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REVIEW ARTICLE

Should ultrasound be used routinely in the diagnosis of rheumatoid arthritis?

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Abstract

Introduction A growing body of evidence indicates the benefits of early diagnosis of rheumatoid arthritis (RA) and prompt treatment with disease-modifying anti-rheumatic drugs (DMARDS) in terms of relieving symptoms, improving prognosis, and reducing long-term complications. There is however some controversy over the most beneficial method of imaging in providing accurate early diagnosis. Though current practice favours clinical and radiological assessment, this is increasingly supplemented by ultrasound techniques (and, to a lesser extent, CT and MRI scanning). While EULAR and ESSR favour the use of ultrasonography (US) as the first-line investigation in cases of suspected RA, a recent NICE review upholds the traditional place of plain film radiographs of hands and feet to detect erosions as early signs of synovitis. This review considers the evidence for US in the early diagnosis of RA and the case for it becoming the primary assessment modality in rheumatology clinics.

Aims This paper aims to assess the current literature on the efficacy of ultrasonography in diagnosing early RA, by comparing US with alternative imaging modalities. The goal is to propose the most appropriate method of diagnosis to improve early initiation of DMARD treatment for optimum disease outcomes.

Methods Searches for related studies and review articles were carried out using electronic databases and hand searches. Additional references were gleaned from the bibliographies of included papers. Related articles and pop-outs from PubMed were also used. The search was refined in PubMed, by only using reviews which were written in English and published in past 10 years and had full free text available.

Results This review confirms that US has a high level of sensitivity in diagnosing RA (and hence a low risk of missing cases of RA which might benefit from early treatment with DMARDs). It also has a high level of specificity (and hence a low risk of falsely diagnosing somebody with RA who may suffer adverse effects of DMARD therapy). US is already widely available and well accepted by clinicians and patients. It does not involve exposure to radiation and can be readily delivered by appropriately trained staff.

Conclusion This review of relevant studies indicates that US should become accepted as the investigation with the most favourable balance of benefits to risks in the early diagnosis of RA. Given the continuing controversy surrounding studies of different imaging techniques in RA, further research into the diagnostic role of US in RA is indicated.

Keywords Diagnosis · Early rheumatoid arthritis · Imaging · Rheumatic disease · Ultrasonography · Ultrasound

Introduction

> 'detecting subclinical arthritis ……. will ultimately improve the quality of life of patients suffering from rheumatoid arthritis'

This review focuses on recent literature regarding role of modern imaging in the diagnosis of rheumatoid arthritis. Early detection is essential in rheumatoid synovitis to avoid disease progression [4, 19, 48].

In 2012, the ESSR (European Society for Musculoskeletal Radiology) considered ultrasound the leading method in peripheral synovitis imaging, irrespective of the disease entity. A growing body of literature demonstrates increasing use of US in rheumatological clinical practice and links US to the

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diagnostic and therapeutic decision-making process of RA [13]. Some clinicians and researchers claim superiority of US when compared with physical examination, plain radiography, and MRI in rheumatic diseases [30]. Despite the available evidence and the diagnostic potential of US findings, many rheumatologists do not utilise this modality to influence their clinical decision-making.

Zhang [86] argues that detecting subclinical arthritis, to assist in improving medical treatment and successfully halt bone erosion, will ultimately improve the quality of life of patients suffering from RA.

Rheumatoid arthritis

RA is a systemic inflammatory polyarthropathy, characterised by chronic inflammation in the synovium, cartilage degradation, and juxta-articular bone erosions [43, 57]. The debilitating disease affects 1% of the population worldwide [27]. Symptoms include pain, stiffness, swelling, and decreased range of motion [11]. RA is also associated with immune cell activation [85] and non-articular complications such as osteoporosis, accelerated atherosclerosis, and increase risk of malignancy and heart disease [9]. The classification criteria of RA are outlined by the American College of Rheumatology (ACR) and European League Against Rheumatoid Arthritis (EULAR).

In Ireland, general practitioners can refer patients to fast access rheumatology clinics if the small joints of the hands or feet are affected symmetrically or other relevant criteria are met. The key stage in the diagnostic process occurs when the patient attends a specialist rheumatology clinic. Traditionally, X-ray of the hands and feet, to identity bony erosions, was the modality of choice to assess severity of inflammation. Presently, US is increasingly utilised, together with clinical assessment and inflammatory biomarkers, due to its improved diagnostic accuracy and assessment of RA.

Ultrasonography as a diagnostic tool for early rheumatoid arthritis

EULAR 2013 recommendations state that diagnostic certainty in RA is improved by imaging in comparison with clinical examination, in addition to accurate assessment of joint inflammation, joint erosion, prediction of treatment response, and disease activity monitoring [10].

The Swiss Sonography in Arthritis and Rheumatism (SONAR) group believe there is rationale for including US assessment for patients with RA in the daily clinical practice of rheumatologists [88] and have developed the SONAR scoring system.

In the initial stages of rheumatoid synovitis, plain film radiographs may not detect preliminary synovial changes, and patients may only experience non-specific musculoskeletal symptoms [87]. Ultrasonography allows direct visualisation of joint structures, with high sensitivity in detecting pathology, lending it a suitable modality for evaluating RA. The ESSR Arthritis Subcommittee recommend a 4-grade scoring system [53, 74] which has proven high reproducibility among rheumatologists and radiologists [62].

For decades, plain film radiograph has been the diagnostic modality of choice in rheumatology. However, in recent years, US is increasingly selected as diagnostic rheumatoid imaging, revealing subclinical inflammation and predicting progression of joint damage [22].

From their findings of US procedures, Zhang and colleagues claim that US is easy to use and interpret, efficient, economical, and reliable for diagnosis of early synovitis [58, 87]. US can directly visualise the inflamed synovium and synovial sheath, including damaged joints and tendons affected by RA [77]. Gutierrez [28] believes that acquiring US skills for specified targets such as spotting bone erosion is simple, using scanning protocols.

Technique

Ultrasound is best suited to assess many different joints for inflammation, relatively quickly [81]. Naredo found that for routine diagnostic and treatment response purposes, 12-joint power Doppler US (PDUS) assessment of synovitis is valid, reliable, sensitive to change, and feasible for therapy monitoring in RA [50]. They argued it is sufficient to assess the anterior and posterior recess of the elbow, the dorsal carpal recess of the wrist, the second and third MCPJ dorsally and palmar, the suprapatellar recess and the lateral parapatellar recess of the knee, the anterior tibiotalar recess of the ankle, and the medial and lateral tendon sheaths in the ankle area. Spencer recommended more concentration on the wrist and MCPJs for examination [72], while Filer found that scanning MCPs, wrist and MTP joints were most likely to demonstrate specificity for RA [20].

Grey-scale ultrasound

Grey-scale ultrasound (GSUS) provides clear grey-scale images of the musculoskeletal system. Zhang et al. [87] reported grey-scale US is precise, valid, inexpensive, and a readily available method for diagnosis of early rheumatoid synovitis of the wrist and finger joints, as supported by the findings in their cross-sectional study. This study showed that GSUS was more effective at detecting early synovitis compared with clinical laboratory investigations ($p = 0.00015$) than plain film radiographs ($p = 0.0002$). While plain film radiography of patients provided precise information of joint erosions, less information was revealed for synovitis. GSUS was more effective at detecting early rheumatoid synovitis and quantified the synovial changes, when compared with X-ray and clinical

investigations. GSUS is helpful to differentiate synovial hypertrophy and tendon pathologies, in addition to bony erosions and joint space narrowing.

Power Doppler ultrasound

PDUS uses the change in the frequency of a sound wave by the movement of its source or receiver. PDUS and colour Doppler are valid techniques to illustrate the level of vascularisation, to accurately assess inflammation and monitor treatment response in joints and soft tissues. PDUS provides clear visible evidence of acute inflammation. Iagnocco et al. [29] argue that US is a reliable and sensitive method for continuous monitoring of disease activity in RA. PDUS can be used to measure blood flow through small vessels to evaluate the extent of inflammation [8, 77]. Naredo et al. [50] claim that PDUS is a relatively low cost, non-invasive, bedside imaging technique that facilitates the visualisation of all peripheral joints at the real-time of consultation, numerous times as required.

Filer et al. claimed that PDUS had a uniquely high specificity and sensitivity for RA [20]. PDUS provides info on synovial and tendon sheath vascularity [3]. PDUS correlates with vascular endothelial growth factor (VEGF), providing evidence of a central role for VEGF in synovial neoangiogenesis [38]. This study evaluated GSUS and PDUS in asymptomatic synovial joints of patients, comprising relevant joints in a RA assessment. A positive correlation between PDUS and serum cytokines involved in synovial inflammation pathogenesis was reported, proving serum VEGF levels are a potential biomarker for synovial vascularity. Ji et al. [31] concluded that PDUS could independently assist the 2010 ACR/EULAR classification criteria in the early diagnosis of RA in those patients who are negative for anti-CCP antibody.

Methods

Inclusion criteria

The structured systematic literature search for related studies was carried out using electronic databases—PubMed, Elsevier, Cochrane library, Wiley online library, and Science Direct using MeSH. Searches included specific syntax such as (Rheumatology OR Rheumatic Disease OR Rheumatoid Arthritis OR Arthropathies OR Inflammatory Arthritis OR Rheuma*) AND (Imaging OR Image OR Images OR Radiology OR Radiological OR Ultrasonography OR Ultrasound OR US OR Ultraso*). Additional references were gleaned from the bibliographies and references of included papers. Related articles and pop-outs appearing in PubMed were also used. All journals had a high impact factor and cited numerous times previously. A total of 88 papers are included in this review, including 20 clinical trials and over 60 reviews, research papers, guidelines, recommendations, and 1 meta-analysis.

Other electronic resources included Glucksman Library E-resources, JSTOR, Thieme, and internet sites including Radiopaedia.org, Rheumatology.org, NICE.org.uk, and arthritisireland.ie. Printed sources included *Journal of Rheumatology*, *European Journal of Rheumatology*, *Radiology*, and *Clinical Radiology*. Grey literature included ResearchGate, British Society for Rheumatology, and *Arthritis Research and Therapy*. The search was not limited in Cochrane or Science Direct. Additional articles were found in the *British Medical Journal*, the *Irish Medical Journal*, ResearchGate, JSTOR, Thieme and reports from the *Annals of Rheumatic Diseases*, and EULAR. The abstracts of each peer-reviewed paper were evaluated to determine if they addressed ultrasonography, diagnosis, or detection of early rheumatoid arthritis. Clinical trials included in this review will be presented in a chronological order. Conclusions drawn from these studies and reviews are compared to determine an appropriate imaging modality for the early diagnosis of RA.

Exclusion criteria

Search terms yielded numerous results, and many were rejected due to irrelevance or non-specific to early rheumatoid arthritis diagnosis and ultrasonography. Any related conditions including juvenile arthritis, gout, SLE, osteoarthritis, polymyalgia rheumatica, and spondyloarthritis were excluded. The search was refined in PubMed by only using reviews which were written in English and published in past 10 years, solely human studies, and had full free text available. Searches for keywords were limited to the title/abstract to maximise relevant data.

Results

Earlier diagnosis and initiation of DMARDS

NICE guidelines recommend early detection of persistent synovitis and prompt commencement of DMARDS. Earlier detection of joint damage and earlier diagnosis of rheumatoid arthritis is now possible, through imaging modalities such as ultrasound and MRI, allowing repair and halting disease progression by novel therapeutic agents. The accessibility of biologics and DMARDS has prompted earlier initiation of therapy, enabling control of RA and joint preservation [81].

Kelly et al. [37] found that routine US in newly referred patients was associated with significantly earlier diagnosis and initiation of DMARD treatment. Ninety-two percent of their patients later clinically diagnosed with RA fulfilled the ACR/EULAR 2010 criteria at 12 months. A window of opportunity

for remission occurs in the earliest stages of RA [82]. It is argued that US improves diagnostic certainty in new patients presenting with seronegative early arthritis [24, 31, 44]. This differs to the Pratt et al., (2013) study; they found that US as routine assessment in an early arthritis clinic did not add substantial discriminatory value for predicting RA.

Evaluation of RA and quickly starting DMARD therapy has advantageous long-term clinical outcomes and socioeconomic benefits. Disease progression can be halted, with improved long-term functional and radiological outcomes. In addition to reduced clinical signs and symptoms of RA, early diagnosis improves long-term outcomes such as pain, structural damage, and disability [54].

Sensitivity and specificity

Studies that compare US and clinical examination have established a higher sensitivity and specificity of RA diagnosis using US [63]. Nakagomi [47] found that US assessment was more sensitive for detecting synovitis than clinical joint examination, (78% sensitivity for GSUS detected synovitis vs 58.5% sensitivity for clinically detected synovitis) thereby minimizing false-negative results and reducing missed diagnosis and loss of benefit of early DMARD treatment. Their study of 41 patients also provided a very specific assessment of synovitis (93.7% specificity for PDUS assessment vs 79.4% specificity for clinically detected synovitis), which is important to eliminate the risk of initiating DMARD therapy, with considerable adverse effects on patients who do not have RA. The NICE report quotes a requirement of sensitivity of > 90% for determining the diagnostic accuracy of US in addition to clinical assessment in diagnosing RA [52] (Table 1).

Main findings of ultrasound in rheumatoid arthritis

The working group in ultrasonography, OMERACT[1], developed outcome measures in rheumatology, including detectable pathologies for synovial hypertrophy, effusion, rheumatoid erosion, enthesopathy, and tenosynovitis [84].

Synovial pathology determined by US correlates with arthroscopic and MRI synovial hypertrophy. Doppler signal correlates with vascularity and histological features of inflammation in biopsies. Keen et al. [36] discovered that US is reliable in detecting synovitis, effusions, tension lesions, tenosynovitis, and erosions. US can predict patients likely to develop radiographic progression, patients most likely to respond to therapy and patients with low levels of disease activity, likely to flare [36].

[1] OMERACT, Outcome Measures in Rheumatology, is an international, informally organised network initiated in 1992 aimed at improving outcome measurement in rheumatology

- Bone erosions
- Synovitis
- Angiogenesis
- Adipose tissue
- Metacarpal cartilage thickness [3]

Bone erosions

A large percentage of patients with RA present with bone erosions. High-frequency transducers detect minute erosions, as revealed by micro-CT analysis [23]. Bone erosions signify joint involvement in RA, and its detection reveals diagnosis, persistence, and severity of disease [39, 57]. In their study, Tamas et al. [76] found a high percentage of patients with RA in the early stage of disease with bone erosions, most frequently located in the fifth metatarsal head, and lateral aspects.

Funck-Brentano et al. [25] claimed that US erosions and PDUS synovitis have prognostic value to predict future radiographic damage and evaluate the potential severity of early arthritis. According to Gutierrez, the ulnar and fifth metatarsal heads are highly reproducible and frequently involve bone erosion in RA, whereas erosions at the volar aspects are less reliable due to technical, anatomical, and pathological issues [28]. Bone erosions are the hallmark of joint damage in RA. The detection of erosive bone damage and increase in quantity or extent indicates poor consequences [70]. Sheane et al. [71] identified that targeted US is a quick and convenient tool in detecting erosions in early RA, providing a better indication of disease severity and prognosis, compared with laboratory tests, in the absence of definite diagnosis.

Numerous studies have demonstrated that US is more sensitive than conventional radiography in the detection of joint damage. US may provide less detail in comparison with MRI; however, it demonstrates articular and peri-articular pathology, assisting treatment provision [34]. US assessment of all affected joints could prove to be quite time-consuming in the clinic; therefore, specific joints most likely to yield diagnosis, such as the 5th MTP, could benefit early therapeutic decision-making [71, 75].

Koevoets et al. [39] demonstrated that bone erosions, more than joint space narrowing in the wrist, are associated with impaired physical functioning in patients with early RA with limited overall damage.

Synovitis

Numerous studies have recognised the association between subclinical synovitis and radiographic progression of joint degradation [22]. Kane et al. [32] claimed that high-resolution US is superior to clinical assessment in detecting and localizing joint and bursal effusion and synovitis, spotting

Table 1 Findings from RCTs and Systematic Reviews of utiliy of US in individuals with Early RA

Author	No. of patients	Patient population	Joints scanned	Ultrasound (GS, PD, erosions)	Conclusions
1. [58]	51	Early IA, not fulfilling 1987 ACR RA criteria	Including shoulder, elbow, wrist, MCP, PIP, knee, ankle, and MTP	GS and erosions	Early detection of synovitis on US in patients later fulfilling the 1987 ACR RA criteria
2. [71]	30	New presentation of synovitis	Bilateral 5th MTP, dorsal, plantar and lateral aspects	PDUS	US of the 5th MTP identifies patients with early joint damage and aids diagnosis in RA. Useful tool to detect erosive disease.
3. [69]	149	Recent onset UA	Bilateral wrist, MCP (2-5), MTP (2-5)	PD	High discriminative ability using a predictive rule including US for the development of RA.
4. [24]	50	Inflammatory symptoms 12 weeks ± synovitis	Bilateral wrist, MCP (1-5) and flexor tendons	GS and PD	US with routine assessment helpful to confirm diagnosis in seronegative early IA
5. [20]	58	Clinically apparent synovitis in at least one joint, 3-month symptom duration	Bilateral shoulder, elbow, wrist, MCP (1-5), PIP (1-5), knee, ankle, MTP (2-5)	GS and PD and erosions	US of the wrists, MCPs, and MTPs added to clinical findings provided optimal data to predict the development of RA
6. [25]	127	Newly diagnosed patients with RA, > 6 weeks, < 6 months not yet receiving DMARDS	Bilateral MCP (2-5) and 5th MTP, i.e. 10 joints per patient	PDUS and B-mode	US is useful to evaluate potential severity of early arthritis. US erosions and synovitis have prognostic value to predict future damage.
7. [35]	69	Early arthritis	Bilateral wrist, MCP (1-5), PIP (1-5), wrist extensor tendons, finger flexor tendons	GS and PD	PDUS with a strong PD signal is very useful to assist the diagnostic performance of the 2010 RA classification criteria in the early recognition of RA
8. [47]	109	Early arthritis or inflammatory symptoms	Bilateral wrist, MCP (1-5), PIP (1-5), wrist extensor tendons, finger flexor, tendons, elbow, shoulder, ankle,	GS and PD	Improved accuracy of ACR/EULAR criteria
9. [51]	45	Polyarthritis	Bilateral wrist, MCP (2-5), PIP (2-5), wrist extensor and flexor tendons, finger flexor tendons	GS and PD	Prevalence of synovitis higher with MRI vs US. High predictive value using US and MRI for the development of RA.
10. [65]	375	Early IA and inflammatory arthralgia	Bilateral MCP (2-4), PIP (2-4), MTP (1+2)	GS and PD and erosions	US in addition to clinical findings and serology not superior to clinical parameters alone to predict early RA
11. [76]	110	30 patients with early arthritis, 80 patients with long-standing RA	Bilateral MCPJ (2+5), 5th MTP	PDUS	US for bone erosions on few target joints was found feasible and superior to clinical exam. High percentage of early RA patients with US bone erosions on 5th MTP and lateral aspects of most frequently involved sites.
12. [67]	103	Suspected IA	Bilateral wrist, MCP (2-5), PIP (2-5), finger flexor tendons (2-5), MTP (2-5)	GS and PD	US added to routine rheumatological investigation increased diagnostic certainty of IA (early RA)
13. [38]	30	Healthy subjects, non-symptomatic	DAS28 joint set, ankles, MTP joints, 60 views in 40 joints, 3600 images	GS and PD	PDUS reliably measures synovial inflammation. PDUS correlated with VEGF, demonstrating neo-angiogenesis
14. [44]	122	Wrist and finger arthralgia/swelling no definitive diagnosis	Bilateral wrist, MCP (1-5) and PIP (1-5)	GS and PD	US contributed to diagnosis of RA (2010 ACR/EULAR criteria).
15. [31]	69	Arthritis in > 1 hand joint anti-CCP negative	Bilateral wrist, MCP (1-5), and PIP (1-5)	GS and PD and erosions	Presence of PD, particularly in the wrists, was predictive of the development of RA in anti-CCP negative IA.

Table 1 (continued)

Author	No. of patients	Patient population	Joints scanned	Ultrasound (GS, PD, erosions)	Conclusions
16. [12]	111	Newly diagnosed RA or undifferentiated arthritis (sx duration < 1 year)	Bilateral MCP (2-3) and MTP (2+5)	PDUS	PDUS led to more intensive treatment but was not associated with significantly better clinical or imaging outcomes than control.
17. [37]	258	Newly referred patients with inflammatory arthritis	Bilateral MCP (1-5), PIP (2-5), MTP (2-5), wrist, elbow, shoulder, knee, ankle, midfoot	PDUS	Use of US was associated with more rapid diagnosis of synovitis and earlier initiation of DMARDS, (beneficial outcomes).
18. [46]	26	Active arthritis in knee joint and recent onset of RA	Medial, lateral, superior knee compartments	PDUS and B-mode	US in large joints such as knee is a reliable tool. Strong correlations between US synovitis grade and histological inflammation score and vascularisation in actively inflamed knee joints of RA patients.
19. [68]	107	Clinically apparent synovitis in 1 more joints for < 3 months	Bilateral PIP (1-5), MCP (1-5), MTP (2-5), wrist, elbow, shoulder, ankle, knee	PDUS and GSUS	US defined tenosynovitis provides independent predictive data for persistent RA development in early RA.
20. [87]	189	Non-specific MS symptoms	Bilateral MCP (2+3), PIP (2+3), MTP (2+5)	GSUS	Findings support the use of GSUS in detection of early rheumatoid synovitis of fingers and wrist. GSUS was more effective at detecting early synovitis than compared with clinical investigation
Summary					18/20 RCTS support use of US for diagnosis of RA
1. [2] Systematic review and meta-analysis	913	Patients with RA (21 studies)	869 joints scanned	GSUS, PDUS, erosions	Intra-observer and interobserver reproducibility in detecting bone erosion. US is more effective for detecting erosion than X-ray and comparable with MRI
2. [10] Systematic review	Not stated	Patients with RA (199 studies inc.)	Not stated	GSUS, PDUS, erosions	Ten key recommendations for the role of imaging in RA was developed using research-based evidence and expert opinion
3. [79] Systematic review	582	Patients with RA (6 studies)	MCP, wrist, MTP joints	GSUS, PDUS	US appears to have added value to clinical examination for diagnosing RA.
4. Numerous Literature reviews See references	N/A	Patients with RA (63 articles)	Various	GSUS, PDUS	US appears to have added value to clinical examination for diagnosing RA.
5. [52] Evidence-based medicine review	Not stated	Patients with RA (4 studies included, 43 studies excluded)	Various	GSUS, PDUS	Evidence on diagnostic accuracy was inconsistent within studies. No evidence was available for any of the clinical effectiveness outcomes.

minute amount of fluids in joints of asymptomatic patients. Filer et al. [20] established a diagnostic benefit of the increased sensitivity of US in an early synovitis population. In their longitudinal study, US joint evaluation significantly increased detection of joint involvement, providing minimal US findings to improve clinical outcomes for RA.

Najm et al. [46] found US in large joints, including the knee, a reliable tool. A positive correlation was realised between the PDUS grade of synovitis, histological inflammation score, and vascularisation score in actively inflamed knee joints ($r = 0.63$; $p = 0.02$). They demonstrated that US examination with both B-mode and power Doppler reflects accurately histological inflammation and vascularisation. They argued that US findings are a useful biomarker for disease activity when compared with synovial histology.

Sahbudin et al. [68] concluded that US of digit flexor tenosynovitis provides independent predictive data for persistent RA development in patients with early arthritis. Filer et al. [20] reported that digit flexor tenosynovitis, determined by MRI (with gadolinium), predicts RA independently; however, US is perceived as a more accessible clinical imaging tool than MRI. They maintained synovitis demarcated by US improves outcomes in RA is superior than serological and clinical variables in early arthritis.

Angiogenesis

Increased synovial vascularity in cartilage, due to angiogenesis, is observed by PDUS and colour Doppler. Blood vessels are not present in healthy cartilage [57]. Despite clinical remission, subclinical inflammatory activity persists in sheaths or joint cavities, causing disease to progress. Increased blood flow in the synovium, detected by PDUS, is a notable risk factor [63].

Adipose tissue

Extra or intra-articular adipose tissue is associated with cartilage and bone erosion [73]. Adipose tissue is infiltrated by inflammatory cells, adipokines, and may be associated with all connective tissue components. Abnormal fat tissue echogenicity is visible in US [57].

Cartilage thickness

Directly measuring cartilage thickness on US in MCPJs and PIPJs is correlated with joint space narrowing in X-ray findings [45]. In their study, Filippucci et al. [21] demonstrated moderate to good interobserver reproducibility of a cartilage damage scoring system, based on morphological changes at MCP joints of patients with RA.

Discussions

Ultrasonography

Ultrasonography (US) uses the physics of sound waves, by converting electrical energy to high-frequency sound via a transducer containing piezoelectrical elements. The transducer directs the sound waves through matter towards the anatomy in question. The waves are affected by both tissue density and frequency of sound waves [36]. The US probe has been likened to the rheumatologist's stethoscope [8]. US in RA can be used to assess structural damage assessment, monitor RA disease activity, and remission [3]. US bears the ability to differentiate between arthralgia and arthritis, to display erosions in early RA which cannot be viewed on X-ray, to scan tendons in enthesopathies, and to image blood vessels [7]. US permits early detection and detailed characterisation of bone erosion, playing a significant role in diagnostic procedures [70].

Advantages of ultrasound for diagnosis of early RA

US presents numerous advantages over other imaging techniques including the following:

- Lack of radiation
- Relatively inexpensive
- Non-invasive
- Acceptable mode of imaging by patients
- Allows assessment of multiple regions easily and readily [8]
- Alter specific sites, allowing dynamic scans and comparison of bilateral sides
- Valid, reproducible, responsive

Given its validity, reproducibility, and responsiveness, US seems a particularly appropriate imaging modality in the early diagnosis RA. It is much more sensitive than clinical examination for detection of inflammation, optimising diagnosis, directing therapy through accurate assessment of disease activity, and understanding the optimal selection of joints for feasible disease monitoring [36]. Due to the excellent soft tissue contrast, US can depict RA at a very early stage.

In patients with RA, US is painless, enables multijoint scanning, offering contralateral and additional anatomic locations, and allows dynamic images immediately and spontaneously [30]. Naredo and others reported US as a useful tool when available as a service in rheumatology clinic [1, 49].

US has demonstrated its success over conventional clinical and serological assessment when evaluating patients with early inflammatory joint disease symptoms. Technological advances in US in recent years have led to advances in the imaging quality of GSUS and the development of progressive forms, including 3D and Doppler US. These enhancements

have improved the validity of US diagnosis, as well as the monitoring of pathology and disease progression. They have also facilitated interventional therapies in rheumatic diseases [18]. PDUS improves the sensitivity and specificity of RA diagnosis, as has been recognised by 2010 ACR/EULAR classification criteria [24].

Kawashiri et al. [35] have shown that US can play a central role in the early diagnosis of RA according to the 2010 classification criteria. US is an easily accessible modality for assessing small joints of the hands for bone erosion, joint effusion, synovial proliferation, and synovitis. Bursae, larger joints, and entheses can be readily examined. US is associated with more rapid diagnosis of synovitis and earlier initiation of DMARDS, and its importance has been recognised by NICE, the UK's National Audit office and Dept. of Health [37].

Disadvantages of ultrasonography for diagnosis or early RA

- Operator dependent
- Variances in interpretation of results
- Significant learning process and period of training
- Scanning times vary—lack of consensus regarding number of joints to be scanned

As US is the most operator-dependent imaging modality, there may be variances in the interpretation of results by individual operators. US has advanced significantly in terms of probes, scanning techniques, and machines. Differences in US positioning can influence findings, and this obviously affects findings in the research and clinical setting. Scanning times can vary and have ranged from 5 to 15 min depending on joints involved in the research setting [16].

There is a significant learning process to master the skills of US, and a substantial period of training before reaching competency [70]. US is carried out in the clinic, and while US equipment is relatively cheap, Durcan et al. [16] claimed that time and training costs can be considerable.

Some studies have questioned the superiority of US. Dale and colleagues in a RCT published in 2016 investigated whether US assessment could improve an intensive early treatment strategy in patients with RA [12]. They found that, while regular assessment of RA disease activity involved a greater intensity of DMARD therapy, the study demonstrated that this was not associated with superior clinical, functional, health-related quality of life or imaging outcomes. This review, contradicting the growing consensus in favour of wider use of US, confirms the need for further studies in this area.

Other authorities have pointed to the lack of consensus regarding the optimal number of joints that should be routinely assessed using US [37]. Meanwhile, OMERACT has published definitions of common pathological lesions in RA, which have been widely accepted, including bone erosion, synovitis, and synovial hypertrophy [84].

US vs conventional radiography

In Ireland, US is a less accessible modality than plain film radiographs. However, studies show that US is superior to X-ray as it facilitates earlier diagnosis and therefore earlier intervention. With the correct technique and focused assessment, US is feasible in clinical practice, with few contraindications.

X-ray images are two-dimensional representations of three-dimensional pathologies; superimposition of normal and abnormal features reduces the diagnostic integrity [55, 59]. X-ray continues to be a common investigative tool due its availability, universal acceptability (despite the risk of background radiation exposure), cost, performance speed, and diagnostic yield [16]. Plain film radiograph is continually utilised for detecting and scoring erosive damage in routine clinical practice, despite its low sensitivity, in comparison with CT, MRI, and US [70]. Pearman et al. [59] advocate for the importance of utilising well-established, routinely practiced conventional radiography and have demonstrated a novel radiographic position for visualizing bones and joint spaces of hands and wrists, with the aim to improve the ability of radiologists and rheumatologists to identify bony lesions. The primary radiographic features for assessment of RA are bony erosions and joint space narrowing [39].

X-rays include a record of cumulative joint damage triggered by rheumatic disease [10]. While X-ray can detect bone erosions, juxta-articular osteoporosis, joint space narrowing, and new bone formation, it cannot portray inflammatory changes [54]. The key limitation of X-ray is its lack of sensitivity in detecting structural changes in joints of patients with early RA assessment [77]. Wakefield, using US, detected up to seven times more erosions than plain radiography in early RA [83].

US vs computerised tomography

In detecting bone erosions, CT is superior to MRI and US [61]; however, it is limited due to the high radiation doses imparted to the patient [40] (Table 2). There is minimal use of peripheral CT in clinical practice due to its inability to visualise soft tissue changes. CT visualises calcified tissue with high resolution. It is seldom used, unless radiography is unclear and MRI unavailable [54]. CT allows visualisation of osteoporosis and new bone formation, in the form of syndesmophytes ligamentous ossification using multiplanar imaging without superimposition of overlying structures [54]. Its usefulness lies in its ability to depict and delineate new bone formation and erosions in rheumatic disease [14, 15].

Table 2 Comparison of imaging modalities—US vs MRI vs X-ray vs CT

Role	US	MRI	X-ray	CT
General use	Advantages			
	Images all RA pathology (except BME) including subclinical synovitis.	Images all RA pathology including subclinical synovitis.	Most accessible and acceptable mode of imaging	Minimal use of peripheral CT in clinical practice
	Maybe available in the clinic for real-time use.	Generally only extremity-MRI available in clinic.	Low cost, high performance speed	
			Exclude other causes of joint disease (OA, pseudogout), assess damage in established RA	
	Well suited when multiple joint sited need to be assessed.		Well established	
	Disadvantages			
	Significant training period required before attaining competency.	MRI contraindications (e.g. claustrophobia, metal foreign objects).	Not as sensitive or specific as US and MRI in detecting early RA	Involved ionizing radiation and therefore is avoided
	Certain joint regions not well visualised due to lack of good acoustic window, potentially reducing detection of pathology.	Use of contrast agents for optimal synovitis detection.	Difficult to distinguish change between two active therapies (DMARDS, biologics)	Its sensitivity to RA soft tissue changes is markedly inferior to MRI and US.
	Cannot detect osteitis or bone marrow oedema	Limited number of joint sites feasible for examination (typically hand and wrist); whole body		Systematic studies of CT of wrist, finger, and toe joints have not been performed.
		MRI under development.		
		Higher operating costs.		
Diagnosis	Advantages			
	Beneficial over conventional assessment in early RA. Can be used in real time to examine multiple joints.	MRI findings combined with clinical data predictive of RA diagnosis.	Detect bone erosions, juxta-articular osteoporosis, joint space narrowing, new bone formation	Visualise osteoporosis, new bone formation without superimposition of overlying structures
	Disadvantages			
	Need to standardise which joints are evaluated.	Contraindications, higher costs.	Cannot detect inflammatory changes	Cannot visualise soft tissue changes
		Need to standardise which joints are evaluated.	Superimposition of normal/abnormal features reduces the diagnostic integrity	
Prognosis	Advantages			
	Both grey-scale and PD synovitis may predict erosion progression	MRI BME consistently predictive of radiographic progression.		
		Synovitis may predict erosion progression.		
	Disadvantages			
	Unable to visualise bone marrow abnormalities	Contraindications, higher costs.		
Outcome measures	Advantages			
	More sensitive than radiography for erosion detection.	More sensitive than radiography for erosion detection.		Can delineate new bone formation and erosions
	Well suited for imaging studies requiring multiple joint sites to be assessed.	Images can be stored and read centrally for multicentre clinical trials.		Seldom used, unless other modalities are unavailable
	Allows in-depth analysis of soft tissue structures.	Validated and internationally accepted semi-quantitative scoring system available.		
	Disadvantages			
	Scoring system developed but requiring further validation for trials.	MRI contraindications and use of contrast agents.	Less sensitive than US/MRI for joint erosions	
	Lack of consensus on optimal number of joints to be scanned in trials.			

US vs magnetic resonance imaging

MRI uses multiplanar tomographic imaging with soft tissue contrast, providing a means to assess all associated structures in RA. MRI can directly and sensitively visualise synovitis (via effusion), synovial hypertrophy, tenosynovitis, tendon rupture, cartilage thickness, periarticular inflammation, bone oedema, bone erosion, and bone proliferation [56]. Synovitis is often present in clinically inactive joints; hence, the presence of subclinical disease activity can be determined using highly sensitive MRI [26]. Bone oedema, a sign of histologic osteitis, is exclusively visualised by MRI and is a strong predictor of structural damage progression [6]. Ionizing radiation is not used and captured images can be filed and analysed centrally [78].

US cannot image bone marrow, to eliminate other pathologies. In suspected cases of bone marrow oedema due to injury or osteoporosis, MRI is modality of choice [5, 6]. In their study of an early RA cohort, Navalho et al. [51] found MRI to have a significantly higher diagnostic capability. Synovitis in flexor tendons and carpal joints revealed by MRI was more powerful than US in predicting progression toward RA.

Ostergaard [54] considered MRI to be the optimum method for detecting inflammation in the spine and sacroiliac joints in early spondylarthritis, but not in RA. In comparison with US, MRI bears higher operation costs. The excessively high costs of MRI and restricted access have contributed to increase in US imaging [66]. Technically, interpreting MRI can be problematic, as similar lesions to bone erosions can be detected in healthy individuals [42]. MRI also carries risk of claustrophobia, and contraindications in metal implantations and in renal failure due to potential exposure to gadolinium-containing contrast agents [78].

In their meta-analysis for the detection of bone erosions, Baillet et al. [2] derived there was no statistically significant difference between MRI and US.[2]

However, in detecting the presence of inflammation in soft tissue, synovitis or tenosynovitis when clinical examination is inconclusive, PDUS is superior to MRI, as it can sense increased blood flow [40, 64].

EULAR and role of imaging

Following the development of DMARDS, the ACR/EULAR revised the diagnostic criteria for RA, assessing joint involvement, blood parameters, and symptom duration. However, imaging was not integrated as part of the primary assessment. Imaging is indicated whereby initial tests deem inconclusive and fail to fulfill the diagnostic criteria [81]. Nineteen experts appointed by EULAR prepared recommendations regarding imaging in RA, to improve diagnosis in patients showing signs of inflammation, detect structural erosions, and forecast the disease course and treatment response.

NICE guidelines

Evidence review A: ultrasound for diagnosis [52]

In July 2018, NICE published guidelines on the role of US in the diagnosis and management of RA [52]. This review concluded that 'No evidence was identified for any of the clinical effectiveness outcomes', of using US as a diagnostic tool for RA. In the view of the NICE committee, the evidence for the diagnostic accuracy of US was inconsistent within studies, dependent on how ultrasound was integrated into the diagnostic process.[3] In contrast to this literature review, which looked at 20 RCTs, only 4 studies satisfied their highly rigorous inclusion criteria. Overall, NICE considered that the limited evidence from their studies was of insufficient quality[4] to support any recommendation regarding the use of US in diagnosis of RA. NICE excluded 43 studies in their report.

However, NICE have acknowledged that US may improve patient outcomes in the event the patient is reluctant to accept their diagnosis of RA and commence treatment. US here can enable clinicians to illustrate objective evidence of joint inflammation and thereby encourage commencement of therapy.

NICE also clarified that further research should help clarify the circumstances where US assessment may be clinically and cost effective in diagnosing RA. They have also agreed to develop recommendations to establish the value of US in diagnosing RA where there is uncertainty following clinical assessment, i.e. symptoms of RA without clinically definite synovitis (Table 3).

Conclusion

US has become an integral element of the diagnostic process in RA by identifying and assessing inflammatory changes in joint cavities, sheaths, and bursae. The ESSR considered US

[2] MRI spotted more erosions than US in MCP (3+4), MTP (), and shoulder joints, whereas US distinguished more erosions in MCP 5, MTP (1+5), and PIP (). US was superior in early RA, while MRI was better in established RA.

[3] The NICE committee found the studies to be highly diverse, with different populations, study designs and reporting data with some conflicting results. Where longer term follow-up (18 months) was not implemented, NICE committee deemed the study low quality and unreliable, regardless of sensitivity and specificity data of the study.

[4] The major defect of the studies found was that patients had established synovitis in most of the RCTs; hence, the studies could not capture the potential benefit of initial US diagnosis before clinical assessment.

Table 3 EULAR recommendations [63]

1. When in diagnostic doubt, use X-ray, US, or MRI
a. US was superior to clinical examination in 75% of patients [1]
2. Presence of inflammation seen with US or MRI can be used to predict the progression to clinical RA from undifferentiated RA
a. Studies with PDUS indicate likelihood of progression of inflammatory arthritis to RA with OR 9.9 if one joint involved, and OR 48.7 if detected in at least 4 joints
3. US and MRI are superior to clinical examination in assessment of joint inflammation.
a. US and MRI detected joint inflammation twice as frequently as clinical exam
4. Plain film radiograph of hands and feet should be initial imaging technique to detect bone erosions. But US/MRI can be used for earlier detection of erosions or if X-ray is negative.
a. US is more sensitive than X-ray in detecting erosions in RA
5. Early joint inflammation detected by US, MRI, or X-ray predicts further joint damage. MRI bone oedema is a strong independent predictor or radiographic progression in early RA.
a. Predictive value of US synovitis for erosive progression detected by MRI occurred superior to MRI synovitis, (Likelihood ratios of 1.75 and 1.45)
6. Imaging showing inflammation may be more predictive of a therapeutic response than clinical features of disease activity.
a. PDUS was the only effective tool for predicting a therapeutic response by measuring inflammatory activity and clinical parameters such as tender and swollen joints, CRP, DAS28, and HAQ at baseline, > 1 year of TNF inhibitor therapy [17].
7 US and MRI may be useful in monitoring disease activity
a. US, together with DAS28 can detect the slightest changes in synovial inflammation throughout treatment [80].
8. X-ray, US, and MRI can be used to monitor disease progression
a. No data on frequency of imaging applied for monitoring progressive joint damage.
9. If cervical spine is involved, use X-ray, then MRI if positive or specific neurological signs
10. US and MRI can be used to assess persistent inflammation.
a. The presence of synovial hypertrophy and PDUS inflammation is an indicator of the risk of structural and radiological progression in asymptomatic joints in 1 year [60].

the modality of choice for imaging peripheral synovitis [63]. ACR/EULAR, in their RA classification criteria, emphasise the role of US in detection of articular inflammatory changes, which may be ambiguous in the clinical situation initially. These criteria can be applied when clinical synovitis, in the form of oedema and tenderness, is identified in at least one joint.

ACR/EULAR state that US can support diagnosis of arthritis, as well as detecting inflammatory activity in subclinical synovitis and predicting progression of inflammatory arthritis to erosional RA. US is more sensitive in detecting rheumatoid erosions than plain film radiographs. Wakefield et al. [83] established that US detects rheumatoid erosions up to seven times more often than X-ray. US is inexpensive, non-invasive, and can be used conveniently by the bedside, with results evaluated immediately. Both Karim et al. [33] and Agrawal et al. [1] support the use of US for diagnostic evaluation in routine clinical practice.

Despite recommendations from ESSR, EULAR, ACR, SONAR, and Baillet et al. in their systematic review and meta-analysis that US should be integrated into routine RA management, especially at disease onset, NICE have published their evidence-based guidelines stating the contrary. However, McAlindon and colleagues, in their evidence-based review of US for the ACR, found it reasonable to use US to assess inflammatory disease activity in undiagnosed patients with RA or other inflammatory arthritis, as US can detect erosions not evident on plain radiographs [41] (Evidence level B).

Recommendations

US allows for an accurate and non-invasive radiological assessment at multiple joints. To orientate US to a specific target or joint, knowledge of the most sites which frequently involve bone erosion is necessary. In agreement with Tamas et al. [76], a systematic approach, aimed at revealing site-specific bone erosion, is efficient and effective, saving time in the clinical setting.

Gutierrez found in their study that following a 4-week focused training programme, a rheumatologist, without prior experience in US, can detect and score bone erosions in joints of hands and feet in patients with RA [28]. Competency in utilising US for RA diagnosis is an important aspect of training. Higher levels of competence can result in better-quality care and lower cost utilisation.

As per Tins and Butler [81], by working closely together, radiologists and rheumatologists can fulfill their duty to utilise imaging modalities in a cost effective manner to provide diagnosis, prognosis, and continuous assessment with minimal risk and inconvenience to the patient.

Due to its relatively low cost and its inherent safe use, US has been widely adopted in rheumatology clinics for the diagnosis of RA. Assessing all these rival claims, as beneficial outcomes with US are frequently observed in everyday clinical practice, this imaging modality should continue to be used as part of the diagnostic process for RA.

Considering the recent NICE guidelines, it is also evident that further research of the role of US in diagnosing RA should help clarify the circumstances where US assessment may be clinically and cost effective in diagnosing RA.

Compliance with ethical standards

Conflict of interest The author declares that she has no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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