication performance of each imaging modality over time. In this analysis, the impact of a publication is determined by the number of citations that it receives. The analysis enables the most influential publications in a research field to be ascertained (431). The co-authorship analysis also included generation of a collaboration world map representing the extent of international author collaborations across the included studies.

In addition, to complement the bibliometric analysis and further explore publication trends over time, linear regression models were used to analyse temporal trends in the use of

each imaging modality over time using SPSS (for example, increased or decreased imaging modality use over time) (Version 26.0. IBM Corp, Armonk, NY). Studies were grouped into decades, based on year of publication. The 2021 publication year was excluded from this analysis due to incomplete data (i.e., data was collected up to and including August 2021).

Results

Characteristics of Included Studies

A total of 1,905 studies were initially identified, of which 158 studies satisfied the inclusion criteria and were included in the final analysis **Figure 6**. Characteristics of the included studies are displayed in **Table 15**. The included studies were published between 1980 and 2021 with an annual percentage growth rate of 9.6%. The majority of included studies employed plain radiography to assess the foot, followed by CT, MRI and USI. Twenty-four studies used two imaging modalities, and the remaining 134 studies used a single imaging modality. When characterised by the Oxford 2011 Level of Evidence, eight (5.1%) studies were Level 2, 58 (36.7%) were Level 3, and 92 (58.2%) were Level 4. One hundred and thirteen (71.5%) studies used imaging to assess a study outcome, nine (5.7%) studies used imaging in the recruitment process to screen participants for inclusion, and 36 (22.8%) used imaging as both a screening tool and outcome measure. The most common foot joint scanned was the first metatarsophalangeal joint (n = 64 studies, 40.5%). **Table 16** presents the proportion of studies assessing each specific joint across each imaging modality.

Assessment of Temporal Changes in the Use of Imaging Modalities

The earliest study was published in 1980 and the most recent study in 2021. The earliest study published using plain radiography to assess foot osteoarthritis was 1980, while the use of CT did not appear until 1995, MRI until 2006, and USI until 2009 **(Figure 7)**. This finding is also consistent with the average years from publication to 2021, which was 8.4 years for studies using plain radiography, 8.1 years for CT, 6.9 years for MRI, and 7.0 years for USI. Each modality showed a significant increase in the number of publications across decades for plain radiography (*P* for trend < 0.001), CT (*P* for trend = 0.001), MRI (*P* for trend <0.001), and USI (*P* for trend = 0.018).

Figure 6. PRISMA flow diagram

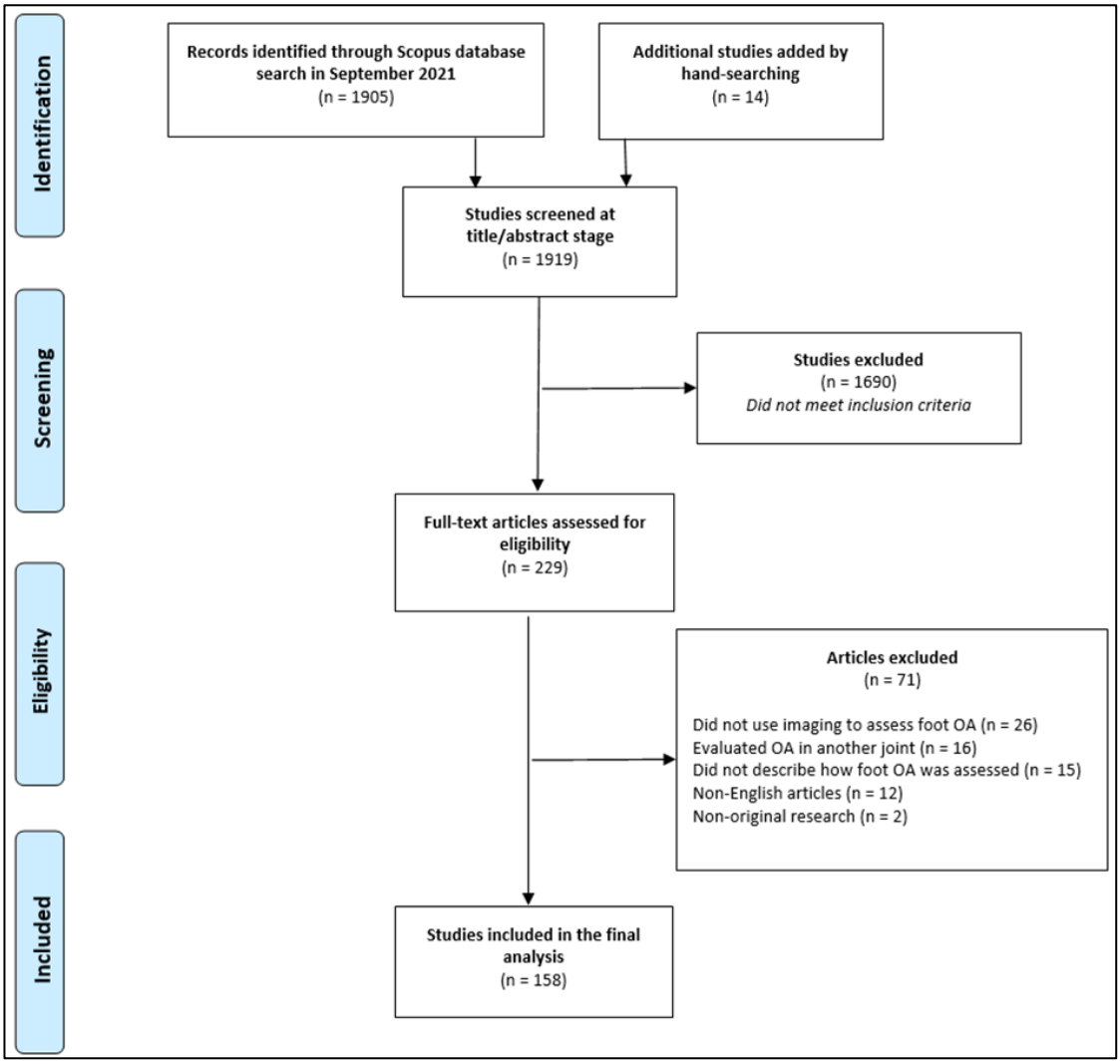


Table 15. Characteristics of the included studies (n = 158)

Timespan, year		1980 to 2021
Annual percentage growth rate, %		9.6%
Oxford 2011 Levels of Evidence, n (%)	Level 2	8 (5.1%)
	Level 3	58 (36.7%)
	Level 4	92 (58.2%)
Imaging modality used, n (%)[a]	Plain radiography	140 (88.6%)
	CT	24 (15.2%)
	MRI	14 (8.9%)
	USI	4 (2.5%)
Reason for imaging, n (%)	Outcome measure	113 (71.5%)
	Participant recruitment	9 (5.7%)
	Both	36 (22.8%)
Foot joint examined with imaging, n (%)[b]	First metatarsophalangeal joint	64 (40.5%)
	Lesser metatarsophalangeal joints	9 (5.7%)
	Interphalangeal joints	7 (4.4%)
	Subtalar joint	50 (31.6%)
	Midfoot joints	82 (51.9%)
	Not specified	6 (3.8%)

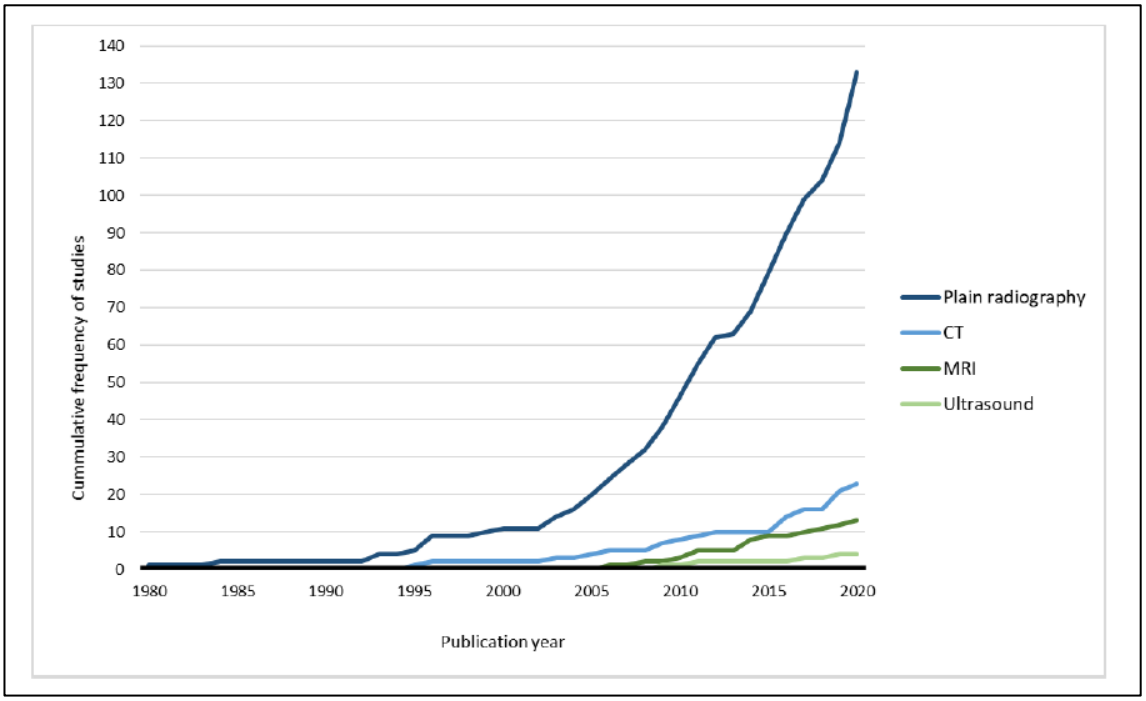
[a]24 studies used more than one imaging modality; [b] 39 studies assessed ≥2 foot joints

Table 16. Foot joints examined across studies for each imaging modality[a]

	Imaging modality				
Joint	**All studies**	**Plain radiography**	**CT**	**MRI**	**USI**
First metatarsophalangeal joint	64	57	5	5	11
Lesser metatarsophalangeal joint (2-5)	9	7	1	1	1
Subtalar joint	50	44	13	4	1
Tarsometatarsal joint	24	21	5	1	1
Naviculocuneiform joint	29	26	4	2	2
Cuneometatarsal joint	18	18	0	0	1
Talonavicular joint	45	42	8	3	2
Calcaneocuboid joint	23	21	6	1	2
Cuboid-navicular joint	3	3	0	0	1
Cuboid-cuneiform joint	1	1	0	0	1
Calcaneonavicular joint	2	2	0	0	0
Interphalangeal joint	1	0	0	1	1
Proximal Interphalangeal joint	3	2	1	0	1
Distal Interphalangeal joint	3	2	1	0	1
Foot joint not specified	6	5	0	3	2

[a]24 studies used ≥2 imaging modalities and 60 studies assessed ≥2 joints.

Figure 7. Cumulative frequency of studies published per year for each imaging modality.
Note: data from studies using more than one imaging modality (n = 24) were counted for each imaging modality used.

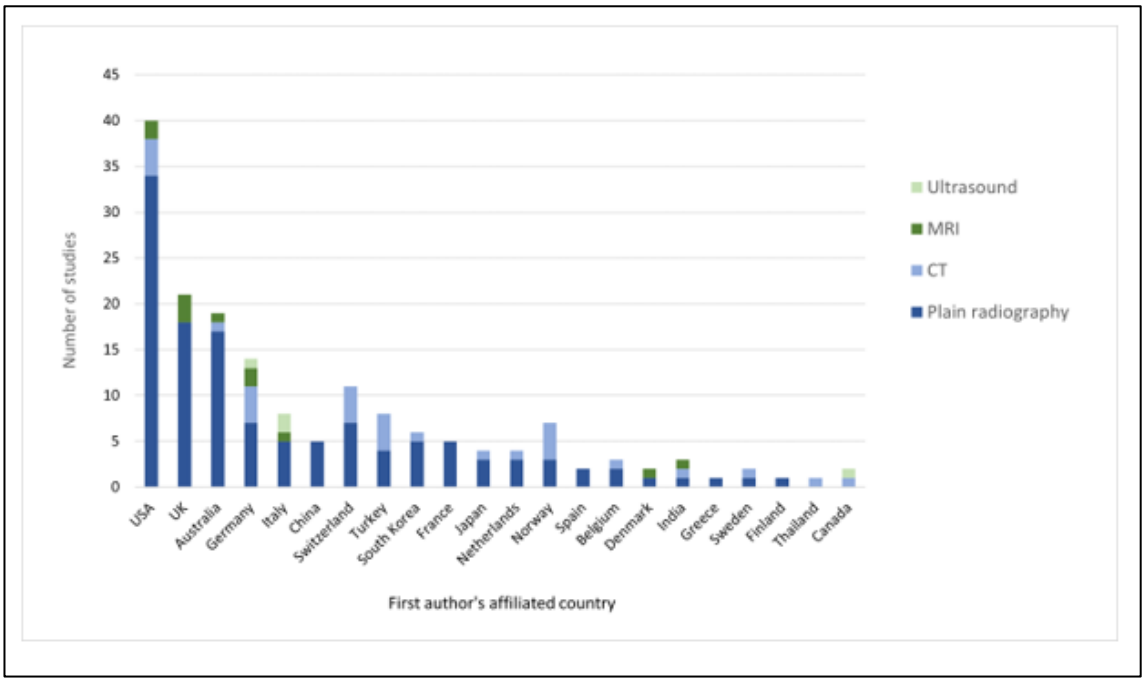


Assessment of Global Differences in the Use of Imaging Modalities

The 158 included studies were published across 22 different countries based on the first author's affiliation **(Figure 8)**. The most productive country was the USA, with 36 (22.8%) included studies based on the first authors affiliation, followed by the United Kingdom, publishing 20 (12.7%), and Australia, publishing 17 (10.8%). The most common first author affiliation for studies using plain radiography was the USA (n = 34 studies), while CT studies were associated with first authors from the USA (n = 4) and Germany (n = 4). The most common first author affiliation for MRI studies was the United Kingdom (n = 3 studies), and for USI studies was Italy (n = 2 studies).

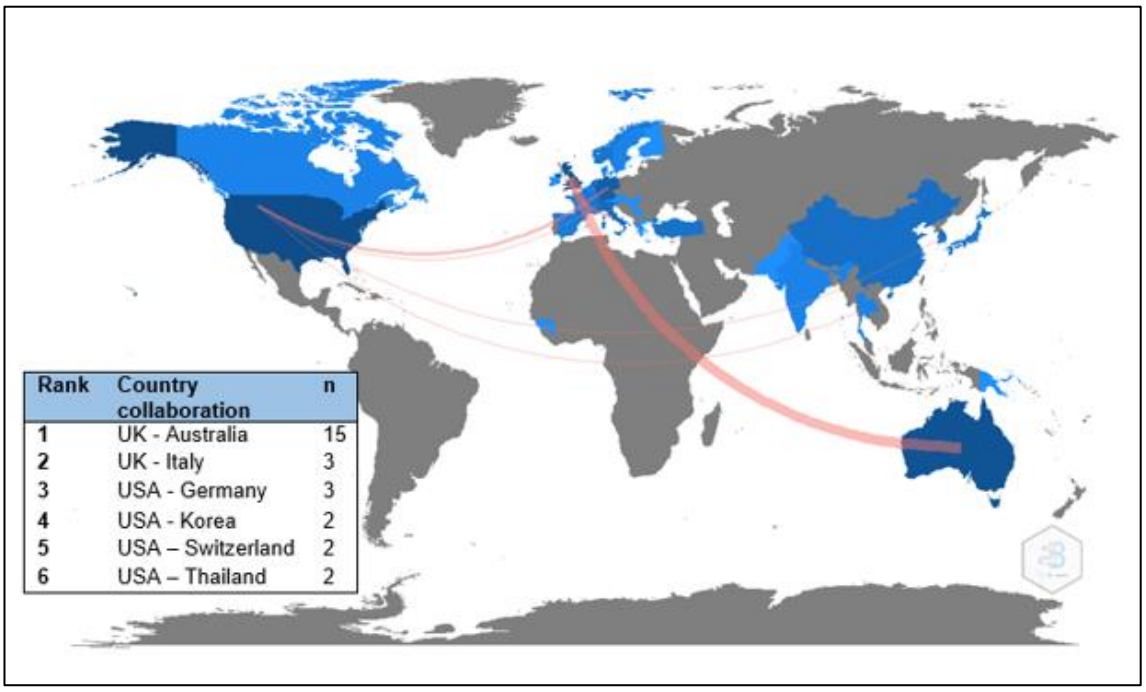
Fifty-seven (36.1%) of the included articles demonstrated international collaboration, 34 (21.5%) articles had bi-national collaboration, 43 (27.2%) articles had evidence of multi-national collaboration, and 24 (15.2%) articles had no collaborative links outside of a single institution. The most frequent international authorship link occurred between the United Kingdom and Australia (15 articles). A world map displaying international collaborative research links by country is displayed in **Figure 9.**

Figure 8. Number of studies associated with the first authors affiliated country for each imaging modality.



Note: data from studies using more than one imaging modality (n = 24) were counted for each imaging modality used.

Figure 9. Visual representation of international collaborative authorship networks.



Rank	Country collaboration	n
1	UK - Australia	15
2	UK - Italy	3
3	USA - Germany	3
4	USA - Korea	2
5	USA – Switzerland	2
6	USA – Thailand	2

Note: Different shades of blue indicate different rates of collaboration between that country with any other country: dark blue = higher collaboration; grey = no collaborations.

Performance Analysis

Citations

The 158 included studies had a total of 3,690 citations, with an average citation rate of 23.4 per study (range: 0-202 citations). Fourteen (8.9%) studies received no citations; however, these had recent publication dates in 2021 (n = 8 studies) and 2020 (n = 6 studies). Total citations, average citations per study, and average annual citation rates per study are displayed in **Table 17**. Although studies using plain radiography had the highest total citations, studies using CT had the highest average citations per study and highest average annual citation rate. A summary of the top five most cited countries based on the first author's country for each imaging modality is displayed in **Table 18**. The most cited study was published by Paley et al. (444) in 1993 and used plain radiography to assess the hindfoot (n = 202 citations). This study represented 5.5% of the total citations for all included studies. The twenty most cited studies represented 50.5% of the total citations. The ten most cited articles are displayed in **Table 19**.

Journals

The 158 included studies were published in 64 different journals **(Table 20)**. *Foot and Ankle International* published the highest proportion of studies (*n* = 24, 15.8%). There were 42 journals (27.6%) where only one of the included articles were published. The journals that published three or more publications accounted for 57.9% of all identified studies. Studies utilising plain radiography were published across 55 different journals, CT across 15 journals, MRI across 14 journals, and USI across four journals. A 2020 IF was available for 51 (79.7%) of the journals where the included articles were published. The mean IF for the included studies was 3.74, median IF was 2.83, with an IF range of 0.51- 19.10. The articles published in *Journal of Bone and Joint Surgery-Series A* were the most cited, with a total of 931 citations, average citations per study of 116 and an average annual citation rate per study of 6.0.

Authorship and Affiliations

A total of 661 authors contributed to the 158 included studies, with a mean of five co-authors per study. Studies using plain radiography had an average author/study count of 5.3, CT had 4.5, and MRI had 5.9. A recent USI study had the largest number of authors listed for a single study (n = 24) [30], bringing the average co-authors per study up to 11.8 for studies using USI. Only one study was authored by a single author (445). **Table 21** displays the ten most published authors based on their appearance as first author, or

as an author listed anywhere in the author list. Hylton Menz had the largest number author appearances (including first author and any author), and total citations.

The 158 included studies were conducted across 232 individual affiliations/institutions. **Table 21** shows the top ten most productive affiliations based on the number of published studies associated with the affiliation of any listed author. La Trobe University located in Australia and Keele University in the United Kingdom were the institutions that published the highest numbers of studies (n = 27 and n = 19, respectively).

Table 17. Citations across imaging modalities

		All	Plain radiography	CT	MRI	USI
Number of studies		158a	140	24	14	4
Total citations		3,690	3,337	616	326	56
Average citations per study		23.4	23.8	25.7	23.3	14.0
Average annual citation rate per study		2.1	2.1	2.2	1.3	1.5
Most cited country	Country	United States of America	United States of America	United States of America	United States of America	Canada
	Number of studies	36	34	4	2	1
	Total citations	1724	1538	216	173	29
	Average citations per study	47.6	45.2	54.0	86.5	29.0
	Average annual citation rate per study	3.1	2.9	3.1	6.9	2.2
Most cited author *(first author)*	Author	Menz HB	Menz HB	Stephens HM	El-Rashidy H	Matsos M
	Number of studies	10	10	1	1	1
	Total citations	254	254	104	107	29
	Average citations per study	25.4	25.4	104	107	29
	Average annual citation rate per study	2.8	2.8	4.0	9.7	2.2
Most cited author *(any author)*	Author	Menz HB	Menz HB	Stephens HM	El-Rashidy H	Matsos M
	Number of studies	27	26	1	1	1
	Total citations	560	558	104	107	29
	Average citations per study	20.7	21.5	104	107	29
	Average annual citation rate per study	2.5	2.6	4.0	9.7	2.2
Most cited journal	Journal	Journal of Bone and Joint Surgery-Series A	Journal of Bone and Joint Surgery-Series A	Foot and Ankle International	Foot and Ankle International	Skeletal Radiology
	Number of studies	8	7	9	1	1
	Total citations	931	824	308	107	29
	Average citations per study	116	117	34	107	29
	Average annual citation rate per study	6.0	5.5	2.4	9.7	2.2

[a]24 studies used ≥2 imaging modalities

Table 18. Top five most cited countries based on first author's country across each imaging modality

	Plain radiography				**CT**				**MRI**				**USI**			
Rank	Most cited country	Total citations	n	Average citations per study	Most cited country	Total citations	n	Average citations per study	Most cited country	Total citations	n	Average citations per study	Most cited country	Total citations	n	Average citations per study
1.	USA	1538	34	45.2	USA	216	4	54.0	USA	173	2	86.5	Canada	29	1	29.0
2.	Australia	456	17	26.8	Switzerland	162	3	54.0	Denmark	49	1	49.0	Italy	20	2	10.0
3.	UK	269	18	14.9	Australia	82	1	82.0	UK	34	3	11.3	Germany	8	1	8.0
4.	Switzerland	203	7	29.0	Germany	42	4	10.5	Germany	18	2	9.0				
5.	Germany	82	7	11.7	Japan	23	1	23.0	Italy	11	1	11.0				

USA, United States of America

Table 19. Characteristics of the ten most cited studies

Rank	Article	Journal	Imaging modality	Total citations	Annual citation rate/study
1	Paley et al. 1993 (444)	Journal of Bone and Joint Surgery-Series A	Plain radiography	202	6.97
2	Dobbs et al. 2006 (446)	Journal of Bone and Joint Surgery-Series A	Plain radiography	176	11.00
3	Graves et al. 1993 (447)	Journal of Bone and Joint Surgery-Series A	Plain radiography	172	5.93
4	Mann et al. 1996 (448)	Journal of Bone and Joint Surgery-Series A	Plain radiography	115	4.42
5	El-Rashidy et al. 2011 (449)	Journal of Bone and Joint Surgery-Series A	MRI	107	9.73
6	Stephens et al. 1996 (450)	Foot and Ankle International	Plain radiography & CT	104	4.00
7	Martel et al. 1980 (451)	American Journal of Roentgenology	Plain radiography	99	2.36
8	Knupp et al. 2009 (452)	Journal of Orthopaedic Research	Plain radiography & CT	88	6.77
9	Menz et al. 2007 (13)	Osteoarthritis and Cartilage	Plain radiography	87	5.80
10	Frawley et al. 1995 (453)	Foot and Ankle International	Plain radiography & CT	82	3.04

Table 20. Characteristics of journals with >3 publications (n = 15 journals)

Journal	Studies, n (%)	Impact Factor	Total citations	Average citations per study	Average annual citation rate/study
Foot and Ankle International	24 (15.2)	2.827	663	27.6	2.1
Arthritis Care and Research	11 (7.0)	4.794	118	10.7	2.0
Osteoarthritis and Cartilage	10 (6.3)	6.576	323	32.3	2.9
Foot and Ankle Surgery	9 (5.7)	2.705	76	8.4	1.3
Journal of Bone and Joint Surgery-Series A[a]	8 (5.1)	5.284	931	116	6.0
Journal of Foot and Ankle Surgery	7 (4.4)	1.286	82	11.7	1.7
Journal of Bone and Joint Surgery-Series B[a]	5 (3.2)	NA	127	25.4	1.6
Injury	4 (2.5)	NA	31	7.8	1.0
American Journal of Roentgenology	3 (1.9)	3.959	107	35.7	1.7
Annals of the Rheumatic Diseases	3 (1.9)	19.103	161	53.7	5.9
Clinical Rheumatology	3 (1.9)	2.98	28	9.3	1.6
European Journal of Radiology	3 (1.9)	3.528	25	8.3	1.3
Foot	3 (1.9)	NA	10	3.3	0.7
Journal of Foot and Ankle Research	3 (1.9)	2.303	4	1.3	0.5
Journal of Orthopaedic Science	3 (1.9)	1.601	25	8.3	1.5

[a]Series A = American volume, Series B = British volume; NA= 2020 IF not available

Table 21. Top 10 most published authors and affiliations

	Authors				Affiliations[a]		
Rank	**Author**	**Any author appearances, n (%)**	**First author appearances, n (%)**	**Total citations**	**Affiliation**	**Studies, n (%)**	**Total citations**
1	Menz HB	27 (17.1)	10 (6.3)	560	La Trobe University	27 (17.1)	559
2	Munteanu SE	17 (10.8)	4 (2.5)	390	Keele University	19 (12.0)	258
3	Roddy E	17 (10.8)	1 (0.6)	254	University of Iowa	6 (3.8)	221
4	Marshall M	11 (7.0)	0 (0)	181	University of Leeds	5 (3.2)	45
5	Auhl M	9 (5.7)	0 (0)	62	New York University	4 (2.5)	155
6	Landorf KB	9 (5.7)	0 (0)	258	University of Southampton	4 (2.5)	8
7	Thomas MJ	9 (5.7)	2 (1.3)	167	Duke University	3 (1.9)	127
8	Tan JM	8 (5.1)	0 (0)	60	Hospital or special surgery	3 (1.9)	89
9	Zammit GV	8 (5.1)	2 (1.3)	328	University of Utah	3 (1.9)	63
10	Rathod T	6 (3.8)	1 (0.6)	171	Oslo University Hospital	3 (1.9)	10

[a]Number of studies based on the affiliation of any listed author

Discussion

This is the first bibliometric analysis of published studies employing musculoskeletal imaging to assess the foot in people with osteoarthritis. The findings have shown a notable increase in the publication of studies in this field over the past four decades. Despite this being a likely generic trend across many healthcare fields, this is of relevance given research in the field of foot osteoarthritis needs to be accelerated (454). Although plain radiography remains the earliest and most widely used in research to assess foot osteoarthritis, CT, MRI, and USI have become increasingly more common in the past decade.

Research specific to foot osteoarthritis is less advanced than that of other joints, including knee and hip osteoarthritis (119, 217-219). However, a notable surge in imaging studies for foot osteoarthritis, particularly at the first metatarsophalangeal joint, was noted in the current analysis, the timeline of which is consistent with publication of the 2017 EULAR recommendations to increase research in this field (17). Although studies using plain radiography have substantially increased over the years, the results from this analysis have shown an increased uptake of more advanced imaging. This is consistent with the reported use of MRI, CT, and USI for general musculoskeletal assessments which have increased 615%, 758%, and 500%, respectively, over the past two decades (455).

To date, one of the most notable imaging advancements specific to foot osteoarthritis was the development of the La Trobe Radiographic Foot Atlas in 2007 (13). The impact of this study was evident by its position among the top 10 most cited studies in this analysis. This atlas has led to significant improvements in the ability to consistently estimate prevalence of this condition (6), as well as understand different patterns of foot joint involvement (226). Although more advanced modalities, including MRI and USI are emerging as more accurate evaluators of both bone and soft tissue abnormalities in foot osteoarthritis (210, 292), it is likely that plain radiography will continue to remain the gold standard until validity of these more advanced techniques are determined. Ongoing research in this area is crucial in determining the capacity of modern imaging modalities to detect early inflammatory changes that precede osseous involvement, therefore informing more timely management approaches that aim to prevent further structural progression (18, 48, 49, 339).

The USA accounted for the largest volume of published studies, based on the first author's affiliation, which primarily utilised plain radiography to assess foot osteoarthritis. This finding is comparable with previous bibliometric studies conducted in other medical fields in which the USA is consistently associated the highest research production (456-458). The USA, despite producing the largest volume of work, had the fewest international collaborations. Studies from this region were published by large numbers of different authors affiliated with several different institutions within the USA. In contrast, studies from the United Kingdom and Australia demonstrated the most frequent international collaborations and tended to involve the same authors affiliated with a small number of institutions. This may reflect the more frequent publication of studies employing CT, MRI and USI in European countries. Clinical-based surveys have shown that specific imaging modalities, for example USI, are more widely used in Europe compared with USA and Australasia (459, 460), which may be due to variations in the structure of musculoskeletal radiology training across countries (461). This finding highlights the importance of ongoing international collaboration in this research field (462-465), with different researchers and institutions contributing different skill sets based on their specific knowledge of different imaging modalities.

The performance analysis confirms the continuing use of plain radiography to assess foot osteoarthritis, with studies using plain radiography having the highest citation rate per study, and seven of the top ten most cited studies employing this modality. Citations are regarded as a measure of the impact or influence of a publication within its field of research (431, 466, 467). The IF of journals are also regarded as an indicator of the influence and quality of their published studies (441, 468). In the current analysis, the median journal IF was 2.83 for included studies, which is a relatively high median for the field based on an analysis by SCI Journal in 2018 (469). SCI Journal found that only 2% of journals have an IF of 10 or more, 13% with IF of 4 or more and 20% with an impact of 3 or more. An IF greater than 2.26 places a journal in the top 40% of medical journals, indicating that the published studies are influential in their field (441, 468). However, the validity of the IF as an accurate, meaningful and useful measure of determining research quality is largely debated (470-474). Despite these limitations, IF is the most commonly used and arguably the best existing metric for evaluating the bibliometric impact of published research (472).

The results of this study have several limitations. Firstly, a single database (Scopus®) was used for study identification and some peer-reviewed journals are not indexed in Scopus®. Although hand-searching of reference lists of included studies was undertaken to address this limitation, it is possible that not all studies employing musculoskeletal

imaging to assess foot osteoarthritis were included. Secondly, the results generated from the search strategy may have been affected by not including individual foot joint names as keywords. Thirdly, non-English studies were excluded from the current analysis which may have resulted in an underrepresentation of the scientific productivity of non-English speaking countries in the current study. Fourthly, in order to provide a comprehensive analysis of all studies in this field, our analysis was not limited to studies in which imaging was used to assess a primary outcome measure. This therefore limits our ability to comment on studies specifically aiming to advance knowledge and progress research in this field. Finally, it should also be acknowledged that the majority of studies included in this analysis were representative of a lower level of evidence according to the OCEBM (Level 3 or 4 evidence) (443), and may not be considered as influential as studies of higher evidence.

Conclusion

In conclusion, published research employing imaging to assess foot osteoarthritis has increased substantially over the past four decades. Although plain radiography remains the gold standard and the most utilised modality for research of foot osteoarthritis, the emergence of MRI, CT and USI in the past two decades continues to advance research in this field. This study has also highlighted the importance of international collaboration in allowing researchers and institutions with different skill sets and knowledge to contribute to ongoing research utilising imaging to evaluate foot osteoarthritis.

Chapter 7

International Multispeciality Consensus on how to Image, Define, and Grade Ultrasound Imaging Features of the First Metatarsophalangeal Joint, a Delphi Consensus Study

Reference

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Molyneux P, Bowen C, Ellis R, Rome K, & Carroll, M. International multispecialty consensus on how to image, define, and grade ultrasound imaging features of first metatarsophalangeal joint osteoarthritis, a Delphi consensus study. *Osteoarthritis and Cartilage Open*. 2023; 5(1):100336
https://doi.org/10.1016/j.ocarto.2023.100336

Preface

The bibliometric analysis presented in chapter 6 reported that published research employing imaging to assess foot OA has increased substantially over the past four decades. Although plain radiography remains the most utilised modality for research on foot OA, the emergence of MRI, CT and USI in the past two decades advances research in this field, providing the required evidence to progress with the utilisation of more advanced imaging. As presented in the reviews in Chapters 4-6, it was unclear which USI procedure should be used to examine the first MTPJ OA. Existing guidelines required further refinement in relation to anatomical landmarks, to establish a standardised imaging procedure and improve the interpretability and reproducibility between studies that evaluate the first MTPJ. The reviews conducted in Chapters 4 and 5 identified the need to develop a standardised USI acquisition procedure and grading system specific for first MTPJ OA. Since the systematic review predominantly included hand OA studies, and the scoping review was not specific to USI of first MTPJ OA, further research was required specific to the USI examination of first MTPJ OA.

To address the knowledge gaps identified in Chapters 4, 5 and 6, an international multi-speciality Delphi study was conducted. The bibliometric analysis also highlighted the importance of international collaboration in allowing researchers and institutions with different skill sets and knowledge to contribute to ongoing research utilising imaging to

evaluate foot OA, providing further evidence for the study presented in Chapter 7 to not only canvas expert opinion, but to do so from an international perspective. The Delphi study was administered through the Osteoarthritis Research Society International (OARSI) Foot and Ankle OA group, the UK Podiatry USI group, and the European League Against Rheumatism (EULAR) USI network, to gain expert consensus concerning which USI features should be assessed and graded, and what USI acquisition procedure should be performed when examining first MTPJ OA. The Delphi results will be incorporated into the methodological development of the USI acquisition procedure presented in Chapter 8 and the USI atlas presented in Chapter 9.

Abstract

Objective

To reach consensus concerning which ultrasound imaging features should be assessed and graded, and what ultrasound imaging procedure should be performed when examining osteoarthritic change in the first metatarsophalangeal joint.

Design

An online Delphi study was conducted over four iterative rounds with 16 expert health professionals. Items were scored from 0-100 (0 = not at all important; 100 = extremely important). Consensus was defined based upon an item receiving a median score of ≥70% acceptance. Items receiving median score of ≤50% were rejected. Items considered ambiguous (median score 51% - 69% of acceptance) were assessed in an additional round. A final round determined the content validity of items through calculation of the content validity ratio and content validity index.

Results

Sixteen items were deemed essential, which included osteophytes graded dichotomously, cartilage damage graded continuously, synovitis and joint space narrowing graded on a semiquantitative scale. The panel deemed essential that the first metatarsophalangeal joint start in a neutral position, then move through range of motion for both dorsal and plantar scanning, orientating the probe in longitudinal and in transverse, whilst using first metatarsal head and proximal phalanx as anatomical landmarks. A supine body position was only deemed essential for a dorsal scan and a neutral foot/ankle position was only rated essential for a plantar scan. The content validity index of the 16 essential items was 0.19.

Conclusion

The consensus exercise has identified the essential components the ultrasound imaging acquisition procedure should encompass when examining first metatarsophalangeal joint osteoarthritis.

Introduction

Osteoarthritis (OA) is a global health burden and leading cause of chronic pain, joint stiffness, functional limitation, and disability among older adults (24, 27). Within the foot, the first metatarsophalangeal joint (MTPJ) is the most commonly affected joint with a prevalence of 8% for individuals aged over 50 years (6). By age 60 years, radiographic first MTPJ OA is present in approximately 46% of women and 32% of men (235).

There has been a fundamental shift in our understanding of OA, from a cartilage-only disease to a whole organ disease, recognising the heterogeneous involvement of multiple joint tissues, including cartilage damage, subchondral bone remodelling, synovial inflammation, and osteophyte development (29, 36, 37). OA is not simply a process of wear and tear, but rather abnormal remodelling of joint tissues driven by a host of inflammatory mediators (29, 46). Attention has now turned to the prognostic value and role of inflammatory markers (29, 35, 46), with several studies reporting an association between active synovitis and structural OA progression (18, 48, 49). Despite this advancement in knowledge our current method of diagnosing foot OA is governed by the findings of conventional radiography (13, 14), which captures OA later in the disease process when irreversible structural damage has already occurred.

Ultrasound imaging (USI) potentially affords inherent advantages for the diagnosis of first MTPJ OA, providing a whole organ assessment with multiplanar acquisitions, enabling a more detailed assessment of pathology (17, 279). USI has gained recognition due to its ability to detect inflammatory joint pathology that is otherwise not detected by clinical examination (36, 307), and reliably quantify both bone and soft tissue abnormalities (17). Given the ability of USI to depict tissue-specific morphological changes before the onset of pain and before the point of irreversible structural damage, USI may play a fundamental role in the earlier detection and assessment of foot OA (320, 475), thus enabling more targeted and timely interventions that may provide capacity to alter disease progression. However, the role of USI for OA diagnosis in foot joints has not been clearly defined.

Currently, the use of USI to categorise OA-related joint changes has several limitations: Firstly, it is not known what USI features are specific to and representative of first MTPJ OA. Secondly, there is no clear consensus as to which type of grading system (e.g. dichotomous or on a semiquantitative scale) should be applied to determine degree of severity for each USI feature. Finally, it is unclear what USI acquisition procedure should

be used to examine the first MTPJ. Therefore, the objective of this research was to adopt a Delphi study design to reach consensus concerning USI imaging of first MTPJ OA.

Methods

Design

An online four-round Delphi study design was undertaken to achieve consensus on which USI features are indicative of first MTPJ OA, how features should be graded, and what USI acquisition procedure is preferable when examining the first MTPJ. The Delphi method is an iterative series of structured rounds that surveys experts to achieve a convergence of opinion in order to gain group consensus (476). Subsequent survey rounds refine and define the items, gauging their accuracy or support from the participants (477). This method is considered an appropriate means of dealing with an absence of guidelines (476). Conducting and rEporting of dElphi Studies (CREDES) recommendations were adopted to provide guidance on a reporting standard (478). Details of how our study reporting aligned with the CREDES recommendations are detailed in **Appendix 8.** The study was approved by *Auckland University of Technology Ethics Committee (AUTEC) (21/117*) (**Appendix 9**).

Participants

Study recruitment occurred via one of two pathways: (1) potential participants were recruited via their association with the Osteoarthritis Research Society International (OARSI) Foot and Ankle OA discussion group, the United Kingdom (UK) Podiatry US group or the European League Against Rheumatism (EULAR) US network group. The three network groups consist of expert health professionals from either a clinical and/or academic background: rheumatologists, sonographers, radiologists, podiatrists, physiotherapists, epidemiologist, academics, researchers, and orthopaedic surgeons. Geographically, members were located in New Zealand, Australia, United Kingdom, United States of America, Canada, Spain, Brazil, Italy, Netherlands, and Japan. Therefore, the three groups were diverse, and a representative group of clinicians and researchers involved in the investigation of foot and ankle OA (479). Alternatively, (2) participants were identified through snowball sampling, in which potential participants were invited to participate through a known contact of the primary researcher (PM). All participants were anonymised to each other, enabling them to share their own thoughts without judgement (480).

Survey Format

The Delphi survey was implemented using online survey platform Qualtrics© (Qualtric Research Suite Provo. UT 2013). Each round of the Delphi was piloted among co-authors (M.C, C.B, R.E and K.R) who were not participants, to refine the format and question design. Participants were requested to consider each question in terms of developing an USI atlas to grade the degree of osteoarthritic related change in the first MTPJ. Consent was obtained prior to the commencement of each round and there was no intra-panel communication. Participants were given a four-week deadline to complete each Delphi round. Reminders were sent via email two weeks following the opening of each round, and participants were given an additional two weeks to complete the round before being classified as a non-responder. After the deadline, the surveys were collated.

Procedure

Delphi Round 1

The Delphi was developed using an evidence driven approach with findings from a systematic review (481) and scoping review (482) used to inform Round 1 open-ended questions. The systematic review investigated what USI features are associated with OA in peripheral joints and how USI features in peripheral joints are defined and graded (481). The scoping review investigated USI acquisition procedures and guidelines used to assess the first MTPJ (482). Round 1 included participant information, online consent, instructions, and the Round 1 survey **(Appendix 10).** Round 1 was divided into two sections: (i) participant characteristic questions and (ii) open-ended questions concerning USI of first MTPJ OA. Due to the inconsistencies reported in both reviews and the dearth of knowledge specific to first MTPJ OA, open-ended questions were specifically aimed to encourage alternative views to determine which USI features are indicative of first MTPJ OA, how should those features be graded, and what USI acquisition procedure should be used to evaluate the first MTPJ.

Survey responses were exported and analysed in Microsoft® Excel®, version 2205 with responses collated into the following sections: Part A: First MTPJ OA USI features; Part B: Grading USI features and Part C: USI acquisition procedure. The USI acquisition procedure was further broken down into two components (I) Patient body and lower limb positioning (dorsal and plantar) and (II) Probe position (longitudinal and transverse). Data were presented as medians and interquartile range unless otherwise noted.

All Round 1 responses were collated with similar responses amalgamated to ensure that the subsequent round was not repetitive and easy to complete. A set of themes were established that mapped USI features, grading systems and USI acquisition procedure; to create items for Round 2 (483). Themes were developed through qualitative descriptive analysis (484, 485) and reviewed by a second author (M.C). Open-ended responses from Round 1 were combined with additional items generated from the systematic and scoping reviews (481, 482), that were not identified by participants in Round 1.

Delphi Round 2

Due to reduced uptake of Round 1, linked to timing in the midst of the COVID pandemic, Round 2 was redistributed to all three network groups, via pathway one and to those that were invited to participate through snowballing method. Potential participants were sent an invitation email containing the Round 2 survey link. Participants were required to rate their level of agreement for each item using a sliding scale from 0-100 (0 = not at all important; 100 = extremely important). The Round 2 survey is detailed in **Appendix 11**. Consensus was defined based upon items receiving a median score of ≥70% of acceptance (486). Items receiving a median score of ≤50% were rejected. Items where there was disagreement, were considered as being ambiguous (answers receiving a median score between 51% - 69% of acceptance) and were taken back to participants for further consideration in Round 3 (477).

Delphi Round 3

An invitation to participate in Round 3 was only sent to those participants who responded to Round 2. In Round 3, participants were asked to accept or reject ambiguous items generated in Round 2 (answers receiving a median score of between 51% - 69% of acceptance). Round 3 provided participants the opportunity to change their answers considering the group's median. To aid in consensus decision making, participants were provided the results from Round 2, which included the group median score and interquartile range (IQR). For Round 3, consensus was defined based upon item statements receiving a median score of ≥70% of acceptance. Statements receiving a median score of <70% were rejected (486, 487). The Round 3 survey is outlined in **Appendix 12.**

Delphi Round 4: Content Validity

Evaluating content validity is a critical step in the development process, which demonstrates the final items are representative of the entire domain the assessment seeks to measure (488), thus ensuring the USI atlas contains the appropriate content to diagnose and grade first MTPJ OA. To determine the content validity of items to be included in the atlas, all participants who participated in Round 3 were asked to rate all accepted items into one of three categories: “essential,” “useful, but not essential,” or “not necessary.” The Round 4 survey is detailed in **Appendix 13.** The content validity ratio (CVR) was used to determine the content validity of each item included in Round 4, using the formula proposed by Lawshe (489). The CVR is a widely applied statistic when quantifying content validity of instruments which involves a panel of 'experts' (488). Items perceived as "essential" by ≥50% of the panel members, provides assurance of content validity(489). A positive CVR indicates more than 50% of the panel members rate the item as essential. Items deemed not essential by ≥50% of panel members were discarded. The content validity index (CVI) was calculated. The CVI is the mean of the CVR values of the retained items and is an indicator of overall content validity (488, 489).

Results

Participant Characteristics

Round 1 of the Delphi exercise received 10 responses. **Table 22** details the characteristics of the 10 participants who completed Round 1. Round 2 received 20 responses. Sixteen participants completed Round 3, of which all 16 participants completed Round 4 (content validity round). Although the invited participants varied with regard to demographics and experience, the respondents were researchers, podiatrists, physiotherapists, sonographers, radiographers and a physiatrist. The characteristics of the 16 participants who completed Rounds 2, 3 and 4 are detailed in **Table 23**. Participants were predominantly female (6 male: 10 female), aged over 40 years old (81%), White British ethnicity (44%) and currently living in the UK (50%). Participants were predominantly podiatrists and/or researchers (44%). Two thirds of the participants reported to have between 0-10 years of musculoskeletal USI experience. Half the participants reported they held no formal qualification relating to musculoskeletal USI.

Table 22. Demographics of participants who completed Round 1

		n (%)
Gender	Male	4 (40)
	Female	6 (60)
Age range	20-29 years old	1 (10)
	30-39 years old	1 (10)
	40-49 years old	5 (50)
	50-59 years old	2 (20)
	Over 60 years old	1 (10)
Ethnicity	Caucasian	1 (10)
	Hispanic	1 (10)
	NZ European	1 (10)
	White British	7 (70)
Country	Australia	1 (10)
	New Zealand	1 (10)
	Spain	1 (10)
	United Kingdom	7 (70)
Profession	Physiotherapist	1 (8.3)
	Podiatrist	6 (50)
	Sonographer	1 (8.3)
	Radiographer	1 (8.3)
	Researcher	3 (25)
Clinical or Academic	Clinical	1 (10)
	Academic	3 (30)
	Both Clinical: Academic	6 (60)
MSK USI experience (years)	0-5 years	4 (40)
	6-10 years	3 (30)
	11-15 years	2 (20)
	Over 20 years	1 (10)
Highest qualification relating to MSK USI	MSc Medical Ultrasound	2 (20)
	PGDip Medical Ultrasound	1 (10)
	PGCert Medical Ultrasound	2 (20)
	Continued professional development course	1 (10)
	No formal USI qualifications	4 (40)

*Some participants selected more than one academic and/or professional background

Table 23. Demographics of participants who completed Round 4

		n (%)
Gender	Male	6 (38)
	Female	10 (62)
Age range	Under 20 years old	0 (0)
	20-29 years old	2 (13)
	30-39 years old	1 (6)
	40-49 years old	6 (40)
	50-59 years old	3 (19)
	Over 60 years old	4 (25)
Ethnicity	Caucasian	3 (19)
	Hispanic	1 (6)
	Irish	1 (6)
	Italian	1 (6)
	NZ European	1 (6)
	White British	7 (44)
	White	2 (13)
Country	Australia	2 (14)
	Canada	1 (6)
	Italy	1 (6)
	Netherlands	1 (6)
	New Zealand	1 (6)
	Spain	1 (6)
	United Kingdom	8 (50)
	United States of America	1 (6)
Profession	Physiatrist	1 (6)
	Physiotherapist	3 (19)
	Podiatrist	7 (44)
	Sonographer	1 (6)
	Radiographer	1 (6)
	Researcher	7 (44)
Clinical or Academic	Clinical	2 (12)
	Academic	6 (38)
	Both Clinical: Academic	8 (50)
MSK USI experience (years)	0-5 years	7 (44)
	6-10 years	4 (24)
	11-15 years	2 (13)
	16-20 years	2 (13)
	Over 20 years	1 (6)
Highest qualification relating to MSK USI	MSc Medical Ultrasound	2 (13)
	PGDip Medical Ultrasound	1 (6)
	PGCert Medical Ultrasound	4 (25)
	Continued professional development course	1 (6)
	No formal USI qualifications	8 (50)

*Some participants selected more than one academic and/or professional background

Delphi Findings

Figure 10 details the number of participants involved in each round and the number of items developed, accepted, and/or rejected from each round. Authors identified 50 open-ended items based on the participants free-text responses in Round 1. These items were combined with an additional 12 items generated from the authors' recent systematic (481) and scoping reviews (482) to be considered in Round 2. Participants rated 62 items in Round 2, 23 items reached consensus (medians score of ≥ 70%), 21 items were considered ambiguous (achieved a median score between 51–69% agreement), and 18 items were excluded (median score ≤ 50%). As a result of two features (tenosynovitis and capsulitis) being excluded their associated grading systems, which were rated as ambiguous were also excluded. In Round 3, participants rated the 21 ambiguous items, three items achieved ≥ 70% agreement and 18 items were excluded. Of the 18 items that were excluded, three were features (synovial hypertrophy, joint effusion and joint erosion) that had previously accepted grading systems from Round 2. For that reason, their associated grading system were now excluded. All accepted items and the round they were accepted are displayed in **Table 24**. Subsequently, 23 accepted items were included in the content validly round (Round 4). Sixteen items were deemed essential by ≥50% of the participants with a CVI of 0.19 **(Table 25)**.

Figure 10. Number of participants involved in each round and the number of items developed, accepted, and/or rejected from each round

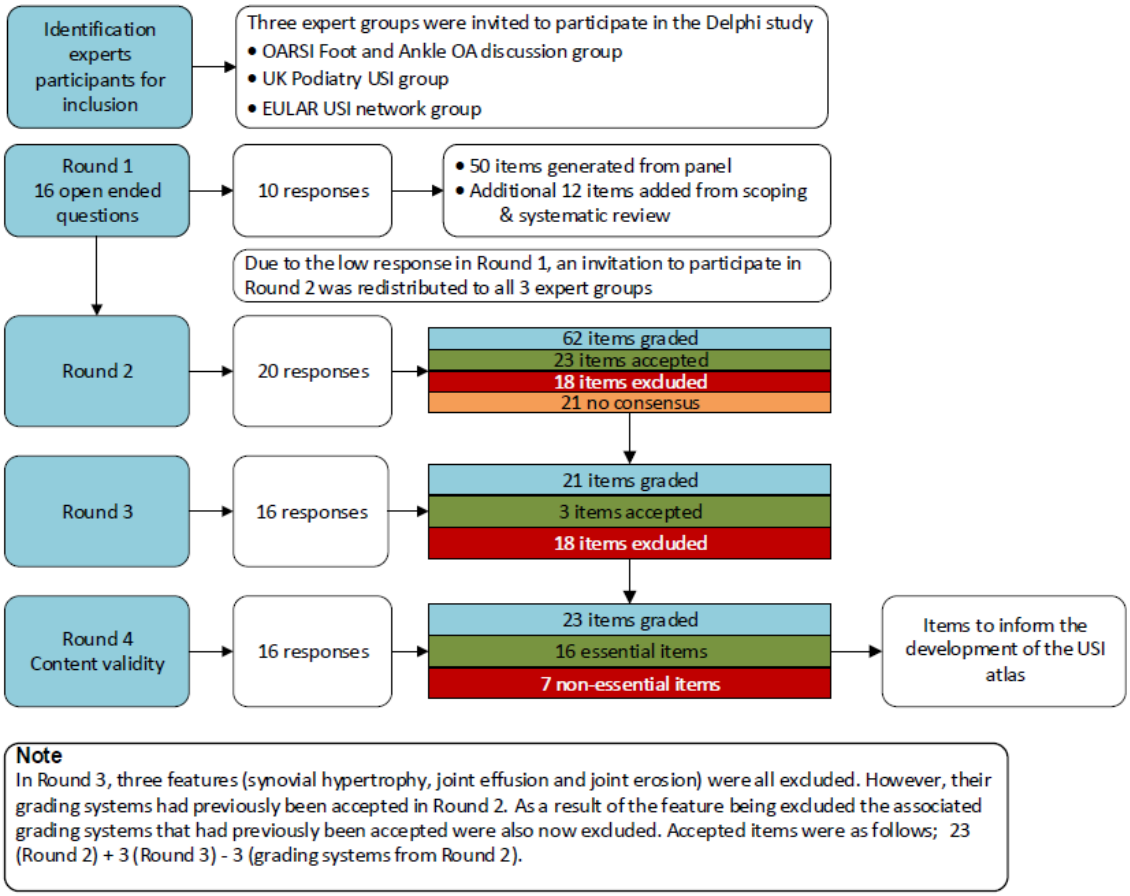


Table 24. All accepted items from the Delphi survey used to inform the methodological development of an USI atlas to grade the degree of osteoarthritic change in the first MTPJ

Item category	Item (round accepted)	Percentage score median (IQR)
PART A: First MTPJ OA ultrasound imaging features	Synovitis (2)	70 (42-80)
	Osteophytes (2)	81 (65-100)
	Cartilage damage (2)	89 (73-94)
	Joint space narrowing (2)	79 (71-93)
PART B: Grading ultrasound imaging features	Synovitis Semiquantitative (3)	74 (55-80)
	Osteophytes Dichotomous (2)	78 (29-84)
	Osteophytes Semiquantitative (3)	70 (51-80)
	Cartilage damage/thickness Cont (mm) (2)	78 (35-84)
	Joint space narrowing Semiquantitative (3)	75 (63-80)
PART C: US Imaging acquisition protocol Patient positioning (Dorsal)	Body position – Supine (2)	86 (73-90)
	Knee position – Flexed (2)	82 (27-87)
	Ankle/foot position – neutral (2)	75 (58-91
	Ankle/foot position – Foot flat on plinth (2)	72 (46-84)
	First MTPJ position – Start in neutral then move through ROM during scanning (2)	84 (67-90
Patient positioning (Plantar)	Knee position – extended	74 (60-92)
	Ankle/foot position – neutral (2)	80 (69-82
	First MTPJ position – Start in neutral then move through ROM during scanning (2)	79 (66-87)
Probe position (Longitudinal)	Dorsal aspect of the forefoot, parallel to the first metatarsal head and proximal phalanx, joint line central to the image (2)	79 (75-90)
	Plantar aspect of the forefoot, parallel to the first metatarsal head and proximal phalanx, joint line central to the image (2)	76 (67-80)
	Medial aspect of metatarsal head and proximal phalanx, joint line central to the image (2)	79 (78-87)
Probe position (Transverse)	Dorsal aspect of the foot, perpendicular to diaphysis of the first metatarsal then move distally to the diaphysis of first proximal phalanx, joint line central to the image (2)	82 (78-92)
	Plantar aspect of the foot, perpendicular to diaphysis of the first metatarsal then move distally to the diaphysis of first proximal phalanx, joint line central to the image (2)	77 (56-90)
	Medial aspect of metatarsal head and proximal phalanx, joint line central to the image (2)	72 (60-76)

Table 25. The content validity ratio (CVR) of each item included in Round 4

Round 4 items	CVR Value	
PART A: FIRST MTPJ OA USI FEATURES		
Synovitis	0	
Osteophytes	0.25	
Cartilage damage	0.13	
Joint space narrowing	0.5	
PART B: GRADING USI FEATURES		
Synovitis Semiquantitative	0	
Osteophytes Dichotomous	0.25	
Osteophytes Semiquantitative		-0.38
Cartilage damage/thickness Cont (mm)	0	
Joint space narrowing Semiquantitative	0.5	
PART C: USI ACQUISITION PROTOCOL (Dorsal)		
Body position - Supine	0.13	
Knee position - Flexed		-0.38
Ankle/foot position - neutral		-0.38
Ankle/foot position - Foot flat on plinth		-0.13
First MTPJ position - Start in neutral then move through ROM during scanning	0	
PART C: USI ACQUISITION PROTOCOL (Plantar)		
Knee position - extended		-0.13
Ankle/foot position - neutral	0.13	
First MTPJ position - Start in neutral then move through ROM during scanning	0.13	
Probe position (Longitudinal)		
Dorsal aspect of the forefoot, parallel to the first metatarsal head and proximal phalanx, joint line central to the image	0.5	
Plantar aspect of the forefoot, parallel to the first metatarsal head and proximal phalanx, joint line central to the image	0	
Medial aspect of metatarsal head and proximal phalanx, joint line central to the image		-0.25
Probe position (Transverse)		
Dorsal aspect of the foot, perpendicular to diaphysis of the first metatarsal then move distally to the diaphysis of first proximal phalanx, joint line central to the image	0.5	
Plantar aspect of the foot, perpendicular to diaphysis of the first metatarsal then move distally to the diaphysis of first proximal phalanx, joint line central to the image	0	
Medial aspect of metatarsal head and proximal phalanx, joint line central to the image		-0.38
CVI	**0.19**	

Discussion

The Delphi study design sought to generate consensus between experts to inform the methodological development of an USI atlas to grade the degree of osteoarthritic related change in the first MTPJ. Through applying a Delphi study design, the panel rated 16 items as ‘essential’ across three domains: first MTPJ OA USI features, grading USI features, and USI acquisition procedure.

OA is characterised by both structural damage and inflammatory abnormalities (356). Four USI features rated as essential to be included in the USI atlas were synovitis, osteophytes, joint space narrowing, and cartilage damage/thickness. It is well understood that inflammation is an important driver of the disease and contributes to the pain experienced and the structural progression of the disease (18, 48, 49). Given the prognostic value of inflammatory features and the sensitivity USI possesses in detecting subclinical inflammatory change (36, 307), the inclusion of multiple inflammatory features may be more helpful in elucidating the role of inflammation in foot OA. In contrast, a recent USI consensus-based study, conducted by Outcome Measures in Rheumatology (OMERACT), for grading hand OA (376), scored grey scale inflammatory abnormalities for synovial hypertrophy and joint effusion separately in addition to power Doppler signal (flow signal detected within synovial hypertrophy to be considered a sign of synovitis) (374, 376). Furthermore, the OMERACT hand OA study reported marked variation in prevalence between grey scale and Doppler detected inflammatory features (376). Grey scale inflammatory features, joint effusion and synovial hypertrophy were frequently observed (40% and 45% respectively). In contrast power doppler signals (considered a sign of synovitis) were reported in 6% of interphalangeal joints (376). Therefore, the exclusion of grey scale features indicative of inflammation may result in OA being underestimated.

The inclusion of synovitis as the only marker of inflammation may be reflective of the inconsistencies in the different entities of synovial pathology indicative of inflammation (481). There has been marked variations across studies in terms of how synovitis, synovial hypertrophy and joint effusion are defined and categorised as USI features (481). The inclusion of synovitis as a core element for the USI evaluation of first MTPJ OA aligns with a preliminary USI grading system for hand OA, that combined synovial hypertrophy and joint effusion into one grey scale synovitis score (350). Whilst the recent OMERACT definition encompasses the whole concept of synovitis being the “presence of a hypoechoic synovial hypertrophy regardless of the presence of effusion or any grade

of Doppler signal" (366), it does necessitate the inclusion of Doppler signal as part of image acquisition when examining synovitis.

To date, one of the most notable imaging advancements specific to foot OA was the development of the La Trobe Radiographic Foot Atlas in 2007 (13). This atlas incorporates both osteophytes and joint space narrowing to provide a quantitative means of assessing foot OA. For that reason, the acceptance of both structural features (osteophytes and joint space narrowing) may have been influenced by their role in the radiographic foot atlas (13). Regardless, USI has been shown to detect more joints with osteophytes than conventional radiography (313, 341). The inclusion of osteophytes and joint space narrowing will allow for comparison between radiographic and sonographic detection and grading, consequently enabling the construct validity between imaging modalities to be determined.

Although the heterogeneous involvement of multiple joint tissues is now well recognised, cartilage damage remains the cornerstone in the pathophysiology of OA (118), this was reflected by its acceptance as an essential USI feature. Unlike radiography, USI can directly visualise some parts of articular cartilage (282). Cartilage damage may not be uniform across the entire joint (490, 491). Therefore, the ability to consistently examine the exact same part of cartilage, with USI, will influence the reliability and validity of this measure. Given the general opinion that USI is heavily operator dependent for image acquisition and interpretation (50, 370), investigating the reliability of grading cartilage damage would be critical before inclusion into the USI atlas. This reinforces the need for further refinement of anatomical landmarks to guide probe positioning to ensure a standardised USI acquisition procedure.

Current USI grading systems applied to OA have been largely extrapolated from those originally designed and validated to quantify inflammatory change in rheumatoid arthritis (RA) (481). Inflammation associated with OA is fundamentally different from that in RA, with OA having lower levels of inflammatory proteins (492), less pronounced synovitis (493, 494), no response to biologic drugs used in RA, and mediated primarily by the innate immune system (46). The distinct difference of inflammation experienced in OA compared to RA(49, 331), reinforces the need for OA-specific grading systems that truly depict the disease progression of first MTPJ OA.

Both dichotomous and semiquantitative grading systems were accepted for osteophytes. However, a dichotomous grading system was deemed essential by the panel members. While dichotomous scoring may be viewed as a simpler method to distinguish between

the absence or presence of a feature, it presents no mechanism to determine the progression of first MTPJ OA over time. Alternatively, a semiquantitative grading system was accepted for synovitis and joint space narrowing. A semiquantitative system enables quantification of disease progression and provides insight into the degree of osteoarthritic change (481). Issues related to the subjectivity of semiquantitative systems have been highlighted, with challenges in interpretation and differentiation between grading of disease severity (331). This may be reflective of the lack of consensus to guide grading and/or studies which have extrapolated RA grading systems to OA. The acceptance of cartilage damage/thickness to be graded using a continuous measure will mitigate issues with distinguishing between grades of severity.

An USI acquisition procedure involves numerous variables that need to be considered as part of examination, these include patient positioning, transducer orientation and surfaces scanned. As it stands only two consensus-based guidelines exist to inform the USI acquisition procedure to assess the first MTPJ (279, 324). Despite this, there has been marked inconsistency in the application of guidelines across studies (482). The 2001 EULAR guidelines included limited instructions on body position, transducer orientation and surfaces of the first MTPJ to scan (supine position for the dorsal scans and prone position for the plantar scans) (324). In 2017 a new EULAR-endorsed task force revised the standardised procedures for USI in rheumatology (279). The updated EULAR guidelines for performing USI of the first MTPJ addressed patient positioning, transducer orientation, probe position (starting point) and, scanning technique (279). Despite this enhancement, the revised guidelines still lack sufficient detail outlining specific anatomical reference points to ensure a standardised USI acquisition procedure.

The Delphi panel considered both patient and lower limb positioning for scanning the dorsal, plantar and medial surface of the first MTPJ. Although accepted, scanning the medial aspect of the first metatarsal head and proximal phalanx, was not rated as an essential item. Eight items were deemed essential when scanning both dorsal and plantar surfaces of the first MTPJ. Unlike previous guidelines, the Delphi panel included first MTPJ positioning. Wherein it was deemed essential that the first MTPJ should start in a neutral position (the position where the foot is neither pronated nor supinated), then move through full range of motion during the scanning procedure for both a dorsal and plantar scans. Consistent with both 2001 (324) and 2017 guidelines (279), a supine body position was deemed essential, however only when performing a dorsal scan. Positioning the ankle/foot in neutral was deemed essential, although only for a plantar scan. This is inconsistent with the 2017 guidelines which reported a dorsiflexed foot position (279). The 2001 guideline (324) provided no further detail on how the lower limb

should be positioned. Regarding knee positioning, a flexed and extended knee were accepted items for both dorsal and plantar scans respectively. Both knee positions are consistent with the 2017 guidelines (279), however neither item were rated as essential.

The Delphi panel also deemed essential that the probe be orientated both longitudinally and transverse when scanning the dorsal and plantar aspect of the first MTPJ. Specifically, for a longitudinal scan the probe should be positioned on the plantar/dorsal aspect of the forefoot, parallel to the first metatarsal head and proximal phalanx, joint line central to the image. In conjunction with a transverse scan, where the probe should be positioned on the plantar/dorsal aspect of the foot, perpendicular to the diaphysis of the first metatarsal then move distally to the diaphysis of first proximal phalanx, joint line central to the image. Previous guidelines provide limited descriptions of anatomical landmarks to guide probe positioning. The revised 2017 guidelines only reported performing a transverse scan when examining articular cartilage (279). The findings of the Delphi support the application of a multiplanar technique when examining the first MTPJ. A multiplanar technique is crucial in cases where one feature (e.g., joint effusion or osteophyte) is obstructing the view of another feature under examination, or when there is severe structural changes, often associated with rheumatic diseases.

A strength of the current study was the inclusion of content validity. Evaluating content validity is a critical step in the development process of instruments used to measure constructs in research (488). Content validity provides evidence to the extent at which items of an assessment instrument are representative of the entire domain the assessment seeks to measure (488). Our findings need to be viewed in the context of several limitations. Firstly, the exercise was primarily dependent upon an expert consensus based approach (495). Therefore, it needs to be acknowledged that it is based on the subjective opinion of the participants, which in the context of evidence-based practice constitutes low level evidence (496). Secondly, the low sample obtained, and level of professional experience may have limited the potential for ideas as well as the number of generated items. The low number of participants maybe reflective of participant recruitment proceeding during the midst of the COVID-19 pandemic. Thirdly, author bias may have been introduced during the amalgamation of Delphi items. However, the authors have attempted to minimise this with transparency of the implemented process. Fourthly, anonymity and confidentiality are suggested requirements of participants in Delphi surveys to minimise the effects, if any, of collusion (476). It cannot be guaranteed that participants remained anonymous to their colleagues, however there was no instance where the author’s believed anonymity was not maintained. All participants were asked to keep both their responses and participation

confidential to minimise this bias risk. Finally, the term ‘expert’ and its application to health practitioners is controversial (480). By inviting members from three different groups (OARSI, UK Podiatry US, and EULAR US network), it is expected that the relevant knowledge, experience, and diversity was reflected in the expert panel members.

Implications for Further Research

The outcomes of the Delphi study will inform future studies into the methodological development of an USI atlas to grade the degree of osteoarthritic change in the first MTPJ. Ongoing research is crucial in determining the capacity of USI to detect early inflammatory changes that precede osseous involvement, therefore informing more timely management approaches that aim to prevent further structural progression.

Conclusion

Sixteen items were accepted as essential for the USI examination of first MTPJ OA. This included osteophytes graded dichotomously, cartilage damage graded on a continuous scale, synovitis and joint space narrowing graded on a semiquantitative scale. The first MTPJ imaged in both dorsal and plantar orientation with the body supine for a dorsal scan and a neutral ankle position for a plantar scan. This data will be the catalyst in developing a USI classification criterion, specific for first MTPJ OA.

Chapter 8

Reliability of an Ultrasound Imaging Acquisition Procedure for Examining Osteoarthritis in the First Metatarsophalangeal Joint

Reference

Molyneux P, Bowen C, Ellis R, Rome K, Fitzgerald K, Clark P, & Carroll M. Reliability of an ultrasound imaging acquisition procedure for examining osteoarthritis in the first metatarsophalangeal joint. *Journal of Foot and Ankle Research*. 2024; 17(1):e12002.

Preface

The systematic review (Chapter 4) identified inconsistencies in the assessment of USI features, the definition of features, and the grading systems used to determine the degree of OA change in peripheral joints. Inconsistencies were identified in the scoping review (Chapter 5) against international guidelines and limited implementation of consensus-based recommendations for USI procedure guidance when evaluating the first MTPJ. It was unclear which USI procedure should be used to examine first MTPJ OA. Current guidelines require further refinement of anatomical landmarks to establish a standardised imaging procedure to improve interpretability and reproducibility between studies that evaluate the first MTPJ. To address these research gaps, a Delphi study (Chapter 7) was undertaken to gain international expert consensus concerning which USI features should be assessed and graded, and what USI procedure should be performed when examining first MTPJ OA. The Delphi study identified the essential components that the USI acquisition procedure should encompass when examining first MTPJ OA.

Chapter 8 outlines the development of a novel USI acquisition procedure and grading system for examining first MTPJ OA and establishes the intra-examiner and inter-examiner reliability of the procedure. The USI acquisition procedure and grading system developed were informed by the systematic review presented in Chapter 4, the scoping review presented in Chapter 5, the Delphi study presented in Chapter 7, and through

underpinning work with an experienced sonographer and radiologists. The reliability study described in Chapter 8 was required to ensure the USI features and their associated grading systems included were reliable across sessions and examiners to inform the methodological development of an USI atlas.

Abstract

Objective

Given the ability of ultrasound imaging (USI) to depict tissue-specific morphological changes before the onset of pain and the point of irreversible structural damage, USI could play a fundamental role in earlier detection and assessment of foot osteoarthritis (OA). Current guidelines require further refinement of anatomical landmarks to establish a standardised imaging procedure to improve interpretability and reproducibility between studies evaluating the first metatarsophalangeal joint (MTPJ). The aims were to develop an USI acquisition procedure and grading system to examine OA features in the first MTPJ and to determine intra-examiner and inter-examiner reliability of a novel USI acquisition procedure.

Design

Thirty participants were included with first MTPJ OA confirmed radiographically with the use of the La Trobe Foot Atlas. An experienced sonographer applied a newly developed USI procedure to examine the following features – joint effusion, synovial hypertrophy, synovitis, joint space narrowing, osteophytes, and cartilage thickness. A semiquantitative grading system was applied to all features. A continuous measure was also examined for osteophyte size, joint space narrowing, and cartilage thickness. To determine intra-examiner and inter-examiner reliability an experienced radiologist and sonographer applied the developed grading system to the images acquired from two imaging sessions. Intra-examiner and inter-examiner reliability were calculated using intraclass correlation coefficients (ICC).

Results

ICCs for intra-examiner between session reliability ranged from 0.58 to 0.92 for semiquantitative grading and 0.39 to 0.94 for continuous measures. Joint effusion and osteophytes achieved the highest intra-examiner reliability (ICC = 0.78-0.94). ICCs for Session one inter-examiner reliability ranged from 0.61 to 1.00 for semiquantitative grading, and all continuous measures had an ICC of 1.00 ICCs for session two inter-examiner reliability ranged from 0.55 to 1.00 for semiquantitative grading and 0.90 to 0.97 for continuous measures. Inter-examiner reliability was good for grading joint effusion (ICC = 0.55-0.62) and was excellent for all other USI features (ICC = 0.77-1.00).

Conclusion

The USI acquisition procedure and grading system are reliable in evaluating first MTPJ osteoarthritis features in participants with radiologically confirmed osteoarthritis. The study was intended to inform the methodological development of an ultrasound atlas for grading the degree of osteoarthritic change in the first MTPJ.

Introduction

Ultrasound imaging (USI) is the most rapidly developing technique in musculoskeletal imaging, with continuing technological advances broadening its application (404). USI potentially affords inherent advantages for the diagnosis of osteoarthritis (OA), due to its ability to detect inflammatory joint pathology that is otherwise not detected by clinical examination (36, 307), and to reliably quantify both bone and soft tissue abnormalities (17). Given the ability of USI to detect tissue-specific morphological changes before the onset of pain and the point of irreversible structural damage, USI may play a fundamental role in the earlier detection and assessment of OA (320, 475). However, the role of USI for OA diagnosis in foot joints, such as the first metatarsophalangeal joint (MTPJ), has not been clearly defined.

The foot is a target region for OA (210), yet foot research is a relatively nascent and evolving discipline within the broader field of OA (12, 17). Within the foot, USI has been shown to significantly increase diagnostic confidence in differentiating OA from other inflammatory arthritis (497). However, current USI grading systems and atlases applied to OA have been largely extrapolated from recommendations originally developed for populations with rheumatoid arthritis (RA) (481). Given that inflammation associated with OA is fundamentally different from that in RA (46, 49, 331, 492-494), the validity of using definitions, grading systems and atlases originally developed for RA must be questioned. This issue reinforces the need for validated OA-specific grading systems that depict the disease progression and may be more helpful in elucidating the role of inflammation in foot OA.

In a recent systematic review, inconsistencies were identified in the assessment of USI features, the definition of features, and the grading systems used to determine the degree of OA change in peripheral joints (481). Inconsistencies were identified in a scoping review against international guidelines and limited implementation of consensus-based recommendations for USI procedure guidance when evaluating the first MTPJ (482). It is currently unclear which USI procedure should be used to examine first MTPJ OA. Current guidelines require further refinement of anatomical landmarks to establish a standardised imaging procedure to improve interpretability and reproducibility across studies that evaluate the first MTPJ. To address these research gaps, a Delphi exercise was conducted to gain consensus concerning which USI features should be assessed and graded, and what USI procedure should be performed when examining first MTPJ OA. The Delphi study identified the essential components that the USI acquisition procedure should encompass when examining first MTPJ OA (498).

The ability to reliably quantify the degree of structural and inflammatory change in first MTPJ OA will provide a more sensitive method for assessing disease severity. Therefore, the study aimed to (1) develop an USI acquisition procedure and grading system to examine OA features in the first MTPJ, and (2) determine the intra-examiner and inter-examiner reliability of the newly developed USI acquisition procedure.

Methods

Study Design

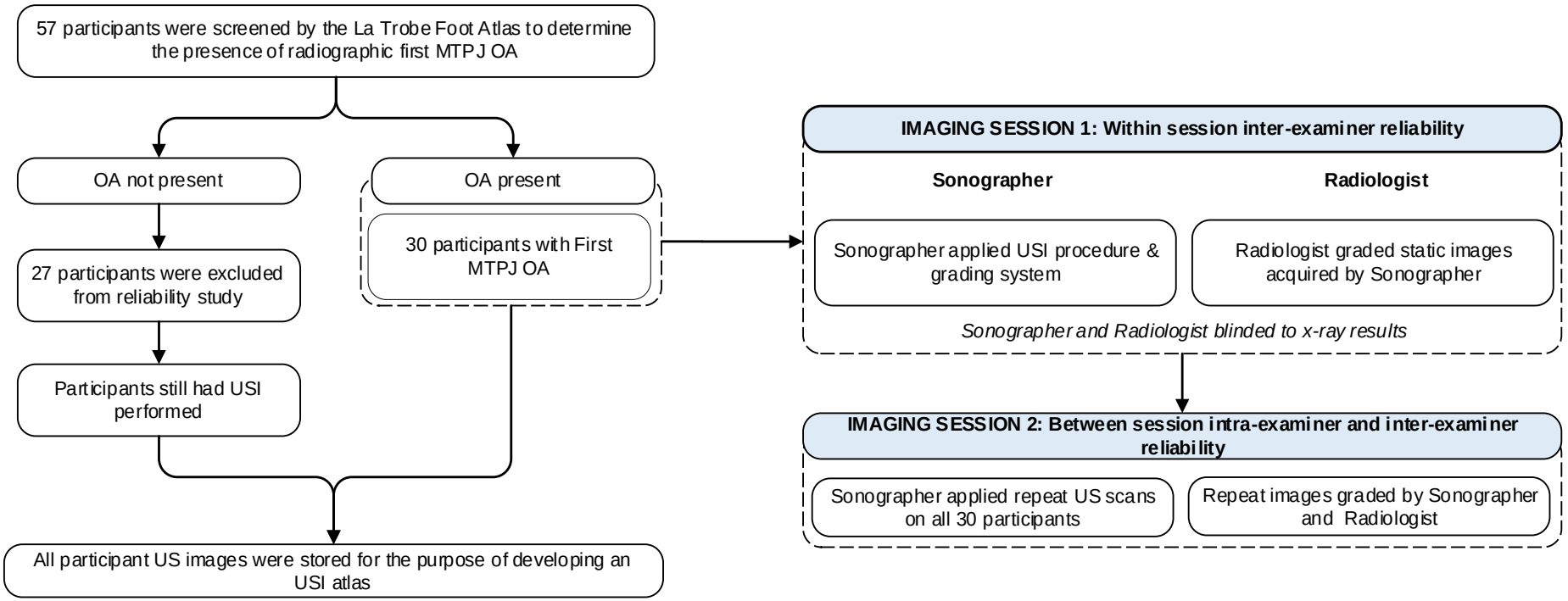
The USI acquisition procedure was developed using an evidence-based approach with findings from a systematic review (481), a scoping review (482) and a Delphi consensus study (498) serving as a basis for development. The feasibility work and the final refinement of the USI acquisition procedure were determined by an experienced sonographer (KF), radiologist (PC) and podiatrist (PM). The examiners (PM, KF and PC) piloted and clarified the USI examination methodology prior to participant recruitment. The purpose of the process was to establish a shared understanding and agreement regarding the USI acquisition procedures, image interpretation and grading. A participant-based exercise was used to determine the reliability of the USI acquisition procedure and grading system for evaluating osteoarthritic change in the first MTPJ. Study details were reported in accordance with the European League Against Rheumatism (EULAR) Recommendation Checklist for Reporting of Rheumatic and Musculoskeletal USI Research **(Appendix 14)** (371). The study was approved by the Southern Health and Disability Ethics Committee, HDEC Ethics Reference: 2022 FULL 12721 **(Appendix 15)**.

Participants

Participants over 20 years of age with suspected or previously diagnosed first MTPJ OA were recruited from the general population in Auckland, New Zealand, through professional interactive networks, social media (Twitter and Facebook) and local newspaper advertisements. Exclusion criteria were pregnancy, the presence of any other inflammatory musculoskeletal condition, history of a first MTPJ surgery, or foot and/or ankle surgery in the last three months. To ascertain reliability of the USI procedure, the La Trobe Foot Atlas (LFA) was used to screen study participants by determining the presence of radiographic first MTPJ OA (13). Fifty-seven participants were screened in the first imaging session, of whom 30 participants had first MTPJ OA radiographically confirmed and then returned for a repeat USI examination in a second imaging session. Each participant was randomly assigned an alphanumeric code upon entry into the study.

Written informed consent was obtained from all participants before the study. **Figure 11** provides a graphical overview of the participant journey.

Figure 11. Overview of the participant journey



Imaging Session One

Imaging session one involved a demographic, radiographic and sonographic assessment, all performed at a private medical imaging facility. All assessments were conducted sequentially within a 60-minute session in total, in three separate rooms. First, demographic data were obtained for each participant (age, sex, height, weight, body mass index, ethnicity, and first MTPJ affected). Second, an X-ray was taken to determine the presence of radiographic first MTPJ OA. Third, participants underwent an USI examination using the USI acquisition procedure and grading system.

Radiographic Assessment and Screening

To determine eligibility for the study, dorsal/plantar and lateral weightbearing radiographs were obtained by an experienced radiographer. The radiologist used the LFA to determine the presence of radiographic first MTPJ OA and to screen participants into the study (13). The LFA considers OA to be present when a score of 2 or greater for osteophytes or joint space narrowing is documented from either the dorsal/plantar or lateral view (13). The radiologist assessed and reported on all radiographs.

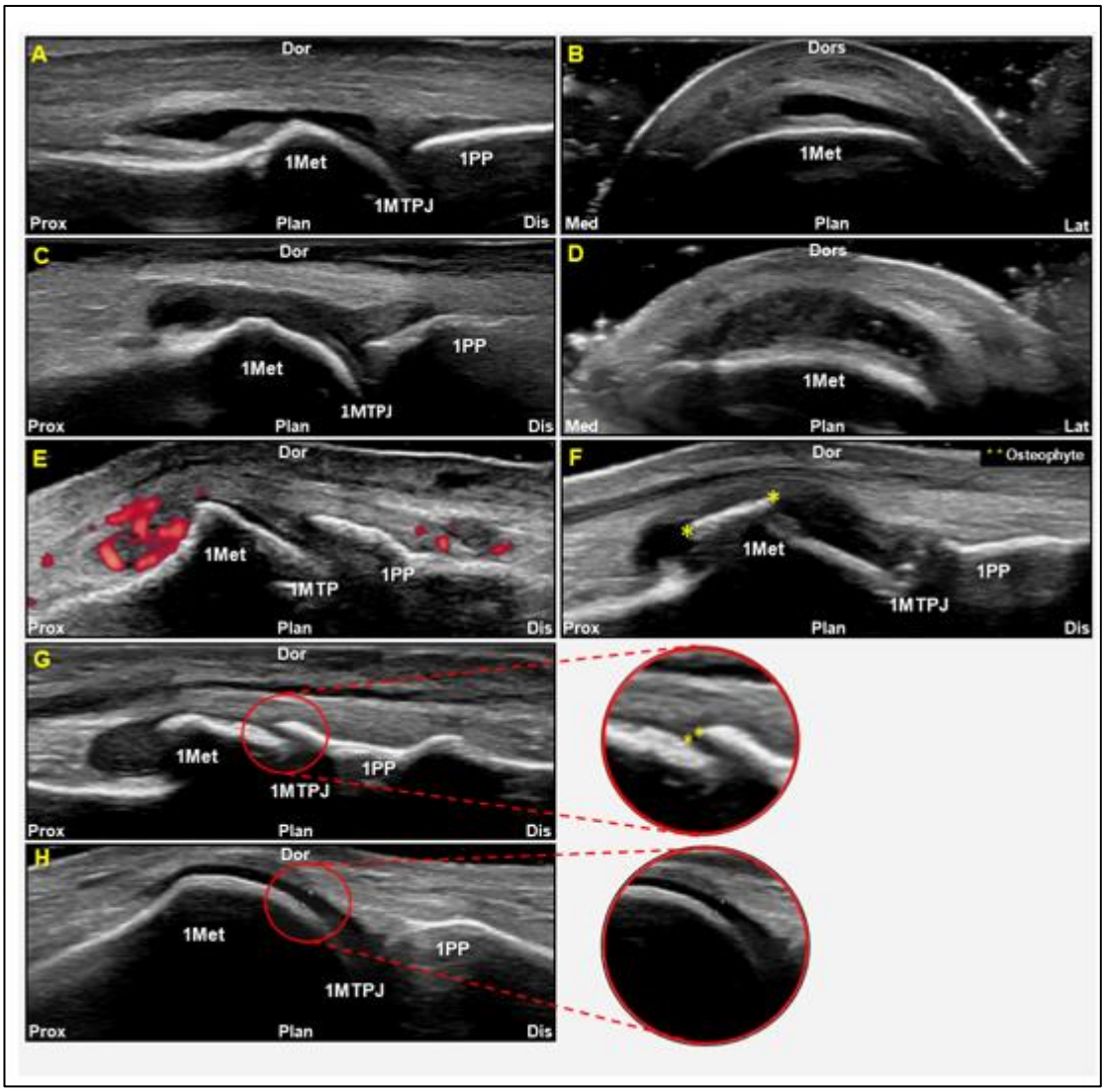
USI Assessment

Directly after the X-ray examination, all 57 participants received an USI examination, regardless of the X-ray result. Only the 30 participants who had confirmed radiographic first MTPJ OA were invited to return for a repeat USI examination in imaging session two. Ultrasound images from all 57 participants were stored for the purpose of developing a USI atlas (as part of a future study). However, the 27 non-OA participants were excluded from the reliability study and did not proceed to the second imaging session.

The USI acquisition procedure and grading system examined the following features of the first MTPJ - joint effusion, synovial hypertrophy, synovitis, joint space narrowing, osteophyte size, and cartilage thickness **(Figure 12)**. All USI features were assessed in the dorsal view with the probe positioned longitudinally; a transverse orientation was also applied to examine joint effusion, synovial hypertrophy, and osteophytes. A semiquantitative grading system was applied to all features (0=Absent, 1=Mild, 2=Moderate, 3=Severe) **(Appendix 16)**. To mitigate problems of inadequate discrimination between intermediary grades of cartilage thickness, a 0-2 semiquantitative grading system was applied, consistent with a recent hand OA study (376). A continuous measure was also examined for osteophyte size (mm), joint space narrowing (mm), and cartilage thickness (mm). For the examination of osteophyte size, the first proximal

phalanx and the first MTPJ head were evaluated as a whole, with the largest osteophyte independently defining the score **(Figure 12F)**. The joint space was measured at the largest joint space from the distal bony edge of the first metatarsal to the most proximal bony edge of the first proximal phalanx **(Figure 12G)**. Cartilage thickness was measured at the sharpest margin of the articular cartilage from the articulating edge **(Figure 12H)**.

Figure 12. USI first MTPJ OA features

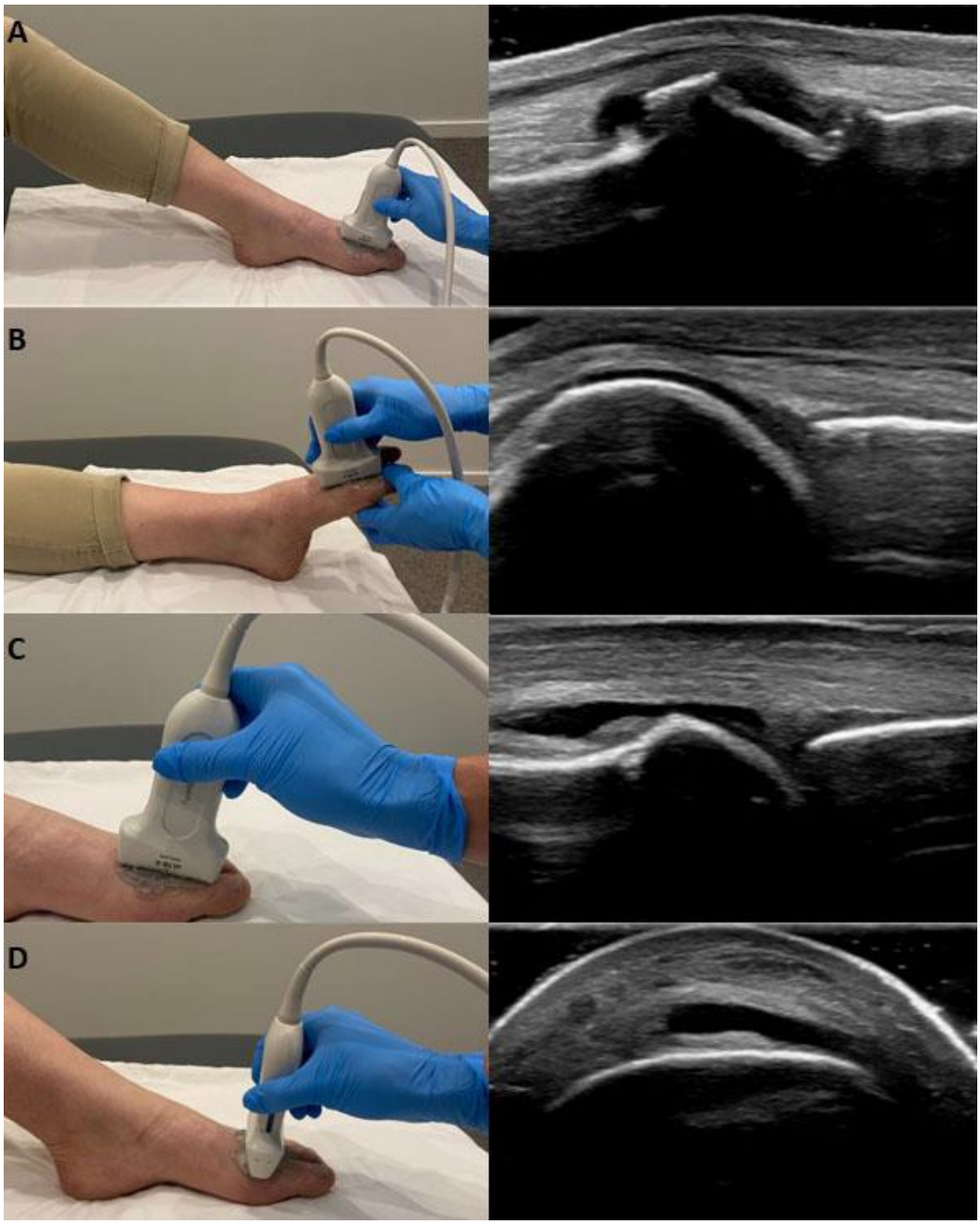


A: Longitudinal ultrasound image of joint effusion. **B**: Transverse ultrasound image of joint effusion. **C**: Longitudinal ultrasound image of synovial hypertrophy. **D**: Transverse ultrasound image of synovial hypertrophy. **E**: Longitudinal ultrasound image of synovitis. **F**: Transverse ultrasound image of synovitis. **G**: Longitudinal ultrasound image of joint space narrowing. **H**: Longitudinal ultrasound image of cartilage thickness.

Participant and probe positioning was informed by the findings of a preceding Delphi study (498). All features were assessed with the participant positioned supine with the knee flexed, the foot flat on the plinth, and the first MTPJ in neutral **(Figure 13A)**. Cartilage was examined with the knee extended, the ankle plantarflexed, and the first

MTPJ positioned in neutral then moved through plantarflexion during scanning **(Figure 13B)**. Positioning the first MTPJ in plantarflexion opened the joint space, optimising the image for examining cartilage thickness. For longitudinal scans the probe was positioned on the dorsal aspect of the forefoot, parallel to the first metatarsal head and proximal phalanx, with the joint line central to the image **(Figure 13C)**. For transverse scans the probe was positioned on the dorsal aspect of the foot, perpendicular to the diaphysis of the first metatarsal, then moved distally to the diaphysis of the first proximal phalanx, with the joint line central to the image **(Figure 13D)**.

Figure 13. Participant and probe positioning



The sonographer (KF, with more than 15 years of experience in musculoskeletal USI) applied the USI acquisition procedure and grading system to evaluate first MTPJ OA. Grading of each USI feature was performed immediately after the imaging session. To determine inter-examiner reliability, the radiologist (PC, with more than 20 years' experience) applied the grading system developed to the static images acquired by the sonographer. Both examiners were blinded to the radiographic results, clinical data, and each other's gradings.

Equipment

A Philips Epiq Elite HW B.2 ultrasound machine, equipped with a multifrequency linear transducer (eL18–4 MHz) (©2015 Koninklijke Philips N.V.), was used to acquire images of the first MTPJ. The USI device did not change during the session or across sessions. Grey scale was used to examine all features (128Hz Gray Map 3, grey scale gain 30-40%, dynamic range 74-68%, Med, 2D Opt Res, SonoCT, XRES 4) and power Doppler was applied for the examination of synovitis (PRF 700Hz, Non-directional Flow Colour Map CPA 3, Colour gain 50-65%, Wall Filter 63Hz, Frequency 6.2MHz). At the beginning of each scanning session, focus was positioned at the level of the region of interest. Colour gain was adjusted below the degree that caused the appearance of noise artefacts.

Imaging Session Two: Repeat USI

To determine intra-examiner between-session reliability, 30 participants with radiographically confirmed first MTPJ OA attended a second USI session for a repeat USI assessment of the same first MTPJ within two weeks of their first USI assessment. The minimum time between USI sessions was one week. The sonographer from session one applied the same USI procedure and grading system. To determine inter-examiner reliability for session two, the radiologist from session one applied the grading system to static images acquired from session two. Both examiners were blinded to session one and each other's gradings.

Statistical Analysis

Statistical analysis was performed using SPSS V.28 (SPSS Chicago, Illinois, USA). Descriptive statistics of categorical data are presented as frequencies and percentages, while means and standard deviations (SD) were calculated for descriptive statistics of continuous variables. Intraclass correlation coefficients (ICCs) and 95% confidence intervals (CIs) using two-way mixed model (ICC 3,1) with absolute agreement were calculated to examine the intra-examiner between-session reliability. ICCs and 95% CIs using two-way random (ICC 2,1) with absolute agreement were calculated to examine the inter-examiner reliability between the sonographer and radiologist for sessions one and two. The following criteria were applied: < 0.40 signified poor reliability; 0.40 – 0.75 fair to good reliability; and > 0.75 excellent reliability (499).

Results

Table 26 details the demographic characteristics of the 30 participants (25 female, 5 male) included in the reliability study. **Table 27** displays the intra-examiner between-session reliability. ICCs for intra-examiner between-session reliability ranged from 0.58 to 0.92 for semiquantitative grading and ranged from 0.39 to 0.94 for continuous measures. Joint effusion and osteophytes achieved the highest intra-examiner reliability. **Table 28** displays the inter-examiner reliability of sessions one and two. ICCs for session one inter-examiner reliability ranged from 0.61 to 1.0 for semiquantitative grading and all continuous measures had an ICC of 1. ICCs for session two inter-examiner reliability ranged from 0.55 to 1.0 for semiquantitative grading and ranged from 0.9 to 0.97 for continuous measures. Inter-examiner reliability was good for grading joint effusion and was excellent for all other USI features.

Table 26. Participant demographic data

Number		30
Age, years, mean (SD)		54.4 (12.5)
Sex, n (%)	Male Female	5 (17%) 25 (83%)
Ethnicity, n (%)	NZ European Māori White British Asian Russian	22 (73%) 4 (14%) 2 (7%) 1 (3%) 1 (3%)
Body mass index, kg/m^2, mean (SD)		29.8 (6.7)
First MTPJ affected	Left Right	13 (43%) 17 (57%)

SD, standard deviation; n, number; MTPJ, metatarsophalangeal joint

Table 27. Intra-examiner between-session reliability

USI feature		ICC	95% CI
Joint effusion	Semiquantitative grade (L)	0.82	0.66-0.91
	Semiquantitative grade (T)	0.78	0.59-0.89
Synovial hypertrophy	Semiquantitative grade (L)	0.65	0.39-0.82
	Semiquantitative grade (T)	0.69	0.44-0.84
Synovitis	Semiquantitative grade	0.61	0.33-0.79
Joint space narrowing	Semiquantitative grade	0.58	0.29-0.78
	Continuous measure	0.67	0.42-0.83
Osteophyte size	Semiquantitative grade	0.92	0.84-0.96
	Continuous measure	0.94	0.87-0.97
Cartilage	Semiquantitative grade	0.68	0.43-0.83
	Continuous measure	0.39	0.06-0.65

ICC, intraclass correlation coefficient; CI, confidence intervals; L, longitudinal plane; T, transverse plane

Table 28. Inter-examiner reliability of session 1 and 2

USI feature		Session 1 ICC (95% CI)	Session 2 ICC (95% CI)
Joint effusion	Semiquantitative grade (L)	0.62 (0.34-0.80)	0.57 (0.27-0.77)
	Semiquantitative grade (T)	0.61 (0.32-0.79)	0.55 (0.22-0.75)
Synovial hypertrophy	Semiquantitative grade (L)	0.82 (0.66-0.91)	0.61 (0.33-0.80)
	Semiquantitative grade (T)	0.77 (0.58-0.88)	0.77 (0.57-0.88)
Synovitis	Semiquantitative grade	0.89 (0.78-0.95)	0.97 (0.93-0.98)
Joint space narrowing	Semiquantitative grade	1.0	1.0
	Continuous measure	1.0	1.0 (0.99-1.0)
Osteophyte size	Semiquantitative grade	1.0	0.96 (0.92-0.98)
	Continuous measure	1.0	0.99 (0.99-1.0)
Cartilage	Semiquantitative grade	0.92 (0.84-0.96)	0.90 (0.80-0.95)
	Continuous measure	1.0 (1.0-1.0)	0.97 (0.93-0.98)

ICC, intraclass correlation coefficient; CI, confidence intervals; L, longitudinal plane; T, transverse plane

Discussion

The USI acquisition procedure and grading system were reliable in evaluating first MTPJ OA features in participants with radiologically confirmed OA. Data revealed that the assessment of joint effusion, synovial hypertrophy, synovitis, joint space narrowing, osteophyte size, and cartilage thickness had good to excellent intra-examiner and inter-examiner reliability. Poor intra-examiner reliability was reported for cartilage thickness only when assessed as a continuous measure. Absolute agreements were excellent for osteophytes and joint space narrowing.

It is well understood that inflammation is an important driver of the disease and contributes to the structural progression of OA (18, 48, 49). Despite this contemporary understanding, clinicians and researchers are currently confined to radiographic grading or grading originally designed for RA when examining foot OA. The distinct difference of inflammation experienced in OA compared to RA and the inability of conventional radiography to detect inflammatory features provides significant limitations. Therefore, the development of our USI grading system is a fundamental step in determining the role of inflammation for first MTPJ OA and the prognostic value for structural progression. Furthermore, it is generally accepted that radiological progression may not always correlate with pain, function and/or impact on activities of daily living. USI may further drive our understanding of factors which may be more important at patient level (i.e. health related quality of life). Therefore, USI may potentially drive more targeted and personalised interventions in the future.

It is a pivotal finding that the USI procedure and grading system reported good to excellent intra-examiner and inter-examiner reliability for all inflammatory OA features, particularly since the marked variations across studies in terms of how synovitis, synovial hypertrophy and joint effusion are defined and categorised as USI features (481). Consequently, it is essential to distinguish the existing disparities among various entities of synovial pathology that serve as indicators of inflammation (481). In line with the Outcome Measures in Rheumatology (OMERACT) hand OA study, we scored grey scale inflammatory abnormalities for synovial hypertrophy and joint effusion separately. Synovitis was examined as a separate entity by power Doppler signal (flow signal detected within synovial hypertrophy was considered a sign of synovitis) (374, 376). Due to the marked variation in prevalence between grey scale and Doppler-detected inflammatory features demonstrated in the hand OA (376), including only grey scale features indicative of inflammation may result in OA being underestimated. A recent study that used magnetic resonance imaging to examine first MTPJ OA was limited by the fact

that it included effusion and synovitis as a combined proxy measure for synovitis, termed “effusion-synovitis” (292). Given the prognostic value of inflammatory features and the sensitivity USI possesses in detecting subclinical inflammatory change (36, 307), the inclusion of multiple inflammatory features that can be reliably quantified as separate entities may be more helpful in elucidating the role of inflammation in OA.

The poor intra-examiner reliability for examining cartilage as a continuous measure may be attributed to scoring cartilage based on a single thickness measurement. It may be that, as cartilage may not be uniform across the entire joint surface, a single measurement of thickness may not provide an accurate representation of cartilage damage across the whole joint surface. Therefore, the ability to consistently examine the exact same part of cartilage across sessions will influence the reliability of this measure. The technique we employed required examiners to measure a vertical line with consistent perpendicular alignment between cartilage borders at a subjective location. Small deviations in the location and orientation can result in thickness differences and measurement variance across sessions and/or examiners (500). This finding is consistent with previous OA and RA studies, which have reported difficulties when examining cartilage damage (292). The poor intra-examiner reliability results for the current study may also be attributable to practical difficulties associated with the scanning of cartilage. To obtain the exact same ultrasound image, the beam angle and location used in session one would need to be precisely replicated in session two. This practice may not have occurred for all repeat scans, which may have influenced the cartilage measurement (490, 491). Conversely the excellent inter-examiner reliability for cartilage thickness as a continuous measure between session one and two may be explained by the fact that the radiologist graded already acquired images of cartilage thickness.

A previous attempt to develop semiquantitative 0-3 grading for cartilage in hand OA found moderate intra-reader and fair inter-reader agreement (50). Even supporting definitions could not help to sufficiently discriminate between intermediary grades. A recent study in people with RA simplified the scoring to a 0-2 scale and reported excellent intra-reader and moderate inter-reader reliability for examining cartilage in the metacarpophalangeal joint (501). Therefore, to mitigate issues with mid-range subjective grading, we opted for a 0-2 semiquantitative scoring system based on the morphological integrity of the superficial interface of the cartilage and the cartilage thickness. To aid in visualisation of cartilage thickness, the acquisition procedure was modified to include plantarflexion of the first MTPJ. Consequently, the degree of plantarflexion achieved between sessions

may have varied, which would undoubtedly have influenced cartilage thickness measures.

Variable intra-examiner and inter-examiner reliability of USI has been reported in the literature (502, 503). Given the general perception that ultrasonography is a highly operator-dependent technique (502, 504), our results are encouraging and represent an important step in support of further application of USI to assess other foot joints. The results of this study will inform the methodological development of an USI atlas for grading the degree of osteoarthritic change at the first MTPJ. It is expected that the accompaniment of an illustrated USI atlas that clearly presents the USI procedure, features and grades will improve the consistency of interpretation and grading and improve the reliability when examining both structural and inflammatory change in first MTPJ OA.

This study must be viewed in the context of possible limitations. First, the USI procedure included solely a dorsal scan of the first MTPJ. USI offers a multiplanar technique, so as the medial and/or plantar aspect of the first MTPJ was not examined, the USI procedure may underestimate the prevalence or severity of features. Second, the poor reliability reported for examining cartilage as a continuous measure could be mitigated by segmenting the entire cross-sectional area of the articular cartilage using ImageJ software (505). With this technique, the average cartilage thickness within standardised regions can be calculated. However, this technique requires additional expertise and overall time to complete the segmentation, which may limit the translation of cartilage thickness assessment to a clinical setting. Third, investigator bias may have occurred, as the same radiologist reported on radiographic screening and graded the acquired ultrasound images. All participants were randomly assigned an alphanumerical code upon entry into the study to minimise risk of researcher bias. Finally, despite efforts to proactively recruit an ethnically diverse population that represents the broader New Zealand population, no Pacific peoples were included. Pacific peoples suffer from significant and longstanding health inequalities and poorer health outcomes compared to other New Zealanders. Therefore, the collection of accurate ethnic OA data is needed to better understand what factors contribute to these inequalities and to provide the capacity to measure progress.

Conclusion

The USI acquisition procedure and grading system developed were reliable in evaluating first MTPJ OA features in participants with radiologically confirmed OA. The USI

procedure demonstrated good to excellent intra-examiner reliability in examining all features, excepting cartilage thickness when evaluated as a continuous measure. Inter-examiner reliability was good for grading joint effusion and excellent for grading all other USI features. With all inflammatory features reporting good to excellent intra-examiner and inter-examiner reliability, coupled with their prognostic value for structural progression, USI affords an opportunity to detect prognostic markers of OA earlier in the disease cascade. The results of this study will be incorporated into the methodological development of a USI atlas for grading the extent of osteoarthritic change in the first MTPJ.

Chapter 9

Development of an Ultrasound Imaging Atlas for Grading Osteoarthritis in the First Metatarsophalangeal Joint

Preface

This programme of work first identified which USI features are indicative of first MTPJ OA and how they should be graded (Chapter 4). The study described in Chapter 5 established which components the USI acquisition procedure should encompass when evaluating first MTPJ OA. The bibliometric analysis highlighted the importance of ongoing international collaboration in this research field, with various researchers and institutions contributing diverse skill sets and knowledge (Chapter 6). To continue to advance knowledge, facilitate international collaboration and address key evidence gaps, an international multi-speciality Delphi study was conducted (Chapter 7). The Delphi study achieved consensus and identified the essential components that the USI acquisition procedure should encompass when examining first MTPJ OA. To further build on the results of the Delphi and address the overarching aim of the present research to develop an USI atlas, a reliability study was conducted (Chapter 8). The results of the Delphi informed the development of a novel USI acquisition procedure and grading system for examining first MTPJ OA. The USI acquisition procedure and grading system were found to be reliable in evaluating first MTPJ OA features in participants with radiologically confirmed OA (Chapter 8).

Finally, the reliable USI procedure was utilised to inform the methodological development of an USI atlas for grading OA in the first MTPJ. To generate the sample of images required to develop the USI atlas, all ultrasound images were acquired and graded by applying the reliable procedure. Chapter 9 details the development of the AUTUSI atlas for grading OA in the first MTPJ.

This multi-study programme of research provided a strong foundation to develop an USI atlas that allows quantification of the presence and severity of pathological changes in first MTPJ OA. Application of the AUTUSI atlas has the potential to advance understanding of the pathological process of first MTPJ OA, provide capacity for earlier detection and standardisation of diagnosis, and broaden the scope and capabilities of targeted interventions. At the time of the thesis submission this chapter was being submitted for peer review to the journal Osteoarthritis and Cartilage.

Abstract

Objective

Ultrasound imaging (USI) may play a fundamental role in the earlier detection and assessment of first metatarsophalangeal joint (MTPJ) osteoarthritis (OA), due to its ability of to depict tissue-specific morphological changes before the onset of pain and before the point of irreversible structural damage. However, the role of USI for OA diagnosis in foot joints has not been clearly defined. Currently, no OA specific USI grading systems exist to support diagnosis. The aims of the study were to develop a semiquantitative USI atlas to grade the degree of osteoarthritic change in the first MTPJ and to evaluate the intra-examiner and inter-examiner reproducibility of using the atlas.

Design

Ultrasound images were obtained from a total of 57 participants (30 participants with radiographically confirmed first MTPJ OA). The USI atlas examined joint effusion, synovial hypertrophy, synovitis, osteophytes, joint space narrowing, and cartilage thickness. To determine the reproducibility of the atlas, six examiners independently graded 24 ultrasound images across two sessions. Intra-examiner and inter-examiner reproducibility were determined using percentage agreement and Gwet's AC2.

Results

Observations using the AUTUSI atlas demonstrated almost perfect-to-perfect inter-examiner agreement (percentage agreement ranged from 96% to 100% and Gwet's AC2 values ranged from 0.81 to 1.00) and moderate-to-perfect intra-examiner agreement (percentage agreement ranged from 67% to 100%, and Gwet's AC2 values ranged from 0.54 to 1.00).

Conclusion

An USI atlas has been developed for evaluating first MTPJ OA. The AUTUSI atlas demonstrated excellent intra-examiner and inter-examiner reproducibility for evaluating first MTPJ joint effusion, synovial hypertrophy, synovitis, joint space narrowing, osteophytes, and cartilage thickness. The AUTUSI atlas will advance understanding of the pathological process of first MTPJ OA and affords an opportunity to detect prognostic markers of OA earlier in the disease cascade.

Introduction

Osteoarthritis (OA) is a prevalent, chronic, progressive and disabling joint disease that imposes a remarkable global health burden, with notable implications for the individuals affected, healthcare systems, and wider socioeconomic costs (24, 25). Foot OA results in functional limitations and significant impairments in balance, strength and locomotor ability, and negatively impacts work ability (5). However, the feet are often overlooked as a site of involvement relative to other joints commonly affected by OA (216). Within the foot, the most commonly reported affected foot site is the first metatarsophalangeal (MTPJ) (6).

The traditional view of OA as a degenerative disorder of articular cartilage resulting from normal bodily wear and tear is obsolete (35, 39, 40). The contemporary concept of OA emphasises the complex pathogenesis of the disease, as a disorder of the joint as a whole organ, which involves not only hyaline cartilage, but an additional and integrated role of bone and synovial tissue (35). Attention has now turned to the prognostic value and role of inflammatory markers (29, 35, 46), with several studies reporting an association between active synovitis and structural OA progression (33, 48-50).

The development of the radiographic La Trobe Foot Atlas (LFA) (13) led to significant improvements in estimating disease prevalence (167), as well as understanding different patterns of foot joint involvement (226). However, the current method of diagnosing OA by conventional radiography remains reactive and captures OA later in the disease process, once the condition is significantly advanced (13, 14). This necessitates a new model of diagnosis and care for OA that is proactive and preventative. More advanced modalities, including magnetic resonance imaging (MRI) and ultrasound imaging (USI) have emerged as more accurate evaluators of both bone and soft tissue abnormalities in foot OA (210, 292). MRI has played a principal role in changing the understanding of OA pathologies when evaluating OA as a whole organ disease (29, 293). Munteanu et al. (292) recently developed an MRI atlas for the assessment of first MTPJ OA which demonstrated excellent intra-examiner and inter-examiner reproducibility (292, 296). However, shortcomings for MRI include high costs, prolonged duration of image acquisition, and limited availability in community care, and it is contraindicated in certain conditions such as metal implants (297, 298). Notably, Oo et al. (2022) demonstrated that the correlations between quantitative knee OA USI features and corresponding MRI findings were very strong (ICC range = 0.85–0.98) (315).

USI potentially affords inherent advantages for the diagnosis of first MTPJ OA. USI can be performed chairside by a clinician experienced in sonography. It has the ability to detect inflammatory joint pathology that is otherwise not detected by clinical examination (36, 307), and can reliably quantify both bone and soft tissue abnormalities (17, 506). USI may play a fundamental role in the earlier detection and assessment of foot OA (320, 475), thus enabling more targeted and timely interventions that may provide capacity to alter disease progression. However, the role of USI for OA diagnosis in foot joints has not been clearly defined. The development of an USI atlas could provide capacity for earlier detection, standardisation of diagnosis, and a more sensitive method to classify and grade the disease process. Therefore, the aims of the current study were to develop a semiquantitative USI atlas (picture-based grading system) to grade the degree of osteoarthritic change in the first MTPJ and to evaluate the intra-examiner and inter-examiner reproducibility of using the atlas.

Methods

Development of the AUTUSI Atlas

Background Work

The AUTUSI atlas was developed using an evidence-based approach with findings from a systematic review (481), a scoping review (482), a Delphi consensus study (498) and a USI reliability study (506), used to inform the development. Our reliability study details the USI acquisition procedure and semiquantitative grading system for evaluating first MTPJ OA features in participants with radiologically confirmed OA (506). The USI acquisition procedure and grading system were found to be reliable in evaluating joint effusion, synovial hypertrophy, synovitis, joint space narrowing, osteophytes and cartilage thickness in participants with radiologically confirmed OA. For semiquantitative grading ICCs for intra-examiner between session reliability ranged from 0.58 to 0.92. Joint effusion and osteophytes achieved the highest intra-examiner reliability (ICC = 0.78-0.94). ICCs for session one inter-examiner reliability ranged from 0.61 to 1.0. ICCs for session two inter-examiner reliability ranged from 0.55 to 1.0. Inter-examiner reliability was good for grading joint effusion (ICC = 0.55-0.62) and was excellent for all other USI features (ICC = 0.77-1.0) (506). The semiquantitative grading of these USI features was incorporated into the methodological development of an USI atlas for grading the extent of osteoarthritic change in the first MTPJ. The study was approved by the Southern Health and Disability Ethics Committee, HDEC Ethics Reference: 2022 FULL 12721 (**Appendix 15**).

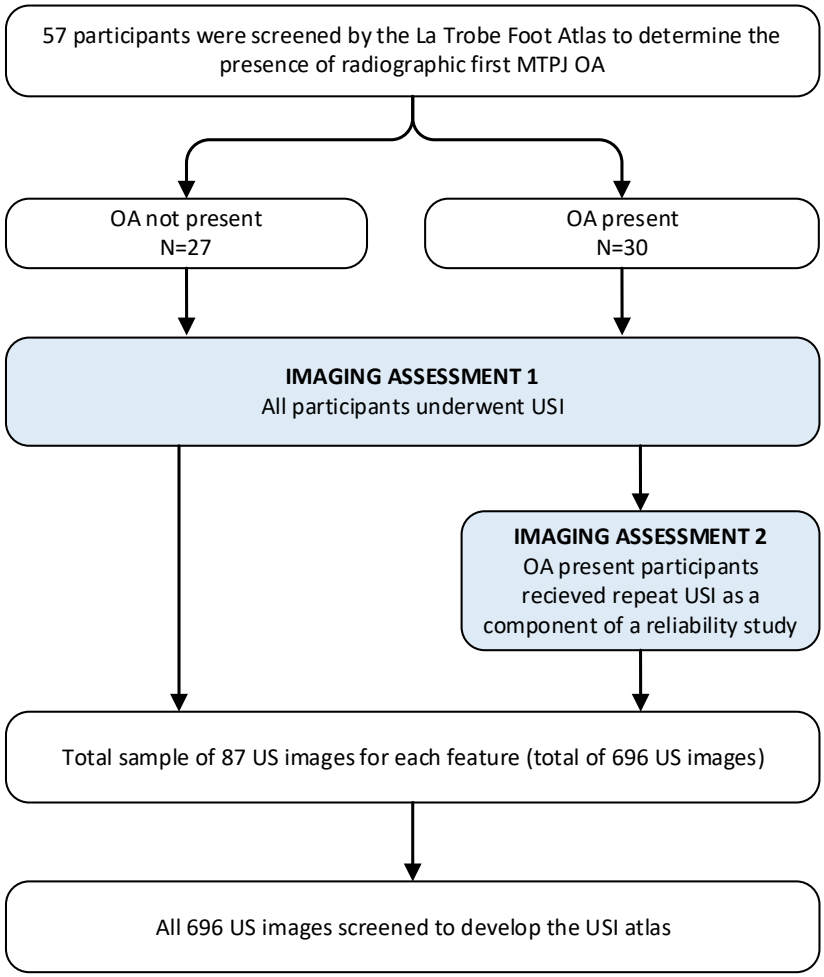
Participants

Ultrasound images were obtained from a total of 57 participants (87 images per USI feature), who participated in an earlier reliability study (506). Participants over 20 years of age with suspected or previously diagnosed first MTPJ OA were recruited from the general population in Auckland, New Zealand. Participants were recruited through professional interactive networks, social media (Twitter and Facebook) and local newspaper advertisements. Exclusion criteria were the possibility of pregnancy, the presence of any other inflammatory musculoskeletal condition, history of a first MTPJ surgery, or foot and/or ankle surgery in the last three months. The LFA was used to screen study participants by determining the presence of radiographic first MTPJ OA (13). Fifty-seven participants were screened in the first imaging session, of whom 30 participants had radiographically confirmed first MTPJ OA and returned for a repeat USI examination, generating a total sample of 87 ultrasound images per feature. Each participant was randomly assigned an alphanumeric code upon entry into the study. Written informed consent was obtained from all participants before the study. **Figure 14** provides an overview of participant engagement and how ultrasound images were acquired to develop the atlas.

Imaging Acquisition Procedure

The USI acquisition procedure was developed in an earlier study that reported good to excellent inter-examiner and intra-examiner reliability for all features graded on a semiquantitative scale (506). All imaging was performed at a private medical imaging facility and was conducted sequentially within a 60-minute session in three separate rooms. First, demographic data were obtained for each participant (age, gender, height, weight, body mass index, ethnicity, and first MTPJ affected). Second, an X-ray was taken to determine the presence of radiographic first MTPJ OA. Third, participants underwent an USI examination using the USI acquisition procedure and grading system.

Figure 14. Atlas development participant journey



Radiographic Assessment and Screening

Weightbearing dorsal/plantar and lateral radiographs were obtained by an experienced radiographer. A radiologist (PC) used the LFA to determine the presence of radiographic first MTPJ OA (13). The LFA considers OA to be present when a score of 2 or greater for osteophytes or joint space narrowing is documented from either the dorsal/plantar or lateral view (13). One radiologist (PC) assessed and reported on all radiographs.

USI Assessment

Directly after the X-ray examination all 57 participants received an USI examination. Thirty participants with confirmed radiographic first MTPJ OA were invited to return for a repeat USI examination, as part of the reliability study, thus providing a total sample of 87 sets of ultrasound images (one static image per feature). All ultrasound images acquired were stored for the purpose of developing the AUTUSI atlas. USI features included in the examination were joint effusion, synovial hypertrophy, synovitis, osteophytes, joint space narrowing, and cartilage thickness. All USI features were

assessed in the dorsal view with the probe positioned longitudinally; a transverse orientation was also applied to examine joint effusion and synovial hypertrophy, to ensure the extent of the effusion and synovial thickening was fully investigated. A semiquantitative grading system was applied to all features (0=Absent, 1=Mild, 2=Moderate, 3=Severe). To mitigate problems with adequate discrimination between intermediary grades of cartilage thickness, a 0-2 semiquantitative grading system was applied **(Appendix 16)** . A sonographer (KF with more than 15 years of experience in musculoskeletal USI) applied the USI acquisition procedure and grading system to evaluate first MTPJ OA. A radiologist (PC with more than 20 years' experience) applied the grading system to the static images acquired by the sonographer. Both examiners were blinded to the radiographic results, clinical data, and each other's gradings.

Equipment

A Philips Epiq Elite HW B.2 ultrasound machine, equipped with a multifrequency linear transducer (eL18–4 MHz), was used to acquire images of the first MTPJ. The USI device did not change during the session or between sessions. Grey scale was used to examine all features (128Hz Gray Map 3, grey scale gain 30-40%, dynamic range 74-68%, Med, 2D Opt Res, SonoCT, XRES 4) and power Doppler was applied for the examination of synovitis (PRF 700Hz, Non-directional Flow Colour Map CPA 3, Colour gain 50-65%, Wall Filter 63Hz, Frequency 6.2MHz). The grey scale and power Doppler settings were adjusted to optimise image resolution and sensitivity to detect flow. At the beginning of each scanning session, focus was positioned at the level of the region of interest. Colour gain was adjusted below the degree that caused the appearance of noise artefacts.

AUTUSI Atlas Image Selection and Consensus

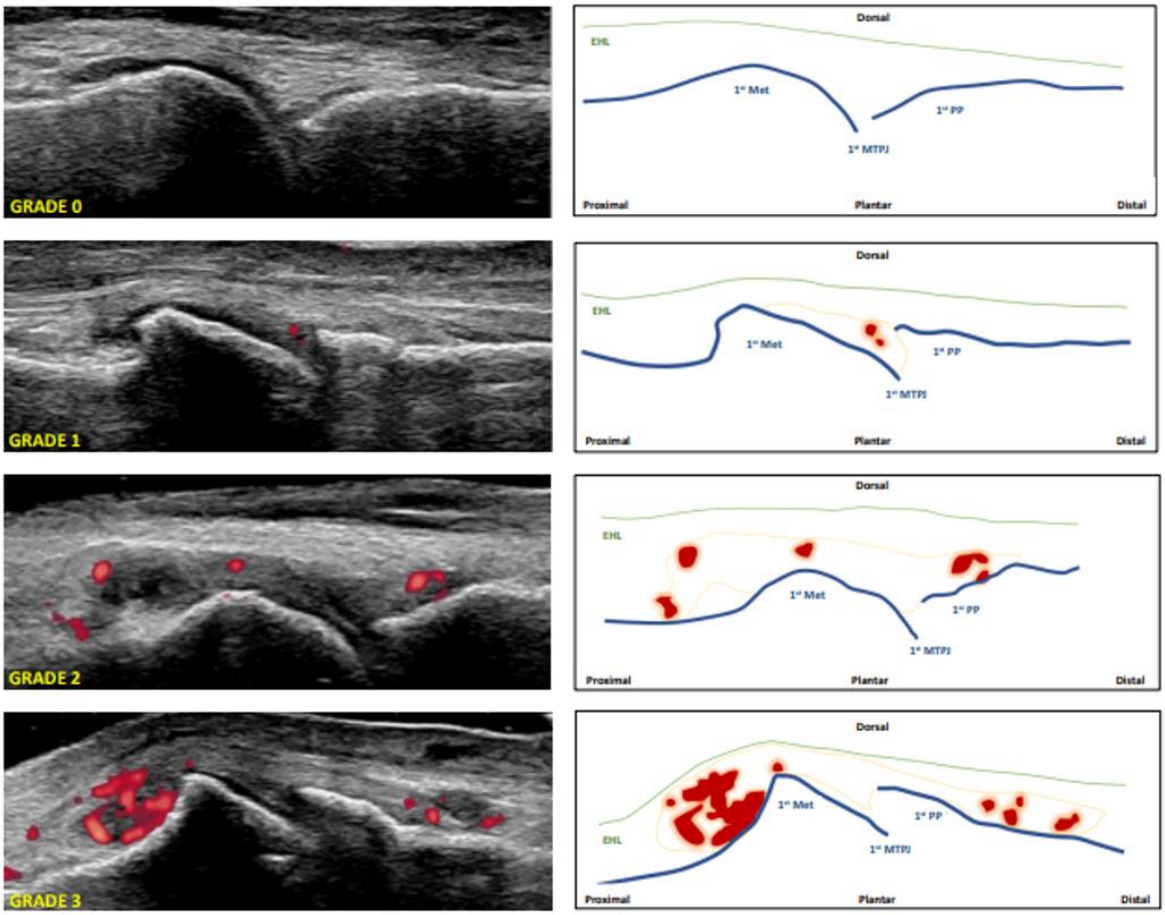
The first MTPJ OA AUTUSI atlas was developed by a podiatrist (PM), sonographer (KF) and radiologist (PC), who were all involved in the reliability study (506). Thus, agreement was already established regarding image interpretation and grading of first MTPJ OA. The three atlas developers (PM, KC and PC) assessed all 87 sets of ultrasound images. Each set of ultrasound images included six longitudinal images illustrating joint effusion, synovial hypertrophy, synovitis, osteophytes, joint space narrowing, cartilage thickness, and two transverse images illustrating joint effusion and synovial hypertrophy. PM categorised all 696 static ultrasound images according to grading by the radiologist and sonographer from the authors' reliability study (506). All 696 static images representing each feature with varying degrees of severity were reviewed to select the most representative examples of each grade of each feature. PM, KF and PC independently selected five images that they believed best represented each

feature definition and rating description. From here the sonographer and radiologist independently selected the best image for each grade of each feature. If there was a disagreement, the image in question was replaced with another image that was considered a better representation. This process was repeated until consensus was achieved. This process led to the final presentation of the first MTPJ OA AUTUSI atlas.

Preparation of Ultrasound Images

An initial atlas was developed consisting of six features with an associated semiquantitative grading system. Joint effusion and synovial hypertrophy also included images in the transverse plane. Therefore, the initial atlas consisted of 31 static ultrasound images. To assist in the differentiation between grades and features, PM designed line drawings to align with each ultrasound image. The initial atlas was distributed to KF and PC for approval. The final atlas was then independently evaluated and confirmed to be appropriate by co-authors (MC, CB, RE, and KR). Agreement was reached regarding image selection and format design. **Figure 15** shows the Atlas images for the assessment of synovitis. Power Doppler signals must be detected within synovial hypertrophy to be considered as a sign of synovitis. The scoring of power Doppler signals was performed according to a semiquantitative scale (0 = No flow in the synovium, 1 = Mild, single vessel signals (one or more), 2 = Moderate, confluent vessel signals in less than half of the area of the synovium, 3 = Severe, vessel signals in more than half of the area of the synovium). The complete AUTUSI atlas is presented in **Appendix 17.**

Figure 15. Atlas images for synovitis of the first MTPJ



Reproducibility of the AUTUSI atlas

Image Selection for Grading

To assess the reproducibility of the atlas, a random sample of 24 ultrasound images were selected from the total sample of 696 available ultrasound images for grading. Ultrasound images were grouped by participant code according to feature and grade using Microsoft® Excel® (version 2307, Microsoft Corp., Redmond, Washington, USA). Participant codes that represented images that had been included in the AUTUSI atlas were deleted from the spreadsheet to ensure atlas examiners would not grade images that had been previously selected as an atlas image. Ultrasound images were randomly selected by row number using a random number generator. Twenty-four ultrasound images (three images per feature) were randomly selected from the remaining 665 images. Selected images were compiled into a document and were sent with the AUTUSI atlas to examiners.

Atlas Examiners

Six examiners with experience in USI from different countries (New Zealand [n=4], United Kingdom [n=1] and Canada [n=1]) and different health professions (radiologists [n=2], podiatrist [n=2], sonographer [n=1], and physical therapist [n=1]) independently rated the randomly selected ultrasound images using the AUTUSI atlas. All examiners were provided with written instructions detailing the AUTUSI atlas, the USI grading sheet, and the tasks required of them for grading session one and two. An additional video outlining the process was also provided. This step included three examiners (PM, KF, and PC) who developed the atlas and three examiners who were not involved in the USI acquisition or the atlas development – a radiologist, a physical therapist, and a podiatrist. To determine inter-examiner reproducibility of the AUTUSI atlas, all six examiners (PM, KF, PC, RG, JW and CD) independently rated the random sample of 24 ultrasound images (3 images per feature of varying severity) using the atlas. To determine intra-examiner reproducibility, this process was repeated 3-4 weeks later (without reference to previous ratings).

Statistical Analysis

Gwet's AC2 values were calculated using the irrCAC package in R, version 1.0, to determine inter-examiner and intra-examiner reliability. Quadratic weighting was used for all calculations due to the ordinal nature of scoring across the USI features. Gwet's AC2 values were interpreted using the following cutoffs: <0 poor; 0.01–0.20 slight; 0.21–0.40 fair; 0.41–0.60 moderate; 0.61–0.80 substantial; 0.81–1.00 almost perfect or 1.00 perfect (507). Gwet's AC1 values were calculated because this approach has been shown to provide a more robust measure of reliability than the traditionally used kappa statistic (508).

Results

Table 29 details the demographic characteristics of the 57 participants (25 female, 5 male) included in the AUTUSI atlas development study.

Table 29. Participant demographic data

Number		57
Age, years, mean (SD)		46.7 (11.7)
Sex, n (%)	Male	11 (19%)
	Female	25 (81%)
Ethnicity, n (%)	NZ European	40 (70%)
	Māori	5 (9%)
	Asian	4 (7%)
	White British	4 (7%)
	Australian	1 (2%)
	Canadian	1 (2%)
	Russian	1 (2%)
	South African	1 (2%)
Body mass index, kg/m^2, mean (SD)		29.1 (6.7)
First MTPJ affected, n (%)	Left	25 (44%)
	Right	32 (56%)

Inter-examiner Reproducibility

Table 30 displays the reproducibility statistics for inter-examiner analyses. Percentage agreement ranged from 96% to 100%. Gwet's AC2 values ranged from 0.81 to 1.00, indicating almost perfect-to-perfect levels of agreement. Inter-examiner reproducibility was similar between session one and session two grading.

Table 30. Inter-examiner reliability of grading sessions one and two

Inter-examiner reliability	Percentage agreement	Gwet's AC2 value (95% CI)	Interpretation
Session 1			
Joint effusion (longitudinal)	100.00%	1.00 (1.00, 1.00)	Perfect
Joint effusion (transverse)	98.02%	0.94 (0.58, 1.00)	Almost perfect
Synovial hypertrophy (longitudinal)	95.80%	0.86 (0.41, 1.00)	Almost perfect
Synovial hypertrophy (transverse)	98.76%	0.96 (0.80, 1.00)	Almost perfect
Synovitis	91.11%	0.82 (0.20, 1.00)	Almost perfect
Osteophytes	96.30%	0.89 (0.84, 0.93)	Almost perfect
Joint space narrowing	97.22%	0.92 (0.52, 1.00)	Almost perfect
Cartilage	97.22%	0.92 (0.52, 1.00)	Almost perfect
Session 2			
Joint effusion (longitudinal)	100.00%	1.00 (1.00, 1.00)	Perfect
Joint effusion (transverse)	98.02%	0.94 (0.58, 1.00)	Almost perfect
Synovial hypertrophy (longitudinal)	97.53%	0.92 (0.73, 1.00)	Almost perfect
Synovial hypertrophy (transverse)	97.53%	0.93 (0.69, 1.00)	Almost perfect
Synovitis	92.22%	0.81 (0.11, 1.00)	Almost perfect
Osteophytes	97.22%	0.92 (0.52, 1.00)	Almost perfect
Joint space narrowing	100.00%	1.00 (1.00, 1.00)	Perfect
Cartilage	97.22%	0.92 (0.52, 1.00)	Almost perfect

Intra-examiner Reproducibility

Table 31 displays the reproducibility statistics for intra-examiner analyses. Percentage agreement ranged from 67% to 100%. Gwet's AC2 values ranged from 0.54 to 1.00, indicating moderate-to-perfect levels of agreement. Intra-examiner reproducibility was similar for the examiners 1, 2, 3, and 5.

Table 31. Intra-examiner between-session reliability

Intra-rater (between session) reliability	Percentage agreement	Gwet's AC2 value (95% CI)	Interpretation
Examiner 1			
Joint effusion (longitudinal)	100.00%	1.00 (1.00, 1.00)	Perfect
Joint effusion (transverse)	100.00%	1.00 (1.00, 1.00)	Perfect
Synovial hypertrophy (longitudinal)	100.00%	1.00 (1.00, 1.00)	Perfect
Synovial hypertrophy (transverse)	100.00%	1.00 (1.00, 1.00)	Perfect
Synovitis	91.67%	0.79 (-0.29, 1.00)	Substantial
Osteophytes	100.00%	1.00 (1.00, 1.00)	Perfect
Joint space narrowing	100.00%	1.00 (1.00, 1.00)	Perfect
Cartilage	100.00%	1.00 (1.00, 1.00)	Perfect
Examiner 2			
Joint effusion (longitudinal)	100.00%	1.00 (1.00, 1.00)	Perfect
Joint effusion (transverse)	100.00%	1.00 (1.00, 1.00)	Perfect
Synovial hypertrophy (longitudinal)	100.00%	1.00 (1.00, 1.00)	Perfect
Synovial hypertrophy (transverse)	100.00%	1.00 (1.00, 1.00)	Perfect
Synovitis	100.00%	1.00 (1.00, 1.00)	Perfect
Osteophytes	100.00%	1.00 (1.00, 1.00)	Perfect
Joint space narrowing	100.00%	1.00 (1.00, 1.00)	Perfect
Cartilage	100.00%	1.00 (1.00, 1.00)	Perfect
Examiner 3			
Joint effusion (longitudinal)	100.00%	1.00 (1.00, 1.00)	Perfect
Joint effusion (transverse)	100.00%	1.00 (1.00, 1.00)	Perfect
Synovial hypertrophy (longitudinal)	100.00%	1.00 (1.00, 1.00)	Perfect
Synovial hypertrophy (transverse)	100.00%	1.00 (1.00, 1.00)	Perfect
Synovitis	100.00%	1.00 (1.00, 1.00)	Perfect
Osteophytes	100.00%	1.00 (1.00, 1.00)	Perfect
Joint space narrowing	100.00%	1.00 (1.00, 1.00)	Perfect
Cartilage	100.00%	1.00 (1.00, 1.00)	Perfect
Examiner 4			
Joint effusion (longitudinal)	100.00%	1.00 (1.00, 1.00)	Perfect
Joint effusion (transverse)	100.00%	1.00 (1.00, 1.00)	Perfect
Synovial hypertrophy (longitudinal)	96.29%	0.88 (0.17, 1.00)	Almost perfect
Synovial hypertrophy (transverse)	100.00%	1.00 (1.00, 1.00)	Perfect
Synovitis	66.67%	0.54 (-2.06, 1.00)	Moderate
Osteophytes	88.89%	0.64 (0.36, 0.91)	Substantial
Joint space narrowing	91.67%	0.79 (-0.29, 1.00)	Substantial
Cartilage	100.00%	1.00 (1.00, 1.00)	Perfect
Examiner 5			
Joint effusion (longitudinal)	100.00%	1.00 (1.00, 1.00)	Perfect
Joint effusion (transverse)	100.00%	1.00 (1.00, 1.00)	Perfect
Synovial hypertrophy (longitudinal)	92.59%	0.76 (0.05, 1.00)	Substantial
Synovial hypertrophy (transverse)	100.00%	1.00 (1.00, 1.00)	Perfect
Synovitis	100.00%	1.00 (1.00, 1.00)	Perfect
Osteophytes	100.00%	1.00 (1.00, 1.00)	Perfect
Joint space narrowing	100.00%	1.00 (1.00, 1.00)	Perfect
Cartilage	100.00%	1.00 (1.00, 1.00)	Perfect
Examiner 6			
Joint effusion (longitudinal)	100.00%	1.00 (1.00, 1.00)	Perfect
Joint effusion (transverse)	100.00%	1.00 (1.00, 1.00)	Perfect
Synovial hypertrophy (longitudinal)	92.59%	0.76 (0.05, 1.00)	Substantial

Synovial hypertrophy (transverse)	96.30%	0.88 (0.17, 1.00)	Almost perfect
Synovitis	100.00%	1.00 (1.00, 1.00)	Perfect
Osteophytes	91.67%	0.79 (-0.29, 1.00)	Substantial
Joint space narrowing	100.00%	1.00 (1.00, 1.00)	Perfect
Cartilage	100.00%	1.00 (1.00, 1.00)	Perfect

Discussion

This study developed an USI atlas for grading OA features in the first MTPJ and assessed its reproducibility. The AUTUSI atlas of first MTPJ OA was developed using an evidence-based approach with findings from a systematic review (481), a scoping review (482), Delphi consensus study (498), and an USI reliability study serving as a basis for development. The AUTUSI atlas of first MTPJ OA evaluates the presence and severity of joint effusion, synovial hypertrophy, synovitis, osteophytes, joint space narrowing, and cartilage thickness. The AUTUSI atlas is expected to enhance unified interpretations of grading USI features between examiners, researchers and clinicians.

Overall, the AUTUSI atlas demonstrated excellent intra-examiner and inter-examiner reproducibility. Although acceptable, the grading of synovitis was not as consistent as other USI features. Despite the randomly selected images representing different grades of severity, the volume of power Doppler signals was similar, which may explain the uncertainty in differentiation between synovitis grades. However, as outlined in the synovitis description of the atlas, power Doppler signals must be detected within synovial hypertrophy to be considered as a sign of synovitis (0 = No flow in the synovium, 1 = Mild, single vessel signals [one or more], 2 = Moderate, confluent vessel signals in less than half of the area of the synovium, 3 = Severe, vessel signals in more than half of the area of the synovium). Alternatively, given the number of choices with a semiquantitative grading scale, synovitis grading variation may be attributed to one examiner overscoring and one underscoring when the image was doubtful. Therefore, additional training of all examiners prior to use of the atlas may improve the performance, to ensure understanding of grading descriptions. This finding may also reflect the use of previous USI grading systems which were originally constructed from RA populations, where the degree of inflammation is distinctly much higher. Additionally, the marked variations across interpretation of how the synovial pathology has been defined and categorised in previous investigations may also be reflected in the scoring variation (481).

To elucidate the role of inflammation in foot OA, grey scale inflammatory abnormalities for synovial hypertrophy and joint effusion were graded separately. Furthermore, synovitis was examined as a separate entity by power Doppler signal (flow signal

detected within synovial hypertrophy was considered a sign of synovitis) (374, 376). Differentiating between inflammatory features addresses past inconsistencies and interpretation of the different entities of synovial pathology. Previous discrepancies of how synovitis, synovial hypertrophy and joint effusion have been defined and categorised as USI features make it unclear if synovial pathology is best represented as separate entities (joint effusion and synovial hypertrophy) or combined as proxy measures for synovitis (481). Furthermore, due to the marked variation in prevalence between grey scale and Doppler-detected inflammatory features demonstrated in hand OA (376), solely including grey scale features indicative of inflammation may result in OA being underestimated. The distinction between inflammatory pathology is further enhanced by our semiquantitative grading system that is specific to OA. To date, USI grading systems applied to OA have been largely extrapolated from those originally designed and validated to quantify inflammatory change in rheumatoid arthritis (RA) (481). The distinct difference of inflammation experienced in OA compared to RA (49, 331), reinforced the need for an OA-specific grading that truly depicts disease progression, as in this work.

The AUTUSI atlas will allow for quantification of the presence and severity of pathologic change occurring in joint tissues in first MTPJ OA. The AUTUSI atlas has the potential to advance understanding of the pathological process of first MTPJ OA, provide capacity for earlier detection, support standardisation of diagnosis, and subsequently broaden the scope and capabilities of targeted interventions. This research demonstrates the role of USI in foot OA and may be the catalyst in developing a classification criteria specific for first MTPJ OA, which could be utilised both clinically and in future research. The AUTUSI atlas will enhance the capability to detect and characterise first MTPJ OA across various stages of disease progression, rather than being restricted solely to the point of irreversible end-stage disease.

Strengths and Limitations

A particular strength of the present study is the inclusion of six examiners from different countries and health professions, and yet all experienced users of USI. Additionally, three reviewers were blinded to the image acquisition and atlas development process. The justification for including six examiners from different professional backgrounds ensures the atlas is reproducible across a range of health professions that are likely to implement the atlas, such as podiatrists, physical therapists, radiologists, sonographers and researchers. In comparison, the radiographic LFA and MRI atlas that were developed to assess first MTPJ OA included the same two examiners for assessing the reproducibility of their atlases (13, 292). A further strength of our study is the accompaniment of supporting images in our atlas which clearly depicts the USI (patient and probe

positioning) acquisition procedure. Given the general perception that USI is a highly operator-dependent technique (502, 504), the authors wanted to ensure that a standardised procedure could be performed for all users of the atlas. Supporting images would ensure correct interpretation and allow subsequent studies to replicate our procedure.

This study must be viewed in the context of its limitations. First, despite examining a total of 24 ultrasound images with the atlas, the reviewers only evaluated three images per feature. Therefore, future research is needed to determine the reproducibility of the atlas when grading a larger sample of images. Second, there may have been examiner bias because the same radiologist reported on radiographic screening and graded the acquired ultrasound images. To minimise the risk of bias we randomly assigned an alphanumerical code to all participants upon entry into the study. Finally, despite efforts to proactively recruit an ethnically diverse population representative of the broader New Zealand population, no Pacific peoples were included. Pacific peoples suffer from significant and longstanding health inequalities and poorer health outcomes compared to other New Zealanders. Therefore, the inclusion of ethnicity related to OA data is needed to better understand what factors contribute to these inequalities and to provide the capacity to measure progress.

Implications for Further Research

This research has laid the foundation for USI-based diagnostic and classification criteria specific to first MTPJ OA. The AUTUSI atlas is the first step in a longitudinal analysis to determine the predictive value of USI features in participants without radiographically confirmed OA. Ongoing research is crucial to determine the capacity of USI to detect early inflammatory changes that precede structural involvement. Finally, further work is needed to determine: which AUTUSI atlas features would be most accurate in the diagnosis of first MTPJ OA compared to radiographic grading; the relationship between the atlas and symptom severity; and how atlas features respond to clinical interventions.

Conclusion

The AUTUSI atlas demonstrated excellent intra-examiner and inter-examiner reproducibility for evaluating first MTPJ joint effusion, synovial hypertrophy, synovitis, joint space narrowing, osteophytes, and cartilage thickness. The AUTUSI atlas affords an opportunity to detect prognostic markers of OA earlier in the disease cascade, which would provide a window of opportunity and broaden the scope and capabilities of

targeted interventions to alter disease progression. The AUTUSI atlas will also advance understanding of the pathological process of first MTPJ OA.

Chapter 10

Thesis Discussion

The aim of this thesis was to develop an USI atlas to grade OA in the first MTPJ. This chapter will discuss the results, including the future directions, clinical implications, strengths, and limitations.

At the start of the research journey eight research questions (RQ) were asked:

1. What USI structural and inflammatory features are indicative of first MTP joint OA and how are they graded?
2. What USI acquisition procedures and guidelines are used to assess the first MTPJ?
3. What is the scope of research utilising imaging to assess foot OA?
4. What are the most valuable sonographic features to diagnose first MTPJ OA?
5. How should severity for each sonographic feature of first MTPJ OA be graded?
6. What USI acquisition protocol should be used to evaluate first MTPJ OA?
7. Is the USI acquisition procedure and grading system reliable for the assessment of structural and inflammatory features of first MTPJ OA?
8. Is the USI atlas reproducible between sessions and between examiners for evaluating first MTPJ OA?

Overview of Main Findings

The research findings have supported the hypothesis that USI affords the utility to quantify inflammatory and structural features of first MTPJ OA. To answer this hypothesis the research undertook six sequential studies. Chapter 4 presented a systematic review that investigated what USI features were associated with OA in peripheral joints, how these features were defined and graded, and the reliability of assessing USI features. The review critically evaluated and summarised relevant studies that had used USI to examine peripheral joint OA (RQ 1). It demonstrated the large degree of variation in what OA features were assessed, how features were defined, and what grading system was applied. The key inconsistency identified was between the different entities of synovial pathology indicative of inflammation. Consequently, it is unclear whether synovial pathology is best represented as separate entities or combined as a single domain termed “synovitis”. The synovial inflammation exhibited in early OA suggests a window of opportunity may exist for interventions targeting the inflammatory processes (364),

thus providing the ability to intervene before end-stage disease where irreversible structural damage occurs (208, 209, 365). USI may also provide an opportunity to identify a point prior to significant inflammation, thus enabling earlier detection, monitoring, and potentially preventative management. However, the use of USI to categorise OA-based change is limited by inconsistencies and the lack of consensus as to which USI features should specifically be evaluated to diagnose and grade peripheral joint OA. How OA features were defined and graded, and atlases applied, has largely been extrapolated from recommendations originally constructed for populations with RA. Given the prognostic value of synovitis for OA progression and the reduced degree of inflammation experienced in OA compared to RA, the validity of applying definitions, grading systems and atlases originally developed for inflammatory arthritis needed consideration. The review strengthened the case for further refinement and validation of OA definitions, grading systems and USI atlases specific to peripheral joints.

Chapter 5 presented a scoping review that investigated the USI acquisition procedures and guidelines used to assess the first MTPJ (RQ 2). Inconsistencies were identified by the scoping review against international guidelines and limited implementation of consensus-based recommendations to guide development and implementation of USI procedures for evaluating the first MTPJ. The variation between studies in USI acquisition procedures used to evaluate the first MTPJ may be attributable to the number of elements the USI acquisition procedure encompasses. The review emphasised the need for further refinement of anatomical reference points used to guide probe positioning. A standardised procedure will improve interpretability and reproducibility between studies.

Chapter 6 presented a bibliometric analysis of published literature used to evaluate the scope of research utilising imaging to assess foot OA (RQ 3). The bibliometric analysis found published research employing imaging to assess foot OA had increased substantially over the past four decades. Despite technological and knowledge advancements, plain radiography has remained the gold standard and the most utilised modality for research of foot OA. The emergence of MRI, CT and USI in the past two decades continues to progress research in this field. The bibliometric analysis also highlighted the importance of international collaboration in allowing researchers and institutions from different health professions with different skill sets and knowledge to contribute to ongoing research utilising imaging to evaluate foot OA. More advanced imaging modalities, including MRI and USI, are emerging as more accurate evaluators of both bone and soft tissue abnormalities in foot OA (210, 292). This contemporary evidence shift has been creating a wave of change and necessitated determining the

validity of these more advanced techniques. To continue improving the understanding of foot OA and acknowledging the heterogeneous involvement of multiple joint tissues, it is pivotal that future research utilises more advanced imaging techniques.

Chapters 4, 5 and 6 addressed RQs 1, 2 and 3 by critically evaluating and summarising relevant studies that had used USI to examine foot OA. Several research gaps were identified. Firstly, it was not known what USI features are specific to and representative of first MTPJ OA, specifically regarding the different entities of synovial pathology. Secondly, there was no clear consensus as to which type of grading system (e.g. dichotomous or on a semiquantitative scale) should be applied to determine the degree of severity for each USI feature. Finally, it was unclear what USI imaging acquisition procedure should be used to examine first MTPJ OA. Therefore, further foundational work was needed as a basis for the development of an USI acquisition procedure and grading system. To address these research gaps, an international multi-speciality Delphi study was conducted to gain consensus concerning which USI features should be assessed and graded, and what USI procedure should be performed when examining first MTPJ OA (RQ's 4, 5 and 6). The Delphi study presented in Chapter 7 identified the essential components that the USI acquisition procedure should encompass when examining first MTPJ OA. Sixteen items were considered as 'essential' across three domains: first MTPJ OA USI features; grading USI features; and USI acquisition procedure. The Delphi findings informed the development of a novel USI acquisition procedure and grading system to examine OA features in the first MTPJ.

Chapter 8 outlined the development of the novel USI acquisition procedure and grading system to examine OA features in the first MTPJ and determined its intra-examiner and inter-examiner reliability (RQ 7). The development of the USI acquisition procedure was informed by the former interconnected studies (systematic review, scoping review and Delphi study) that have been completed iteratively. Feasibility work and final refinement clarified the USI examination methodology to establish a shared understanding and agreement regarding the USI acquisition procedures, image interpretation and grading. The new USI acquisition procedure and grading system demonstrated reliability in evaluating first MTPJ OA features in participants with radiologically confirmed OA. The USI procedure demonstrated good to excellent intra-examiner reliability in examining all features except cartilage thickness when evaluated as a continuous measure. Inter-examiner reliability was good for grading joint effusion and excellent for grading all other USI features. With all inflammatory features reporting good to excellent intra-examiner and inter-examiner reliability, coupled with their prognostic value for structural

progression, it was concluded that USI affords an opportunity to detect prognostic markers of OA earlier in the disease process.

With all semiquantitative grading of USI features reporting good to excellent inter-examiner and intra-examiner reliability, all USI features were incorporated into the methodological development of the AUTUSI atlas for grading the extent of osteoarthritic change in the first MTPJ. It is now well understood that OA is a whole organ disease, and USI is superior in assessing this, over and above antiquated methods such as conventional radiography. The development of an USI atlas which evaluates inflammatory and structural features will advance the understanding of the pathological process of first MTPJ OA and provide a more sensitive method to classify and grade the disease process.

Chapter 9 presents the final study of the research which outlines the development of an USI atlas for examining first MTPJ OA. The intra-examiner and inter-examiner reproducibility of the AUTUSI atlas was also assessed (RQ 8). Each study has built upon the findings of the former to generate the AUTUSI atlas. The AUTUSI atlas evaluates the presence and severity of joint effusion, synovial hypertrophy, synovitis, osteophytes, joint space narrowing, and cartilage thickness of the first MTPJ. To assist in the differentiation between grades and features, the atlas also included USI feature definitions, grading descriptions, and graphical images to align with each ultrasound image. To determine the intra-examiner and inter-examiner reproducibility of the new atlas, six examiners independently rated a random sample of ultrasound images using the atlas. The atlas demonstrated excellent intra-examiner and inter-examiner reproducibility for evaluating first MTPJ joint effusion, synovial hypertrophy, synovitis, joint space narrowing, osteophytes, and cartilage thickness.

The AUTUSI atlas affords an opportunity to detect prognostic markers of OA earlier in the disease cascade. The ability to detect OA before the point of irreversible structural change and should provide a window of opportunity where individuals may be more responsive to interventions, thus broadening the scope and capabilities of targeted interventions to alter disease progression and symptomatic consequence, preserving joint function and mobility, and preventing disability. This research will make an important contribution to advancing clinicians contemporary understanding of OA. The AUTUSI atlas will play a pivotal role in transforming the narrative from illness management to proactive disease mitigation. Early diagnosis will provide patients with the knowledge and tools to participate actively in their healthcare, empowering individuals to make informed decisions about modifiable risk factors, treatment options and self-

management strategies. Targeting OA in its early stages may lead to more cost-effective management of OA. Consequently, healthcare resources may be utilised more efficiently, reducing the demand for more extensive costly interventions (i.e. total joint replacements), which are significant contributors to the global burden of OA. With the capability for earlier disease detection, the AUTUSI atlas affords an opportunity to create a meaningful clinical and socioeconomic impact. Furthermore, the AUTUSI atlas will make a significant contribution to the field of foot OA research.

Future Directions

The research demonstrated that USI is an extremely valuable diagnostic and monitoring tool in OA, providing prognostic information as well as advancing clinical decision-making to reduce the burden of OA. Given the high prevalence and unmet need for OA, this research and planned future work will promote an area of research of major value in the field of foot and ankle OA.

As it stands, this thesis reveals the extremely valuable contribution that USI provides in the diagnosis of OA, identifying radiography as an outdated method that is limited by its inability to detect early disease critical to guide proactive treatments at a time when they are most needed. Future research will determine the reproducibility of the AUTUSI atlas when grading a larger sample of images. To assess the reproducibility of the new atlas, a random sample of 30 ultrasound images per feature (total sample of 240 images) will be randomly selected from a new library of acquired images, to confirm the inter-examiner and intra-examiner reproducibility of the atlas. To ensure the external validity of the AUTUSI atlas, the inclusion of multiple examiners from different countries, institutions and health professions will be continued. This approach ensures the application of the atlas by users not involved in the atlas development process should be reproducible.

Once that step has been completed, future work is planned to investigate how the AUTUSI atlas could be extrapolated to other foot joints commonly affected by OA. Promising opportunities exist to take advantage of USI ability to provide excellent resolution of superficial tissues and structures. Therefore, extending the AUTUSI atlas to the cuneo-metatarsal joints, navicular-cuneiform joint and talonavicular joint will assist in delineating different phenotypes of foot OA that require distinct management approaches.

Future research will then determine, variously: which AUTUSI atlas features would be most accurate in the diagnosis of first MTPJ OA; whether additional features could further enhance the AUTUSI atlas; the relationship between USI atlas features and symptom severity; and how AUTUSI atlas features respond to clinical interventions. Construct validity will be determined, to evaluate the utility and appropriateness of the AUTUSI atlas for grading first MTPJ OA, by comparing AUTUSI atlas features against radiographic features graded by the LFA. To determine the construct validity of early disease detection, sonographic features will be compared against MRI features, clinical features, and/or blood inflammatory markers.

There is a paucity of data on what symptomatic features occur in the early stages of OA and whether the frequency, intensity, type and duration of symptoms can differentiate between early- and late-stage OA. Clinical assessment data was obtained from the participants involved in the reliability and atlas development studies as exploratory outcome measures. Future work will investigate the relationship between USI features and clinical findings, such as symptom severity. Despite the high prevalence and disabling nature of first MTPJ OA, only a few interventions - orthoses, shoe-stiffening inserts, rocker-sole footwear, and intra-articular hyaluronan - have been trialled, with inconclusive results (509-513). Ultimately, the goal is the inclusion of the AUTUSI atlas into clinical trials that investigate the efficacy of interventions for first MTPJ OA, investigating targeted interventions at different stages along the pathological process, and providing clinicians with a means to inform early interventions that prevent or halt progression of subsequent joint damage and improve patient outcomes. To efffectively reduce the burden of OA, the current reactive model of care needs to change. This necessitates a shift towards prevention and/or early detection. The focus should be on identifying those individuals most at risk of OA development. The AUTUSI atlas could be utilised in prospective cohort studies where a group of vulnerable participants (i.e. previous trauma to first MTPJ) are followed, to plot the course of disease.

Future work would then need to determine the minimal important difference of the AUTUSI atlas for diagnosing first MTPJ OA. The receiver-operating characteristic (ROC) method can be used to ascertain the minimal important difference, which increases the precision and accuracy of estimates (514). A ROC curve provides a graphical representation of the balance between sensitivity and specificity, the point of optimal true positives and false negatives (230). That analysis would provide information as to how well the first MTPJ OA AUTUSI atlas can discriminate between the presence and absence of first MTPJ and investigate which combination of USI features from the atlas are most predictive of first MTPJ OA.

The AUTUSI atlas will be the first step in a longitudinal analysis to determine the predictive value of USI features in participants without radiographically confirmed OA. The incorporation of the AUTUSI atlas as an outcome measure in population-based cohort studies (e.g. the Johnston County OA Project) could provide valuable insight into early detection. The Johnston County OA Project new enrolment (2019) includes a younger and ethnically diverse cohort of participants. Future USI research of foot OA will be improved by including populations that are diverse in ethnicity and age, since the prevalence and burden of OA is not uniform across demographic groups. Thus, implementation of the AUTUSI atlas in a longitudinal analysis provides capacity to determine which USI features may progress to radiographic change. Consequently, the AUTUSI atlas has the potential to lay the foundation for USI-based diagnostic and classification criteria for early detection of first MTPJ OA. The ability to identify early OA provides the opportunity to determine the natural history of the disease, how the disease progresses, what the different trajectories are, and who experiences more accelerated progression and/or greater severity, and to examine what factors are contributing to disparities across demographic groups.

Interrupting the advancement of structural progression and halting symptomatic or functional consequences are crucial objectives and essential outcomes in the development of disease-modifying OA drug development. The effectiveness of OA drug development might be hindered by the involvement of individuals already experiencing established or end-stage OA, when pharmacologic interventions may be less effective (515). Currently there is no established definition for early-stage OA (516), nor validated classification criteria to identify potential participants for inclusion in clinical trials. OARSI is currently in the initial phase of an initiative to develop classification criteria for early-stage knee OA (516). The primary objective is to identify individuals early in the disease course, before potentially irreversible structural damage/disability occurs, that may be more responsive to interventions. Relying on radiographic OA to define early-stage OA identifies individuals who already have more established structural joint damage and/or functional limitations, which could reflect disease that might be beyond the optimal timeframe for specific effective disease-modifying treatments. The implementation of USI as a classification criterion for defining early-stage foot OA has real potential to make a significant impact on how the pathological process is diagnosed and monitored. Unfortunately, knowledge of OA in the foot is extremely limited in comparison to the knee, which is 30 years more advanced, even though foot OA has a similar prevalence to knee OA (237). With OARSI currently developing a classification criterion for early-stage knee

OA, it is crucial the foot isn't left behind once more. The time to define early-stage foot OA is now.

Clinical Implications

Current care for people with OA is variable and frequently inconsistent with clinical guideline recommendations (517). Consistent evidence-practice gaps in OA care are observed in primary care settings globally (518). Building workforce capacity to deliver high-value care requires a contemporary understanding of OA. Lack of knowledge is one of the main reasons why people with OA are not getting appropriate care (518). The traditional view of OA resulting from normal bodily wear and tear is obsolete, but terms such as 'wear and tear', 'bone on bone' and 'degenerative' are still being widely used, despite being inaccurate descriptors of the disease. These misconceptions that some health clinicians portray have consequences, often influencing the management of OA (519, 520). Clinicians' levels of understanding and language use can be detrimental to the patient's belief of how their OA can be managed well (517). The present research will make an important contribution to advancing clinicians' understanding of OA, helping shift the focus to appreciating OA as a disease of the whole joint. The new atlas will help shift the clinical focus from symptom management to proactive disease mitigation.

There is a dearth of evidence to inform best practice and guide treatment efficacy of first MTPJ OA. There are few clinical trials investigating conservative treatment for first MTPJ OA (509, 510, 513), and all included participants based on the presence of radiographic first MTPJ OA. Findings from the present research have underscored the need to change the current model of studying end-stage disease. The AUTUSI atlas may provide an opportunity to detect inflammatory features before the point of pain and before the point of irreversible structural damage. The application of the atlas may provide clinicians with a greater window of opportunity to intervene at a point where they could provide the greatest impact. Earlier detection of OA would broaden the scope and capabilities of targeted interventions to alter the progression of the disease.

The atlas will not only provide clinicians the capacity to make an earlier diagnosis but also the means to monitor disease progression, informing appropriate timing of management modifications and referral pathways. Furthermore, it provides a tool to investigate interventions at different stages along the pathological process, which may provide valuable insight into treatment efficacy along the course of disease to optimise individuals' long-term outcomes. The translation and implementation of USI into clinical

practice can create a paradigm shift, reshaping both the diagnosis of and model of care for first MTPJ OA. The clinical application of the AUTUSI atlas has potential to advance clinical decision-making, increasing the workforce capability of diverse healthcare professionals and improving healthcare provision, access and outcomes with early disease detection.

Strengths

This research demonstrated several methodological strengths. Importantly, this was a novel study that comprehensively investigated USI for the examination of first MTPJ to inform the development of an USI acquisition procedure, grading system and USI atlas specific to first MTPJ OA. The outputs of the iterative research approach have been informed using an evidence-based approach with findings from extensive reviews and an international multispeciality Delphi consensus study serving as a basis for development. Furthermore, feasibility and reliability work have led to the development of the AUTUSI atlas for evaluating first MTPJ OA.

Given the focal output of the research is an assessment instrument, a strength of the research was the inclusion of content validity in the Delphi study. Evaluating content validity is a critical step in the development process of instruments used to measure constructs in research (488). Content validity provides evidence to the extent at which items of an assessment instrument are representative of the entire domain the assessment seeks to measure (488).

A particular strength in the development of the atlas was the inclusion of six examiners from different countries, institutions and health professions to determine the reproducibility of the AUTUSI atlas, including three reviewers who were blinded to the image acquisition and atlas development processes. The rationale for including six examiners from different professional backgrounds ensured the atlas was reproducible across a range of health professions that are likely to implement the AUTUSI atlas.

A further strength of this research work is the accompaniment of supporting images in the atlas which clearly depicted the USI acquisition procedure (patient and probe positioning). Given the general perception that USI is a highly operator-dependent technique (502, 504), it was essential to ensure that a standardised procedure could be performed for all users of the atlas. Supporting images also ensure correct interpretation, which in turn will enable subsequent researchers or clinicians to replicate the acquisition procedure. Furthermore, to assist in the differentiation between features and grades, the

atlas also included line drawings to align with each ultrasound image, representing each feature definition and grading description. It is expected that the accompaniment of supporting images and descriptions will enhance unified interpretations of grading USI features between examiners, researchers and clinicians.

Limitations

The research must be viewed in the context of several limitations. Firstly, it is important to acknowledge the coronavirus pandemic and associated lockdowns during the research period which were disruptive and challenging. New Zealand experienced four substantial lockdowns, the longest being four months in 2021. These disruptions significantly impacted the research timelines by delaying the ability to recruit participants and commence data collection. The less than desired number of participants who participated in the Delphi study may be reflective of participant recruitment proceeding during the midst of the COVID-19 pandemic. Once data collection was authorised to commence for the reliability and atlas development studies, retaining participants was difficult due to the number of people contracting COVID-19 and having to cancel or reschedule their imaging examinations due to lengthy isolation periods. Furthermore, due to the potential risk and fear of being exposed to COVID-19, potential participants may have avoided healthcare venues like imaging facilities. Consequently, potential participants may have been less willing to participate in our research.

The Delphi study presented in Chapter 7 was primarily dependent upon an expert consensus-based approach (495). Therefore, the analysis was based on the subjective opinion of the participants, which in the context of evidence-based practice constitutes low-level evidence (496). The small sample obtained, and level of professional experience may have limited the potential for ideas as well as the number of items generated. Investigator bias may have been introduced during the amalgamation of Delphi items. However, attempts were made to minimise bias through transparency in the process implemented. The term ‘expert’ and its application to health practitioners is controversial (480). By inviting members from three different groups (OARSI, UK Podiatry US, and EULAR US network), it was expected that the relevant knowledge, experience and diversity was reflected in the expert panel members.

The USI procedure presented in Chapter 8 included solely a dorsal scan of the first MTPJ. USI offers a multiplanar technique, and as the medial and/or plantar aspect of the first MTPJ was not examined, the procedure developed may underestimate the prevalence or severity of features. However, feasibility work with an experienced

radiologist and sonographer determined that the extra time taken to acquire the additional images did not add further value to the examination of first MTPJ OA. Furthermore, a transverse orientation technique was applied to examine joint effusion and synovial hypertrophy, to ensure the extent of the effusion and synovial thickening was fully investigated. The poor reliability reported for examining cartilage as a continuous measure could be mitigated by segmenting the entire cross-sectional area of the articular cartilage using ImageJ software (505). With this technique, the average cartilage thickness within standardised regions can be calculated. However, this technique requires additional expertise and overall time to complete the segmentation, which may limit the translation of cartilage thickness assessment to a clinical setting. However, this may be an important step to address in research settings where more time may be available.

There may have been examiner bias in studies five and six because the same radiologist reported on radiographic screening and graded the acquired ultrasound images. All participants were randomly assigned an alphanumerical code upon entry into the study to minimise this risk of bias. Despite examining a total of 24 ultrasound images with the AUTUSI atlas, the reviewers only evaluated three images per feature, due in part to time limitations of the research. However, it is a crucial first step in determining the reproducibility of the AUTUSI atlas across a range of examiners. This step allowed the opportunity for revision of images selected or feature descriptions given the initial reproducibility results. Now that the AUTUSI atlas has demonstrated excellent intra-examiner and inter-examiner reproducibility for evaluating first MTPJ joint effusion, synovial hypertrophy, synovitis, joint space narrowing, osteophytes, and cartilage thickness, future research is planned to determine the reproducibility of the atlas when grading a larger sample of images.

Finally, despite efforts to proactively recruit an ethnically diverse population representative of the broader New Zealand population, no Pacific peoples were included in the reliability study or atlas development study. Pacific peoples and Māori experience significant and longstanding health inequalities and poorer health outcomes compared to other New Zealanders. Consequently, Māori and Pacific peoples are living with the burden of this disease for longer. Therefore, to achieve health equity, it is necessary to shift resources to prevention and earlier diagnosis. The collection of accurate ethnic OA data is needed to better understand what factors contribute to these inequalities and to provide the capacity to measure progress. To mitigate this issue and improve potential participation of Pacific peoples and Māori for future research, we need to better understand their community needs. Future research will aim to involve Pacific and/or

Māori research assistants and/or collaborators, to ensure our research includes capacity-building for both their workforces and communities, ultimately creating change in an underserved community.

Conclusion

The current method of diagnosing OA by conventional radiographs remains reactive and captures OA later in the disease process once the condition is significantly advanced and irreversible structural damage may have already occurred. This issue necessitates a new model of care for OA, where the diagnosis and management are proactive and preventative. The aim of this research was to develop an USI atlas to grade OA in the first MTPJ. The AUTUSI atlas recognises the heterogeneous involvement of multiple joint tissues, thus providing a reliable means of evaluating both structural and inflammatory features specific to first MTPJ OA. The AUTUSI atlas affords an opportunity to detect prognostic inflammatory features earlier in the disease course before potentially irreversible damage or disability occur. Therefore, the first MTPJ OA AUTUSI atlas can be the catalyst in developing a USI classification criterion for defining and detecting early first MTPJ OA when the joint may be more responsive to interventions. Ultimately, the AUTUSI atlas will advance the understanding of OA, provide capacity for earlier detection and standardisation of diagnosis, and provide a more sensitive method to classify and grade the disease process.

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Appendices

Appendix 1

Evaluation of Osteoarthritic Features in Peripheral Joints by Ultrasound Imaging: A Systematic Review - Study Design and Participant Demographics

Foot OA

Author	Study aim	Study design/participant/sample size	Definition of OA cohort (inclusion criteria)
Zabotti (1)	Evaluate the level of agreement on US lesions among highly experienced sonographers as well as the intraobserver and interobserver reliability of inflammatory and structural US lesions in patients with foot OA	Delphi and cross-sectional reliability study design. Participants mean (SD) age 67.8 (NSD) years, *n* = 12 (M:F = 2:10)	• Reported foot pain on weight bearing • diagnosis of foot OA based on clinical examination • radiographic criteria based on the LaTrobe Foot Atlas (2)
Iagnocco (3)	To investigate the prevalence of US abnormalities in the feet of patients with OA and to compare them with clinical findings	Cross-sectional study design. Participants mean (SD) age 65.4 (10.8) years, disease duration (SD) years 1.1 (0.9), *n* = 100 (M:F = 43:57)	Clinical and radiographic signs of OA involving the feet

Hand OA

Author	Study aim	Study design/participant/sample size	Definition of OA cohort (inclusion criteria)
Fjellstad (4)	Explore whether US-detected gray-scale synovitis and PD activity in the interphalangeal and first carpometacarpal joints are associated with pain and physical function in patients with hand OA	Cross-sectional study design. Data from the baseline examination of the Nor-Hand study. Participants mean (SD) age 60.9 (NSD) years, BMI 25.5 (NSD) kgm^2, *n* = 290 (M:F = 34:256)	Clinical examination or presence of osteophytes determined by US
Steen (5)	Examine the association of structural and inflammatory features of hand OA with local pressure pain thresholds in the Nor-Hand Study	Cross-sectional study design. Participants mean (SD) age 61 (NSD) years, disease duration (SD) years 6 (NSD), BMI 26 (5) kgm^2, *n* = 285 (M:F = 34:251)	Evidence of hand OA by ultrasound and/or clinical examination performed by a rheumatologist
Besselink (6)	Assess performance of optical spectral transmission in assessing synovitis in hand and wrist OA. Then compare optical spectral transmission levels between joints with and without US synovitis	Cross-sectional study design. Participants mean (SD) age 64.5 (9.9) years, *n* = (M:F = 5:42)	Recruited from rheumatology clinic. Participants were eligible if they had at least one swollen finger or wrist joint

Author	Study aim	Study design/participant/sample size	Definition of OA cohort (inclusion criteria)
Oo (7)	Determine the associations of OA US features with the extent of pain, function, strength and radiographic scores in symptomatic thumb-base OA	Cross-sectional study design. Participants mean (SD) age 67.0 (7.0) years, disease duration 3.1 (1.1) years, BMI 29.4 (6.7) kgm^2, *n* = 93 (M:F = 73:20)	• Thumb-base pain at least half of the days in the past month • Average pain ≥40 on a 100mm VAS • Functional Index for HOA • scores ≥6 (Dreiser, Maheu, Guillou, Caspard, & Grouin, 1995) • KL grade ≥2 in the index thumb-base joint
Kroon (8)	Investigate the associations between US and MRI inflammatory features, structural damage and pain in the thumb base of hand OA patients	Cross-sectional study design. Participants mean (SD) age 60.3 (8.8) years, BMI 27.2 (4.5) kgm^2, *n* = 87 (M:F = 16:71)	ACR criteria for hand OA (9)
Sivakumaran (10)	Investigate the usefulness of a standardised US examination protocol for hand joints in diagnosing OA	Cross-sectional study design. Participants mean (SD) age 51.1 (15.3) years, disease duration 4 (NSD) years, *n* = 62 (M:F = 12:50)	Hand OA based on EULAR recommendations (11)
Magnusson (12)	To explore whether smoking and alcohol use are associated with hand OA features in two different OA cohorts	Cohort study design. Radiographic hand OA (MUST cohort) age 65.3 (8.0) years, BMI 28.4 (4.8) kgm^2, *n* = 530 (M:F = 155:375) Oslo hand OA cohort age 61.6 (5.7) years, BMI 25.6 (4.1) kgm^2, *n* = 187 (M:F = 17:170)	**MUST cohort** (selected from the general population with self-reported or physician-based or X-ray-diagnosed OA) radiographic hand OA (KL grade ≥2) 57.4% of these fulfilled the ACR criteria for hand OA **Oslo hand OA cohort** (consists of people visiting specialist care for their hand OA) 92.5% had radiographic hand OA (KL grade ≥2) 83.4% fulfilled the ACR criteria for hand OA
Mathiessen (13)	Determine whether US detected osteophytes (in radiographically and clinically normal finger joints) predicted the development of radiographic and clinical hand OA five years later	Prospective cohort study design. *N* = 78 From the Oslo Hand OA cohort	ACR criteria for hand OA (9)
Spolidoro, (14)	To assess the correlation between inflammatory sonographic findings and clinical and functional assessments in hand OA and correlate the intraobserver and interobserver reliability	Cross-sectional study design. Participants mean (SD) age 60.7 (8.2) years, disease duration 5.0 (3.6) years, *n* = 60.7 (8.2) (M:F = 2:58)	• ACR criteria for hand OA (9) • Older than 40 years • VAS pain score (0-10cm)

Author	Study aim	Study design/participant/sample size	Definition of OA cohort (inclusion criteria)
Hammer (15)	Explore the reliability of highly experienced sonographers in performing semiquantitative US scoring of cartilage pathology and osteophytes in the finger joints of patients with hand OA	Cross-sectional study design. Participants mean (SD) age 74.5 (NSD) years, BMI 23.2 (3.1) kgm^2, *n* = 10 (M:F = 0:10)	ACR criteria for hand OA (9)
Haugen (16)	To compare the prevalence of synovitis, pain and radiographic progression in non-erosive and erosive hand OA and to explore whether the different rate of disease progression is explained by different levels of synovitis and structural damage	Prospective cohort study design. Participants of the Oslo hand OA cohort **Non-erosive OA** Participants mean (SD) age 68.3 (4.6) years, disease duration 16 (NSD) years, BMI 26.5 (3.9) kgm^2, *n* = 31 (M:F = 4:27) **Erosive OA** Participants mean (SD) age 67.4 (6.0) years, disease duration 17 (NSD) years, BMI 26.8 (3.9) kgm^2, *n* = 34 (M:F = 2:32)	ACR criteria for hand OA (9)
Kortekaas (17)	Investigate the association between features of US detected inflammation and development of erosive disease in patients with hand OA over 2.3 years of follow-up	Longitudinal cohort study design. Participants mean (SD) age 61.2 (8.9) years, disease duration 4 (NSD) years, BMI 27.6 (4.6), *n* = 56 (M:F = 8:48)	ACR criteria for OA (9)
Mathiessen (18)	To examine whether US predicts radiographic hand OA progression after 5 years	Longitudinal cohort study. Participants mean (SD) age 67.8 (5.2) years, disease duration 18.5 (7.9) years, BMI 25.4 (3.7), *n* = 78 (M:F = 7:71)	ACR criteria for OA (9)
Kortekaas (19)	Investigate whether inflammatory US features are associated with structural radiographic damage after long-term follow-up of 2-3 years and to investigate the course of inflammatory ultrasound features over long-term follow-up	Longitudinal observational cohort study design Participants mean (SD) age 61.2 (8.9) years, BMI 27.6 (4.6), *n* = 56 (M:F = 8:48)	ACR criteria for hand OA (9)

Author	Study aim	Study design/participant/sample size	Definition of OA cohort (inclusion criteria)
Mancarella (20)	To evaluate the association between US detected inflammation at baseline and subsequent development of new bone erosions at follow-up in patients with hand OA	Case control study design. Participants of the Oslo hand OA cohort **Controls** Participants mean (SD) age 66.8 (9.0) years, BMI 24.9 (3.4) kgm^2, *n* = 10 (M:F = 2:8) **Non-erosive OA** Participants mean (SD) age 67.0 (7.5) years, BMI 25.8 (4.7) kgm^2, *n* = 12 (M:F = 2:10) **Erosive OA** Participants mean (SD) age 63.9 (8.2) years, BMI 25.2 (2.9) kgm^2, *n* = 13 (M:F = 0:13)	ACR criteria for hand OA (9)
Abraham (21)	To measure the prevalence of features of OA in the dominant hand using US, within the Newcastle Thousand Families birth cohort	Prospective cohort study design. Participants mean (SD) age 63 (NSD) years, BMI 26.5 (4.2), *n* = 311 (M:F = 140:171)	The presence of at least one osteophyte in one hand joint
Kortekaas (22)	Investigate inflammatory US features and pain over a 3-month period in hand OA	Prospective cohort study design. Participants mean (SD) age 60 (8.8) years, BMI 28.0 (4.3), *n* = 25 (M:F = 9:16)	ACR criteria for hand OA (9)
Usón (23)	To describe and compare the clinical, radiographic and US findings in patients with OA of the PIP and/or DIP joints with and without pain	Cross-sectional study design. Participants mean (SD) age 61.9 (NSD) years, disease duration 6.8 (NSD) years, *n* = 20 (M:F = 0:20)	ACR criteria for hand OA (9)
Kortekaas (24)	To compare inflammation as assessed by US between patients with the subset erosive hand OA versus non-erosive OA	Cross-sectional study design. **Non-erosive OA** Participants mean (SD) age 58.0 (8.9) years, BMI 26.9 (NSD) kgm2, *n* = 27 (M:F = 5:22) **Erosive OA** Participants mean (SD) age 65.0 (8.5) years, BMI 27.6 (NSD) kgm^2, *n* = 28 (M:F = 3:25)	ACR criteria for hand OA (9)
Mathiessen (25)	To investigate the reliability of US assessment of osteophytes and clinical joint examination in patients with hand OA	Cohort study design. Participants mean (SD) age 68.6 (5.8) years, BMI 25.3 (3.6) kgm^2 disease duration 18.3 (7.2) years, *n* = 127 (M:F = 11:116)	ACR criteria for hand OA (9)

Author	Study aim	Study design/participant/sample size	Definition of OA cohort (inclusion criteria)
Vlychou (26)	To compare structural and inflammatory features in small joints of the hand between patients with erosive OA and nodal hand OA by the use of high resolution US and MRI	Case control study design. **Non-erosive OA** Participants mean (SD) age 62.0 (5.8) years, disease duration 5.9 (5.2) years, *n* = 7 (M:F = 0:7) **Erosive OA** Participants mean (SD) age 61.6 (8.6) years, disease duration 6.9 (4.4) years, *n* = 13 (M:F = 1:12) **Controls** Participants mean (SD) age 43.8 (4.3) years, *n* = 5 (M:F = 2:3)	ACR criteria for hand OA (9) Diagnosis of hand OA was further supported by a KL grade >2 in any IP joint Nodal OA was defined as hand OA with Heberden's or Bouchard's nodes and no evidence of erosions on radiograph
Iagnocco (27)	To assess the reliability of US in detecting cartilage abnormalities at the MCPJ in people with cartilage pathology	Cross-sectional study design. Participants mean (SD) age 65 (NSD) years, disease duration 3.2 (NSD) years, *n* = 8 (M:F = 2:6)	ACR criteria for hand OA (9)
Arrestier (28)	To describe non-structural US abnormalities in finger OA to establish the prevalence of these abnormalities with healthy controls, and to evaluate correlations linking US abnormalities to clinical symptoms and radiographic damage	Case control study design. **Cases** Participants mean (SD) age 61.4 (8.6) years, disease duration 5 (NSD) years. *n* = 55 (M:F = 4:51) **Controls** Participants mean (SD) age 25.5 (4.3) years. *n* = 46 (M:F = 13:33)	ACR criteria for finger OA (9)
Kortekaas (29)	Investigate the association between structural abnormalities on US and pain in hand OA	Cohort study design. Participants mean (SD) age 61.4 (9.3) years, BMI 27.7 (4.5) kgm^2 disease duration 5.0 (NSD) years. *n* = 55 (M:F = 8:47)	ACR criteria for hand OA (9)
Kortekaas (30)	To investigate the association of US features: grey scale synovitis, synovial thickening, effusion, and PD signal with symptoms in hand OA	Cross-sectional study design. Participants mean (SD) age 62.0 (8.9) years, BMI 27.7 (4.5) kgm^2 disease duration 5.0 (NSD) years. *n* = 55 (M:F = 7:48)	ACR criteria for hand OA (9)

Author	Study aim	Study design/participant/sample size	Definition of OA cohort (inclusion criteria)
Mancarella (31)	To examine US features of synovitis in hand OA joints, and to evaluate their relationship with radiological damage severity and US-detected cartilage thickness	Case control study deign. **Controls** Participants mean (SD) age 66.8 (9.0) years, BMI 24.9 (3.4) kgm^2. *n* = 10 (M:F = 2:8) **Non-erosive OA** Participants mean (SD) age 67.0 (7.5) years, duration of disease 6 (NSD) years, BMI 25.8 (4.7) kgm^2. *n* = 12 (M:F = 2:10) **Erosive OA** Participants mean (SD) age 63.9 (8.2) years, duration of disease 7 (NSD) years, BMI 25.2 (2.9) kgm^2. *n* = 13 (M:F = 0:13)	ACR criteria for hand OA (9)
Vlychou (32)	Compare sonographic and radiographic imaging for the detection of erosions and osteophytes in hand joints of erosive OA patients and evaluate additional sonographic findings using grey scale and PD imaging	Cross-sectional study design. Participants mean (SD) age 62.5 (NSD) years, duration of disease 4.2 (NSD) years. *n* = 22 (M:F = 2:20)	ACR criteria for hand OA (9)
Keen (33)	To develop a preliminary US hand OA scoring system, initially focusing on relevant pathological features with potentially high reliability	Cross-sectional study design. Seven participants no further information was reported.	NR
Keen (34)	Compare the detection of osteophytosis and joint space narrowing by US and radiographic in hand OA	Cross-sectional study design. Participants median (IQR) age 57 (53-66) years, duration of disease 4.2 (2.7-7.8) years. *n* = 37 (M:F = 6:31)	ACR criteria for hand OA (9) OR with symptoms and radiographic structural changes consistent with OA such as sclerosis, joint space narrowing or osteophytes.
Keen (35)	Determine the extent of US detected pathology and investigate its relationship with symptoms in hand OA	Case control study deign. **OA group** Participants mean (SD) age 58 (NSD) years. *n* = 36 (M:F = 5:31) **Controls** Participants mean (SD) age 58 (NSD) years. *n* = 19 (M:F = 6:13)	ACR criteria (9) OR had radiographic changes consistent with hand OA who reported hand pain.

US, Ultrasound; OA, Osteoarthritis; PD, power Doppler; ACR, American College of Rheumatology; KL, Kellgren and Lawrence; M, Male; F, Female; BMI, Body mass index; SD, Standard deviation; NSD, No standard deviation; IQR, Interquartile range; NR, Not reported

Appendix 1 References

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Appendix 2

Defining and Grading Sonographic Features of Osteoarthritis

Author	Joint	US feature	Definition	Atlas included	Origin of US atlas	Grading system	US acquisition protocol	Sonographer	Reliability
Zabotti (1)	Foot: First MTPJ Midfoot	Synovial hypertrophy	NR	No	NA	Absent /present (2)	NR	11 rheumatologists all experts in US and members of OMERACT group	Intraobserver reliability κ = 0.64 Interobserver round 1 κ = 0.50 Interobserver round 2 κ = 0.64
						Semiquantitative (0-3) (3)			Intraobserver reliability κ = 0.48 Interobserver round 1 κ = 0.63 Interobserver round 2 κ = 0.59
		PD Signal	NR			Semiquantitative (0-3) (3)			Intraobserver reliability κ = 0.90 Interobserver round 1 κ = 0.87 Interobserver round 2 κ = 0.89
		Joint effusion	NR			Absent /present (2)			Intraobserver reliability κ = 0.67 Interobserver round 1 κ = 0.80 Interobserver round 2 κ = 0.61
		Osteophytes	NR			Semiquantitative (0-3) 0 = none 1 = minor 2 = moderate 3 = major size of osteophytes (4)			Intraobserver reliability κ = 0.63 Interobserver round 1 κ = 0.54 Interobserver round 2 κ = 0.58
		Cartilage damage First MTPJ only due to probe positioning	Loss of anechoic structure and/or thinning of cartilage layer (5)			Absent/ present (5)			Intraobserver reliability κ = 0.64 Interobserver round 1 κ = 0.60 Interobserver round 2 κ = 0.63
Iagnocco Iagnocco, Filippucci (6)	Foot: STJ TNJ NCJ-M NCJ-I MTPJ 1-5	Joint effusion	Abnormal hypoechoic or anechoic intra-articular material that is displaceable and compressible but does not exhibit PD signal (7)	No	NA	All lesions were registered according to a dichotomous (present of absent) score	Loqiq9 machine equipped with a multi-frequency linear probe, operating at 14 MHz. According to the EULAR guidelines for MSK US in rheumatology, in all cases, longitudinal and transverse multiplanar scans were performed at the level of the dorsal, lateral and medial aspects of the foot (8)	Single sonographer who was a rheumatologist experienced in MSK US and was blinded to the clinical and laboratory findings.	NR
		Synovial hypertrophy	Abnormal hyopechoic intraarticular tissue that is nondisplaceable and poorly compressible and which may exhibit PD signal (7)						
		PD vascularisation	NR						
		Osteophytes	Cortical protrusion at the joint margin seen in two planes (9)						

Author	Joint	US feature	Definition	Atlas included	Origin of US atlas	Grading system	US acquisition protocol	Ultrasonographer	Reliability
Fjellstad (10)	Hand: DIP PIP CMC 1	Synovitis	NR	Yes	NR	Semiquantitative (0–3) (11)	The joints were scanned dorsally with longitudinal projection, from the radial to the ulnar side. An additional transverse scanning was carried out when presence of pathology was uncertain	A trained medical student performed the US examination. Scoring was performed in consensus with an experienced ultrasonographer	DIP/PIP κ = 0.80 CMC1 κ = 0.92
		PD Signal	NR						DIP/PIP κ = 0.85 CMC1 κ = 0.92
		Osteophytes	NR						DIP/PIP κ = 0.72 CMC1 κ = 0.80
Steen Pettersen (12)	Hand: DIP PIP	Synovitis	NR	No	NA	Semiquantitative (0-3) (11)	All hand joints were scanned dorsally with longitudinal projection from the radial to the ulnar side of each joint. An additional transverse scan was performed when the presence of pathologic features of OA was uncertain	A trained medical student performed the US examinations. Initial scorings were done in consensus with an experienced ultrasonographer	Inter-reader reliability of the assessments of the DIP/PIP joints in 10 participants between the medical student and the ultrasonographer was good (κ = 0.80 for gray-scale synovitis grades 0–3)
		PD activity	NR			Semiquantitative (0-3) Due to the low frequency of grade (2–3) PD activity, this variable was later dichotomised Grade 0 versus grades (1-3) (11)			Inter-reader reliability was good for the absence/presence of PD activity (κ = 0.79)
Besselink (13)	Hand: DIP 2-5 PIP 1-5 CMC 1 MCP 1	US Synovitis	Refers to previous manuscript (14)	No	NA	Semiquantitative (0-3) (2)	Mylab 60 system (Esaote, GEN Patient and probe positioning were performed according to EULAR guidelines (15)	US examination was performed by a single experienced examiner	NR
		PD synovitis	Refers to previous manuscript (14)			Semiquantitative (0-3) (2)			NR
		Osteophytes	Refers to previous manuscript (14)			Absent /present			NR
		Erosions	Refers to previous manuscript (14)			Absent /present			NR
Oo (16)	Hand: CMC	Synovitis (effusion and synovial hypertrophy)	Effusion was defined as hypoechoic or anechoic fully compressible material Synovial hypertrophy was defined as echogenic or hypoechoic slightly compressible or non-compressible intra-articular tissue (17)	No	NA	Synovial hypertrophy and effusion were considered together as a single domain “synovitis” 0 = absent 1 = mild 2 = moderate 3 = severe (11)	The thumb-base joint was scanned on the longitudinal and transverse plane of the palmar and dorsal aspect according to the OMERACT ultrasound definitions and scanning methods (11)	Sonographer, experience in MSK US	Intra-rater reliability κw = 0.77
		PD signal	Doppler signal as a pulsating colour spot found within the synovial structure (7)	No	NA	Absent /present (7)			Intra-rater reliability unweighted κ = 0.89
		Osteophytes	cortical protrusions at the joint margin seen in two planes (7)	Yes	(4)	Semi-quantitatively using an atlas (0–3), based on the largest osteophyte (4)			Intra-rater reliability κ = 0.79
		Erosions	Intra-articular discontinuity of the bone surface that is visible in two perpendicular planes (7)	No	NA	Absent /present			NR

Author	Joint	US feature	Definition	Atlas included	Origin of US atlas	Grading system	US acquisition protocol	Sonographer	Reliability
Kroon (18)	Hand: CMC	Synovial thickening	NR	No	NA	semiquantitative scale: 0 = none 1 = mild 2 = moderate 3 = severe (19)	NR	Two ultrasonographers, who scored together in consensus during the examination	NR
		Joint effusion	NR						NR
		PD signal	NR						NR
Sivakumaran (20)	Hand: 1st CMC MCP PIP DIP	PD signal	Active joint inflammation refers to (21)	No	NR	Semiquantitative (1-3) (21)	Dorsal longitudinal and transverse views of wrists and MCP, PIP, DIP and carpometacarpal 1 [CMC-1] joints	Clinician with 6 years' experience in US.	NR
		Synovitis	NR but refers to (21)			Semiquantitative (1-3) (21)			
		Synovial thickening	NR but refers to (21)			Semiquantitative (1-3) (21)			
		Joint effusion	NR but refers to (21)			Present or absent (21)			
		Erosions	An intra-articular discontinuity of the bone surface that is visible in two perpendicular planes (7)			Present or absent (7)			
		Osteophytes	Hyperechoic signal in the area of the attachment of the joint capsule to the bony cartilaginous margin that correspond with the eventual appearance of osteophytes visualised on the PR (22)			Present or absent			
Magnusson (23)	Hand: CMC 1 MCP 1-5 PIP 2-5 DIP 2-5	Synovitis	NR	Yes	US RA atlas was used as a reference (17)	Present or absent A previously published atlas for RA was used as a reference (17)	NR	Three medical students trained in US	NA
Mathiessen (24)	Hand: CMC 1 IP 1 PIP 2-5 DIP 2-5	Osteophytes	NR	No	NA	Semiquantitative (0–3) (4)	Longitudinal and transverse US examination was performed on both hands on the volar and dorsal sides	Two sonographers performed assessments and reached consensus on each scoring They were the same sonographers from Mathiessen, Haugen (4) and Mathiessen, Slatkowsky-Christensen (25)	NR
Spolidoro Paschoal (26)	Hand: DIP PIP	Synovial hypertrophy	NR	No	NA	Semiquantitative 0 = no fluid 1 = a minimal amount of fluid 2 = a moderate amount of fluid (without distension of the joint capsule) 3 = extensive amount of fluid (with distension of the joint capsule) (27)	NR	Two rheumatologists experienced in MSK US	Distal joint: Intraobserver reliability Dorsal: κ = 0.673 Palmer: κ = -0.044 Interobserver reliability Dorsal: κ = 0.617 Palmer: κ = 0.498 Proximal joint: Intraobserver reliability Dorsal: κ = 0.664 Palmer: κ = 0.640 Interobserver reliability Dorsal: κ = 0.390 Palmer: κ = 0.525
		Synovial blood flow (PD signal)	NR			Semiquantitative 0 = no flow in the synovia 1 = single vessel signals 2 = confluent-vessel signals in less than half of the area of the synovia 3 = vessel signals in more than half of the area of the synovia (7, 27)			Power Doppler signals were found in only 1.7% of the sample, precluding statistical analysis.

Author	Joint	US feature	Definition	Atlas included	Origin of US atlas	Grading system	US acquisition protocol	Sonographer	Reliability
Hammer (28)	Hand: CMC 1 MCP 1-5 PIP 1-5 DIP 2-5	Osteophyte	Formation of excess bone at the joint margins	Yes	US atlas was used as a reference (4)	Semiquantitative 0 = none 1 = minor 2 = moderate 3 = major size of osteophytes (4)	Five identical General Electric logic E9 machines (GE Medical Systems, Milkaukee, Wisconsin, USA), equipped with two multifrequency linear probes (hockey stick 8-18MHz used for scoring cartilage and regular probe 6-15 MHz used for scoring osteophytes) Osteophytes were assessed by longitudinal scanning on extended joints with swiping of the probe from side to side of the dorsal aspect of MCP, PIP and DIP joints and at the radiopalmar side of CMC1 joints. For the evaluation of cartilage, the MCP joints were kept in maximal flexion (ie, close to 90°) and a longitudinal dorsal scan was performed at the level of the mid portion of the metacarpal head	10 sonographers (9 were rheumatologists, experts in MSK US and members of the OMERACT US group and one trainee fellow in rheumatology, highly experienced and had participated in the development of the US atlas	Osteophyte scores were evenly distributed, and the intraobserver and interobserver reliabilities were substantial to excellent κ range = (0.68–0.89) mean Day 1 κ = 0.65 Day 2 κ = 0.67
		Cartilage	NR		Developed new US atlas for scoring cartilage damage	Semiquantitative 0 = normal cartilage 1 = loss of anechoic structure and/or focal thinning of cartilage layer OR irregularities and/or loss of sharpness of at least one cartilage margin; 2 = loss of anechoic structure and/or focal thinning of cartilage layer AND irregularities and/or loss of sharpness of at least one cartilage margin; 3 = focal absence or complete loss of the cartilage			Cartilage scores were unevenly distributed, and the intraobserver and interobserver reliability was fair to moderate κ range = (0.46–0.66) mean: Day 1 κ = 0.39 Day 2 κ = 0.33
Haugen (29)	Hand: DIP 2-5 PIP 1-5	Synovitis	grey-scale synovitis, including both thickened synovium and fluid	Yes	US RA atlas was used as a reference (17)	Semiquantitative 0 = none 1 = minor 2 = moderate 3 = major presence of US pathology (17)	Each joint was scanned longitudinally from the radial to the ulnar side, and transverse scanning was performed if there was uncertainty about the presence of pathology (4)	A trained medical student and an experienced rheumatologist performed the US assessments together and reached consensus on each scoring	NR
		PD activity	Presence of vascularisation			Semiquantitative 0 = none 1 = minor 2 = moderate 3 = major presence of US pathology (17)			NR
Kortekaas (30)	Hand: All DIPJ All PIPJ	PD signal	NR	No	NA	Semiquantitative 0 = none 1 = mild 2 = moderate 3 = severe (19)	NR	One experienced ultrasonographer while always in the presence of a second ultrasonographer, scoring together in consensus	NR
		Synovial thickening	NR						NR
		Joint Effusion	NR						NR
Mathiessen (25)	Hand: CMC 1 MCP 1-5 PIP 1-5 DIP 2-5	Synovitis	A combined score of thickened synovium and joint effusion	Yes	(17)	Semiquantitative 0 = none 1 = minor 2 = moderate 3 = major presence of US Pathology (17)	Each joint was scanned longitudinally from the radial to the ulnar side, and transverse scanning was performed if there was uncertainty about the presence of pathology	One trainee and one experienced rheumatologist performed the US assessments together and reached consensus on each scoring	Good inter-reader reliability for synovitis (κw = 0.74) Intra-reader reliability was very good for both features (κw > 0.86)
		PD activity	Represented presence of vascularisation						Inter-reader reliability for PD (κw > 0.93)
Kortekaas (31)	Hand: All DIPJ All PIPJ 1st IPJ 1st CMC MCP	Synovial thickening	NR	No, but radiographic progression of osteophytes and joint space narrowing were scored using the OARSI atlas	(32)	Semiquantitative 0 = none 1 = mild 2 = moderate 3 = severe (19)	Hand joints were scanned on the dorsal side in longitudinal and transverse planes	One experienced ultrasonographer, scoring together in consensus with a second ultrasonographer. Both blinded to clinical findings	Intraobserver reliability was tested by performing a second ultrasound in 10% (randomly chosen) of patients ICC = 0.93
		Effusion							ICC = 0.84
		PD activity							ICC = 0.62
Mancarella (33)	Hand: PIP 1-5 DIP 2-5	PD activity	A signal within a region of GS synovitis	No	NA	Present or absent (7)	Longitudinal and transverse US examination was performed on both hands on the volar and dorsal sides	Two experienced MSK sonographers	Intra-observer variability depicted by κ coefficient was 0.78
		Synovial thickening	GS synovitis			Present or absent (7)			Intra-observer variability depicted by κ coefficient was 0.84
		Joint effusion	OMERACT definitions (7)			Present or absent (7)			Intra-observer variability depicted by κ coefficient was 0.83
		Erosions	An intra-articular discontinuity of the bone surface that is visible in two perpendicular planes on imaging (7)			NR			Intra-observer variability depicted by κ coefficient was 0.87

Author	Joint	US feature	Definition	Atlas included	Origin of US atlas	Grading system	US acquisition protocol	Sonographer	Reliability
Abraham (34)	Hand: 1st CMC Index: MCP PIP DIP	Osteophytes	Cortical protrusions seen in two planes (35)	No	NA	Present or absent (Present if at least one osteophyte in the individual joint)	Mylab 70 XVG machine (ESAOTE, Genoa, Italy). Dominant hand imaged using a 10-18 MHz linear transducer Dynamic approach with the probe in a longitudinal position and being swept across the whole of the joint for DIP and PIP joints from the anterior to posterior aspect, and across accessible areas for the MCP and CMC joints. The hand joints were placed in a neutral position for all examinations	Trained MSK Ultrasonographers	The κ inter-rater reliability for HOA was moderate to substantial, with values ranging from 0.50 to 0.69
Kortekaas (36)	Hand: CMC 1 MCP 1-5 PIP 1-5 DIP 2-5	PD signal	As described previously (19)	No	NA	All ultrasound features were scored on a 4-point semiquantitative scale: 0 = none 1 = mild 2 = moderate 3 = severe (19)	Scanned on the dorsal side in longitudinal and transverse planes	US assessment by one ultrasonographer and scored together with a second ultrasonographer	NR
		Synovial thickening							NR
		effusion							NR
Usón (37)	Hand: PIP DIP	Osteophytes	Hyperechoic cortical protrusions visualised in two planes	No	NA	Absent/present	A General Electric Logic 9 ultrasoundmachine with an M12 linear probe. In their longitudinal and transverse axis, the dorsal, palmar, lateral and medial aspects of each PIP and DIP joint, with the hand outstretched on the table.	An ultrasound expert rheumatologist	NR
		Joint impingement	Decrease in the space between the cortical margins			Absent/present			NR
		US synovitis (effusion and/or synovial hypertrophy)	Distension of the joint capsule ≥1.5 mm in its anteroposterior diameter with compressible material			Absent/present			NR
		PD signal	Intraarticular Doppler signal			Absent/present			NR
		Erosions	Intraarticular cortical defect visualised in three planes			Absent/present			NR
		Cartilage	The display or non-display of an anechoic band over the head of the phalanx was assessed			Absent/present			NR
Kortekaas (38)	Hand: PIP DIP	PD signal	NR	No	NA	All ultrasound features were scored on a 4-point Semiquantitative scale: 0 = none 1 = mild 2 = moderate 3 = severe Synovial thickening and effusion were scored in accordance with the scoring system for inflammatory signs in RA (27)	Scanned from the dorsal and lateral side only in longitudinal and transverse planes, in accordance with a group of experts in order to develop a scoring system for ultrasound for hand OA (11) Features had to be present in both planes	US assessment by one ultrasonographer and scored together with a second ultrasonographer	Intra-observer variability was tested by performing a second ultrasound in 10% (five) of all patients. Intra-observer variability ICC = 0.57
		Effusion	The definition of synovial thickening and effusion followed the outcome measures in rheumatoid arthritis clinical trials definitions (7)						Intra-observer variability ICC = 0.73
		Synovial thickening							Intra-observer variability ICC = 0.73
		Osteophytes	NR						Intra-observer variability ICC = 0.71
Mathiessen (4)	Hand: CMC 1 MCP 1-5 PIP 1-5 DIP 2-5	Osteophyte	Cortical protrusions (7)	Developed new US atlas of osteophytes	Trainee sonographer collected still images from US exam and developed novel US atlas	Semiquantitative 0 = none 1 = minor 2 = moderate 3 = major size of osteophytes (11, 17)	A linear array transducer was used 5–13 MHz, Each joint was scanned longitudinally from the radial to the ulnar side, and transverse scanning was performed if there was uncertainty about the presence of pathology	One trainee and one experienced sonographer performed the ultrasound assessments together and reached consensus on each scoring	Excellent intra and inter-reader reliability for both readers and scoring sessions (κw > 0.91)

Author	Joint	US feature	Definition	Atlas included	Origin of US atlas	Grading system	US acquisition protocol	Sonographer	Reliability
Vlychou (39)	Hand: MCP PIP DIP	Effusion	Completely transonic, compressible, and with no increase in PD signal	No	NA	Present/absent	Protocol included transverse and longitudinal scanning (40) The sonographic scanning process and the definitions of findings have been published previously (41)	Radiologist experienced in MSK US	Agreement between US and MRI for features of hand OA κ = 0.87
		Osteophytes	Intra-articular discontinuity of the bone surface that is visible in two perpendicular planes; bone proliferation is osseous proliferation of the cortex in the area adjacent to the joint						Agreement between US and MRI for features of hand OA κ = 0.79
		Synovitis	An anechoic or hypoechoic intra-capsular area, different from cartilage with or without PD signal						Agreement between US and MRI for features of hand OA κ = 0.82
		Tenosynovitis	A hypoechoic rim around tendon with or without PD signal						Agreement between US and MRI for features of hand OA κ = 0.83
		Erosions	NR						Agreement between US and MRI for features of hand OA κ = 0.84
Iagnocco (5)	2-5 MCP	Cartilage	Loss of anechoic structure and/or thinning of cartilage layer, and irregularities and/or loss of sharpness of at least one cartilage margin	No, but consensus was obtained on image interpretation of normal and pathological US findings from static images during a training session	Delphi method to reach consensus on which definitions they would recommend for testing the reliability of US in hand OA	Present/ absent In addition, the following basic lesions were evaluated: loss of anechoic structure and/or thinning of the cartilage layer, and irregularities and/or loss of sharpness of at least one cartilage margin	Eight identical MyLab 70 X-Vision gold machines, equipped with a mulit-frequency (6-8 MHz) linear probe operating at a frequency of 18 MHz ere used Joints were examined with a longitudinal dorsal scan, performed at the level of the median portion of the MCP joints	Nine rheumatologists, all experts in MSK US. All members of the OMERACT US group and the OMERACT/OARSI US task force	Intra-observer κ values ranged from 0.52 - 1 for global cartilage abnormalities κ values ranged from 0.54 - 0.94 for loss of anechoic structure and/or thinning of cartilage layer κ values ranged from 0.59 - 1 for irregularities and/or loss of sharpness of at least one cartilage margin Values of κ for inter-observer reliability were 0.80 for global cartilage abnormalities, 0.62 for loss of anechoic structure and/or thinning of cartilage layer, and 0.39 for irregularities and/or loss of sharpness of at least one cartilage margin
Arrestier (42)	Hand: 2-5 PIP 2-5 DIP	Joint effusion	Echo-free zone, OMERACT criteria (7)	No	NA	Semiquantitative 0 = no effusion 1 = effusion under the tendon 2 = moderate effusion without distension of the joint capsule 3 = large effusion with distension of the capsule (27)	Estaote (Technos MP) machine and a 10-13 MHz linear array transducer. Power Doppler was performed using a frequency of 8.3 MHz and a pulse repetition frequency of 750 MHz Ultrasonography method recommended by EULAR. The volar and palmar aspects of the joints were scanned longitudinally	Two sonographers, both rheumatologists with over two years' experience in OA USI	NR
		PD signal	Hypervascularisation			semi-quantitatively (0 - 3)			
		Synovitis	Intracapsular hypoechogenic zone, OMERACT criteria (7)			NR			
Kortekaa(43)	Hand: CMC 1 MCP 1 IPJ 1-5 PIP 1-5 DIP 2-5	Osteophytes	NR	No	NA	Semiquantitative 0 = none 1= mild 2 = moderate 3 = severe (19)	Scanned from the dorsal side only in the longitudinal and transverse planes, covering the dorsal and lateral sides of the joint, in accordance with a preliminary US scoring system for hand OA (11)	Two ultrasonographers blinded to clinical findings and PR scores	Intraobserver variability was tested by performing a second US in 10% of randomly selected patients Intraobserver variability ICC= 0.71
		PD signal	NR						Intraobserver variability ICC= 0.57
		Joint effusion	NR						Intraobserver variability ICC= 0.73
		Synovial thickening	NR						Intraobserver variability ICC= 0.73
Kortekaa(19)	Hand: CMC 1 MCP 1 IPJ 1-5 PIP 1-5 DIP 2-5	Synovitis	A composite of effusion and synovial thickening (11)	No	NA	Semiquantitative 0 = none 1 = mild 2 = moderate 3 = severe(11)	Hand joints were scanned on the dorsal side in longitudinal and transverse planes (11) Features had to be present in both planes	Two ultrasonographers	Intraobserver variability was tested by performing a second US scan in 10% of randomly selected patients NR for synovitis
		Synovial thickening	Abnormal hypoechoic intra-articular material that is non-displaceable and poorly compressible and may exhibit PDS						Intraobserver variability κ = 0.73
		Effusion	Abnormal hypoechoic or anechoic intra-articular material that is displaceable and compressible and does not exhibit PDS						Intraobserver variability κ = 0.73
		PD signal	NR						Intraobserver variability κ = 0.57

Author	Joint	US feature	Definition	Atlas included	Origin of US atlas	Grading system	US acquisition protocol	Sonographer	Reliability
Mancarella (44)	Hand: MCP 1-5 PIP 1-5 DIP 2-5	Synovitis (synovial hypertrophy and joint effusion)	Characterised by evaluating Synovial hypertrophy and effusion, using the OMERACT definitions developed for RA (7)	No	NA	Present/ absent (11)	Longitudinal and transverse US examination was performed on both hands on the volar and dorsal sides	Single sonographer experienced in MSK US, blinded to PR data	The intra-observer reliability was excellent with κ values of 0.910 for synovial hypertrophy
									The intra-observer reliability was excellent with κ values of 0.943 for joint effusion
		PD signal	A signal within a region of GS synovitis			Present/absent (11)			The intra-observer reliability was almost excellent with a κ value of 0.86
		Cartilage thickness	Well-defined anechogenic or homogeneously hypoechogenic band between the chondrosynovial and osteochondral margins (22)			Measured in mm			ICC for cartilage thickness was excellent with a value of 0.926
Vlychou (41)	Hand: CMC MCP PIP DIP	Osteophytes	Intra-articular discontinuity of the bone surface that is visible in two perpendicular planes; bone proliferation is osseous proliferation of the cortex in the area adjacent to the joint	No	NA	Present/absent	Scanned using a multiplanar technique. Sagittal scans were performed in both volar and dorsal aspect of hand joints, complemented by axial views. PD US was applied in all joints, in order to detect the presence of inflamed synovium (40)	Trained radiologist with a 4-year experience in MSK US. Blinded to radiographic and clinical data	The intra-observer κ value for agreement for the sonographic detection of erosions and other findings was 0.81
		Erosions	According to Outcome Measurement in Rheumatoid Arthritis (RA) and Connective Tissue (OMERACT)						
		Joint effusion	A completely anechoic fluid collection that is fully compressible, and with no Doppler signal						
		Synovitis	An anechoic or hypoechoic intra-capsular area, different from cartilage with or without PD signal						
		Tenosynovitis	A hypoechoic rim around tendon with or without PD signal						
		PD activity	NR						
Keen (11)	Hand: 1st CMC MCP 1-5 PIP 1-5 DIP 2-5	Osteophytes	Cortical protrusions seen in two planes	No	NA	Dichotomous 0 = present 1 = absent AND 0 = absent 1 = mild 2 = moderate 3 = Severe	LA 435 linear multifrequency transducer of 8-14 MHz. The B mode frequency used was 13 MHz. The power frequency was 10 MHz The entire dorsal surface of the joint was imaged in the longitudinal plane	15 experts in OA, US and outcome measures, met under the auspices of the Disease Characteristics in Hand OA Group	intrareader reliability κ values of 0.087–1.0 Inter-reader reliability κ values of 0.530
		Synovitis (synovial hypertrophy and effusion)	OMERACT definition of Synovial hypertrophy and effusion developed for RA was applied (7)			Dichotomous 0 = present 1= absent and Semiquantitative 0 = no synovitis 1 = mild synovitis 2 = moderate synovitis 3 = Severe synovitis			intrareader reliability κ values of 0.444–1.0 Inter-reader reliability κ values of 0.398
		PD signal	A signal within a region of grey scale synovitis			Dichotomous 0 = present 1 = absent and Semiquantitative 0 = no 1= mild 2 = moderate 3 = Severe			intrareader reliability κ values of 0.211–1.0 Inter-reader reliability κ values of 0.327
Keen (9)	Hand: 1st CMC MCP 1-5 PIP 1-5 DIP 2-5	Osteophytes	Cortical protrusion at the joint margin seen in two planes	No	NA	Present/absent (11)	Philips HDI 5000 SonoCT scanner. The joints were assessed with a 15-7 MHz hockey stick probe Scanning across the longitudinal and transverse planes on the dorsal and palmar surfaces of the hand ensuring the medial and lateral regions of the joints were also visualised. The finger joints were held in a neutral position but extended and flexed as required to visualise pathology	Single ultrasonographer	The intra-reader reliability for the presence of osteophytosis κ = 0.832
		Joint space narrowing	Documented as normal when the distances between superficial cortical surfaces of phalanges appeared normal			Normal or narrowed			The intra-reader reliability for US detected joint space narrowing κ = 0.641

Author	Joint	US feature	Definition	Atlas included	Origin of US atlas	Grading system	US acquisition protocol	Sonographer	Reliability
Keen (45)	Hand: 1st CMC MCP 1-5 PIP 1-5 DIP 2-5	Synovitis	A composite of synovial hypertrophy and effusion according to the OMERACT definition (7)	No	NA	Semiquantitative 0 = no synovitis 1 = mild synovitis 2 = moderate synovitis 3 = Severe synovitis (11)	Joints were assessed globally, scanning on both the dorsal and palmar aspects of the hand in both the longitudinal and transverse planes	Single ultrasonographer	Intrareader reliability κw = 0.62
		PD signal	Areas of color signal within the joint capsule, when the gain was adjusted to exclude only background noise			Semiquantitative 0 = no 1 = mild 2 = moderate 3 = Severe (11)			Intrareader reliability κw = 0.97
		Osteophytes	Cortical protrusions seen in two planes			Scored by counting the number of osteophytes at each joint			Intrareader reliability was almost perfect κ = 0.83
		Joint space narrowing	The joint space was considered reduced when the space between the superficial cortical margins appeared reduced, or was assumed to be reduced because osteophytes prevented visualisation			A surrogate of radiographic joint space narrowing was used			Intrareader reliability was substantial κ = 0.64

Appendix 2 References

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Appendix 3

CASP Checklist Scores of Included Studies

1. CASP Checklist for Cohort Studies
2. CASP Checklist for Case Control studies

	CASP criteria														
	1	2	3	4	5 (a)	5 (b)	6 (a)	6 (b)	7	8	9	10	11	12	Quality Score
Abraham (1)	Y	CT	CT	CT	N	N	NA	NA	Y	Y	Y	Y	Y	Y	7/14
Besselink (2)	Y	Y	CT	Y	Y	Y	NA	NA	Y	Y	Y	CT	CT	CT	8/14
Fjellstat (3)	Y	Y	Y	CT	Y	Y	NA	NA	Y	Y	Y	Y	Y	Y	11/14
Hammer (4)	Y	Y	Y	Y	N	CT	NA	NA	Y	Y	Y	CT	Y	Y	9/14
Iagnocco (5)	Y	Y	Y	Y	N	CT	NA	NA	Y	CT	Y	CT	Y	Y	8/14
Iagnocco (6)	Y	Y	CT	CT	N	CT	NA	NA	Y	CT	Y	CT	CT	Y	5/14
Keen (7)	Y	CT	CT	CT	N	CT	NA	NA	Y	CT	Y	CT	CT	Y	4/14
Keen (8)	Y	Y	Y	Y	N	CT	NA	NA	Y	CT	Y	Y	Y	Y	9/14
Kortekaas (9)	Y	Y	Y	Y	Y	Y	NA	NA	Y	Y	Y	Y	Y	Y	12/14
Kortekaas (10)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	14/14
Kortekaas (11)	Y	Y	Y	Y	Y	Y	NA	NA	Y	Y	Y	Y	Y	Y	12/14
Kortekaas (12)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	14/14
Kortekaas (13)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	14/14
Kortekaas (14)	Y	Y	Y	Y	Y	Y	NA	NA	Y	Y	Y	Y	Y	Y	12/14
Kroon (15)	Y	Y	CT	Y	Y	Y	NA	NA	Y	Y	Y	Y	Y	Y	11/14
Magnusson (16)	Y	Y	CT	CT	Y	Y	NA	NA	Y	Y	Y	Y	Y	CT	10/14
Mathiessen (17)	Y	CT	Y	Y	N	N	NA	NA	Y	CT	Y	Y	Y	Y	8/14
Mathiessen (18)	Y	CT	CT	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	12/14
Mathiessen (19)	Y	CT	CT	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	12/14
Oo (20)	Y	CT	Y	Y	Y	Y	NA	NA	Y	Y	Y	Y	Y	Y	11/14
Spolidoro (21)	Y	CT	Y	CT	N	N	Y	Y	Y	CT	Y	Y	Y	Y	9/14
Steen Pettersen (22)	Y	CT	CT	CT	Y	Y	NA	NA	Y	Y	Y	Y	Y	Y	9/14
Sivakumaran (23)	Y	CT	Y	Y	N	N	NA	NA	Y	CT	Y	Y	Y	Y	8/14
Uson (24)	Y	CT	Y	Y	N	N	NA	NA	Y	CT	Y	CT	Y	Y	7/14
Vlychou (25)	Y	Y	Y	Y	N	N	NA	NA	Y	CT	Y	CT	Y	Y	8/14
Zabotti (26)	Y	CT	Y	Y	N	N	NA	NA	Y	CT	Y	CT	CT	Y	6/14

1	Clearly focused issue stated
2	Appropriate recruitment
3	Exposure accurately measured to minimise bias
4	Outcome accurately measured to minimise bias
5 (a)	Confounding factors identified
5 (b)	Confounding factors accounted
6 (a)	Subjects follow up is complete
6 (b)	Subjects follow-up is long enough
7	Clear results
8	Precise statistical results
9	Results are believable
10	Ability to generalise results to local population
11	Interpretation related to the existing evidence
12	Clear implications of this study for practice

Y: Yes; N: No; CT: Can’t Tell; NA: Not Applicable

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CASP Checklist for Case Control studies

CASP criteria

	1	2	3	4	5	6 (a)	6 (b)	7	8	9	10	11	Quality score
Arrestier (1)	Y	Y	Y	CT	CT	Y	N	NA	NA	Y	Y	CT	6/12
Haugen (2)	Y	Y	Y	Y	Y	CT	Y	NA	NA	Y	Y	Y	8/12
Keen (3)	Y	Y	Y	Y	Y	Y	CT	NA	NA	Y	Y	Y	8/12
Mancarella (4)	Y	Y	Y	CT	Y	Y	Y	NA	NA	Y	Y	Y	8/12
Mancarella (5)	Y	Y	Y	CT	Y	Y	CT	NA	NA	Y	Y	Y	7/12
Vlychou (6)	Y	Y	Y	CT	Y	CT	N	NA	NA	Y	Y	CT	5/12

1	Clearly focused issue stated
2	Appropriate method to answer question
3	Cases recruited in an acceptable way
4	Controls recruited in an acceptable way
5 (a)	Exposure accurately measured to minimise bias
5 (b)	Groups treated equally
6 (a)	Account of the potential confounding factors in the design and/or in their analysis
6 (b)	How large was the treatment effect?
7	Precise estimate of the treatment effect
8	Results are believable
9	Ability to generalise results to local population
10	Interpretation related to the existing evidence

Y, Yes; N, No; CT, Can't Tell; NA, Not Applicable

Appendix 3 References

1. Arrestier S, Rosenberg C, Etchepare F, Rozenberg S, Foltz V, Fautrel B, et al. Ultrasound features of nonstructural lesions of the proximal and distal interphalangeal joints of the hands in patients with finger osteoarthritis. Joint Bone Spine. 2011;78(1):65-9.
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Appendix 4

Reliability of Grading of OA Features Using US Imaging

		Intra-rater reliability			Inter-rater reliability			
US feature	**Study**	**Semiquantitative**	**Dichotomous (present or absent)**	**Continuous (mm)**	**Semiquantitative**	**Dichotomous (present or absent)**	**Continuous (mm)**	**Sonographer**
Synovial hypertrophy	Zabotti (1)	κ = 0.48	κ = 0.64	NR	κ = 0.63 and 0.59	κ = 0.50 and 0.64	NR	Eleven rheumatologists all experienced in US and members of the OMERACT group
	Mancarella (2)	NR	κ = 0.84	NR	NR	NR	NR	Two experienced MSK sonographers
	Spolidoro, (3)	Dorsal κ = 0.67 Palmer κ = 0.44	NR	NR	Dorsal κ = 0.62 Palmer κ = 0.50	NR	NR	Two experienced rheumatologists in MSK US
	Kortekaas (4)	ICC = 0.84	NR	NR	NR	NR	NR	One experienced ultrasonographer, scoring together in consensus with a second ultrasonographer. Both blinded to clinical findings
	Kortekaas (5)	ICC = 0.73	NR	NR	NR	NR	NR	US assessment by one ultrasonographer and scored together with a second ultrasonographer.
	Kortekaas (6)	ICC = 0.73	NR	NR	NR	NR	NR	Two ultrasonographers blinded to clinical findings and PR scores
	Kortekaas (7)	ICC = 0.73	NR	NR	NR	NR	NR	Two ultrasonographers

		Intra-rater reliability			Inter-rater reliability			
US feature	**Study**	**Semiquantitative**	**Dichotomous (present or absent)**	**Continuous (mm)**	**Semiquantitative**	**Dichotomous (present or absent)**	**Continuous (mm)**	**Sonographer**
Power Doppler signal	Fjellstad (8)	NR	NR	NR	κ = 0.85 and κ = 0.92	NR	NR	A trained medical student performed the US examination. Scoring was performed in consensus with an experienced ultrasonographer
	Zabotti (1)	κ = 0.90	NR	NR	κ= 0.87 and 0.89	NR	NR	Eleven rheumatologists all experienced in US and members of the OMERACT group
	Mancarella (2)	NR	κ = 0.78	NR	NR	NR	NR	Two experienced MSK sonographers
	Kortekaas (4)	ICC = 0.62	NR	NR	NR	NR	NR	One experienced ultrasonographer, scoring together in consensus with a second ultrasonographer. Both blinded to clinical findings
	Kortekaas (5)	ICC = 0.57	NR	NR	NR	NR	NR	US assessment by one ultrasonographer and scored together with a second ultrasonographer
	Kortekaas (6)	ICC = 0.57	NR	NR	NR	NR	NR	Two ultrasonographers blinded to clinical findings and PR scores
	Kortekaas (7)	ICC = 0.57	NR	NR	NR	NR	NR	Two ultrasonographers
	Oo (9)	NR	κ = 0.89	NR	NR	NR	NR	Sonographer, experience in MSK US
	Steen (10)	NR	NR	NR	κ = 0.79	NR	NR	A trained medical student performed the US examinations. Initial scorings were done in consensus with an experienced ultrasonographer
	Keen (11)	κ = 0.09-1.0	κ = 0.21-1.0	NR	κ = 0.23	κ = 0.33	NR	15 experts in OA, US and outcome measures, met under the auspices of the Disease Characteristics in Hand OA Group. Reliability exercise involved seven examiners
	Keen (12)	κ=0.97	NR	NR	NR	NR	NR	Single ultrasonographer
	Mathiessen (13)	NR	NR	NR	κ=0.93	NR	NR	One trainee and one experienced rheumatologist performed the US assessments together and reached consensus on each scoring
	Vlychou (14)	NR	κ = 0.81	NR	NR	NR	NR	Trained radiologist with a 4-year experience in MSK US. Blinded to radiographic and clinical data
	Mancarella (15)	NR	κ = 0.86	NR	NR	NR	NR	Single sonographer experienced in MSK US, blinded to PR data

		Intra-rater reliability			Inter-rater reliability			
US feature	**Study**	**Semiquantitative**	**Dichotomous (present or absent)**	**Continuous (mm)**	**Semiquantitative**	**Dichotomous (present or absent)**	**Continuous (mm)**	**Sonographer**
Synovitis	Fjellstad (8)	NR	NR	NR	κ = 0.80 and κ = 0.92	NR	NR	A trained medical student performed the US examination. Scoring was performed in consensus with an experienced ultrasonographer.
	Mancarella (2)	NR	κ = 0.90	NR	NR	NR	NR	Two experienced MSK sonographers
	Steen (10)	NR	NR	NR	κ = 0.80	NR	NR	A trained medical student performed the US examinations. Initial scorings were done in consensus with an experienced ultrasonographer
	Oo (9)	κ = 0.77	NR	NR	NR	NR	NR	Sonographer, experience in MSK US
	Mathiessen (13)	κ = 0.86	NR	NR	κ = 0.74	NR	NR	One trainee and one experienced rheumatologist performed the US assessments together and reached consensus on each scoring
	Keen (12)	κ = 0.62	NR	NR	NR	NR	NR	Single ultrasonographer
	Vlychou (14)	NR	κ =0.8	NR	NR	NR	NR	Trained radiologist with a 4-year experience in MSK US. Blinded to radiographic and clinical data
	Keen (11)	κ = 0.17-1.0	κ = 0.07- 1.0	NR	κ = 0.25	κ = 0.40	NR	15 experts in OA, US and outcome measures, met under the auspices of the Disease Characteristics in Hand OA Group. Reliability exercise involved seven examiners
	Vlychou (16)	NR	Agreement between US and MRI κ = 0.82	NR	NR	NR	NR	Radiologist experienced in MSK US
Joint effusion	Zabotti (1)	NR	κ =0.67	NR	NR	κ = 0.80 and 0.61	NR	Eleven rheumatologists all experienced in US and members of the OMERACT group
	Mancarella (2)	NR	κ = 0.83	NR	NR	NR	NR	Two experienced MSK sonographers
	Kortekaas (4)	ICC = 0.84	NR	NR	NR	NR	NR	One experienced ultrasonographer, scoring together in consensus with a second ultrasonographer. Both blinded to clinical findings
	Kortekaas (5)	ICC = 0.73	NR	NR	NR	NR	NR	US assessment by one ultrasonographer and scored together with a second ultrasonographer

	Kortekaas (6)	ICC = 0.73	NR	NR	NR	NR	NR	Two ultrasonographers blinded to clinical findings and PR scores
	Kortekaas (7)	ICC = 0.73	NR	NR	NR	NR	NR	Two ultrasonographers
	Vlychou (14)	NR	κ = 0.81	NR	NR	NR	NR	Trained radiologist with a 4-year experience in MSK US. Blinded to radiographic and clinical data
	Vlychou (16)	NR	Agreement between US and MRI κ = 0.87	NR	NR	NR	NR	Radiologist experienced in MSK US
	Mancarella (15)	NR	κ = 0.94	NR	NR	NR	NR	Single sonographer experienced in MSK US, blinded to PR data

		Intra-rater reliability			Inter-rater reliability			
US feature	**Study**	**Semiquantitative**	**Dichotomous (present or absent)**	**Continuous (mm)**	**Semiquantitative**	**Dichotomous (present or absent)**	**Continuous (mm)**	**Sonographer**
Osteophytes	Fjellstad (8)	NR	NR	NR	κ = 0.72 and κ = 0.80	NR	NR	A trained medical student performed the US examination. Scoring was performed in consensus with an experienced ultrasonographer
	Zabotti (1)	NR	κ=0.63	NR	NR	κ = 0.54 and 0.58	NR	Eleven rheumatologists all experienced in US and members of the OMERACT group
	Abraham (17)	NR	NR	NR	NR	κ = 0.50- 0.69	NR	Trained MSK Ultrasonographers
	Oo (9)	κ = 0.79	NR	NR	NR	NR	NR	Sonographer, experience in MSK US
	Hammer (18)	κ = 0.69-0.89	NR	NR	κ = 0.65-0.67	NR	NR	10 sonographers (9 were rheumatologists, experts in MSK US and members of the OMERACT US group and one trainee fellow in rheumatology, highly experienced and had participated in the development of the US atlas
	Vlychou (14)	NR	κ = 0.81	NR	NR	NR	NR	Trained radiologist with a 4-year experience in MSK US. Blinded to radiographic and clinical data
	Vlychou (16)	NR	Agreement between US and MRI κ = 0.79	NR	NR	NR	NR	Radiologist experienced in MSK US
	Keen (11)	κ = 0.17-0.91	κ= 0.09-1.0	NR	κ = 0.38	κ = 0.53	NR	15 experts in OA, US and outcome measures, met under the auspices of the Disease Characteristics in Hand OA Group. Reliability exercise involved seven examiners
	Keen (19)	NR	NR	NR	NR	κ = 0.83	NR	Single ultrasonographer
	Keen (12)	NR	NR	NR	NR	κ = 0.83	NR	Single ultrasonographer
	Mathiessen (20)	κ = 0.91	NR	NR	κ = 0.91	NR	NR	One trainee and one experienced sonographer performed the ultrasound assessments together and reached consensus on each scoring
	Kortekaas (5)	ICC = 0.71	NR	NR	NR	NR	NR	US assessment by one ultrasonographer and scored together with a second ultrasonographer
	Kortekaas (6)	ICC = 0.71	NR	NR	NR	NR	NR	Two ultrasonographers blinded to clinical findings and PR scores.

		Intra-rater reliability			Inter-rater reliability			
US feature	**Study**	**Semiquantitative**	**Dichotomous (present or absent)**	**Continuous (mm)**	**Semiquantitative**	**Dichotomous (present or absent)**	**Continuous (mm)**	**Sonographer**
Cartilage damage	Zabotti (1)	NR	κ = 0.64	NR	NR	κ = 0.60	NR	Eleven rheumatologists all experienced in US and members of the OMERACT group
	Iagnocco (21)	NR	κ = 0.5-1.0	NR	NR	κ = 0.39 - 0.80	NR	Nine expert MSK ultrasonographers
	Hammer (18)	κ = 0.46-0.66	NR	NR	κ = 0.33- 0.39	NR	NR	10 sonographers (9 were rheumatologists, experts in MSK US and members of the OMERACT US group and one trainee fellow in rheumatology, highly experienced and had participated in the development of the US atlas
	Mancarella (15)	NR	NR	ICC = 0.93	NR	NR	NR	Single sonographer experienced in MSK US, blinded to PR data.
Erosions	Mancarella (2)	NR	κ = 0.87	NR	NR	NR	NR	Two experienced MSK sonographers
	Vlychou (16)	NR	Agreement between US and MRI κ = 0.84	NR	NR	NR	NR	Radiologist experienced in MSK US
	Vlychou (14)	NR	κ = 0.81	NR	NR	NR	NR	Trained radiologist with a 4-year experience in MSK US. Blinded to radiographic and clinical data
Joint space narrowing	Keen (19)	NR	κ = 0.64	NR	NR	NR	NR	Single ultrasonographer
	Keen (12)	NR	κ = 0.64	NR	NR	NR	NR	Single ultrasonographer
Tenosynovitis	Vlychou (16)	NR	Agreement between US and MRI κ = 0.83	NR	NR	NR	NR	Radiologist experienced in MSK US
	Vlychou (14)	NR	κ = 0.81	NR	NR	NR	NR	Trained radiologist with a 4-year experience in MSK US. Blinded to radiographic and clinical data.

NR, Not reported; κ, Kappa; ICC, Intraclass correlation coefficient; US, Ultrasound; MRI, Magnetic resonance imaging; MSK, Musculoskeletal; OMERACT, Outcome Measures in Rheumatology.

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Appendix 5

Ultrasound Imaging Acquisition Procedures for Evaluating the First Metatarsophalangeal Joint: A Scoping Review

Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	Page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	Page 3-5
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	Page 5
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	NA
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	Page 6
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	Page 5-6
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	Page 25
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	Page 6 and Figure 1
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	Page 7
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	Page 7
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	NA
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	Page 7
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	Figure 1
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	Supplementary File 2 and 3

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	NA
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	Supplementary File 2 and 3
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	Page 7-11
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	Page 11- 15
Limitations	20	Discuss the limitations of the scoping review process.	Page 15
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	Page 16-17
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	Page 17

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.
* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.
† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).
‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.
§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.

Appendix 6

Study Design and Participant Demographics

Author	Study aim	Study design/participant/sample size	Cohort pathology
Bhadu (1)	Determine the preferred sites of urate crystal deposition in asymptomatic hyperuricemic individuals by US	Cross-sectional study design **Cases** Participants mean (SD) age 45.5 (13.7) years, BMI 27.9 (5.8) kgm^2 *n* = 24 (M:F = 17:7) **Controls (serum uric acid <7mg/dl)** Participants mean (SD) age 48.5 (11.5) years, BMI 24.8 (3.7) kgm^2 *n* = 50 (M:F = 43:7)	Asymptomatic hyperuricemia
Bhadu (2)	To compare US-detected abnormalities at two sites (knee and first MTPJ versus six sites (knee joint, first MTPJ, radiocarpal joint, talar joint, patellar tendon and triceps tendon) in gout patients	Cross-sectional study design **Cases** Participants mean (SD) age 49.4 (14.4) years, BMI 24.1 (4.7) kgm^2 *n* = 47 (M:F = 43:4) **Controls (serum uric acid <7mg/dl)** Participants mean (SD) age 48.5 (11.5) years, BMI 24.8 (3.7) kgm^2 *n* = 50 (M:F = 43:7)	Gout (diagnosed based on ACR clinical criteria)
Blandin (3)	Determine the correlation between tophus size and characteristics of Hallux valgus in gouty patients	Case control study design **Cases** Participants mean (SD) age 63.9 (12.2) years, BMI 27.3 (4.8) kgm^2 *n* = 56 (M:F = 49:7) **Controls (serum uric acid <7mg/dl)** Participants mean (SD) age 59.0 (12.8) years *n* = 41 (M:F = 37:4	Gouty patients positive for MSU crystals in synovial fluid.
Das (4)	Assess the sensitivity and specificity of USI features of gout in intercritical and chronic stages and compared USI features of gout between patients with persistent high serum uric acid and patients with low serum uric acid	Prospective case–control study design **Cases** Participants mean (SD) age 49.1 (9.1) years, BMI 24.9 (3.1) kgm^2 *n* = 62 (M:F = 60:2) **Controls (serum uric acid <7mg/dl)** Participants mean (SD) age 47.6 (10.6) years, BMI 22.1 (2.0) kgm^2 *n* = 30 (M:F = 29:1)	Gout confirmed by demonstration of MSU

| Author | Study aim | Study design/participant/sample size | Cohort pathology |

Das (5)	To detect evolution of US signs of deposition of monosodium urate crystals in gouty joints by serial USI after initiation of urate-lowering therapy	Prospective observational study design Participants mean (SD) age 50.0 (11.0) years, BMI 25.4 (1.8) kgm^2 *n* = 38 (M:F = 38:0)	Gout confirmed by demonstration of MSU
Delle (6)	To investigate, by US examination, the prevalence and the features of foot involvement in psoriatic arthritis and to describe their correlations with clinical findings	Cross-sectional study design Participants mean (SD) age 50.8 (12.5) years *n* = 101 (M:F = 44:57)	Patients with psoriatic arthritis
Elsaman (7)	Evaluate the sonographic features of gouty arthritis and correlate findings with disease duration	Descriptive cross-sectional study design Participants mean (SD) age 53.1 (6.1) years *n* = 100 (M:F = 55:45)	Episodic mono- or oligo-arthritis of the lower limb (defined as effusion in the knee or first MTPJ based on clinical evaluation)
Filippucci (8)	Investigate the relationship between clinical and US findings together with the prevalence and distribution of US findings indicative of MSU deposition within the foot in patients with gout	Prospective Cohort study design Participants mean (SD) age 58.5 (12.0) years *n* = 46 (M:F = 43:3)	Definite diagnosis of gout
Hammer (9)	Explore the most frequent locations for depositions, the extent of erosions in the first MTPJ as well as the resolution of the different forms of US detected MSU depositions in patients with gout	Prospective, observational study design Participants mean (SD) age 56.4 (13.8) years *n* = 209 (M:F = 199:10)	Gout confirmed by demonstration of MSU
Harman (10)	Analyse the longitudinal changes in GS US and PD US parameters and correlated them with clinical, functional, and radiologic outcomes in patients with newly diagnosed RA	Cross-sectional study design Participants mean (SD) age 55.9 (15.9) years BMI 27.6 (3.0) kgm^2 *n* = 72 (M:F = 21:51)	Newly diagnosed RA
Hiraga (11)	Investigate the low-echoic synovial area of non-arthritic MTPJ in healthy subjects to provide standard reference values for each MTPJ and to determine the factors which independently influence the measurements	Cross-sectional study design Participants mean (SD) age 42.2 (9.3) years *n* = 100 (M:F = 27:73)	Healthy subjects free of arthritic symptoms were studied

Author	Study aim	Study design/participant/sample size	Cohort pathology
Howard (12)	Compare MSUS findings and interreader concordance in patients with different likelihoods of having MSU deposition, i.e., gout versus patients with AH versus controls	Cross-sectional study design **Gout** Participants mean (SD) age 73 (NSD) years, BMI 31.1 (NSD) kgm^2 *n* = 14 (M:F = 14:0) Ethnicity, no. (%) White 4 (29) African American 9 (64) Hispanic 1 (7) Asian 0 (0) Other 0 (0) **Asymptomatic Hyperuricemia** Participants mean (SD) age 66 (NSD) years, BMI 30.4 (NSD) kgm^2 *n* = 17 (M:F = 17:0) Ethnicity, no. (%) White 7 (41) African American 6 (35) Hispanic 3 (18) Asian 0 (0) Other 1 (6) **Control** Participants mean (SD) age 69 (NSD) years, BMI 27.5 (NSD) kgm^2 *n* = 19 (M:F = 19:0) Ethnicity, no. (%) White 8 (42) African American 5 (26) Hispanic 6 (32) Asian 0 (0) Other 0 (0)	Gout assessment using ACR clinical criteria and serum UA level was assessed for all subjects. Subjects were categorised as belonging to 1 of 3 diagnostic groups: 1) gout (those meeting ACR clinical criteria) 2) AH (no gout per ACR clinical criteria, UA level _6.9 mg/dl) 3) controls (no gout, UA level _6.8 mg/dl)
Huppertz (13)	Compare the diagnostic accuracy for detecting MSU deposits between dual-energy CT and US	Case control study design Participants mean (SD) age 62 (11.3) years, BMI 30.4 (6.1) kgm^2 *n* = 60 (M:F = 49:11)	Clinical suspicion of gout by the attending rheumatologist
Iagnocco (14)	To investigate the prevalence of US abnormalities in the foot of patients with osteoarthritis and to compare them with clinical findings	Cross-sectional study design Participants mean (SD) age 65.4 (10.8) years *n* = 100 (M:F = 43:57)	Clinical and radiographic signs of osteoarthritis involving the feet

Author	Study aim	Study design/participant/sample size	Cohort pathology
Kang (15)	Identify the characteristic US findings of the first MTPJ in acute gout attack and to evaluate the efficacy and safety of US-guided intraarticular corticosteroid injection of the MTPJ	Cross-sectional study design Participants mean (SD) age 64.2 (17.7) years, BMI 25.1 (3.1) kgm^2 *n* = 21 (M:F = 18:3)	Patients with acute gout attack that involved the first MTPJ unilaterally were enrolled
Keen (16)	To examine the relationship between pain, function and US-detected pathology in the first MTPJ	Cohort study design **Symptomatic** Participants mean (SD) age 53.2 (11.9) years, *n* = 33 (M:F = 8:25) **Controls** Participants mean (SD) age 60.3 (11.6) years, *n* = 20 (M:F = 7:13)	Subjects (symptomatic group) with first MTPJ pain on most days over the past 4 weeks
Le Bodedec (17)	To evaluate concordance between Clinical joint examination and US (B-US, PDUS, and both modes in combination) for detecting synovitis in patients with active RA	Prospective cohort study design Participants mean (SD) age 55.0 (13.0) years, *n* = 76 (M:F = 12:64)	Patients older than age 18 years who met 1987 ACR criteria for RA
Lu (18)	Compare the difference of clinical and US features between gout patients with and without US detected tophus and identify risk factors associated with the presence of ultrasonographic tophus in gout patients	Case–control study design **Tophaceous** Participants mean (SD) age 57.1 (15.2) years, BMI 25.9 (4.4) kgm^2 *n* = 54 (M:F = 51:3) **Non-tophaceous** Participants mean (SD) age 48.9 (16.0) years, BMI 25.7 (4.4) kgm^2 *n* = 31 (M:F = 26:5)	All patients fulfilled the 2015 ACR/ EULAR classification criteria for gout
Machado (19)	Assess these measurements among small-, medium- and large-sized joints in asymptomatic volunteers, with the aim of identifying the recesses with the highest/worst US measurements in each of these three groups of joints	Cross-sectional study design. Participants mean (SD) age 44.8 (14.6) years, BMI 25.9 (4.5) kgm^2 *n* = 130 (M:F = 30:100)	Participants without joint disease, absence of pain and joint swelling
Naredo (20)	To assess the responsiveness and repeatability of volumetric PD US evaluation of synovitis and bone erosions in RA	Prospective observational longitudinal study Participants mean (SD) age 52.7 (12.6) years, *n* = 33 (M:F = 14:19)	Patients with RA according to the ACR criteria

Author	Study aim	Study design/participant/sample size	Cohort pathology
Norkuviene (21)	To identify the optimal sites for classification of early gout by ultrasonography	Case–control study design **Early gout group** Participants mean (SD) age 52.6 (12.4) years, BMI 32.4 (5.9) kgm^2 *n* = 25 (M:F = 19:6) **Late gout group** Participants mean (SD) age 54.6 (10.1) years, BMI 32.4 (4.6) kgm^2 *n* = 35 (M:F = 33:2) **Healthy control group** Participants mean (SD) age 51.5 (16.0) years, BMI 26.8 (4.4) kgm^2 *n* = 36 (M:F = 28:8)	Diagnosis of gout as stated by a rheumatologist and confirmed by the study investigators according to the presence of MSU crystals
Peiteado (22)	Investigate the usefulness of a short US assessment in gout	Cross-sectional study design Participants mean (SD) age 58.0 (NSD) years *n* = 29 (M:F = 27:2)	Gout, history suggestive of gout and at least one symptomatic acute attack in the last three months
Pineda (23)	Investigate ultrasonographic US changes suggestive of gouty arthritis in the hyaline cartilage, joints and tendons from asymptomatic individuals with hyperuricemia	Cross-sectional study design **Hyperuricemic** Participants mean (SD) age 55.7 (16.6) years *n* = 50 (M:F = 33:17) **Normouricemic** Participants mean (SD) age 47.3 (10.9) years *n* = 52 (M:F = 35:17)	Patients with serum urate concentrations ≥7.0 mg/dL on at least two occasions within the past 2 years
Reuss (24)	Investigate the frequency of gout-specific US findings in a cohort of hyperuricemic patients with various musculoskeletal complaints	Cohort study design **Gout** Participants mean (SD) age 54.2 (NSD) years, BMI 30.0 (NSD) kgm^2 *n* = 27 (M:F = 22:5) **Asymptomatic hyperuricemia** Participants mean (SD) age 54.7 (16.6) years, BMI 31.5 (NSD) kgm^2 *n* = 31 (M:F = 19:12) **Normouricemic control** Participants mean (SD) age 52.5 (NSD) years, BMI 28.6 (NSD) kgm^2 *n* = 16 (M:F = 9:7)	Patients in an inpatient rehabilitation program for musculoskeletal problems

Author	Study aim	Study design/participant/sample size	Cohort pathology
Roddy (25)	To assess the sonographic frequency of synovial effusion, synovial hypertrophy, synovitis, and double contour sign at joints commonly affected by gout and whether these features differ according to serum urate levels, disease duration, and use of urate-lowering therapy	Cross-sectional observational study design Participants mean (SD) age 64.5 (13.5) years *n* = 40 (M:F = 31:9)	Diagnosis of gout based upon either identification of MSU crystals on compensated polarised light microscopy of aspirated synovial fluid/tophaceous material or fulfilment of the 1977 American Rheumatology Association preliminary criteria for the acute arthritis of primary gout
Scirè (26)	This study aimed to evaluate the usefulness of a systematic MSUS assessment in the detection of residual disease activity in patients with early RA who achieved clinical remission	Cross-sectional observational study design Participants mean (SD) age 59.5 (14.4) years *n* = 106 (M:F = 31:75)	ACR criteria for RA
Stewart (27)	To determine the association between US features and clinical characteristics of the first MTPJ in people with gout, asymptomatic hyperuricaemia and age- and sex-matched normouricaemic individuals	Cross-sectional study design **Gout** Participants mean (SD) age 58.0 (14.0) years, BMI 30.8 (3.8) kgm^2 *n* = 23 (M:F = 23:0) Ethnicity, no. (%) European 14 (61) Māori 1 (4) Pasifika 4 (17) Asian 4 (17) **Asymptomatic hyperuricemia** Participants mean (SD) age 58.0 (19.0) years, BMI 29.3 (5.9) kgm^2 *n* = 29 (M:F = 29:0) Ethnicity, no. (%) European 24 (83) Māori 0 (0) Pasifika 3 (10) Asian 2 (7) **Normouricaemic control group** Participants mean (SD) age 58.0 (14.0) years, BMI 25.0 (2.9) kgm^2 *n* = 34 (M:F = 34:0) Ethnicity, no. (%) European 30 (88) Māori 1 (3) Pasifika 0 (0) Asian 3 (9)	Participants with gout fulfilled the 1977 preliminary American Rheumatism Association (ARA) classification criteria for gout (28) Asymptomatic hyperuricaemic group (serum urate ≥ 6.9 mg/dL) Normouricaemic control group (serum urate < 6.9 mgl/dL)

Author	Study aim	Study design/participant/sample size	Cohort pathology
Stewart (29)	Identify US features of the first MTPJ in people with gout and people with asymptomatic hyperuricemia compared with normouricemic controls	Case control study design **Gout** Participants mean (SD) age 58.0 (14.0) years, BMI 30.8 (3.8) kgm^2 *n* = 23 (M:F = 23:0) Ethnicity, no. (%) European 14 (61) Māori 1 (4) Pasifika 4 (17) Asian 4 (17) **Asymptomatic hyperuricemia** Participants mean (SD) age 58.0 (19.0) years, BMI 29.3 (5.9) kgm^2 *n* = 29 (M:F = 29:0) Ethnicity, no. (%) European 24 (83) Māori 0 (0) Pasifika 3 (10) Asian 2 (7) **Normouricaemic control group** Participants mean (SD) age 58.0 (14.0) years, BMI 25.0 (2.9) kgm^2 *n* = 34 (M:F = 34:0) Ethnicity, no. (%) European 30 (88) Māori 1 (3) Pasifika 0 (0) Asian 3 (9)	Participants with gout fulfilled the 1977 preliminary American Rheumatism Association (ARA) classification criteria for gout (28) Asymptomatic hyperuricaemic group (serum urate ≥ 6.9 mg/dL) Normouricaemic control group (serum urate < 6.9 mgl/dL)
Tan (30)	To identify joints commonly exhibiting bone erosions using an extended 36-joint US examination in patients with RA and to study bone erosion in relation to US-detected joint inflammation	Cross-sectional study design Participants mean (SD) age 61.7 (9.1) years, *n* = 30 (M:F = 2:28) Ethnicity, no. (%) Chinese 23 (77) Other NR	RA with at least one swollen and/or tender joint
Terslev (31)	To test the reliability of the consensus-based US definitions of elementary gout lesions in patients	Cross-sectional study design Participants mean (SD) age 67.0 (NSD) years, *n* = 8 (M:F = 8:0)	Polyarticular, tophaceous gout, verified by polarization microscopy

Author	Study aim	Study design/participant/sample size	Cohort pathology
Wiell (32)	To assess US for the detection of inflammatory and destructive changes in finger and toe joints, tendons, and entheses in patients with psoriasis-associated arthritis by comparison with MRI, projection radiography, and clinical findings.	Cross-sectional study design **PsA** Participants mean (SD) age 57.0 (NSD) years, *n* = 15 (M:F = 4:11) **RA** Participants mean (SD) age 48.0 (NSD) years, *n* = 8 (M:F = 0:5) **Healthy controls** Participants mean (SD) age 63.0 (NSD) years, *n* = 5 (M:F = 1:4)	Fifteen patients with PsA, 5 with RA, and 5 healthy control persons were examined with US
Wright (33)	To compare high-resolution US with conventional radiography in the detection of erosions in the first MTPJ of patients with gout and to identify the characteristic sonographic features of gout	Case control study design **Gout** Participants mean (SD) age 52.0 (11.0) years, BMI 30.0 (4.0) kgm^2 *n* = 39 (M:F = 39:0) **Controls** Participants mean (SD) age 53.0 (16.0) years, BMI 26.0 (6.0) kgm^2 *n* = 22 (M:F = 19:3)	Gout, participants either had crystal confirmation of gout after joint aspiration or were diagnosed on the basis of the American Rheumatism Association guidelines (28)
Wu (34)	To determine the prevalence, distribution, and factors associated with bone erosion detectable by US in patients with gout	Retrospective cohort study design **Non-bone erosion** Participants mean (SD) age 47.0 (16.2) years, BMI 26.2 (3.5) kgm^2 *n* = 549 (M:F = 518:31) **Bone erosion** Participants mean (SD) age 54.6 (14.7) years, BMI 26.0 (3.9) kgm^2 *n* = 431 (M:F = 406:25)	History of gout based on the 2015 American College of Rheumatology/ European League Against Rheumatism diagnostic criteria to undergo imaging investigations (35)
Yin (36)	To assess the value of MicroPure, a new USI processing technique, in identifying microcalcifications (formed by monosodium urate crystals) in the first MTPJs attacked by gout compared to GS US images	Cross-sectional study design Participants mean (SD) age 55.9 (11.3) years *n* = 36 (M:F = 27:9)	Patients met the standards of American Rheumatism Association guidelines (28) and the first MTPJ had a history of acute gouty arthritis
Zhang (37)	Evaluated the distribution of US features of lower-limb joints and the risk factors of tophus in gout patients	Observational cross-sectional study design Participants mean (SD) age 49.4 (15.6) years *n* = 98 (M:F = 93:5)	Gout according to 2015 American College of Rheumatology and the EULAR gout classification criteria (35)

US, ultrasound; MSU, monosodium urate crystals; ACR, American College of Rheumatology; EULAR, European League Against Rheumatism

Appendix 6 References

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Appendix 7

Reported USI Acquisition Procedures Evaluating the First MTPJ

Author	Anatomical region	Patient position	US mode and settings	Probe position/orientation and surfaces scanned	Scanning procedure
Bhadu (1)	First MTPJ	First MTPJ in neutral position, tibiotalar joint with slight plantar flexion	Linear array multi-frequency (8–13 MHz) transducer of Logiq E (GE Medical Systems US) was used for US examination, on B mode GS Settings of machine: GS frequency of 11–13 MHz, dynamic range of 40–50 dB and GS gain of 60 dB	Both horizontal and longitudinal views were taken to minimise any artefactual findings Probe positioned at medial side of dorsal aspect	NR
Bhadu (2)	First MTPJ	First MTPJ in neutral position, tibiotalar joint with slight plantar flexion	Linear array multi-frequency (8–13 MHz) transducer of Logiq E (GE Medical Systems US) was used for US examination, on B mode GS Settings of machine: GS frequency of 11–13 MHz, dynamic range of 40–50 dB and GS gain of 60 dB	Both horizontal and longitudinal views were taken to minimise any artefactual findings Probe positioned at medial side of dorsal aspect	NR
Blandin (3)	First MTPJ	To analyse the presence of double contour sign in first MTPJ, toes were flexed to visualise a wider portion of the hyaline cartilage and for dynamic assessment of the cartilage	Esaote MyLab70 echograph (linear probe, 10-18 MHz)	Lateral and dorsal surfaces were scanned in the longitudinal plane	NR
Author	**Anatomical region**	**Patient position**	**US mode and settings**	**Probe position/orientation and surfaces scanned**	**Scanning procedure**

Das (4)	First MTPJ	NR	(MyLab25Gold, Esaote systems, Via di Caciolle, 15-50127 Firenze, Italy) using high frequency (12–18 MHz) linear array transducer PD assessment was performed with a PRF of 400–500 Hz	Dorsal, medial and planter aspects in long and short axes	NR
Das (5)	First MTPJ	NR	US examinations were done with MyLab25Gold, Esaote systems with high-frequency (12–18 MHz) linear array transducer	Dorsal, medial and planter aspects in long and short axes	NR
Delle (6)	First MTPJ	Patient in supine position with the foot in neutral extended position and with the knee flexed at 30°	Logiq 9 (General Electrics Medical Systems, Milwaukee, WI), with a linear probe operating at 14 MHz The setting parameters were standardised as follows: GS gain was initially set in order to obtain the maximal contrast between the different tissues under examination, and successively reduced to the lowest level allowing the visualisation of only hyperechoic structures using the bony cortex as reference PRF of 500 Hz, Doppler frequency of 7.5 MHz and Doppler gain to avoid random noise visualisation	A US multiplanar examination was performed according to the EULAR guidelines for MSUS in rheumatology (7) Dorsal transverse and longitudinal scans	NR

Author	Anatomical region	Patient position	US mode and settings	Probe position/orientation and surfaces scanned	Scanning procedure
Elsaman (8)	First MTPJ	NR	A linear probe (Medison, Sonoace R3, made in South Korea) with a frequency of 8–12 MHz was used The same US settings (frequency, depth, focusing) were used for all patients	Dorsal, lateral and plantar views in the longitudinal and transverse planes (7, 9, 10)	NR
Filippucci (11)	First MTPJ	To obtain maximal access of the metatarsal head hyaline cartilage, MTPJ were examined in maximal flexion	US examinations were performed using two US systems a Logiq 9 (General Electrics Medical Systems, Milwaukee, WI) and a My Lab70 XVG (Esaote SpA, Genoa, Italy). They were equipped with a multi-frequency linear probe operating at a frequency higher than 13 MHz	Scanning technique described in detail by Delle Sedie et al. (6) was adopted and the EULAR guidelines were followed (7) Dorsal transverse and longitudinal scans	NR
Hammer (12)	First MTPJ	Joint positioned in flexion	US was performed using a GE E9 or E10 machine with a 6-15 MHz probe, scoring GS pathologies at 15 MHz.	Examined the whole dorsal circumference of all the joints/cartilage with flexion of the joint as needed	NR
Harman (13)	First MTPJ	NR	A US platform featuring a 5–13-MHz linear array transducer was employed to this end (LOGIQ P5; General Electric, New York, NY)	Scanned at plantar and dorsal sites	NR
Hiraga (14)	First MTPJ	Patients lay in a supine position, keeping the sole flat, with the ankle and toes relaxed. The knee was flexed to a right angle	HI VISION Ascendus with a linear array multi-frequency transducer (5-18 MHz for GS) (Hitachi Medical Corporation, Tokyo, Japan) Machine settings were not changed throughout the study period with a B mode gain at 17 dB and a dynamic range of 70 dB	Dorsal aspect of the first MTPJ was assessed Each joint was scanned in a longitudinal imaging plane which was perpendicular to the bone surface at midline of the toe The transducer was placed approximately parallel to the skin surface above the joint space, where the anisotropy of joint capsule was minimal	NR

Author	Anatomical region	Patient position	US mode and settings	Probe position/orientation and surfaces scanned	Scanning procedure
Howard (15)	First MTPJ	NR	MyLab25 machine (Biosound Esaote), with a frequency of 18 MHz	Longitudinal dorsal and medial views	NR
Huppertz (16)	First MTPJ	The feet were scanned in supine position	MyLab Twice system (Esaote SpA, Milan, Italy) using a 6–18 MHz probe	The joint was examined circumferentially in long and short axis	NR
Iagnocco (17)	First MTPJ	Patients were asked to adopt a supine position with the foot resting on the examination table and the knee flexed at 60°	Logiq9 machine (General Electrics Medical Systems, Milwaukee, WI), equipped with a multi-frequency linear probe, operating at 14 MHz. PD was applied (frequency 7.5 MHz; gain 50%; PRF 750 Hz) Colour gain was adjusted just below the degree that caused the appearance of noise artefacts (18) US was performed in B-mode to detect morphological changes and PD technique, searching for local abnormal vascularisation	Longitudinal and transverse multiplanar scans were performed at the level of the dorsal, lateral and medial aspects of the joint, according to the EULAR guidelines for MSUS in rheumatology (7)	NR
Kang (19)	First MTPJ	NR	All scans were performed using a Siemens, Auscon S2000 machine (CA, USA) with a 6–18 MHz linear array transducer	Scanned in longitudinal and transverse planes on dorsal, medial, and plantar sides	NR
Keen (20)	First MTPJ	NR	Philips HDI 5000 sonoCT scanner with a multilinear 15-7 MHz hockey stick probe A PD signal was assessed with a PRF of 750 Hz, medium wall filter and gain adjusted until background signal removed	Dorsal surface in the transverse and longitudinal planes	NR

Author	Anatomical region	Patient position	US mode and settings	Probe position/orientation and surfaces scanned	Scanning procedure
Le Bodedec (21)	First MTPJ	NR	Esaote Technos MPX, Toshiba Aplio, Esaote MyLab, Philips HD11, or BK Mini Focus and multifrequency linear transducers (7–12 MHz) US scanning techniques, GS (B-mode) and PD machine settings, were standardised before the study. PD measurements were adjusted to the lowest permissible PRF to maximise sensitivity, which led to PRF values as low as 750 Hz. Low-wall filters were used. Color gain was set just below the level at which color noise appeared in the underlying bone	Multiplanar greyscale (B-mode) and PD images were obtained	NR
Lu (22)	First MTPJ	Maximum degree of dorsiflexion and plantarflexion to ensure direct visualisation of the articular structure	Aplio 500 (Made in Japan, 2015) diagnostic machine with a 12–14 MHz linear array transducer	Dorsal, plantar, and medial aspects of the first MTPJ were scanned in both transverse and longitudinal planes	NR
Machado (23)	First MTPJ	Participants were positioned with the joint at rest	MyLab 60 Xvision US machine (Esaote Biomedical, Genoa, Italy) and a linear multifrequency (6–18 MHz) probe An US wall filter was set to capture low-speed flows. The gain was adjusted to the level at which artifacts appeared and then gradually decreased until disappearance of the flow signals below the bone. The PRF was maintained between 500 and 1000Hz. The frequency varied between 6.3 and 10 MHz	Dorsal in longitudinal plane Evaluation of PD was held in the longitudinal direction in the areas of interest, which included bone margins, joint space and a view of the surrounding tissues	NR

Author	Anatomical region	Patient position	US mode and settings	Probe position/orientation and surfaces scanned	Scanning procedure
Naredo (24)	First MTPJ	NR	Logiq 9; GE Medical Systems Ultrasound and Primary Care Diagnostics LLC). The scanner was equipped with multifrequency electromechanical 3D dedicated VP (8–15 MHz) B-mode and PD machine settings were standardised among investigators These settings were as follows: dynamic range of 66 dB, GS frequency of 15 MHz, Doppler frequency of 7.5 MHz, GS gain of 66 dB, color gain of 39 dB, low-wall filters, PRF of 900 Hz	Dorsal aspect in the longitudinal and transverse plane. Probe was placed over the central part of the investigated joint areas	A volumetric sweeping on the longitudinal plane was performed at each studied site
Norkuviene (25)	First MTPJ	NR	The LOGIQ e US system with a 12-MHz linear transducer on a B-mode scale was used for all US examinations	Scanned in the longitudinal plane on the dorsal side	NR
Peiteado (26)	First MTPJ	NR	The assessment was completed using Logiq 9 equipment (General Electric Medical Systems, Milwaukee, WI, USA) with a 9-14-MHz probe for GS and a 5-7.5-MHz probe for Doppler The Doppler gain was adjusted to a level just below its disappearance under the bony cortex	Dorsal, medial and plantar aspects	Performed by scanning across the joints and moving the probe from the medial to lateral aspect and from the proximal to distal aspect
Pineda (27)	First MTPJ	Patient in a supine position with the knee in flexion (30°)	US examinations were performed in GS mode and PD GS mode: MyLab25 (Esaote Biomedica, Genoa, Italy) equipped with a 6-18-MHz broadband linear transducer Blood flow was examined with a PRF of 750 KHz and a Doppler frequency between 6 - 8 MHz	All of the US examinations were performed using a multiplanar technique in accordance with the EULAR guidelines for MSUS in rheumatology (7)	Dynamic examination with flexion-extension was carried out to investigate the superficial margin of the hyaline cartilage in the first MTPJs

Author	Anatomical region	Patient position	US mode and settings	Probe position/orientation and surfaces scanned	Scanning procedure
Reuss (28)	First MTPJ	NR	All US examinations were performed using a MyLab 70 XVG (Esaote SpA, Genoa, Italy) equipped with 2 multifrequency linear probes operating at a frequency spectrum from 7-15 MHz Scanned in GS mode to detect structural changes and PD technique to detect abnormal blood flow	Unclear	Performed in two dimensions by scanning across the joints and moving the probe from medial to lateral and from distal to proximal
Roddy (29)	First MTPJ	NR	Sonographic examinations were performed using the LOGIQe US system (GE healthcare) with a 12 MHz linear transducer To optimise sensitivity the Doppler settings were adjusted to a PRF of between 800 and 1000 Hz and the colour gain was set just below the level at which noise appeared. Low wall filters were also used	The US scanning technique adopted standard scans for the assessment of the relevant joints as described in the EULAR MSUS guidelines (7) The joints were scanned from medial to lateral in longitudinal plane and from proximal to distal in transverse plane	Dynamic manoeuvres were performed to distinguish the double contour sign from artefactual enhancement of the superficial margin of the cartilage
Scirè (30)	First MTPJ	Joint in extension	Toshiba Nemio scanner with a multi-frequency linear array transducer (8–14 MHz) PD calibrations were adjusted at the lowest permissible PRF to maximize sensitivity Colour gain was set just below the level that causes the appearance of noise artefacts. Flow was demonstrated in two perpendicular planes and confirmed by pulsed wave Doppler spectrum to exclude artefacts (18)	Transverse and longitudinal scanning of medial and lateral dorsal view of the joint according to EULAR guidelines (7)	NR

Author	Anatomical region	Patient position	US mode and settings	Probe position/orientation and surfaces scanned	Scanning procedure
Stewart (31)	First MTPJ	Bilateral first MTPJs were scanned with participants positioned supine with legs extended MTPJ was maximally dorsiflexed and plantarflexed by the radiologist during scanning to ensure direct visualisation of the articular surface of the first metatarsal head	Phillips iU22 diagnostic US machine (Bothell, Washington, USA) with a 10 MHz, 55 mm linear array transducer was used. All B-mode settings, including frequency, focal zones, gain and depth were standardised across participants Scanned in B-mode GS and PD PD involved the use of a standardised pulse repetition frequency of 400 to 500 Hz and low wall filters with the gain adjusted to a level just below the disappearance of the colour signs within the bony cortex (32, 33)	The dorsal, medial and plantar aspects of each joint were scanned using a multi-planar technique, in which transverse and longitudinal planes were imaged	A dynamic technique was adopted in which the probe insonation angle was manipulated by the sonographer to reduce the occurrence of the cartilage interface sign
Stewart (34)	First MTPJ	Bilateral first MTPJs were scanned with participants positioned supine with legs extended MTPJ joint was maximally dorsiflexed and plantarflexed by the radiologist during scanning to ensure direct visualisation of the articular surface of the first metatarsal head	Phillips iU22 diagnostic US machine (Bothell, Washington, USA) with a 10 MHz, 55 mm linear array transducer was used Scanned in B-mode GS and PD PD involved the use of a standardised pulse repetition frequency of 400 to 500 Hz and low wall filters with the gain adjusted to a level just below the disappearance of the colour signs within the bony cortex (32, 33)	The dorsal, medial and plantar aspects of each joint were scanned using a multi-planar technique, in which transverse and longitudinal planes were imaged	NR
Tan (35)	First MTPJ	NR	US was performed using an EPIQ 5G scanner with a 5-18 MHz linear probe (Philips Healthcare, Andover, Massachusetts) For PD a Doppler frequency of 8-9.3 MHz and a PRF of 700 to 850 Hz were used	Standardised MSUS examination was performed based on the EULAR guidelines (7) Dorsal surface scanned	NR

Author	Anatomical region	Patient position	US mode and settings	Probe position/orientation and surfaces scanned	Scanning procedure
Terslev (36)	First MTPJ	NR	8 Esaote MyLab Twice/Class machines, equipped with 6-18 MHz broadband linear array transducers	Examined dorsally, from medial to lateral	Bilateral B-mode US examination (including dynamic examination)
Wiell (37)	First MTPJ	All views were obtained with feet in a neutral position	US was performed with a GE LOGIQ 9 unit (General Electric Medical Systems, Buckinghamshire, UK) using a high-frequency 9-14-MHz linear array transducer The setting for grey-scale US was 14 MHz, and the PRF for the PD signal was set at 500 Hz.	The palmar, dorsal and medial aspects were examined in a longitudinal plane. A transverse view was added in case of doubt concerning the type of the detected finding or for confirmation of an erosion	NR
Wright (38)	First MTPJ	NR	All scans were performed using a Sonoline Antares (Siemens, Munich, Germany) machine with a 5–13 MHz linear array transducer PD assessment of each joint was carried out with settings standardised to a PRF of 400–500 Hz and low wall filters. The PD colour gain was adjusted to a level just below the disappearance of colour signs under the bony cortex as recommended by Rubin et al. (39)	Scanned in both longitudinal and transverse planes on both dorsal and medial sides	NR
Wu (40)	First MTPJ	NR	Aplio 500 (Toshiba), which was equipped with a multifrequency linear transducer (12–14 MHz). On each scanner, the factory setting for superficial musculoskeletal assessment was used	The dorsal, volar, and lateral aspects of all anatomical sites were explored on both longitudinal and transverse views	NR

Author	Anatomical region	Patient position	US mode and settings	Probe position/orientation and surfaces scanned	Scanning procedure
Yin (41)	First MTPJ	NR	All subjects underwent both GS US and MicroPure imaging during the same examination The Aplio 500 TUS-A500 (Toshiba Medical Systems Corporation, Tochigi, Japan) with an 18-MHz broadband linear array probe was used The physical parameters were adjusted to obtain the optimising images and then were kept constant	Transverse and longitudinal static images were obtained	NR
Zhang (42)	First MTPJ	Unclear	The examinations were conducted using a Toshiba Aplio500 scanner (Toshiba, Tokyo, Japan) with a 5-12 MHz linear array transducer	Dorsal, plantar, and medial views in the longitudinal and transverse planes according to the scanning technique described in the European guidelines for MSUS (9)	NR

MTPJ, Metatarsophalangeal joint; US, Ultrasound; GS, Grey scale; PD, power Doppler; MSUS, Musculoskeletal ultrasound; PRF, Pulse repetition frequency NR, not reported

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Appendix 8

International Multispeciality Consensus on how to Image, Define, and Grade Ultrasound Imaging Features of the First Metatarsophalangeal Joint, A Delphi Consensus Study

CREDES Recommendations

Recommendations for the Conducting and REporting of DElphi Studies (CREDES)	
Recommendation	Location where recommendation is reported
Rationale for the choice of the Delphi technique	
1. Justification:	The Introduction and Design section highlight the current knowledge gaps and lack of guidelines concerning the use of US imaging to categorise OA-related joint changes, (Lines: 1-54)
Planning and design	
2. Planning and process:	No modifications were made.
3. Definition of consensus:	A priori criterion for consensus was defined. Consensus was defined based upon an item receiving a median score of ≥70% acceptance. Under the 'Procedure' heading, each Delphi Round outlines criterion for consensus, how to proceed with items in the next round and procedures to be followed when consensus is not reached for each item. Round 2: Lines (125-129), Round 3: Lines (138- 140) and Content validity Round: Lines (153- 158)
Study conduct	
4. Informational input:	Each round of the Delphi was piloted among co-authors (MC, CB, RE and KR) who were not participants, to refine the format and question design (Lines: 81-82).
5. Prevention of bias:	By providing open ended questions to Round 1 ensured the researchers did not directly or indirectly influence the experts' judgements. The authors had acknowledged a potential bias which is outlined in the limitation section (Lines: 339-341). "Thirdly, author bias may have been introduced during the amalgamation of Delphi items. However, the authors have attempted to minimise this with transparency of the implemented process." The authors have no conflicts of interest.
6. Interpretation and processing of results:	The results section outlines the processing of results. The Discussion section provides interpretation and acknowledges the consensus does not necessarily imply the 'correct' answer or judgement. The authors considered the panel's decision of items. For example, the inclusion of multiple inflammatory features (Lines: 214- 225). The discussion provides insight into the different perspectives concerning US imaging of first MTPJ OA.
7. External validation:	The outcomes of the Delphi have been discussed with two experienced radiologists and an experienced sonographer to better inform the development of the atlas. As part of the atlas development, future research will include external validity. The Delphi panel will be invited to apply the developed US atlas to determine agreement of analysing US images and grading features.
Reporting	
8. Purpose and rationale:	The objective of this research is outlined on Lines: 37-40. A Delphi technique was rationalised due to the inconsistencies and lack of published guidelines.
9. Expert panel:	Criteria for the selection of experts and how the expert panel were recruited is outlined on Lines: 57-69. Table 1 and Table 2. Display demographic information of the participants who completed Round 1 and Round 4 respectively. Response rates are reported in the results section (Lines: 164-167) and are displayed in Figure 1.
10. Description of methods:	The methods section described the methods employed. Which included preparatory steps on available evidence (systematic and scoping reviews). Each round of the Delphi was piloted among co-authors (MC, CB, RE and KR) who were not participants, to refine the format and question design (Lines: 81-82). The number and design of survey rounds, methods of data analysis, processing, and synthesis of experts' responses to inform the subsequent survey round were reported.
11. Procedure:	Figure 1. Illustrates the stages of the Delphi process. The Figure has been amended to address comment 10.
12. Definition and attainment of consensus:	Consensus for Rounds 2 and 3 were defined in the methods section and were repeated in the Results section. *"Consensus was defined based upon an item receiving a median score of ≥70% acceptance."* Abstract (Lines: 37-38) Manuscript *Methods* (Round 2, Lines: 124-125, Round 3, Line 138-139) Results (Round 2, Lines 185-186, Round 3, Lines 190-191)

13. Results	Each round was reported separately to make the evolving of consensus over the rounds transparent. The manuscript includes Figure 1., which outlines the Delphi study process. Table 3. displays which round items were accepted to inform the methodological development of an US atlas to grade the degree of osteoarthritic change in the first MTPJ. Table 4. Displays the content validity ratio of each item included in Round 4.
14. Discussion of limitations:	Several limitations were identified and discussed. To address the reviewer comments (Reviewer 1, comment 13) and (Reviewer 2, comment 5) the limitations sections has been amended to include the following (Lines: 336-341) “Secondly, the low sample obtained, and level of professional experience may have limited the potential for ideas as well as the number of generated items. It must be acknowledged that the low number of participants maybe reflective of participant recruitment proceeding during the midst of the COVID-19 pandemic, with different countries moving between various phases of lockdowns.”
15. Adequacy of conclusion:	The conclusion adequately reflects the outcomes of the Delphi study. To address comment 13, the implications of the work have been added to the conclusion (Lines: 372-374).
16. Publication and dissemination:	The accepted and essential items are displayed in Table 4. The essential items were further reported in the discussion and conclusion. Essential items are clearly identifiable in Table 4. The implications of the findings for clinical practice and future research have been added under the heading ‘Implications for further research’ on Lines: (353-361).

Appendix 9

Auckland University of Technology Ethical Approval (21/117)

Auckland University of Technology Ethics Committee (AUTEC)

Auckland University of Technology
D-88, Private Bag 92006, Auckland 1142, NZ
T: +64 9 921 9999 ext. 8316
E: ethics@aut.ac.nz
www.aut.ac.nz/researchethics

8 June 2021

Matthew Carroll
Faculty of Health and Environmental Sciences

Dear Matthew

Re Ethics Application: **21/117 International multispecialty consensus on how to image, define, grade ultrasound imaging features of first metatarsophalangeal joint osteoarthritis, a Delphi consensus study.**

Thank you for providing evidence as requested, which satisfies the points raised by the Auckland University of Technology Ethics Committee (AUTEC).

Your ethics application has been approved for three years until 8 June 2024.

Standard Conditions of Approval

1. The research is to be undertaken in accordance with the Auckland University of Technology Code of Conduct for Research and as approved by AUTEC in this application.
2. A progress report is due annually on the anniversary of the approval date, using the EA2 form.
3. A final report is due at the expiration of the approval period, or, upon completion of project, using the EA3 form.
4. Any amendments to the project must be approved by AUTEC prior to being implemented. Amendments can be requested using the EA2 form.
5. Any serious or unexpected adverse events must be reported to AUTEC Secretariat as a matter of priority.
6. Any unforeseen events that might affect continued ethical acceptability of the project should also be reported to the AUTEC Secretariat as a matter of priority.
7. It is your responsibility to ensure that the spelling and grammar of documents being provided to participants or external organisations is of a high standard and that all the dates on the documents are updated.

AUTEC grants ethical approval only. You are responsible for obtaining management approval for access for your research from any institution or organisation at which your research is being conducted and you need to meet all ethical, legal, public health, and locality obligations or requirements for the jurisdictions in which the research is being undertaken.

Please quote the application number and title on all future correspondence related to this project.

For any enquiries please contact ethics@aut.ac.nz. The forms mentioned above are available online through http://www.aut.ac.nz/research/researchethics

(This is a computer-generated letter for which no signature is required)

The AUTEC Secretariat
Auckland University of Technology Ethics Committee

Cc: prue.susan.molyneux@aut.ac.nz; nick.garrett@aut.ac.nz; keith.rome@outlook.com; richard.ellis@aut.ac.nz

Appendix 10

Delphi Round 1

AUT

Information Sheet:

Project Title

International multispecialty consensus on how to image, define, and grade ultrasound imaging features of first metatarsophalangeal joint osteoarthritis, a Delphi consensus study.

An Invitation

Thank you for considering the opportunity to participate in the Delphi study. My name is Prue Molyneux, I am a podiatrist and a PhD candidate. This study is one of six interconnected studies that will be completed in series as part of my PhD. Along with my supervision team Associate Professor Matthew Carroll, Professor Catherine Bowen, Associate Professor Richard Ellis and Professor Keith Rome, we are conducting a Delphi study to achieve expert consensus concerning ultrasound (US) imaging of first metatarsophalangeal joint (MTPJ) osteoarthritis (OA). This project will advance our understanding of US imaging for first MTPJ OA. If you do choose to participate, you will be contributing to a foundation study that will inform future research and practice.

Participation in this study is completely voluntary. You may withdraw at any time during this study.

What is the purpose of this research?

As it stands our knowledge of OA in the foot is extremely limited in comparison to the knee and hip which is 30 years more advanced. The use of US imaging to categorise OA-based change is limited by major gaps in knowledge. First, it is not known what US features are specific to and representative of first MTPJ OA. Second, there is no validated classification criteria to grade severity of first MTPJ OA. Thirdly, it is unclear what US acquisition protocol should be used to

examine the first MTPJ. To answer these gaps in knowledge a Delphi study design will be adopted in order to gain a group consensus of opinion via a structured communication process. The outcomes of the Delphi study will inform the methodological development of an US atlas to grade the degree of osteoarthritic change in the first MTPJ.

How was I identified and why am I being invited to participate in this research?

Two methods have been used to identify and invite participants into this research:

1. You were identified through your membership of the Osteoarthritis Research Society International (OARSI) Foot and Ankle OA group, the UK Podiatry USI group, and the European League Against Rheumatism (EULAR) USI network (expert health professionals from either a clinical or academic background).
2. You have been identified through a cascade/snowballing protocol. You have been identified and invited to participate through a known contact on the primary researcher's behalf.

A Delphi method involves a group of expert panel members, who possess the relevant knowledge and experience and whose opinions are respected within their field. Ideally to be a representative group, there needs to be inclusion of a wide range of professions, from a range of clinical backgrounds and from a wide geographical diversity.

How do I agree to participate in this research?

Your participation in this research is voluntary (it is your choice) and whether or not you choose to participate will neither advantage nor disadvantage you. By completing and submitting this survey you are agreeing to have your answers used in the study. You can withdraw from the study between each round of the Delphi. However, once responses from the previous round have fed into the next round, removal of your data may not be possible. Consent will be gained through completing the online Consent Form prior to starting Delphi Round 1.

What will happen in this research?

This research will be conducted using the Delphi technique consisting of four questionnaires (known as rounds) aiming to achieve consensus. The introduction email contains a link to direct you to round one of the Delphi study using the online survey software (Qualtrics XM, Provo, UT). Before proceeding to the first round of the Delphi study, you will have to complete the online

Consent Form. After providing informed consent, you will have access to round one, including: round one instructions, and the Delphi questionnaire.

Delphi round 1: will consist of 8 demographic questions and 13 specific open-ended questions concerning USI of the first MTPJ.
The open-ended questions will specifically answer the following research questions:

1. What US features are indicative of first MTPJ OA?
2. How should US features indicative of first MTPJ OA be graded?
3. What US imaging acquisition protocol should be used to evaluate first MTPJ OA?

Potential participants who express interest in participating in the study will be given a four-week deadline to complete the questionnaire. At two weeks, a reminder email will be sent if you had not returned the round 1 questionnaire. You will be given an additional week to complete the questionnaire before being classified as a non-responder. You will only receive one reminder per round. After the deadline, the questionnaires will be collated and terminology will be made consistent by the researcher (Prue Molyneux). Responses of the first round will be used to develop a list of recommendations. A set of themes will be established that will map US features, grading systems and US imaging acquisition technique; to create items for round two.

Delphi round 2: Responses from round one will develop a list of items to be graded in round 2. You will be asked to grade Delphi items using a nine-point Likert scale (1 = not at all important; 9 = absolutely essential). Items where there is disagreement will be considered ambiguous and will be taken back to you for further consideration in round three.

Delphi round 3: You will all be emailed a copy of your individual responses from round two. Round 3 will give you the opportunity to change your answers in light of the group's average.

Delphi round 4: Content validity will be determined in the Delphi study, where you will rate which items are essential to be included in the US atlas to grade first MTPJ OA. A level of 50% agreement provides assurance of content validity. This will be determined as an acceptable marker to capture the most valued items to be included in the US atlas to grade first MTPJ OA.

The survey takes approximately 20 minutes to complete. On completion you will be asked to submit the survey, the answers will then be submitted to the researcher (Prue Molyneux). There are no right or wrong answers to the questions. This study is seeking your expert opinion. The submitted answers will be confidential to all other participants.

What are the discomforts and risks?

There are no anticipated discomforts or risks with completing this survey.

What are the benefits?

You will gain satisfaction in participating in a foundation study that will inform future research and practice. The nature of a Delphi study technique will allow you to reflect on your own practices in light of the responses from other experts. Therefore, the results of this research may contribute to reshaping the scope of musculoskeletal US imaging in their individual fields. This research will assist Prue Molyneux in obtaining her Doctor of Philosophy degree.

How will my privacy be protected?

Your name, birthdate and any personal information that could identify you as an individual will not be used in this study or published in any medium. All the information that is provided by you will be confidential and strict access will only be available to the researchers and yourself upon request. Your identity will be protected and remain confidential to all other participants at all stages of the study. All collected information will be confidential and stored securely at the researcher's office for six years. You will not be identified in research outputs, i.e., publications or conference presentations.

What are the costs of participating in this research?

There will be no financial cost to you if you decide to participate in this research, other than your time. It is anticipated that each round of the Delphi will take approximately 20 minutes to complete.

What opportunity do I have to consider this invitation?

You will have four weeks to decide whether or not you would like to accept this invitation. Please make sure you thoroughly read this Information Sheet and have any concerns answered before you participate.

Will I receive feedback on the results of this research?

You will receive feedback following each round of the Delphi. You will be emailed a copy of your individual responses from each round and will be given the opportunity to change your answers in light of the group's average.

The results will be sent to you in the form of a written summary and any papers that may be published as a result of this study can be accessed upon request.

The final results of the Delphi study will be published in a peer-reviewed journal.

What do I do if I have concerns about this research?

Any concerns regarding the nature of this project should be notified in the first instance to the Project Supervisor, Associate Professor Matthew Carroll (matthew.carroll@aut.ac.nz) or phone 09 9219999 x7305.

Concerns regarding the conduct of the research should be notified to the Executive Secretary of AUTEC, ethics@aut.ac.nz , (+649) 921 9999 ext 6038.

Whom do I contact for further information about this research?

You are also able to contact the research team as follows:

Researcher Contact Details:

Prue Molyneux (prue.susan.molyneux@aut.ac.nz)

Project Supervisor Contact Details:

Associate Professor Matthew Carroll (matthew.carroll@aut.ac.nz) or phone 09 9219999 x7305

The research was approved by the Auckland University of Technology Ethics Committee (AUTEC) on 6 May 2021, AUTEC Reference number 21/117.

Informed consent

Project title: International multispecialty consensus on how to image, define, and grade ultrasound imaging features of first metatarsophalangeal joint osteoarthritis, a Delphi consensus study
Project Supervisor: Associate Professor Matthew Carroll
Researcher: Prue Molyneux

*** Please note you must check the first six boxes to proceed to Round One of the survey**

1. I have read and understood the information provided about this research project in the Information Sheet dated 6 May 2021.
2. I have had an opportunity to ask questions and to have them answered.
3. I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time without being disadvantaged in any way.
4. I understand that if I withdraw from the study then I will be offered the choice between having any data that is identifiable as belonging to me removed or allowing it to continue to be used. However, once the findings have been produced, removal of my data may not be possible.
5. I understand if I miss a deadline of a round, I can choose to re-enter the Delphi.
6. I agree to take part in this research.

I wish to receive a summary of the research findings

Welcome to this Delphi consensus study, thank you for your participation.

The first round of this Delphi will ask you 9 characteristic questions and 16 open-ended questions concerning ultrasound (US) imaging of the first metatarsophalangeal joint (MTPJ) relating to osteoarthritis (OA). There are spaces for you to provide answers. Please be as detailed in your response as possible.

Thank you for your interest in completing this survey. The survey is aimed at developing an US atlas to grade the degree of osteoarthritic change in the first metatarsophalangeal joint This survey will take approximately 20 minutes to complete. Your participation in this research is voluntary. You have the right to withdraw at any point during the study.

If you have any questions or queries, please contact Prue Molyneux prue.susan.molyneux@aut.ac.nz

This project has been approved by the Auckland University of Technology Ethics Committee on May 6, 2021, AUTEC Reference number 21/117

Best regards

Prue Molyneux

Please enter your name so we know who has answered the survey. *(Your response will remain confidential and blinded to other participants)*

Please enter your email address so we know how to contact you. *(Your address will remain confidential and blinded to other participants)*

PARTICIPANT CHARACTERISTIC QUESTIONS

1. Gender. Please identify?

Female

Male

Non-binary

Prefer not to say

Prefer to self-describe, below

2. What is your age range?

Under 20 years old

20-29 years old

30-39 years old

40-49 years old

50-59 years old

Over 60 years old

3. What is your ethnicity?

4. Which country do you currently live in?

5. What is your academic and/or professional background?

- Rheumatologist
- Sonographer
- Radiologists
- Radiographer
- Podiatrist
- Physiotherapist
- Researcher
- Orthopedic surgeon
- Other *please specify below

6. Is your job role clinical, academic, or a combination of both?

- Clinical
- Academic
- Clinical and academic

7. If your job role is a combination of both clinical and academic, please indicate what percent of your job role comprises clinical and academic practice. *(Please move the slider to indicate your percentage)*

0 10 20 30 40 50 60 70 80 90 100

Clinical

Academic

8. How many years of musculoskeletal US imaging experience do you have?

0-5 years

6-10 years

11-15 years

16-20 years

Over 20 years

9. What is your highest qualification relating to musculoskeletal US imaging?

Delphi Consensus Questions

The next series of questions will specifically ask about your perceptions on:

Part A: First MTPJ OA US features
Part B: Grading US features
Part C: US imaging acquisition protocol

PART A: FIRST MTPJ OA ULTRASOUND IMAGING FEATURES

PART A: FIRST MTPJ OA ULTRASOUND IMAGING FEATURES

10. What US features (e.g., synovitis and osteophytes) do you think are the most important to identify first MTPJ OA?

PART B: GRADING ULTRASOUND IMAGING FEATURES

PART B: GRADING ULTRASOUND IMAGING FEATURES

11. For each US feature listed in the previous question, what US grading system do you apply to determine the degree of osteoarthritic change? (e.g., dichotomous or semiquantitative)

12. If you have applied a semiquantitative system (i.e., 0-3) to grade an US feature, can you please outline what each grade represents.

13. Are there any specific published or standardised measurements or approaches that you use when performing an US examination of the first MTPJ?

14. Do you apply a standardised US atlas (visual-based grading system) when evaluating OA US features of the first MTPJ? If yes, please state the source.

I. Patient body and lower limb positioning

PART C: ULTRASOUND IMAGING ACQUISITION PROTOCOL

I. Patient body and lower limb positioning

15. What position are your patients in (e.g., prone lying or sitting) when you perform an US examination of the first MTPJ?

16. What position is the foot of your patients in when you perform an US examination of the first MTPJ?

II. Probe positioning

II. Probe positioning

17. When performing an US examination of the first MTPJ what anatomical landmarks do you use to guide your probe position?

18. What probe orientation(s) do you use when performing an US examination of the first MTPJ?

19. What surfaces do you scan (e.g., dorsal or plantar) when performing an US examination of the first MTPJ?

20. When scanning the first MTPJ, is your examination dynamic? (i.e., the probe is moved along the first MTPJ during the US examination)

21. Do you use any US machine accessories, for example, a ‘standoff pad’ to examine the first MTPJ?

22. Do you have any other comments about ensuring optimal probe positioning for image acquisition?

III. Machine optimisation

III. Machine optimisation

23. What are the machine settings that you think are optimal for performing an US examination of the

first MTPJ? (i.e. frequency, depth, use of colour doppler, etc)

PART E: WHEN CONSIDERING THOSE WITH FIRST MTPJ OSTEOARTHRITIS

PART D: WHEN CONSIDERING THOSE WITH FIRST MTPJ OSTEOARTHRITIS

24. Are there any special considerations that you think need to be taken into account when using US to examine the first MTPJ for signs of osteoarthritis? If so, please describe below.

25. Do you have any other comments about optimising US of the first MTPJ?

Appendix 11

Delphi Round 2

Question Tour Block 1

International multispecialty consensus on how to image, define, and grade ultrasound imaging features of first metatarsophalangeal joint osteoarthritis, a Delphi consensus study- Round Two

Welcome to Round two of this Delphi consensus study, thank you for your participation. We remind participants that this survey is aimed at developing an ultrasound imaging (USI) atlas to grade the degree of osteoarthritic change in the first metatarsophalangeal joint (MTPJ). This survey will take approximately 20 minutes to complete.

Instructions

The second round of this Delphi lists all the responses generated from round one. These responses have been collated and similar responses have been amalgamated to ensure that the questionnaire is not repetitive and easily completed. The meaning of the responses has not been changed. Responses from round one have been combined with additional items generated from a systematic and scoping review; creating items for round two.

You will be asked to accept or reject each item. Please move the slider along the scale (0-100) to the point which you feel best describes your level of agreement for each Delphi item. Items

where there is disagreement will be considered ambiguous and will be taken back to participants for further consideration in round three. These numbers correspond to a response as below:

Consensus will be defined by the RAND Corporation/ University of California Los Angeles (UCLA) disagreement index whereby values >1 indicate disagreement and values <1 indicate agreement. Medians, 30^{th} and 70^{th} percentile ranges will be calculated for each item. Items that have median scores, or where there is disagreement (RAND/UCLA DI >1) will be considered ambiguous and will be taken back to participants for further consideration in Round three.

If you have any questions or queries please contact Prue Molyneux prue.susan.molyneux@aut.ac.nz

This project has been approved by the Auckland University of Technology Ethics Committee on **21st October 2021**, AUTEC Reference number **21/117**.

Please enter your name and email address so we know who has answered the survey and how to contact you (your responses will remain confidential and blinded to other participants).

Please select yes if you consent to proceeding with the survey

- ○ YES
- ○ NO

Question Tour Block 2

Please enter your name so we know who has answered the survey. *(Your responses will remain confidential to other participants).*

Please enter your email address so we know how to contact you. *(Your address will remain confidential and blinded to other participants)*

Question Tour Block 3

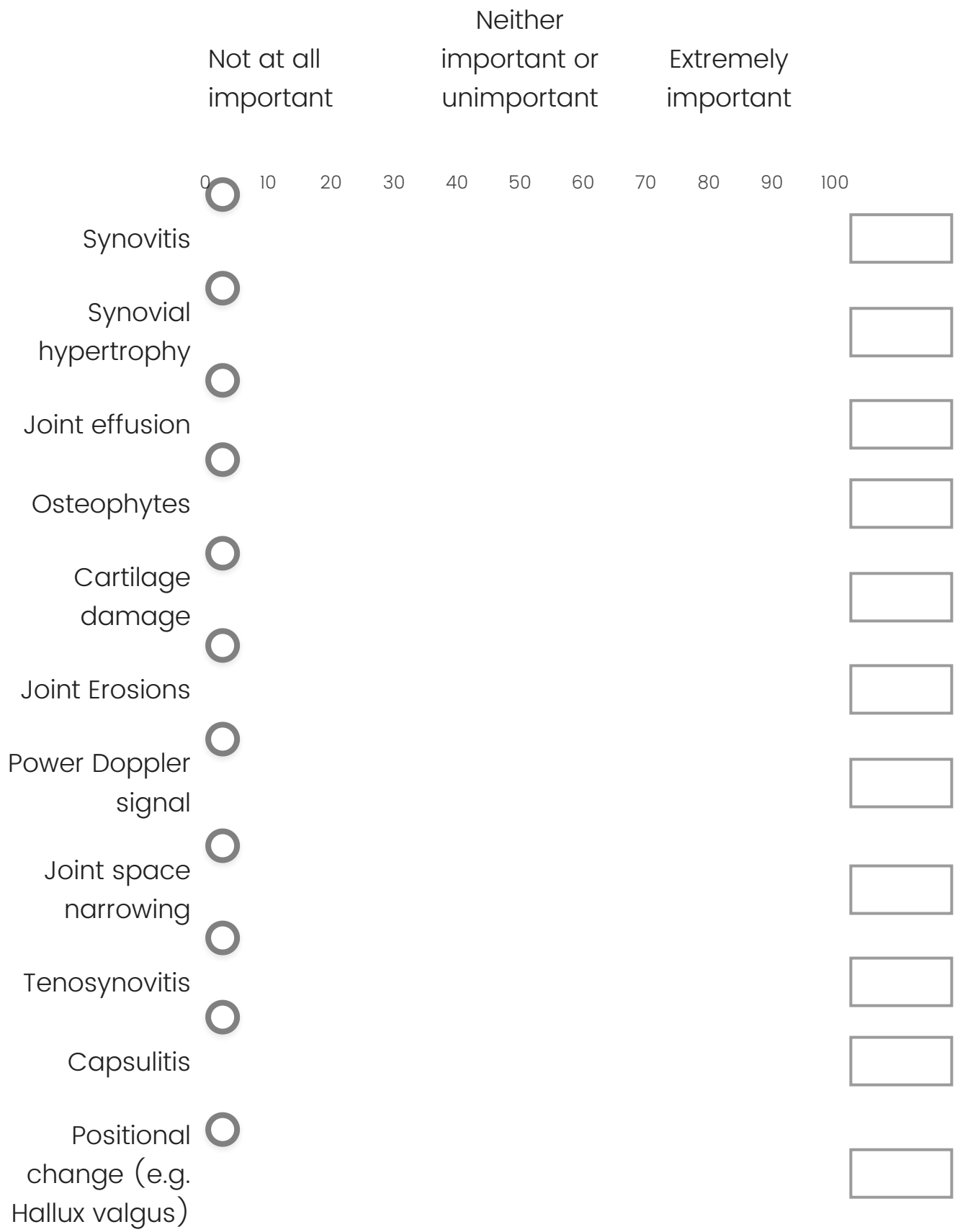
PART A: FIRST MTPJ OA ULTRASOUND IMAGING FEATURES

Please select on a scale of 0-100 how important you feel each of the following USI features are for the diagnosis of first MTPJ OA.

0 = Not at all important

50 = Neither important or unimportant

100 = Extremely important



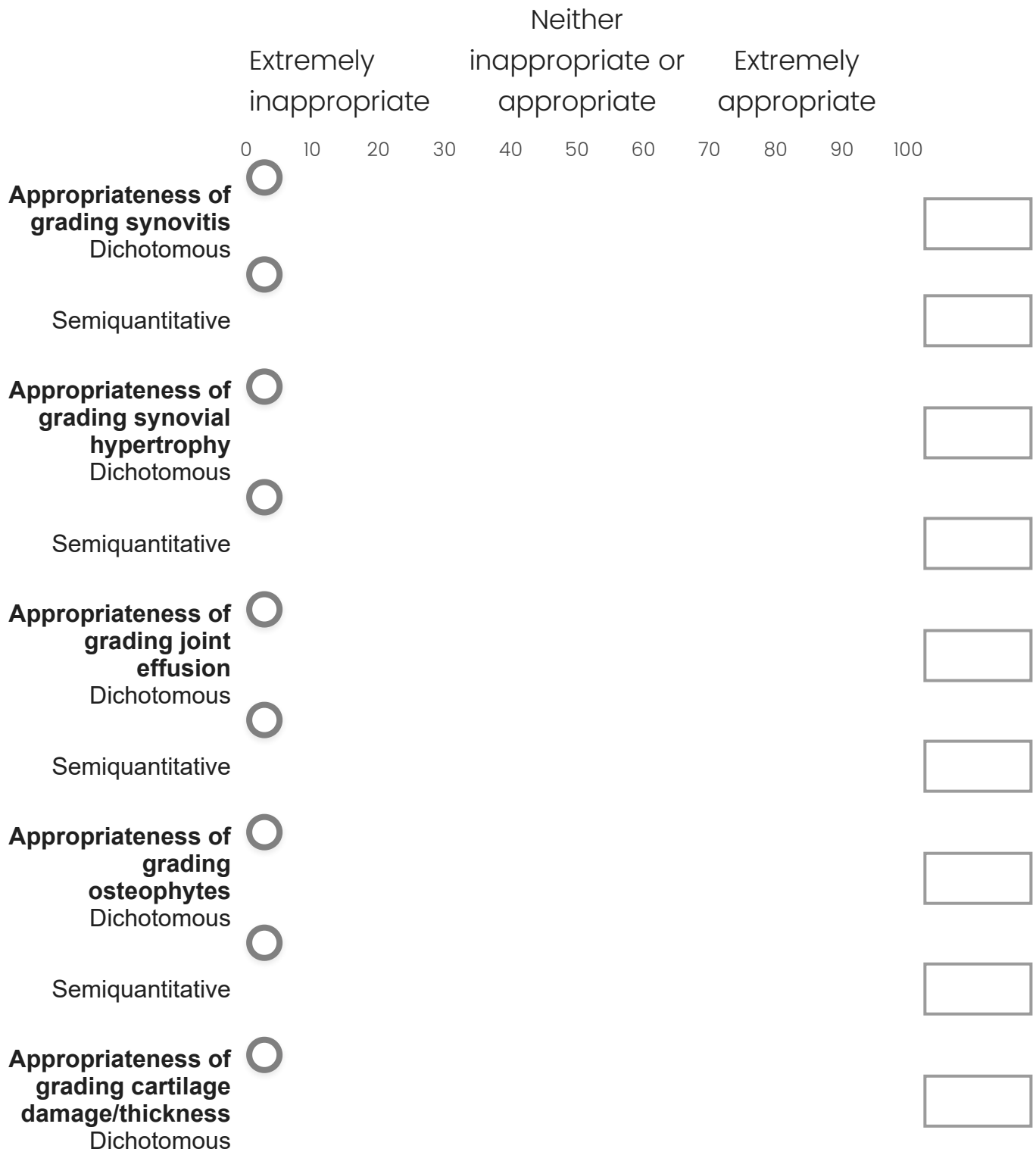
PART B: GRADING ULTRASOUND IMAGING FEATURES

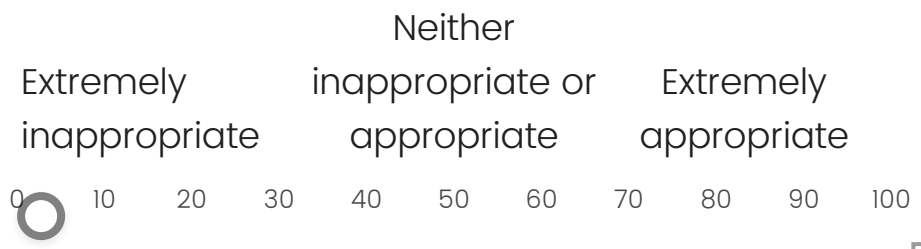
Please select on a scale of 0-100 which grading system you believe is the most appropriate to determine the degree of osteoarthritic change for each USI feature.

0 = Extremely inappropriate

50 = Neither inappropriate or appropriate

100 = Extremely appropriate





Semiquantitative

Continuous measure (mm)

Appropriateness of grading joint erosions
Dichotomous

Semiquantitative

Appropriateness of grading power Doppler signal
Dichotomous

Semiquantitative

Appropriateness of grading joint space narrowing
Dichotomous

Semiquantitative

Continuous measure (mm)

Appropriateness of grading tenosynovitis
Dichotomous

Semiquantitative

Appropriateness of grading capsulitis
Dichotomous

Semiquantitative

Extremely inappropriate | Neither inappropriate or appropriate | Extremely appropriate

0 10 20 30 40 50 60 70 80 90 100

Appropriateness of grading positional change (e.g. Hallux valgus)
Dichotomous

Semiquantitative

PART C: USI ACQUISITION PROTOCOL

I. Patient body and lower limb positioning

When performing a **DORSAL** USI examination of the first MTPJ, how important on a scale of 0-100 do you feel the following positions are when acquiring your image?

0 = Not at all important

50 = Neither important or unimportant

100 = Extremely important

Not at all important | Neither important or unimportant | Extremely important

0 10 20 30 40 50 60 70 80 90 100

Body position: Supine

Body position: Prone

	Not at all important				Neither important or unimportant					Extremely important
	0	10	20	30	40	50	60	70	80	90	100
Knee position: Flexed											
Knee position: Extended											
Ankle/foot position: Plantarflexed											
Ankle/foot position: Dorsiflexed											
Ankle/foot position: Neutral											
Ankle/foot position: Foot flat on the plinth											
First MTPJ position: Plantarflexed											
First MTPJ position: Dorsiflexed											

Not at all important | Neither important or unimportant | Extremely important

0 10 20 30 40 50 60 70 80 90 100

First MTPJ position: Start in neutral then move through ROM during scanning

PART C: USI ACQUISITION PROTOCOL

I. Patient body and lower limb positioning

When performing a **DORSAL** USI examination of the first MTPJ, how important on a scale of 0-100 do you feel the following positions are when acquiring your image?

0 = Not at all important

50 = Neither important or unimportant

100 = Extremely important

Not at all important | Neither important or unimportant | Extremely important

0 10 20 30 40 50 60 70 80 90 100

Body position: Supine

	Not at all important				Neither important or unimportant					Extremely important
	0	10	20	30	40	50	60	70	80	90	100
Body position: Prone											
Knee position: Flexed											
Knee position: Extended											
Ankle/foot position: Plantarflexed											
Ankle/foot position: Dorsiflexed											
Ankle/foot position: Neutral											
Ankle/foot position: Foot flat on the plinth											
First MTPJ position: Plantarflexed											
First MTPJ position: Dorsiflexed											

	Not at all important				Neither important or unimportant					Extremely important
	0	10	20	30	40	50	60	70	80	90	100
First MTPJ position: Start in neutral then move through ROM during scanning											

When performing a **PLANTAR** USI examination of the first MTPJ, how important on a scale of 0-100 do you feel the following positions are when acquiring your image?

0 = Not at all important

50 = Neither important or unimportant

100 = Extremely important

	Not at all important				Neither important or unimportant					Extremely important
	0	10	20	30	40	50	60	70	80	90	100
Body position: Supine											
Body position: Prone											
Knee position: Flexed											

	Not at all important				Neither important or unimportant				Extremely important	
	0	10	20	30	40	50	60	70	80	90	100
Knee position: Extended	○										
Ankle/foot position: Plantarflexed	○										
Ankle/foot position: Dorsiflexed	○										
Ankle/foot position: Neutral	○										
First MTPJ position: Plantarflexed	○										
First MTPJ position: Dorsiflexed	○										
First MTPJ position: Start in neutral then move through ROM during scanning	○										

II. Probe positioning

When performing a **LONGITUDINAL** USI examination of the first MTPJ, please select how

important on a scale of 0-100 the following anatomical landmarks are:

0 = Not at all important

50 = Neither important or unimportant

100 = Extremely important

	Not at all important				Neither important or unimportant					Extremely important
	0	10	20	30	40	50	60	70	80	90	100
Dorsal aspect of the forefoot, parallel to the first metatarsal head and proximal phalanx, joint line central to the image											
Plantar aspect of the forefoot, parallel to the first metatarsal head and proximal phalanx, joint line central to the image											

	Not at all important				Neither important or unimportant						Extremely important
	0	10	20	30	40	50	60	70	80	90	100
Medial aspect of metatarsal head and proximal phalanx, joint line central to the image											

When performing a **TRANSVERSE** USI examination of the first MTPJ, please select how important on a scale of 0-100 the following anatomical landmarks are:

0 = Not at all important

50 = Neither important or unimportant

100 = Extremely important

	Not at all important			Neither important or unimportant						Extremely important
	0	10	20	30	40	50	60	70	80	90	100
Dorsal aspect of the foot, perpendicular to diaphysis of the first metatarsal then move distally to the diaphysis of first proximal phalanx, joint line central to the image											
Plantar aspect of the foot, perpendicular to diaphysis of the first metatarsal then move distally to the diaphysis of first proximal phalanx, joint line central to the image											
Medial aspect of metatarsal head and proximal phalanx, joint line central to the image											

Appendix 12

Delphi Round 3

International multispecialty consensus on how to image, define, and grade ultrasound imaging features of first metatarsophalangeal joint osteoarthritis, a Delphi consensus study- Round Three

Welcome to Round 3 of this Delphi consensus study, thank you for your participation.

We remind participants that this survey is aimed at developing an ultrasound imaging (USI) atlas to grade the degree of osteoarthritic change in the first metatarsophalangeal joint (MTPJ). This survey will take approximately 5 minutes to complete.

Instructions

In Round 3, participants will be asked to accept or reject ambiguous items generated in Round 2 (ANSWERS RECEIVING A MEDIAN 51% - 69% OF ACCEPTANCE). Each item will include the results from Round 2, the group median rating and interquartile range (IQR). Round 3 will give participants the opportunity to change their answers considering the group's average. If the median score on ambiguous items remains unchanged between rounds, these items will be confirmed as ambiguous and will be rejected. Consensus will be defined based upon items statements receiving ≥70% of acceptance. Statements receiving <70% will be rejected.

Please see the responses from round 2 and rate all undecided items. Where agreement on a response has already been reached (i.e. ≥70% = accepted or ≤50% = rejected) there will be no requirement for you to rate this response further. For each item, please move the slider along the scale (0-100) to the point which you feel best describes your level of agreement for each Delphi item.

If you have any questions or queries please contact Prue Molyneux prue.susan.molyneux@aut.ac.nz

This project has been approved by the Auckland University of Technology Ethics Committee on **21st October 2021**, AUTEC Reference number **21/117**.

Please enter your name and email address so we know who has answered the survey and how to contact you (your responses will remain confidential and blinded to other participants).

Please select yes if you consent to proceeding with the survey

- ○ YES
- ○ NO

Question Tour Block 2

Please enter your name so we know who has answered the survey. *(Your responses will remain confidential to other participants).*

Please enter your email address so we know how to contact you. *(Your address will remain confidential and blinded to other participants)*

Question Tour Block 3

PART A: FIRST MTPJ OA ULTRASOUND IMAGING FEATURES

How important you feel each of the following USI features are for the diagnosis of first MTPJ OA.

Round 2 results

Synovitis	≥70% = ACCEPTED
Osteophytes	≥70% = ACCEPTED
Cartilage damage	≥70% = ACCEPTED
Joint space narrowing	≥70% = ACCEPTED
Tenosynovitis	≤50% = REJECTED
Capsulitis	≤50% = REJECTED

Round 3

PLEASE SEE THE RESULTS OF THE UNDECIDED ITEMS BELOW

Please rate all undecided items from round 2. For each undecided item, please move the slider along the scale (0-100) to the point which you feel best describes your level of agreement.

*Consensus will be defined based upon items statements receiving ≥70% of acceptance

PART B: GRADING ULTRASOUND IMAGING FEATURES

Which grading system you believe is the most appropriate to determine the degree of osteoarthritic change for each USI feature.

Round 2 results

Synovial hypertrophy	Dichotomous	≥70% = ACCEPTED
	Semiquantitative	≤50% = REJECTED
Joint effusion	Dichotomous	≥70% = ACCEPTED
	Semiquantitative	≤50% = REJECTED
Osteophytes	Dichotomous	≥70% = ACCEPTED
Cartilage damage/thickness	Dichotomous	≤50% = REJECTED
	Continuous measure (mm)	≥70% = ACCEPTED
Joint Erosions	Dichotomous	≥70% = ACCEPTED
	Semiquantitative	≤50% = REJECTED
Positional change	Dichotomous	≤50% = REJECTED
	Semiquantitative	≤50% = REJECTED

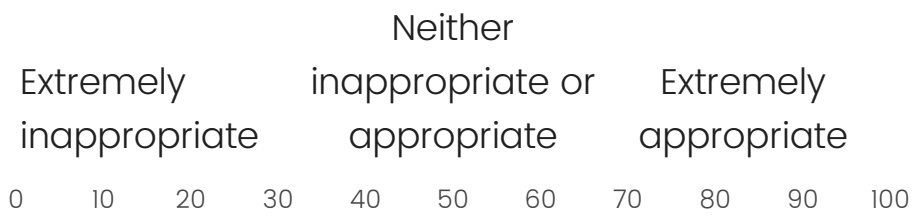
*As tenosynovitis and capsulitis were rejected from Part A they are now not applicable for Part B.

Round 3

PLEASE SEE THE RESULTS OF THE UNDECIDED ITEMS BELOW

Please rate all undecided items from round 2. For each undecided item, please move the slider along the scale (0-100) to the point which you feel best describes your level of agreement.

*Consensus will be defined based upon items statements receiving ≥70% of acceptance



Appropriateness of grading synovitis
Dichotomous
Round 2 Median = 55
IQR = [13-73]

Semiquantitative
Round 2 Median = 59
IQR = [37-81]

Appropriateness of grading osteophytes
Semiquantitative
Round 2 Median = 59
IQR = [27-74]

Appropriateness of grading cartilage damage/thickness
Semiquantitative
Round 2 Median = 65
IQR = [28-78]

Appropriateness of grading power Doppler signal
Dichotomous
Round 2 Median = 55
IQR = [8-77]

Semiquantitative
Round 2 Median = 64
IQR = [33-71]

Appropriateness of grading joint space narrowing
Dichotomous
Round 2 Median = 64
IQR = [16-85]

Semiquantitative
Round 2 Median = 64
IQR = [41-72]

Continuous measure (mm)
Round 2 Median = 68
IQR = [20-90]

PART C: USI ACQUISITION PROTOCOL

I. Patient body and lower limb positioning

When performing a **DORSAL** USI examination of the first MTPJ, how important do you feel the following positions are when acquiring your image?

Round 2 results

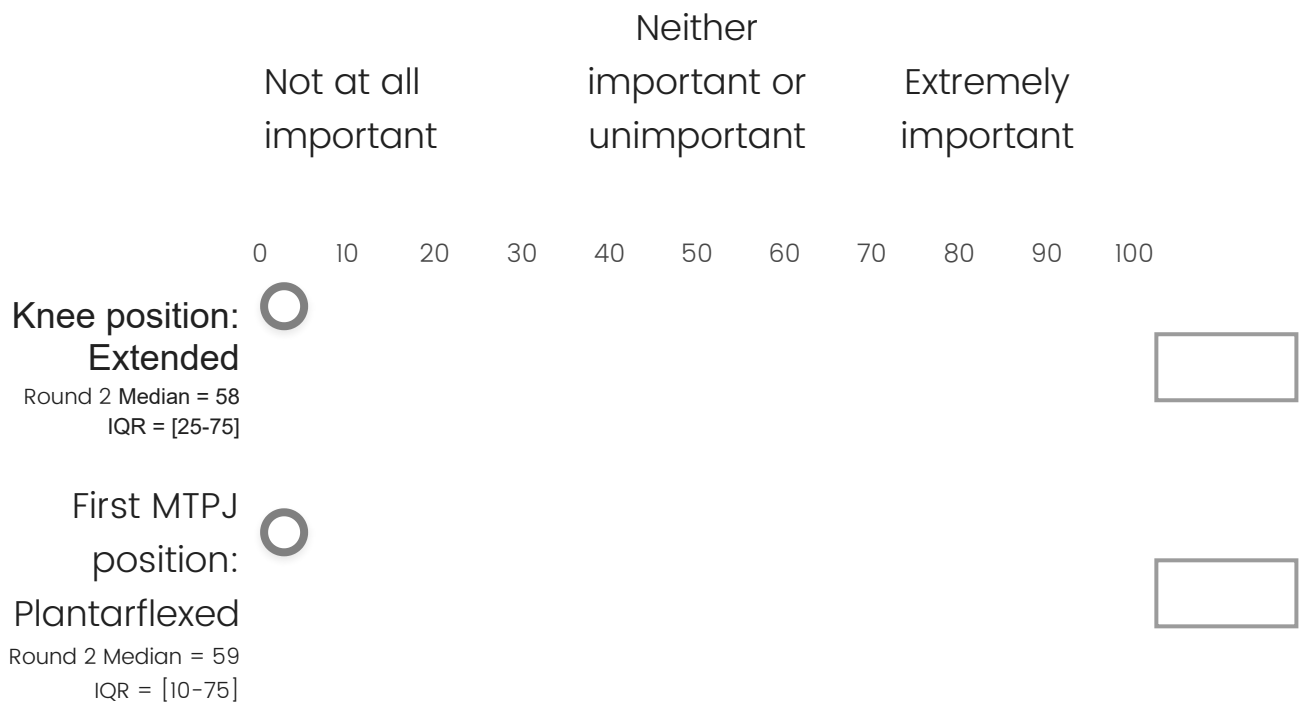
Body position	Supine position	≥70% = ACCEPTED
	Prone position	≤50% = REJECTED
Knee position	Knee flexed	≥70% = ACCEPTED
Ankle/foot position	Plantarflexed	≤50% = REJECTED
	Dorsiflexed	≤50% = REJECTED
	Neutral	≥70% = ACCEPTED
	Foot flat on the plinth	≥70% = ACCEPTED
First MTPJ position	Dorsiflexed	≤50% = REJECTED
	Start in neutral then move through ROM during scanning	≥70% = ACCEPTED

Round 3

PLEASE SEE THE RESULTS OF THE UNDECIDED ITEMS BELOW

Please rate all undecided items from round 2. For each undecided item, please move the slider along the scale (0-100) to the point which you feel best describes your level of agreement.

*Consensus will be defined based upon items statements receiving ≥70% of acceptance



When performing a **PLANTAR** USI examination of the first MTPJ, how important do you feel the following positions are when acquiring your image?

Round 2 results

Knee position	Knee flexed	≤50% = REJECTED
	Knee extended	≥70% = ACCEPTED
Ankle/foot position	Plantarflexed	≤50% = REJECTED
	Neutral	≥70% = ACCEPTED
First MTPJ position	Start in neutral then move through ROM during scanning	≥70% = ACCEPTED

Round 3

PLEASE SEE THE RESULTS OF THE UNDECIDED ITEMS BELOW

Please rate all undecided items from round 2. For each undecided item, please move the slider along the scale (0-100) to the point which you feel best describes your level of agreement.

*Consensus will be defined based upon items statements receiving ≥70% of acceptance

Not at all important | Neither important or unimportant | Extremely important

0 10 20 30 40 50 60 70 80 90 100

Body position: Supine
Round 2 Median = 62
IQR = [50-83]

Body position: Prone
Round 2 Median = 65
IQR = [28-82]

Ankle/foot position: Dorsiflexed
Round 2 Median = 55
IQR = [8-80]

First MTPJ position: Plantarflexed
Round 2 Median = 51
IQR = [0-74]

First MTPJ position: Dorsiflexed
Round 2 Median = 60
IQR = [9-73]

Appendix 13

Delphi Round 4

International multispecialty consensus on how to image, define, and grade ultrasound imaging features of first metatarsophalangeal joint osteoarthritis, a Delphi consensus study- Content Validity

Welcome to the final round, which will determine the content validity of the Delphi consensus study, thank you for your participation. We remind participants that this survey is aimed at developing an ultrasound imaging (USI) atlas to grade the degree of osteoarthritic change in the first metatarsophalangeal joint (MTPJ). This survey will take approximately 5 minutes to complete.

Instructions

Content validity provides evidence to the extent at which items of an assessment instrument are representative of the entire domain the assessment seeks to measure. For instance, whether or not the USI atlas contains the appropriate content to grade first MTPJ OA.

The content validity round of this Delphi lists all the accepted items generated from Rounds 2 and 3. To determine the content validity of items to be included in the atlas, you will be asked to rate items into one of three categories: **“essential,” “useful, but not essential,” or “not necessary.”** Items deemed “essential” by ≥50% of panel members will be included in the USI

atlas to grade first MTPJ OA, with items failing to achieve this critical level discarded. A content validity ratio will be used to quantify content validity of each item recommended to be included in the USI atlas.

If you have any questions or queries please contact Prue Molyneux prue.susan.molyneux@aut.ac.nz

This project has been approved by the Auckland University of Technology Ethics Committee on **21st October 2021**, AUTEC Reference number **21/117**.

Please enter your name and email address so we know who has answered the survey and how to contact you (your responses will remain confidential and blinded to other participants).

Please select yes if you consent to proceeding with the survey

- ○ YES
- ○ NO

Question Tour Block 2

Please enter your name so we know who has answered the survey. *(Your responses will remain confidential to other participants).*

Please enter your email address so we know how to contact you. *(Your address will remain confidential and blinded to other participants)*

Block 3

PARTICIPANT CHARACTERISTIC QUESTIONS

1. Gender. Please identify?

- ◯ Female
- ◯ Male
- ◯ Non-binary
- ◯ Prefer not to say
- ◯ Prefer to self-describe, below

2. What is your age range?

- ◯ Under 20 years old
- ◯ 20-29 years old
- ◯ 30-39 years old
- ◯ 40-49 years old
- ◯ 50-59 years old
- ◯ Over 60 years old

3. What is your ethnicity?

4. Which country do you currently live in?

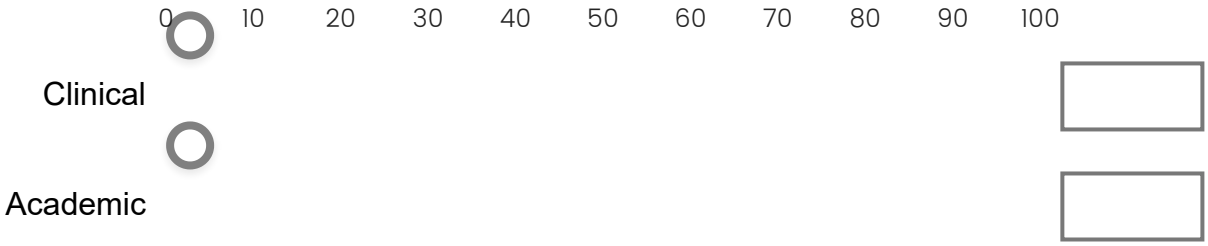
5. What is your academic and/or professional background?

- ☐ Rheumatologist
- ☐ Sonographer
- ☐ Radiologist
- ☐ Radiographer
- ☐ Podiatrist
- ☐ Physiotherapist
- ☐ Researcher
- ☐ Orthopedic surgeon
- ☐ Other *please specify below

6. Is your job role clinical, academic, or a combination of both?

- ◯ Clinical
- ◯ Academic
- ◯ Clinical and academic

7. If your job role is a combination of both clinical and academic, please indicate what percent of your job role comprises clinical and academic practice. *(Please move the slider to indicate your percentage)*



8. How many years of musculoskeletal US imaging experience do you have?

- ◯ 0-5 years
- ◯ 6-10 years
- ◯ 11-15 years
- ◯ 16-20 years
- ◯ Over 20 years

9. What is your highest qualification relating to musculoskeletal US imaging?

Question Tour Block 3

PART A: FIRST MTPJ OA ULTRASOUND IMAGING FEATURES

Please rate how essential you feel each of the following USI features are for the diagnosis of first MTPJ OA. Please rate each USI feature into one of three categories: **“essential,” “useful, but not essential,” or “not necessary.”**

	ESSENTIAL	USEFUL, BUT NOT ESSENTIAL	NOT NECESSARY
Synovitis	○	○	○
Osteophytes	○	○	○
Cartilage damage	○	○	○
Joint space narrowing	○	○	○

PART B: GRADING ULTRASOUND IMAGING FEATURES

Please rate how essential each of the assigned grading systems are to determine the degree of osteoarthritic change for each USI feature. Please rate each grading system into one of three categories: **“essential,” “useful, but not essential,” or “not necessary.”**

	ESSENTIAL	USEFUL, BUT NOT ESSENTIAL	NOT NECESSARY
Grading Synovitis Semiquantitative	○	○	○
Grading Osteophytes Dichotomous	○	○	○
Grading Osteophytes Semiquantitative	○	○	○
Grading cartilage damage/thickness Continuous measure (mm)	○	○	○
Grading Joint Space Narrowing Semiquantitative	○	○	○

PART C: USI ACQUISITION PROTOCOL

I. Patient body and lower limb positioning

When performing a **DORSAL** USI examination of the first MTPJ, please rate how essential the following positions are when acquiring your image into one of three categories: **"essential," "useful, but not essential," or "not necessary."**

	ESSENTIAL	USEFUL, BUT NOT ESSENTIAL	NOT NECESSARY
Body position: Supine	○	○	○

	ESSENTIAL	USEFUL, BUT NOT ESSENTIAL	NOT NECESSARY
Knee position: Flexed	○	○	○
Ankle/foot position: Neutral	○	○	○
Ankle/foot position: Foot flat on the plinth	○	○	○
First MTPJ position: Start in neutral then move through ROM during scanning	○	○	○

When performing a **PLANTAR** USI examination of the first MTPJ, Please rate how essential the following positions are when acquiring your image into one of three categories: **“essential,” “useful, but not essential,” or “not necessary.”**

	ESSENTIAL	USEFUL, BUT NOT ESSENTIAL	NOT NECESSARY
Knee position: Extended	○	○	○
Ankle/foot position: Neutral	○	○	○
First MTPJ position: Start in neutral then move through ROM during scanning	○	○	○

II. Probe positioning

When performing a **LONGITUDINAL** USI examination of the first MTPJ, please select how essential the following anatomical landmarks are into one of three categories: **"essential," "useful, but not essential," or "not necessary."**

	ESSENTIAL	USEFUL, BUT NOT ESSENTIAL	NOT NECESSARY
Dorsal aspect of the forefoot, parallel to the first metatarsal head and proximal phalanx, joint line central to the image	○	○	○
Plantar aspect of the forefoot, parallel to the first metatarsal head and proximal phalanx, joint line central to the image	○	○	○
Medial aspect of metatarsal head and proximal phalanx, joint line central to the image	○	○	○

When performing a **TRANSVERSE** USI examination of the first MTPJ, please select how essential the following anatomical landmarks are into one of three categories: **"essential," "useful, but not essential," or "not necessary."**

	ESSENTIAL	USEFUL, BUT NOT ESSENTIAL	NOT NECESSARY
Dorsal aspect of the foot, perpendicular to diaphysis of the first metatarsal then move distally to the diaphysis of first proximal phalanx, joint line central to the image	○	○	○
Plantar aspect of the foot, perpendicular to diaphysis of the first metatarsal then move distally to the diaphysis of first proximal phalanx, joint line central to the image	○	○	○

	ESSENTIAL	USEFUL, BUT NOT ESSENTIAL	NOT NECESSARY
Medial aspect of metatarsal head and proximal phalanx, joint line central to the image	○	○	○

Appendix 14

Reliability of an Ultrasound Imaging Acquisition Procedure for Examining Osteoarthritis in the First Metatarsophalangeal Joint

EULAR US Reporting Recommendations

Recommendations checklist for reporting studies using ultrasound in rheumatic and musculoskeletal diseases			
Topic	Number	Item to report	Location where item is reported
Objective	1	Objective of the ultrasound measurement in the study (eg, description, prediction, diagnosis, validation…)	Page: 5 Lines: 128-131
Design	2	Study design (eg, cross- sectional, case- control, cohort, randomised clinical trial, …)	Page: 6 Lines: 134-144
	3	Prospective or retrospective data collection*	Pages: 7-10 Lines: 165-244
150-Participants	4	Informed consent procedure (written, oral)	Page: 7 Lines: 162-163
	5	Source, selection criteria and sampling of the participants (including controls where appropriate)	Page: 7 Lines: 151-156
Blinding	6	Procedures for blinding of sonographers and participants	Page: 9 Lines 223-224
Ultrasound features	7	a. Broad domain* of interest (eg, inflammation or structural damage) b. Target domain* with corresponding theoretical ultrasound definition(s)* (eg, synovitis: synovial hypertrophy plus increased synovial blood flow) c. Domain components (ie, elementary lesions)* with corresponding operational definitions* (eg, synovial hypertrophy: increased thickness of synovium with hypoechoic appearance)	Pages: 8-9 Lines: 190-202 Figure 2
Scanning/acquisition procedures	8	a. Anatomical region(s)* or structure(s)* that were studied b. Rationale for choosing these anatomical region(s)/structure(s)	Pages: 5 Lines: 102-111
	9	a. Patient position (eg, prone, supine…) b. Anatomical region position (eg, neutral…) c. Surfaces scanned (eg, volar, dorsal) d. Transducer position (eg, transverse, longitudinal) e. Whether the examination was dynamic*	Page: 9 Lines: 204-217 Figure 3

Ultrasound scoring system	10	Scoring system used: a. Type (eg, quantitative, semiquantitative, binary) b. Level: (eg, patient level, joint/anatomical region level)	Page: 8 Lines: 192-202 Additional file 2
	11	For existing scoring systems: a. References or results of previous validity and reliability studies b. Score range (minimum- maximum), and meaning of the score (eg, higher is ……) c. Rationale for any thresholds or cut- offs d. Training session details if performed e. The reliability* of the scoring system in the hands of the study sonographers/readers	NA
	12	For new scoring systems: a. Rationale for developing a new scoring system b. Detailed description of the scoring system c. Reliability assessment: I. Type of reliability: inter- reader, other ii. Training session if performed iii. The reliability of the scoring system as applied by the study sonographers/readers iv. Whether reliability was assessed on static images, video- clips or real- time examination of patients v. Sample size of the reliability study vi. Reliability results (eg, kappa or ICC with 95% CI and type of kappa or ICC, prevalence of observed lesions, smallest detectable change, SE of measurement)	Page: 5 a) Lines: 113-125 b) Lines: 192-202 & Additional file 2 c) i. Page: 10, Lines: 250-256 ii. Page: 6, Lines: 137-142 iii. Pages: 10-11, Lines: 250-256 iv. Page 9, Lines: 219-224 v. Page 10, Lines: 238-240 & Figure 1 vi. Page 11, Lines 258-268
Sonographer(s)/reader(s)	13	a. Whether acquisition and reading were performed at the same time b. Whether acquisition and reading were performed by the same person c. Number of sonographers or readers d. In longitudinal studies, whether the same sonographer scanned the same patient at each assessment	Pages: 9-10 Lines: 219-244
	14	Optional: Information about the experience of sonographer(s) and reader(s) (eg, numbers of scanned performed, certification, qualification…)	Page: 9 Lines: 219-222
Equipment	15	a. Brand and model of the ultrasound device b. Type and model of the transducer c. Whether the ultrasound device (or software) was changed during the study	Page: 10 Lines: 226-235
	16	Ultrasound modalities* and settings a. Grey scale	Page: 10 Lines: 229-235

		b. Doppler c. Other	
Images (pictures and drawings)	17	For images included into the manuscript, verify that: a. Information identifying patient is deleted b. Essential targets in the image(s) are clearly labelled c. Images match the content of the manuscript d. Quality of the images is adequate	No images that could identify a participant are included in the manuscript
Contextual factors	18	Duration of ultrasound examination when relevant for the study question	NA
	19	*Optional:* *a. Whether ambient conditions (eg, temperature, time of day) were kept stable during the study* *b. Potential confounding factors (eg, exercise, alcohol, caffeine, smoking)*	NA
Statistical analysis	20	a. Existence of a pre- specified statistical analysis plan and specification of post- hoc analyses b. Analyses performed c. Whether the analyses were performed at patient or at joint/region level d. Extent of missing data e. Handling of missing data	Pages: 10-11 Lines 246- 256
Disclosures	21	Potential conflicts of interest including those related to ultrasound	Pages: 16-17 Lines: 391-425

Appendix 15

Health and Disability Ethics Committee Approval. Ethics Reference: 2022 FULL 12721

Health and Disability Ethics Committees
Ministry of Health
133 Molesworth Street
PO Box 5013
Wellington
6011
hdecs@health.govt.nz

Ethics reference: 2022 FULL 12721

17 June 2022

Ms Prue Molyneux

90 Akoranga Drive
Northcote
Auckland
0627
New Zealand

Tēnā koe Ms Molyneux

APPROVAL OF APPLICATION

Study title: Development of an ultrasound imaging atlas to grade first metatarsophalangeal joint osteoarthritis

I am pleased to advise that your application was **approved** by the Southern Health and Disability Ethics Committee (the Committee). This decision was made through the FULL pathway.

Conditions of HDEC approval

HDEC approval for this study is subject to the following conditions being met prior to the commencement of the study in New Zealand. It is your responsibility, and that of the study's sponsor, to ensure that these conditions are met. No further review by the Southern Health and Disability Ethics Committee is required.

Standard conditions:

- Before the study commences at *any* locality in New Zealand, all relevant regulatory approvals must be obtained.
- Before the study commences at *each given* locality in New Zealand, it must be authorised by that locality in Ethics RM. Locality authorisation confirms that the locality is suitable for the safe and effective conduct of the study, and that local research governance issues have been addressed.

After HDEC review

Please refer to the *SOPs* for HDEC requirements relating to amendments and other post-approval processes.

Your next progress report is due by 16 June 2023.

Participant access to compensation

The Southern Health and Disability Ethics Committee is satisfied that your study is not a clinical trial that is to be conducted principally for the benefit of the manufacturer or distributor of the medicine or item being trialed. Participants injured as a result of treatment received as part of your study may therefore be eligible for publicly-funded compensation through the Accident Compensation Corporation.

Further information and assistance

Please contact the HDECs Secretariat at hdecs@health.govt.nz or visit our website at www.ethics.health.govt.nz for more information, as well as our General FAQ and Ethics RM user manual.

Nāku noa, nā

Mr Anthony Fallon

Chair

Southern Health and Disability Ethics Committee

Encl: Appendix A: documents submitted

Appendix A: Documents submitted

Document Type	File Name	Date	Version
Scientific Peer Review	Appendix 2_Confirmation of Candidature MOLYNEUX Prue 0952234		
Protocol	Appendix 1_Development of an USI atlas to grade first MTPJ OA_Study Protocol		
Evidence of Consultation	Appendix 3_Māori consultation		
Advertisement	Appendix 4_Development of an USI procedure and atlas to grade first MTPJ OA_Advertisement		
PIS/CF	Appendix 5_ Development of an USI procedure and atals to grade first MTPJ OA_Information Sheet		
PIS/CF	Appendix 6_ Development of an USI procedure and atlas to grade first MTPJ OA_Consent Form		
Data Management Plan	Appendix 7_HDEC-data-only-management-template-Oct-2021		
CV for Coordinating Investigator	Appendix 8_Prue Molyneux_CV		
Response to PA Document	Appendix 1_Development of an USI atlas to grade first MTPJ OA_Study Protocol_Revised version		
Response to PA Document	Appendix 1_Development of an USI atlas to grade first MTPJ OA_Study Protocol_Clean version		
Response to PA Document	Appendix 4_Development of an USI procedure and atlas to grade first MTPJ OA_Advertisement_Revised version		
Response to PA Document	Appendix 4_Development of an USI procedure and atlas to grade first MTPJ OA_Advertisement_Clean version		
Response to PA Document	Appendix 5_ Development of an USI procedure and atals to grade first MTPJ OA_Information Sheet_Revised version		
Response to PA Document	Appendix 5_ Development of an USI procedure and atals to grade first MTPJ OA_Information Sheet_Clean version		
Response to PA Document	Appendix 6_ Development of an USI procedure and atlas to grade first MTPJ OA_Consent Form_Revised version		
Response to PA Document	Appendix 6_ Development of an USI procedure and atlas to grade first MTPJ OA_Consent Form_Clean version		
Response to PA Document	Appendix 7_HDEC-data-only-management-template-Oct-2021_Revised version		
Response to PA Document	Appendix 7_HDEC-data-only-management-template-Oct-2021_Clean version		
Response to PA Document	Cover letter_HDEC		

Appendix 16

USI Grading Sheet

USI feature	USI acquisition procedure		Grading system				
Joint Effusion	Dorsal	Longitudinal	0	1	2	3	
		Transverse	0	1	2	3	
Synovial Hypertrophy	Dorsal	Longitudinal	0	1	2	3	
		Transverse	0	1	2	3	
Synovitis	Dorsal	Longitudinal with power Doppler	0	1	2	3	
Joint Space Narrowing	Dorsal	Longitudinal – scan right through joint	0	1	2	3	mm
Osteophytes	Dorsal	Longitudinal – scan right through joint	0	1	2	3	mm
		Transverse	0	1	2	3	mm
Cartilage	Dorsal	Longitudinal – scan right through joint	0	1	2	X	mm

Scoring

- **0 = Absent**
- **1 = Mild**
- **2 = Moderate**
- **3 = Severe**

Appendix 17

AUTUSI Atlas for First MTPJ

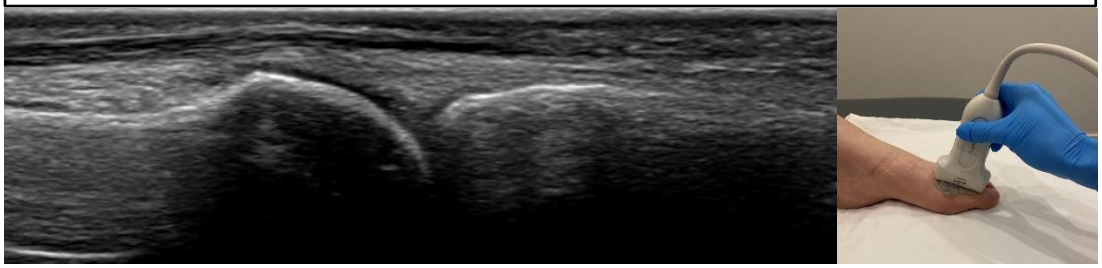
Ultrasound atlas for first metatarsophalangeal joint osteoarthritis

PATIENT AND PROBE POSITIONING FOR USI OF FIRST MTPJ OA

- All features are assessed with the patient body positioned supine, knee flexed, foot flat on the plinth and the first MTPJ in neutral, except for cartilage.
- All USI features are assessed in the dorsal view with the probe positioned longitudinally.
- A transverse orientation is also applied to examine joint effusion and synovial hypertrophy.

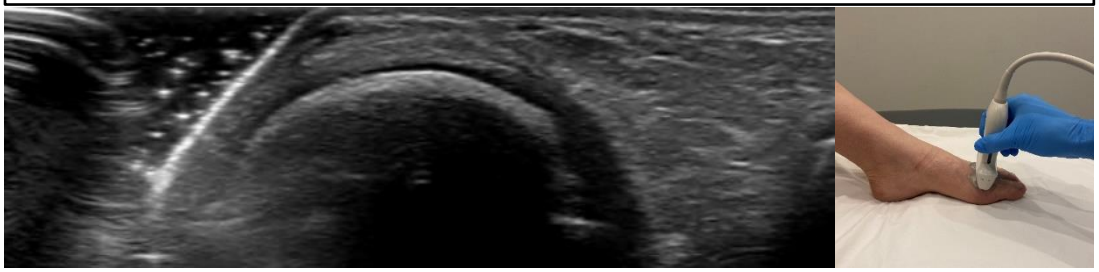
LONGITUDINAL SCANS

For longitudinal scans the probe is positioned on the dorsal aspect of the forefoot, parallel to the first metatarsal head and proximal phalanx, with the joint line central to the image.



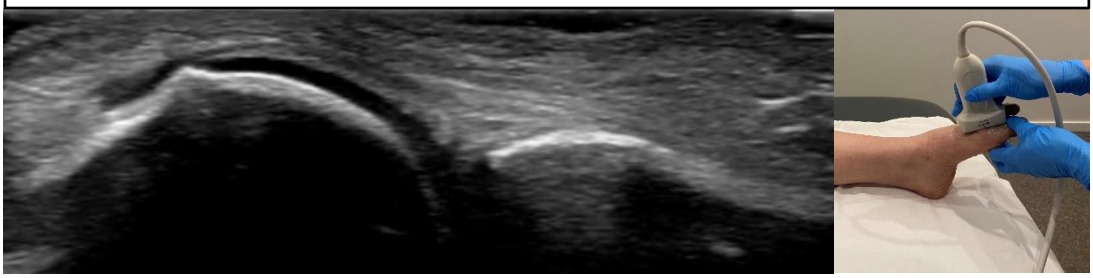
TRANSVERSE SCANS

For transverse scans the probe is positioned on the dorsal aspect of the foot, perpendicular to the diaphysis of the first metatarsal then moved distally to the diaphysis of the first proximal phalanx, with the joint line central to the image.



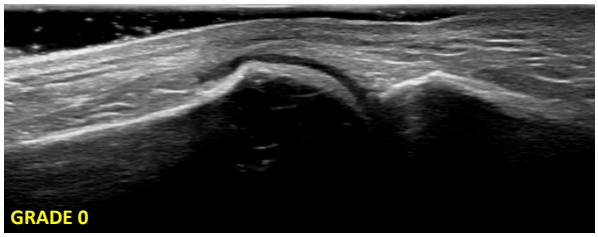
CARTILAGE

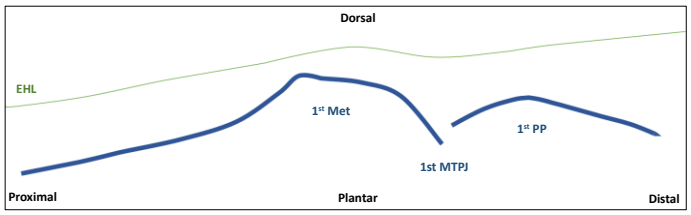
Cartilage is examined with the knee extended, ankle plantarflexed and first MTPJ positioned in neutral then moved through plantarflexion during scanning.

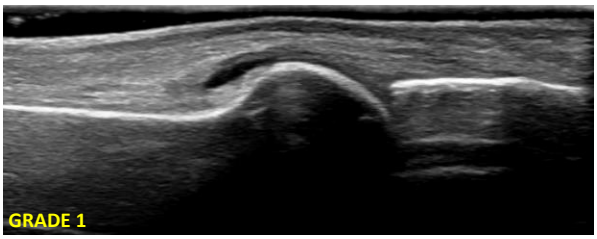


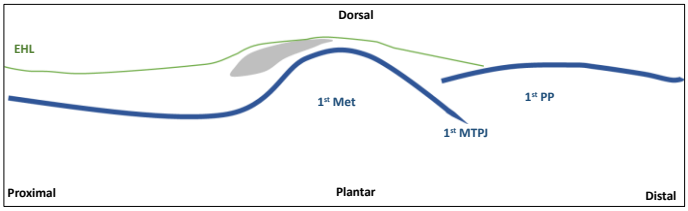
JOINT EFFUSION (LONGITUDINAL)

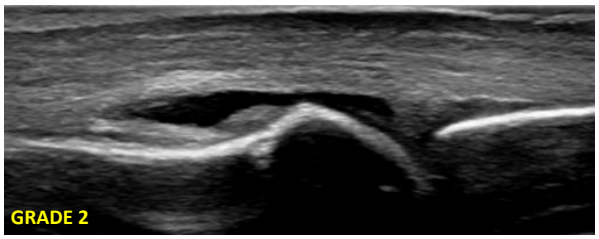
Definition	Grade	Description
Grey scale joint effusion is defined as an abnormal, intraarticular anechoic or hypoechoic material that is displaceable and compressible. Joint effusion score relative to maximal size of effusion	0	Absent
	1	Mild
	2	Moderate
	3	Severe

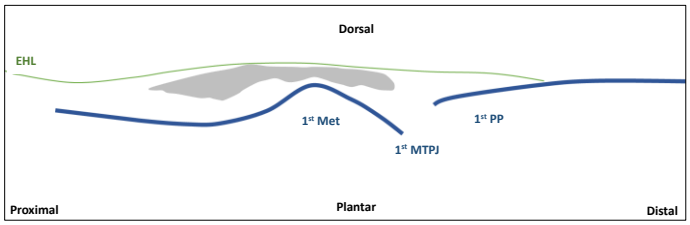


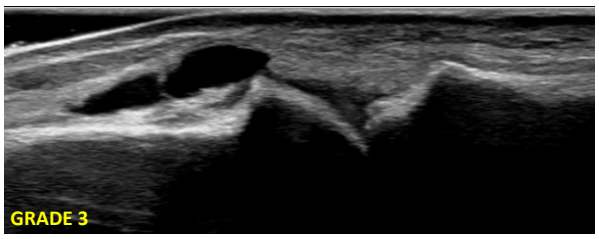


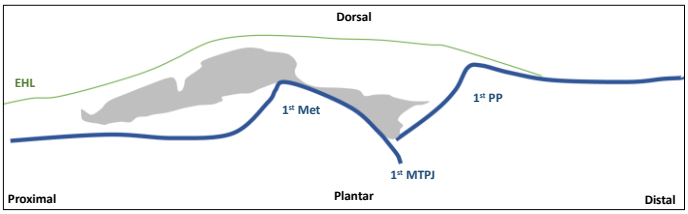






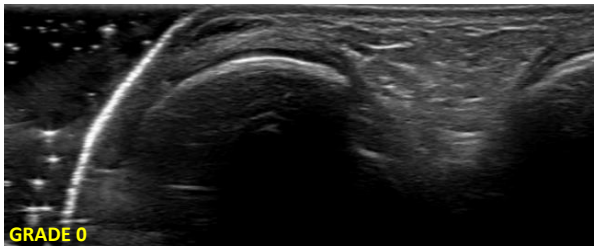


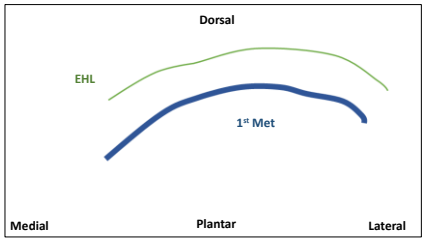


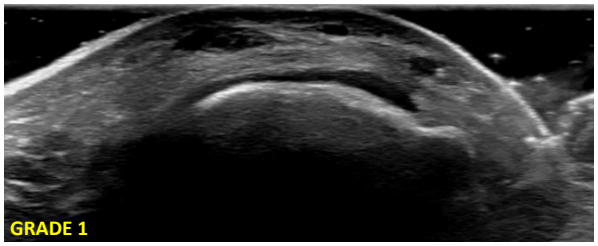


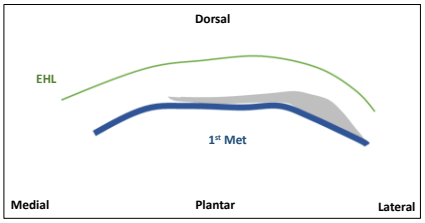
JOINT EFFUSION (TRANSVERSE)

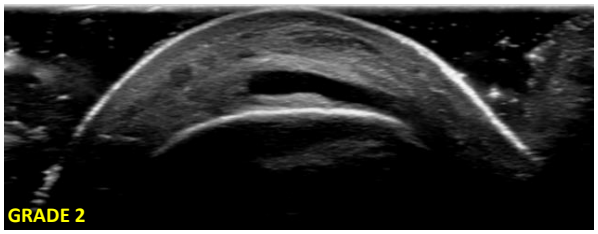
Definition	Grade	Description
An abnormal, intraarticular anechoic or hypoechoic material that is displaceable and compressible. Joint effusion score relative to maximal size of effusion	0	Absent
	1	Mild
	2	Moderate
	3	Severe

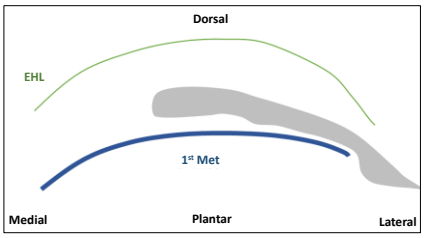


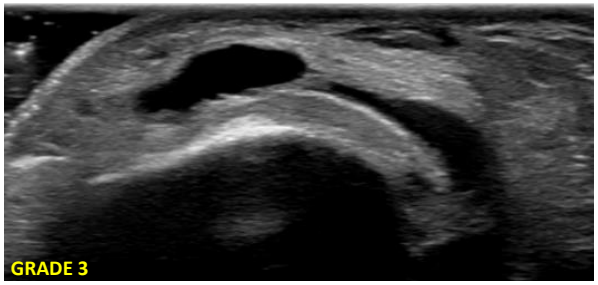


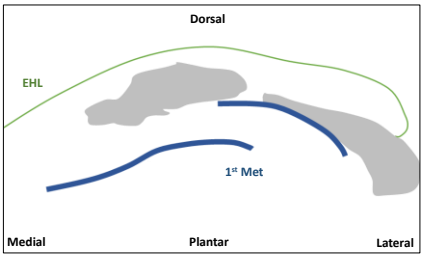






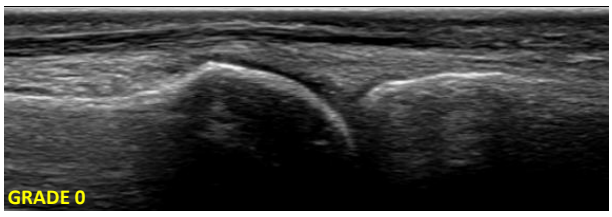


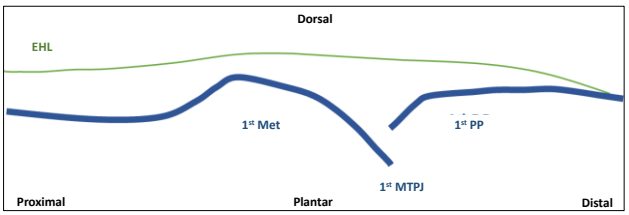


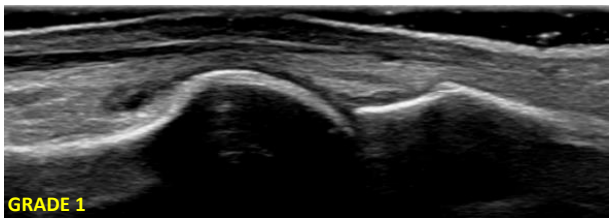


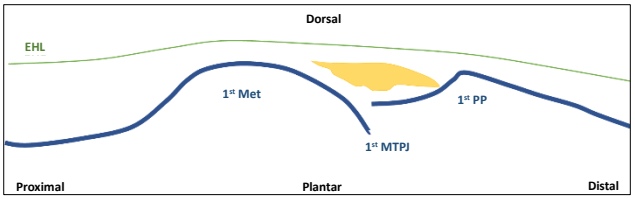
SYNOVIAL HYPERTROPHY (LONGITUDINAL)

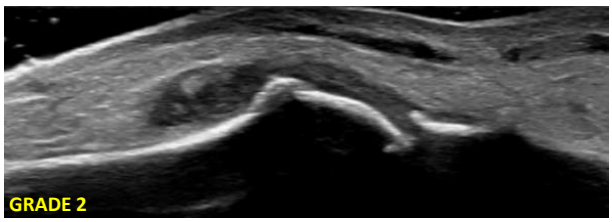
Definition	Grade	Description
An abnormal, intraarticular, hypoechoic material that is non-displaceable and poorly compressible. The scoring of synovial hypertrophy is performed according to a semiquantitative scale	0	Absent
	1	Mild, hypoechoic synovial hypertrophy up to the imaginary horizontal line connecting bone surfaces of the joint
	2	Moderate, hypoechoic synovial hypertrophy extending/protruding beyond joint line but with upper surface concave or flat
	3	Severe, hypoechoic synovial hypertrophy extending beyond joint line but with upper surface convex

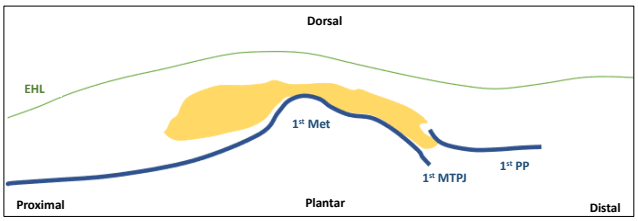


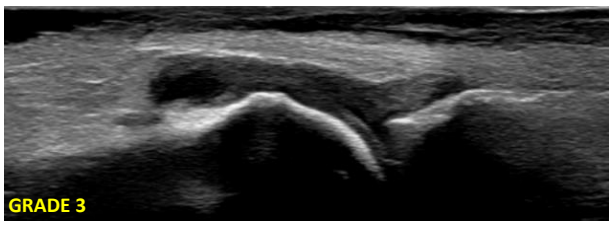


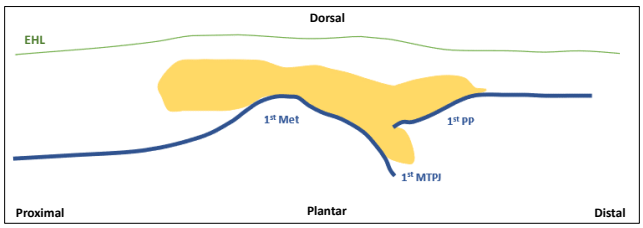






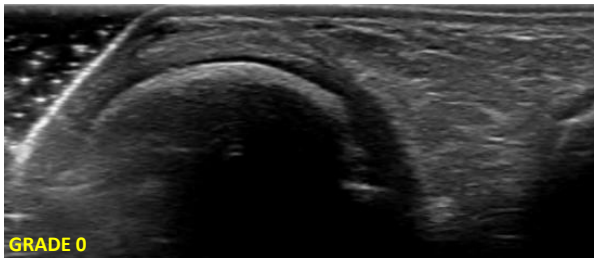


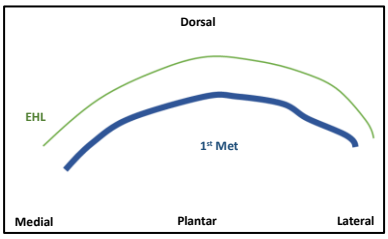


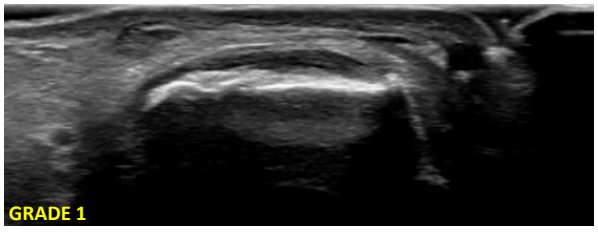


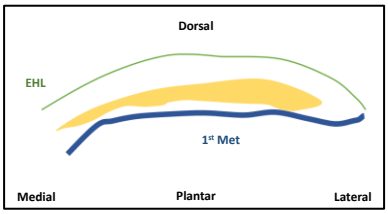
SYNOVIAL HYPERTROPHY (TRANSVERSE)

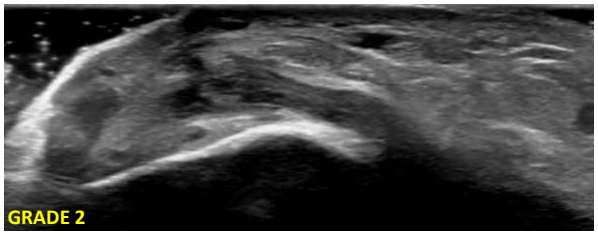
Definition	Grade	Description
An abnormal, intraarticular, hypoechoic material that is non-displaceable and poorly compressible. The scoring of synovial hypertrophy is performed according to a semiquantitative scale	0	Absent
	1	Mild, hypoechoic synovial hypertrophy
	2	Moderate, hypoechoic synovial hypertrophy, with upper surface concave or flat
	3	Severe, hypoechoic synovial hypertrophy, with upper surface convex

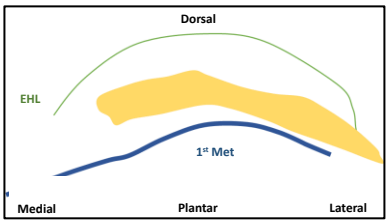


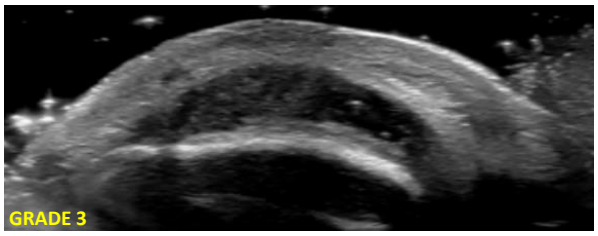


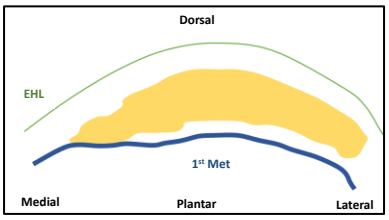






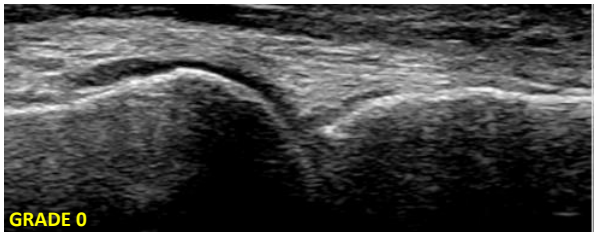


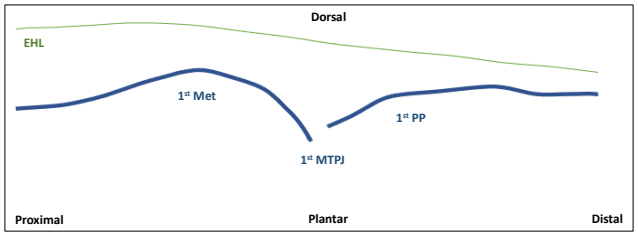


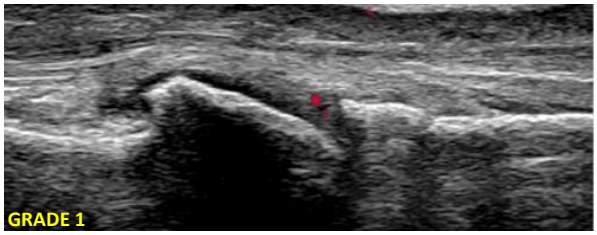


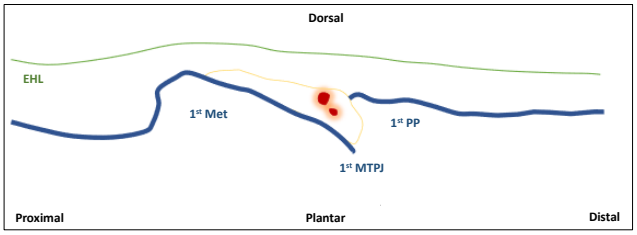
SYNOVITIS

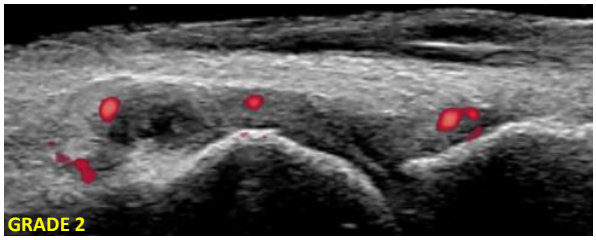
Definition	Grade	Description
Power Doppler signals must be detected within synovial hypertrophy to be considered as a sign of synovitis. The scoring of power Doppler signals are performed according to a semiquantitative scale	0	No flow in the synovium
	1	Mild, single vessel signals (one or more)
	2	Moderate, confluent vessel signals in less than half of the area of the synovium
	3	Severe, vessel signals in more than half of the area of the synovium

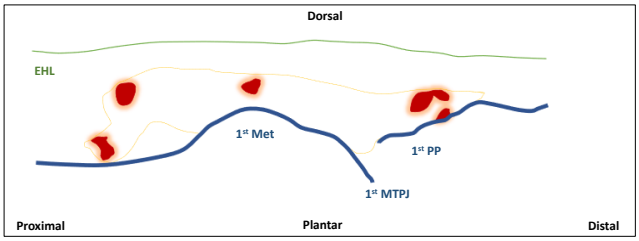


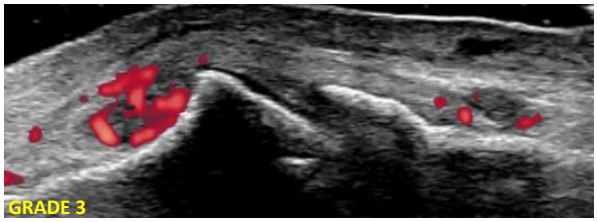


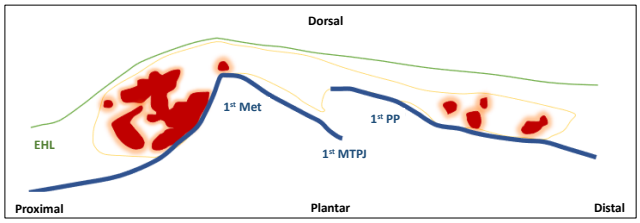








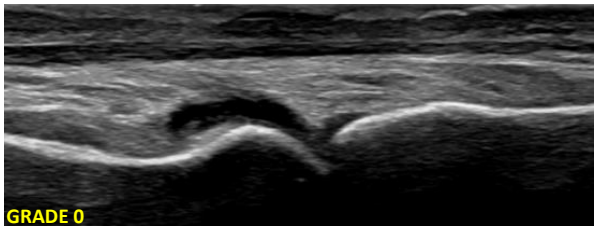


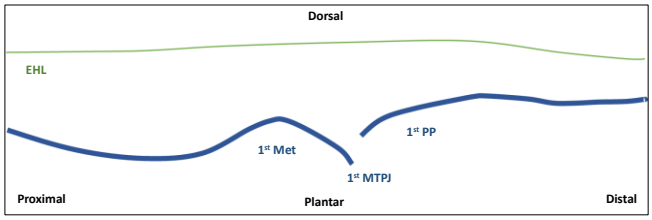


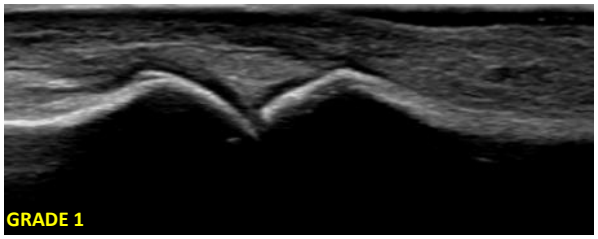
OSTEOPHYTES (LONGITUDINAL)

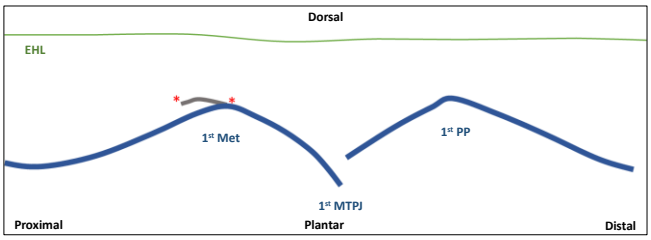
A clear, step-up cortical prominence at the bony margin that is visible in 2 perpendicular planes. The first proximal phalanx and the first MTPJ head were evaluated as a whole, with the largest osteophyte independently defining the score.

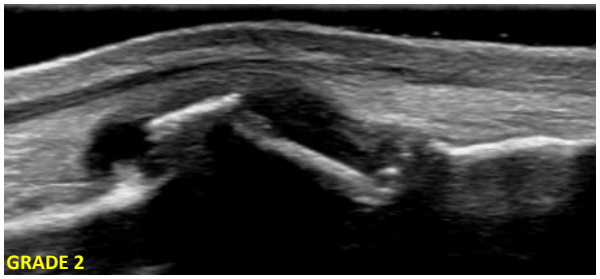
Definition	Grade	Description
Ultrasound semiquantitative scoring system for osteophytes	0	No osteophytes, i.e. a smooth cortical surface.
	1	Small and distinct cortical protrusion(s) of the bony surface (1-4mm)
	2	Larger protrusion(s) which may have broad base(s) (5-9mm)
	3	Very large protrusion(s) which may have very broad base(s) (≥ 10mm)

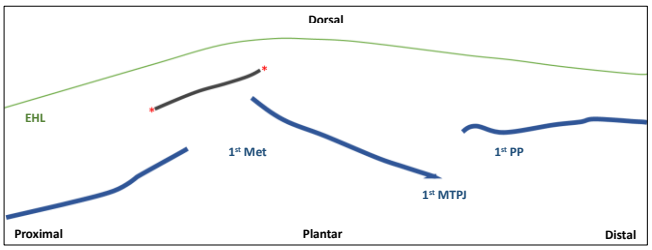


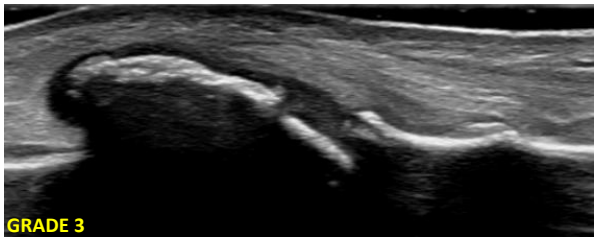


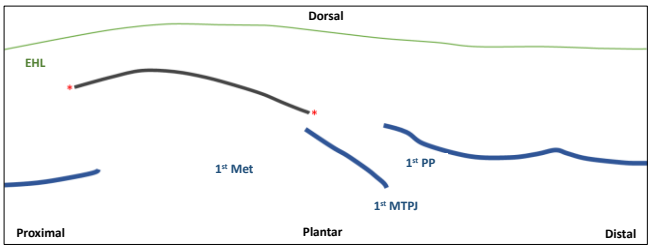


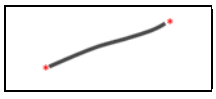










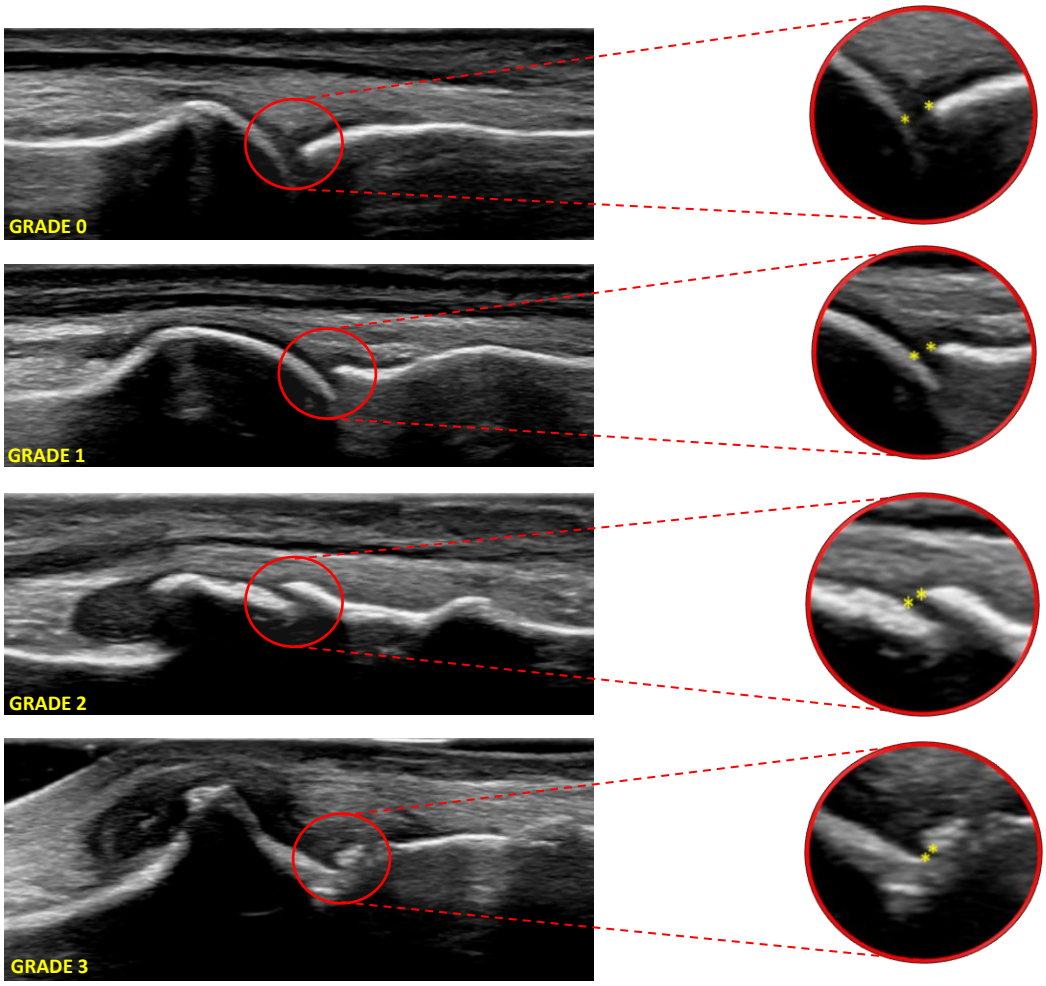


Osteophyte

JOINT SPACE NARROWING

The joint space was measured at the largest joint space from the distal bony edge of the first metatarsal to the most proximal bony edge of the first proximal phalanx.

Definition	Grade	Description
Ultrasound semiquantitative scoring system for joint space narrowing	0	≥1.0mm
	1	0.6-0.9mm
	2	0.2-0.5mm
	3	≤0.1mm



CARTILAGE

Definition	Grade	Description
Ultrasound semiquantitative scoring system for cartilage abnormalities	0	Normal cartilage (anechoic structure with visible margins (=echoic interphase) of cartilage).
	1	Loss of anechoic structure and/or focal thinning of cartilage layer and/or loss of sharpness of at least one cartilage margin.
	2	Focal absence or complete loss of cartilage.