Healthcare Improvement Scotland

evidence note

In response to an enquiry from the Scottish Society for Rheumatology

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In patients with suspected rheumatoid arthritis, does the use of musculoskeletal ultrasound increase the ability of rheumatologists to confirm or rule out a diagnosis of rheumatoid arthritis at an earlier stage compared to routine diagnostic assessment?

What is an evidence note?

Evidence notes are rapid reviews of published secondary clinical and cost-effectiveness evidence on health technologies under consideration by decision makers within NHSScotland. They are intended to provide information quickly to support time-sensitive decisions. Information is available to the topic referrer within a 6-month period and the process of peer review and final publication of the associated advice is usually complete within 6–12 months. Evidence notes are not comprehensive systematic reviews. They are based on the best evidence that Healthcare Improvement Scotland could identify and retrieve within the time available. The reports are subject to peer review. Evidence notes do not make recommendations for NHSScotland, however the Scottish Health Technologies Group (SHTG) produces an Advice Statement to accompany all evidence reviews.

Key points

- Musculoskeletal ultrasound is a rapid, non-radioactive method of imaging that may be effective for early diagnosis of rheumatoid arthritis.
- Evidence from two overlapping systematic reviews indicates that adding musculoskeletal ultrasound imaging to clinical assessment and laboratory testing improves early diagnosis of rheumatoid arthritis.
- A cohort study in patients with non-specific musculoskeletal symptoms and positive anti-CCP antibody tests reported that abnormalities detected using power Doppler ultrasound were associated with future development of inflammatory arthritis.
- In a single observational study with methodological limitations, musculoskeletal ultrasound imaging reduced the time from first rheumatology clinic visit to diagnosis by 1.15 months and time to initiation

of disease modifying anti-rheumatic drugs (DMARDs) by 1.35 months in patients with suspected rheumatoid arthritis.

- Patient and clinician satisfaction with a musculoskeletal ultrasound clinic was high in a small Scottish evaluation study.
- There is evidence from a small number of studies, with some methodological weaknesses, that adding musculoskeletal ultrasound imaging to routine diagnostic assessment in rheumatology aids in the early diagnosis of rheumatoid arthritis compared to clinical examination and laboratory testing alone.

Definitions

Musculoskeletal ultrasound: imaging of soft tissues, cartilage, bone surfaces, and fluid containing structures using pulses of high frequency sound[1, 2].

Synovitis: inflammation of the synovial tissue lining a joint, leading to swelling and pain around the joint[3].

Synovial hypertrophy: enlargement or proliferation of cells within the synovial tissue lining a joint, sometimes as a result of inflammation (synovitis)[3].

Literature search

Methods

A systematic search of the secondary literature was carried out between 24–30 January 2017 to identify systematic reviews, health technology assessments and other evidence-based reports. Medline, Medline ePub ahead of print and in process, Embase, Cinahl and Web of Science databases were also searched.

The primary literature was systematically searched between 24–30 January 2017 using the following databases: Medline, Medline ePub ahead of print and in process, Embase, Cinahl and Web of Science.

Key websites were searched for guidelines, policy documents, clinical summaries and economic studies. All search results were limited to English language from 2007 onwards.

Concepts used in all searches included: inflammatory or rheumatoid arthritis, musculoskeletal ultrasound, ultrasonography, early diagnosis, first appointment or consultation and early discharge. A full list of resources searched and terms used are available on request.

Introduction

Rheumatoid arthritis is a chronic autoimmune condition where an individual's immune system attacks the synovial tissue lining the body's joints causing inflammation, pain, stiffness and joint damage[4, 5]. Rheumatoid arthritis usually affects both sides of the body in a similar pattern, beginning in the small joints of the hands and feet before spreading to other joints[5]. Rheumatoid arthritis can also affect organs of the body such as the lungs, heart and eyes[5]. The exact cause of rheumatoid arthritis is unknown but it appears to involve an environmental trigger initiating a series of changes in the immune system causing it to mistake the body's tissues for foreign tissue which the immune system then attacks. Untreated, rheumatoid arthritis can cause irreversible joint damage, restrict an individual's ability to perform everyday tasks such as dressing, cooking or going to work, and reduce quality of life[6]. Life expectancy can be reduced by 3–7 years in patients with rheumatoid arthritis who remain untreated and patients with severe disease may live 10–15 years less than expected[6].

Although there is no cure for rheumatoid arthritis, adequate management of the disease allows most people diagnosed today to lead full and active lives[5]. Treatment of rheumatoid arthritis involves using disease modifying anti-

rheumatic drugs (DMARDs), painkillers, anti-inflammatory drugs and steroids to reduce disease activity, preserve physical function and prevent further joint damage[7]. The initial weeks and months after an individual begins showing symptoms of rheumatoid arthritis are referred to as a 'window of opportunity' where it is important that patients with the disease begin appropriate treatment[6, 8, 9]. Early initiation of treatment in patients diagnosed with rheumatoid arthritis can prevent joint damage, improve long term physical function, help maintain regular employment and increase the likelihood of achieving clinical remission[6, 8, 9] (Dr N McKay, Consultant Rheumatologist, NHS Lothian. Personal communication, 24 Apr 2017). This has resulted in clinical interest in ways to ensure prompt referral and recognition of rheumatoid arthritis, including the use of musculoskeletal ultrasound imaging.

Diagnostic assessment of people with suspected rheumatoid arthritis has traditionally involved a clinical examination, blood tests and X-ray imaging of the affected joints[10]. X-ray is considered the gold standard for imaging in rheumatoid arthritis but has low sensitivity for detecting early structural damage which limits its usefulness in diagnosis[11]. Musculoskeletal ultrasound is a rapid, non-radioactive method of imaging that can be performed in routine clinical practice and may be more effective than conventional X-ray for early diagnosis of rheumatoid arthritis and assessment of disease activity[12, 13]. Musculoskeletal ultrasound imaging distinguishes between healthy and pathological tissues based on the detection of fluid build-up in the joint; synovitis and sub-clinical synovitis which is not visible on clinical examination; synovial hypertrophy; erosions of the bone surface; inflammation of synovial tissue surrounding tendons (tenosynovitis) and inflammation at the point where tendons attach to bones[2]. The presence of synovitis, tenosynovitis or early bone erosions on ultrasound images appear to predict future progression of bone erosion[11]. Consequently, guidelines from the European League Against Rheumatism (EULAR) have recommended using ultrasound when there is diagnostic doubt or when no damage is detected using conventional X-ray imaging in patients with suspected rheumatoid arthritis[11].

This evidence note evaluates the effectiveness of adding musculoskeletal ultrasound to clinical examination and laboratory testing for diagnosing rheumatoid arthritis at an earlier stage compared to routine diagnostic assessment using clinical examination, laboratory testing and X-ray where appropriate.

Health technology description

Musculoskeletal ultrasound is the imaging of soft tissues, cartilage, bone surfaces and fluid containing structures using high frequency sound[1, 2]. In rheumatoid arthritis, patients' ultrasound imaging is used to detect pathological features of the disease such as synovitis, tenosynovitis and bone erosions[14].

In the past decade there have been improvements in image definition, size, portability and cost of ultrasound machines[2]. Most ultrasound machines now have built-in settings for musculoskeletal imaging[2]. Each ultrasound machine comprises a computer processing unit and a transducer[1]. The transducer produces pulses of high frequency sound, inaudible to the human ear, that reflect back from body tissues as echoes which are picked up by the transducer and passed to the computer processing unit[1]. The computer processing unit interprets the echoes to produce images of the body tissues[1].

There are three main musculoskeletal ultrasound modalities: grey-scale/B-mode ultrasound, colour Doppler ultrasound and power Doppler ultrasound[14]. Grey-scale ultrasound produces anatomical structural images in black, white and shades of grey, allowing the visualisation of synovial hypertrophy, synovitis and/or effusion[2, 14]. The more dense a body tissue is, the more it reflects sound back to the transducer and the whiter it appears in the image[1, 2]. Doppler ultrasound uses the principle that sound echoes differently from

objects that are moving towards or away from the transducer (the 'Doppler effect') to visualise blood in tissues[1, 2, 14]. Colour Doppler ultrasound estimates the mean Doppler frequency shift to provide information on the velocity and distribution of red blood cells[1]. Power Doppler ultrasound measures the amplitude of the Doppler signal to estimate the volume of blood present in the tissue[1]. In patients with active synovitis, blood flow through small blood vessels in the synovial tissues surrounding the affected joints increases and can be detected by Doppler ultrasound. Colour and power Doppler ultrasound images appear as colour superimposed onto the grey-scale ultrasound image[2].

Image resolution and depth of tissue penetration with ultrasound varies depending on the frequency of sound used. Low frequency sound penetrates to greater depths but produces poorer image resolution[1]. Musculoskeletal ultrasound imaging uses sound frequencies of 7 MHz and above to provide sufficient tissue penetration and image resolution[1]. Many other factors influence the quality of the image obtained using musculoskeletal ultrasound such as the type of machine, transducer settings, transducer pressure and patient position[2]. For musculoskeletal ultrasound, a linear array which has a flat surface and produces rectangular images is preferred[1, 2].

The potential benefits of using ultrasound in rheumatoid arthritis patients include the ability to carry out imaging in rheumatology clinics or at the patient bedside, low running costs and less image corruption by metal artifacts than computed tomography (CT) or magnetic resonance imaging (MRI) scanning[2]. Counter-balancing these benefits are initial equipment costs, the resource impact of training staff to use ultrasound, and dependency on operator skills and experience[1, 2].

Epidemiology

Rheumatoid arthritis can develop at any age with peak incidence in people aged 40– 60 years old[5].

In the UK, the main source of epidemiological data on rheumatoid arthritis is the Arthritis Research UK-funded Norfolk Arthritis Register (NOAR). Based on NOAR data, incidence rates for rheumatoid arthritis appear to be stable with an estimated 1,851 new cases in Scotland in 2009[15]. An estimated 36,835 people in Scotland were living with rheumatoid arthritis in 2009; approximately 73% of these patients were women[15]. Incidence and prevalence estimates for rheumatoid arthritis in Scotland derived from NOAR data should, however, be interpreted with caution due to geographical variation in clinical practice[15].

The National Rheumatoid Arthritis Society estimates that 1% of the UK population has rheumatoid arthritis[5]. Prevalence estimates from the 2014 Quality and Outcomes Framework indicator on rheumatoid arthritis put prevalence in Scotland at 0.6% (approximately 32,085 people)[16]. With an increasing older population in Scotland, the prevalence of rheumatoid arthritis is expected to increase in the future[15].

Clinical effectiveness

Two systematic reviews with complete overlap of included studies, one primary study published after the systematic reviews, and an unpublished primary study were identified in the literature search.

A recent systematic review by Lage-Hansen et al (2017) evaluated the role of ultrasound in early diagnosis of people with suspected rheumatoid arthritis or arthralgia (joint pain)[17]. Three cross-sectional studies and 12 prospective cohort studies with a total of 1,407 participants were included in the review. Although the authors stated they assessed study quality, they only report study design and sample size as quality criteria. No meta-analysis was conducted due to

heterogeneity. Six of the included studies enrolled patients with unclassified clinically evident arthritis (n=321) and nine studies enrolled arthralgia patients with or without clinically evident arthritis (n=1,086). The majority of studies (11 studies) in the review used a combination of grey-scale and power Doppler ultrasound to assess joints for signs of inflammation. Thirteen studies demonstrated that musculoskeletal ultrasound added value to early rheumatoid arthritis diagnosis compared to clinical examination and laboratory testing alone by increasing detection of inflammation, improving prediction of future development of disease, increasing the number of correct clinical diagnoses, and increasing diagnostic certainty. Four studies in the review analysed results based on the serology status of participants: sero-negative or sero-positive. The review authors do not state whether the participants in these studies were sero-negative or sero-positive for rheumatoid factor, anti-cyclic citrullinated protein (anti-CCP) antibodies, or both. Two studies that incorporated only sero-positive patients found that ultrasound was moderately effective at predicting progression to arthritis. However, in two studies that incorporated both sero-positive and sero-negative patients, the probability of developing arthritis was significantly greater in sero-negative patients with ultrasound evidence of inflammation compared with sero-negative patients without ultrasound detected inflammation (probability increase from 30% pre-test to 94% post-test).

An older systematic review (2013) incorporated six studies on diagnosis of early arthritis which were all reported in the analysis by Lage-Hansen et al (2017)[17, 18]. However, this older review can be considered to provide better quality evidence as they assessed and reported the quality of included studies using the recognised QUADAS-2 tool, whereas Lage-Hansen et al (2017) only report study design as a quality assessment criterion[18]. All the studies incorporated in the Ten Cate (2013) review appear to have limitations based on QUADAS-2 criteria. Meta-analysis was again precluded due to heterogeneity and all the included studies were small. Participants in the six included diagnostic cohort studies (n=582) had symptoms of inflammatory arthritis, undifferentiated arthritis, oligoarthritis, or arthralgia. Two studies using combined gray-scale and power Doppler ultrasound reported that ultrasound was more likely to predict progression to inflammatory arthritis within 1–2 years: odds ratio (OR) 5.50, 95% confidence interval (CI) 2.57 to 11.9 and pre-test probability 6% to post-test probability 94%, respectively. In three studies that compared ultrasound diagnosis with clinical diagnosis of rheumatoid arthritis 18 months to 2 years later, ultrasound reclassified 10– 15% of patients as having rheumatoid arthritis. A final study that added ultrasound to clinical examination found that one third of patients could be reclassified based on ultrasound results but 8% of joints with clinical synovitis appeared normal on ultrasound imaging.

A cohort study (n=136), published after the two systematic reviews above, evaluated the ability of musculoskeletal ultrasound to predict progression to inflammatory arthritis in a subgroup of undiagnosed patients with non-specific musculoskeletal symptoms, a positive anti-CCP antibody test, and no clinical synovitis[19]. Ultrasound scans were performed every 3 months for the first year and then annually or until the patient developed inflammatory arthritis (defined as one or more tender or swollen joint). All ultrasound examinations were performed by the same rheumatologist who was blinded to the results of participant clinical tests in “the majority of cases”. It is not explained in the study why the rheumatologist was not blinded to clinical results for all patients. Approximately 42% (n=57) of participants developed some form of inflammatory arthritis after a median follow-up of 18 months (range 0.1 months to 79.6 months); in 86% (n=49) of these patients rheumatoid arthritis was diagnosed based on the EULAR criteria.

At least one abnormality was detected on ultrasound at baseline in 86% of patients who proceeded to develop inflammatory arthritis

compared with 67% of patients who did not develop arthritis (X^2=6.3, p=0.012). In a patient level analysis, a power Doppler ultrasound score of two or more (hazard ratio (HR) 3.7, 95% CI 2.0 to 6.9, p<0.001) or presence of one or more joint erosions on ultrasound (HR 2.9, 95% CI 1.7 to 5.1, p< 0.001) were associated with a significantly higher risk of developing inflammatory arthritis. The authors report a second patient level analysis where they excluded ultrasound scans of the metatarsophalangeal (MTP) joints. In this second analysis, a grey-scale ultrasound score of two or more was associated with progression to inflammatory arthritis (HR 2.3, 95% CI 1.0 to 4.9, p=0.038). It is not clear why the authors decided to exclude the MTP joint ultrasound results in this second analysis and the confidence interval is only borderline significant. Therefore, the results of this analysis are not reported in detail here. In a joint level analysis, any grey-scale or power Doppler ultrasound score above zero was associated with a significantly increased risk of developing clinical synovitis at that joint (p<0.001). The presence of bone erosions was not significantly associated with increased risk of progression to inflammatory arthritis in the joint-level analysis.

A good quality, prospective diagnostic cohort study which was included in the review by Lage-Hansen et al (2017) is described separately here because it specifically reported on the impact of ultrasound on rheumatologists' decision-making at a first rheumatology referral visit[10, 17]. Other studies included in the Lage-Hansen et al (2017) review considered the impact of musculoskeletal ultrasound on detection of inflammation and prediction of future development of arthritis using a deterministic analysis comparing ultrasound with clinical examination or X-ray. In the study by Rezaei et al (2014), the authors took a probabilistic approach that acknowledged the clinical reality that there is a range of diagnostic uncertainty from highly likely to highly unlikely[10, 17].

One hundred and three patients were enrolled in the cohort study; 36.9% were later diagnosed with rheumatoid arthritis based on American College of Rheumatology (ACR) or EULAR criteria[10]. All patients were assessed twice: once after clinical examination and laboratory tests, and again after performance of musculoskeletal ultrasound. The same rheumatologist assessed both sets of results for an individual patient. After each assessment, the rheumatologist recorded their judgement of the likelihood that the patient had rheumatoid arthritis using a five-point scale. The sonographer who conducted the ultrasound scan and the four participating rheumatologists were not blinded to the results of the clinical examination and laboratory tests which could have introduced bias to the analysis. Patients with a likelihood of rheumatoid arthritis < 20% or ≥ 80% were classed as having the highest diagnostic certainty (highly unlikely or highly likely to have rheumatoid arthritis respectively). For the likelihood of rheumatoid arthritis, the proportion of patients in the group with highest diagnostic certainty increased by 31.1% (31 more patients) following ultrasound scan results (p<0.001). The number of individuals in the group with the highest diagnostic uncertainty (likelihood 40% to 60%) for rheumatoid arthritis decreased by 18 patients (17.4%) after musculoskeletal ultrasound results were provided, p=0.08. These results suggest a substantial improvement in rheumatologists' diagnostic certainty following the addition of musculoskeletal ultrasound to clinical examination and laboratory tests in patients with suspected rheumatoid arthritis. When compared to the final patient diagnosis based on ACR or EULAR criteria after 1 year of follow-up, adding ultrasound to the diagnostic assessment of suspected inflammatory arthritis patients resulted in more patients being correctly diagnosed as having or not having inflammatory arthritis/rheumatoid arthritis.

An unpublished UK-based observational study was identified which aimed to describe the impact of ultrasound on time from first clinic visit to formal diagnosis, and time from first clinic visit to initiation of DMARD therapy, in suspected rheumatoid arthritis patients (Dr S Kelly, Consultant Rheumatologist, Barts Health

NHS Trust. Personal communication, 13 Mar 2017). This study was included in this rapid review, despite its unpublished status, as it specifically addressed key aspects of the research question: the use of ultrasound for diagnosis at a first rheumatology clinic visit and the impact of ultrasound diagnosis on time to initiation of treatment. Study participants were patients with suspected new onset inflammatory arthritis referred to one of four rheumatology clinics through routine local referral practices. Some of the rheumatology clinics used ultrasound in patient assessment and other clinics did not use ultrasound for patient assessment. Whether a clinic used ultrasound or not, and which clinic each patient was referred to, was not randomised or altered in any way from routine practice. Of the 258 patients enrolled in the study, 114 were later diagnosed with rheumatoid arthritis. It is not clear how the diagnosis of rheumatoid arthritis was confirmed in this group. In the sub-set of study participants later diagnosed with rheumatoid arthritis ultrasound (n=56/134) resulted in earlier diagnosis and initiation of DMARD therapy compared to no ultrasound (n=58/124). The median time to diagnosis was significantly shorter at 0.23 months in the ultrasound group compared to 1.38 months in the non-ultrasound group. At the first rheumatology clinic visit, 41% of the ultrasound group received a diagnosis compared to 19% of patients not undergoing ultrasound (Fisher's exact test, p=0.01). Time to initiation of DMARD therapy in the ultrasound group was significantly less than the non-ultrasound group (median 0.46 months and 1.81 months respectively, p<0.001). It should be noted that confounding factors related to differences in rheumatologists' practice other than ultrasound use may have influenced the study results and the clinical significance of a 6-week reduction in time to DMARD therapy is not clearly established.

Patient and clinician experiences

A small non-comparative observational study evaluated clinical usefulness of, and patient satisfaction with, a pilot musculoskeletal ultrasound clinic in Inverness, Scotland[12]. Over a 6-month period, 10 evening ultrasound clinics were organised. Clinicians were encouraged to refer patients with suspected or diagnosed inflammatory arthritis to the ultrasound clinic based on four pre-specified indications: assisting with early or subclinical diagnosis; aiding treatment decision-making; monitoring disease activity or response to treatment; and performing ultrasound guided procedures. Forty-three clinicians (rheumatologists, rheumatology nurses, physiotherapists) and 43 patients were sent a questionnaire following patient attendance at one of the ultrasound clinics. Survey response rates were 96% for clinicians (n=39) and 44.2% for patients (n=19).

Patients expressed high satisfaction with the ultrasound clinic[12]. On a Likert scale of 0–10, average patient satisfaction scores were 9.5 or higher for explanations of the procedure and findings, lack of discomfort during the procedure, improved understanding of their condition, length of appointment, and willingness to return for future ultrasounds. Clinicians reported that ultrasound results were used to assist in early or subclinical diagnosis in 35% of patients referred to the pilot clinic (n=15)[12]; 44% (n=19) of clinicians used the ultrasound results to aid treatment decision-making and 39% (n=17) found the ultrasound useful for monitoring disease activity or treatment response. Average clinician scores on usefulness of ultrasound for the referral indications ranged from 8.0 to 8.7 on a 10-point Likert scale. The clinicians scored the musculoskeletal ultrasound clinic an average 9.0 out of 10 for providing valuable support to the rheumatology team.

Safety

No adverse events relating to the use of musculoskeletal ultrasound in patients with suspected rheumatoid arthritis were identified.

Cost effectiveness

No primary or secondary cost-effectiveness evidence was identified specifically relating to musculoskeletal ultrasound in people with suspected rheumatoid arthritis. However, an NHSScotland report and associated economic model on rheumatoid arthritis suggested that early diagnosis and treatment resulted in medium term cost savings for the NHS[15, 20].

Conclusion

Two systematic reviews with complete overlap in included studies reported that addition of musculoskeletal ultrasound to clinical examination and laboratory testing in patients with suspected inflammatory arthritis increased detection of joint inflammation, improved prediction of future rheumatoid arthritis development, improved accurateness of clinical diagnoses and increased diagnostic certainty compared to clinical assessment and laboratory testing alone.

In two primary studies (one included in the systematic reviews and one unpublished), musculoskeletal ultrasound added to the diagnostic assessment of suspected rheumatoid arthritis patients, increased diagnostic certainty and reduced time to formal diagnosis or initiation of DMARD therapy. Evidence from a single cohort study in a subgroup of undiagnosed patients with musculoskeletal symptoms and positive anti-CCP antibody tests reported that abnormalities detected using power Doppler ultrasound were significantly associated with the development of inflammatory arthritis.

A small Scottish evaluation study reported high patient and clinician satisfaction with a pilot musculoskeletal ultrasound clinic within a rheumatology service.

No adverse events relating to the use of musculoskeletal ultrasound in patients with suspected rheumatoid arthritis were identified.

No primary or secondary evidence was identified which assessed cost effectiveness of musculoskeletal ultrasound in people with suspected rheumatoid arthritis.

There is evidence from two overlapping systematic reviews to support the clinical effectiveness of adding musculoskeletal ultrasound to clinical assessment and laboratory testing to diagnose rheumatoid arthritis at an earlier stage of the disease. Results from three primary studies with methodological weaknesses suggest that musculoskeletal ultrasound can increase rheumatologists' diagnostic certainty, predict progression to inflammatory arthritis and decrease the time to diagnosis or initiation of DMARD therapy in patients with suspected rheumatoid arthritis.

Identified research gaps

Published, peer reviewed observational or randomised studies comparing diagnostic assessment using both clinical and ultrasound assessment with clinical diagnostic assessment alone, and reporting the time from first clinic visit to diagnosis or first clinic visit to treatment initiation are required.

Cost-effectiveness analyses with a UK perspective are required to evaluate use of musculoskeletal ultrasound for the early diagnosis of people with suspected rheumatoid arthritis.

Equality and diversity

Healthcare Improvement Scotland is committed to equality and diversity in respect of the nine equality groups defined by age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion, sex, and sexual orientation.

The process for producing evidence notes has been assessed and no adverse impact across any of these groups is expected. The completed equality and diversity checklist is available on www.healthcareimprovementscotland.org

About evidence notes

This evidence note will be considered for review 2 years post-publication, and at 2-yearly intervals thereafter. For further information about the evidence note process see:

www.healthcareimprovementscotland.org/our_work/clinical__cost_effectiveness/shtg/standard_operating_procedures.aspx

To propose a topic for an evidence note, email shtg.hcis@nhs.net

References can be accessed via the Internet (where addresses are provided), via the NHS Knowledge Network www.knowledge.scot.nhs.uk, or by contacting your local library and information service.

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