Applications of Real Time Musculoskeletal Ultrasonography in Rheumatology Practice

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SUMMARY

In early arthritis, it is important to make a diagnosis before structural damage has occurred, with early disease-modifying therapy effective in improving long term outcomes. Conventional radiographs are relatively insensitive for diagnosing early rheumatoid arthritis (RA), therefore there may be a role for high resolution ultrasound (HRUS) in assessment of synovial inflammation.

The first part of this thesis addresses the deficiency in our current knowledge of standardisation and reproducibility of ultrasound (US) findings. Chapter 2 describes a standardised protocol developed for assessing the metacarpophalangeal (MCP) joints and novel measurements of synovial inflammation. These US measurements were highly reproducible with a rapid learning curve. A reference range of normative values was established based on data obtained from control participants without inflammatory arthritis. In a sub study using obese participants, the impact of body mass index on measurements is summarised.

The correlation of US with clinical observations is not well established. Chapter 3 compares early arthritis subjects to a control group, and showed significantly more US synovitis and abnormally increased measurements, with extensor tenosynovitis (ET) and power Doppler (PD) positivity highly specific to the early arthritis group. US was more sensitive in detecting synovitis than clinical examination, suggesting significant sub clinical synovitis. Additionally, a "reduced joint count" assessment was developed and validated.

Chapter 4 validates HRUS findings in a subset of subjects using magnetic resonance imaging (MRI) as the reference standard. US measurements developed significantly correlated with MRI measurements. MRI was superior for detection of erosions, joint effusion and flexor tenosynovitis, whilst US demonstrated more ET and synovitis than MRI. Advantages of each imaging method are critically discussed.

Longitudinal studies in the musculoskeletal US field are few in number, in particular addressing response to treatment. Chapter 5 presents longitudinal data which suggests that clinical swelling and PD positivity at the MCP joints were the most sensitive to change as a result of disease-modifying therapy. Currently, the prognostic value of US abnormalities for radiographic progression is unknown. Potentially important predictors of treatment response and remission using DAS28 criteria were identified. Baseline predictors of disease persistence were clinical symmetry, ESR and a measurement of joint distension (M1) due to synovial proliferation or effusion. Potential candidates for prediction of radiographic erosions at one year were abnormal M1 and US erosions at baseline.

Chapter 6 validates an US assessment tool developed based on "sentinel joints" whilst factors that may help to differentiate subjects with polyarthralgias from those with early RA are identified in Chapter 7.

The results of this study suggest that early RA needs to be redefined in the light of our US findings. The prognostic value of early US abnormalities will continue to be investigated.

DECLARATION

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

I give consent to this copy of my thesis, when deposited in the University Library, being available in all forms of media, now and hereafter known.

Anita Tin Yun Lee

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DEDICATION

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PUBLICATIONS

Publications and presentations arising from this thesis

Publications

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Lee A, Proudman S, Wilkinson M, McWilliams L, Cleland L. Development of a Screening Protocol Using High Resolution Musculoskeletal Ultrasound in Early Arthritis. Australian Rheumatology Association 49th Annual Scientific Meeting, Perth May 2006

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ABBREVIATIONS

HRUS = high resolution ultrasound

MRI = magnetic resonance imaging

RA = rheumatoid arthritis

EA = early arthritis

PA = polyarthralgias

ESR = erythrocyte sedimentation rate

CRP = C-reactive protein

RF = rheumatoid factor

Anti-CCP = anti-cyclic citrullinated peptide

M1 = measurement one

M2 = measurement two

M3 = measurement three

BMI = body mass index

DAS = disease activity score

ACR = American College of Rheumatology

DMARD = disease-modifying anti-rheumatic drug

NSAID = non-steroidal anti-inflammatory drug

MCP = metacarpophalangeal

PIP = proximal inter-phalangeal

ET = extensor tenosynovitis

FT = flexor tenosynovitis

PD = power Doppler

ANOVA = analysis of variance

SD = standard deviation

ROC = receiver-operated characteristics

AUC = area under curve

cv = coefficient of variation

DEFINITIONS OF COMMONLY USED TERMS

Terms commonly used in musculoskeletal ultrasonography

Anisotropy: appearance of structures which are specular reflectors such as tendon and muscle are affected by the angle of approach of the US beam (if not perpendicular to structure being scanned), potentially resulting in artefacts

TGC: time gain compensation (or depth gain compensation). The gain level (or amplification) is set by each slide control in a TGC system on the US machine corresponding to specific depths within a subject. For example, greater amplification is required for returning echoes from deeper tissues to compensate for more attenuation with increased path length back to the transducer (increased attenuation as the beam passes through more tissues). The TGC settings utilised require constant adjustment throughout the US examination and depend on the depth of the area of interest.

CHAPTER 1

Introduction

1.1 Introduction

Musculoskeletal ultrasonography (US) is a useful and versatile technique for assessing soft tissue abnormalities (Gibbon 1996, Grassi 1998), with a rapidly expanding role in diagnostic and therapeutic areas of rheumatology. Kane et al recently reviewed the history of US "from bats and ships to babies and hips" (Kane 2004). Spallanzani's experiments in the 1790s investigated the ability of bats to navigate flight despite being blindfolded, and the first sonar device was later built by Fessenden after the sinking of the Titanic (Hill 1973). In 1972, the first documented use of US for human joints was for evaluation of popliteal cysts and subsequently of congenital dislocation of the hip (McDonald 1972, Graf 1980).

Several review articles have been published recently on musculoskeletal US, reflecting a growing interest in this imaging modality (Benson 1991, Chhem 1994, Jacobson 1998, Hashimoto 1999, Winter 2001). To date, US has been used primarily as an extension of the clinical examination to provide greater anatomical definition and for guiding needle aspiration, biopsy and injection of joints, bursae and tendon sheaths (Balint 1997, Koski 2000). There is increasing interest in research into the significance of sub clinical findings (Karim 2001, Wakefield 2004c).

Joint US is useful especially when performed by appropriately trained clinicians who can interpret the results within the context of the history and physical examination findings (Manger 1995, Backhaus 2001). In comparison to other imaging techniques,

US is safe since no ionising radiation is involved (Wakefield 1999, Canoso 2000). It is non-invasive and relatively inexpensive (Winter 2001, Wakefield 2004b), which is important for containing health care costs. The newer machines are fully mobile and suited to use in an outpatient clinic setting and at the bedside (Leeb 1995, Manger 1995, Jacobson 1999), thereby allowing an immediate change in diagnosis and management plan if indicated (Karim 2001). Positioning of the patient is not limited by the constraints of the machine, unlike computed tomography (CT) or magnetic resonance imaging (MRI) (Lin 2000).

More recently, high resolution US (HRUS) machines have been developed for scanning superficial structures more accurately, and this has enabled small joints to be visualised clearly (Backhaus 1999, Hau 1999, Wakefield 2000). This improved resolution has also made US more accessible to non-radiologists (Wakefield 1999). Real time imaging allows the dynamic evaluation of joints, including provocative manoeuvres to enhance pathological features (Manger 1995, Jacobson 1999, Wakefield 1999). The multi-planar scanning capabilities of US permit examination of areas not visualised by conventional radiography (Grassi 2001b). In rheumatology, musculoskeletal US has been used in the evaluation of rheumatoid arthritis (RA), spondyloarthritis (Lehtinen 1994, Olivieri 1998), osteoarthritis (Grassi 1999a), scleroderma (Ihn 1995, Scheja 1997), Sjogren's syndrome (Makula 1996) and temporal arteritis (Schmidt 1997).

US can be performed frequently and be repeated at will to monitor progression of the early phases of inflammatory arthritis. Since a short scanning time is required for each joint, multiple joints can be scanned on the same occasion (Wakefield 1999). Comparisons can be made with the contralateral side (when unaffected) to enable

significant findings to be distinguished from normal variants (van Vugt 1998, Lin 2000). US is a dynamic interactive process between the operator, transducer and patient and therefore is the most operator-dependent mode of image capture. The advantages of interpretation of findings in real time extend this operator dependency to the interpretation of images (Canoso 2000, Wakefield 2004a, Wakefield 2004b). The dynamic aspect of US offers advantages but also a tendency to error and artefacts, and a training period is required. Formulating images requires a high level of hand-eye coordination and acquisition and maintenance of perceptual and manual skills. Some differences in results between research studies may be explained by variability in operator performance.

In the assessment of arthritis, US can aid in determination of likely aetiopathogenesis, in diagnosis, especially early when radiographic signs may be absent, in prognostication and in monitoring disease activity. US can also be used to assess response to interventions and to help guide treatment decisions. More validation studies are required especially regarding the issue of inter-scanner variability and sensitivity to change of current scoring systems (Ostergaard 2005, Hunter 2006). US may potentially be utilised to tailor therapy to the individual requirements depending on the presence of poor prognostic signs, such as ultrasonographically detected periarticular bony erosions, which may warrant more intensive treatment to guard against progressive joint damage and cumulative disability.

In recent years, there has been increasing use of US in rheumatology clinics within Europe and the UK, especially in clinics designed for the early detection and management of polyarthritis. Notwithstanding, there remain unresolved issues

regarding validity and reproducibility and a paucity of longitudinal data with which to assess the prognostic implications of early findings (Keen 2005). Studies have often been limited to small numbers of patients with no "gold standard" such as surgical or histopathologic correlation being utilised (Jacobson 1999). The long-term implications of sub-clinical synovitis, extensor tenosynovitis (ET) and erosions found with US early in the polyarthritis upon longer-term disability and radiographically evident joint damage are unknown. Whether earlier diagnosis of synovitis and erosions will favourably alter treatment given and hence outcome remains to be seen.

The issues of competency, training and core knowledge and skills required of rheumatologists to practice US in their clinics all need to be addressed. In the short-term, rheumatologists may be disinclined to use outpatient US due to the cost of HRUS machines, which can be prohibitive, and the long period of training and intensity of continuing practice required to achieve and maintain operator competence. There is scant evidence available on what constitutes appropriate training. British and European training courses have been developed, but these are not for certification of competency. Lack of suitable arrangements for remuneration for US by rheumatologists and the opportunity cost for the time required for its performance are further barriers to the routine adoption of this technology in rheumatology practice.

A recent article from a working party in musculoskeletal US provides extensive documentation on the indications for musculoskeletal US and the knowledge base and basic skills required for its performance (Brown 2005). The article identified eight indications, which include inflammatory arthritis, with particular reference to monitoring disease activity and progress of structural changes. The hand and wrist are

included among eight anatomic regions identified. Fourteen categories of knowledge and skills are detailed. Relevant physics, anatomy and recognition of artefacts are examples. The desirability of partnerships between radiologists with extensive US experience and the clinical skills of interested rheumatologists is acknowledged.

The basic physics of US have recently been summarised by Conaghan et al. (Conaghan 2005). US uses the various physical properties of sound waves to create images. These properties include reflection, absorption and differing speeds of transmission within different tissues. Sound waves with frequencies higher than those sensed by human hearing are used, hence the term 'ultrasound'. Higher frequency transducers provide good resolution of superficial structures, such as small peripheral joints, but lack penetration and are therefore unsuitable for assessment of deeper structures, such as hip joints and internal organs. Typically, US images are portrayed in black and white, also known as gray-scale US, with fluid in black and bone surface in white. Doppler US depends on moving cells, with power Doppler (PD) sonography being more sensitive to low flow blood vessels such as those in the synovial proliferation of RA. The importance of the availability of the PD functionality as an adjunct to gray-scale US includes the ability to detect hypervascularity in synovial tissues, which implies ongoing active inflammation. In a recent study of established RA with low-level activity clinically and normal inflammatory markers, PD response to therapy was found helpful in the decision regarding intensity of treatment (Conaghan 2005).

1.2 Use of HRUS in early arthritis

1.2.1 Need for early diagnosis

Information on the presence of inflammatory joint disease, erosions and other prognostic factors are required early for prompt treatment, which can reduce inflammation during the window of opportunity when disease-modifying anti-rheumatic drugs (DMARDs) have the best chance of altering the outcome (Emery 2002, Taylor 2004). Early RA should be differentiated from self-limiting synovitis, since, on the one hand, there are risks associated with medications prescribed for RA and, on the other, these treatments may not necessarily be helpful with regard to the spontaneous resolution of a self-regulating process. Tunn et al. (Tunn 1993) at a patient's first visit were unable to identify clinical or laboratory features or profiles that allowed one to predict whether recent onset, symmetrical polyarthritis would be self-limiting or persistent. Detailed history taking and a thorough physical examination can fail to confirm or exclude a diagnosis of polyarthritis in patients with painful joints of recent onset.

Current criteria for the diagnosis of RA are not designed to detect early disease. The American College of Rheumatology (ACR) classification criteria, published in 1987 (Arnett 1988), were poor at predicting the subsequent development of RA in patients with recent onset inflammatory joint symptoms (also referred to as early arthritis, or EA) at their first visit. In a French study of 270 EA patients with disease duration of less than one year, the ACR classification criteria at baseline did not predict RA at two years if the opinion of the rheumatologist was excluded (Saraux 2001).

Structural damage occurs early in active RA, and the higher rates of progression of radiographic scores of joint damage have been seen in the first 2 years of RA in longer term studies of patients receiving usual therapy (van der Heijde 1995). Early disease-modifying anti-rheumatic drug (DMARD) treatment is effective in improving long-term outcomes (Ostergaard 1999, Emery 2002), which include reduced radiographically evident joint damage (Boers 2001). The MCP and PIP joints are often first to be affected in RA and are representative of overall joint damage (Drossaers-Bakker 2000), since small joint involvement correlates with large joint involvement. Therefore detailed assessment of small joints is warranted.

The MCP joints are have been chosen for study in early RA as their anatomy allows the most reproducible and interpretable documentation of the relationship between synovitis and bone damage at the joint level (Conaghan 2003), in contrast to other joints such as the MTP joints of the feet. Clinically evident soft tissue swelling about an MCP joint can be due to synovial thickening, effusion, tenosynovitis, swollen skin or prominent subcutaneous fat. The rate of radiographic progression varies for an individual and relates to disease activity (especially if the rheumatoid factor (RF) is present). The link between progression of radiographic changes and functional impairment is strongest in established disease (Breedveld 2005), although in early disease, joint damage also correlates with functional impairment. When radiographs are normal and inflammatory arthritis is suspected, US can provide valuable information regarding the presence of synovitis. Studying patients with polyarthritis early allows disease related changes to be assessed in the absence of the potentially confounding effects of medications and other interventions (Conaghan 2003).

1.2.2 Assessment of periarticular inflammation and erosive changes

Factors which can correlate with rates of joint damage as assessed radiographically include seropositivity for RF, certain genetic factors (Combe 2001) and disease activity, both with regard to severity, persistence and duration (Giovagnoni 1998). There is a relationship between joint damage on conventional radiographs and functional disability, both of which increase with duration of disease (van der Heijde 2001). Patients with early erosive changes have a poorer prognosis (Boers 2001).

Up to 70% of all early RA patients have erosions on plain radiographs within the first one to two years of the onset of symptoms (van der Heijde 2000). Conventional radiography has been regarded as the gold standard for judging progression of joint damage but lacks sensitivity in detecting the evolution of erosive changes, since destructive proliferative synovitis (pannus) is not visualised (Backhaus 1999, Wakefield 2000). Radiographs are useful for detecting erosions later in the course of RA, but early inflammatory changes can only be visualised indirectly by detecting soft tissue swelling or periarticular osteopenia (Newman 1996). Specialised radiographic views improve resolution and can detect erosions with sensitivity approaching that of US, (van der Heijde 1996), but at the cost of significantly increased radiation exposure and poor reproducibility. Accordingly, these views have not found a place in routine practice (Wakefield 2000). Erosions can only be diagnosed on conventional 2D radiographs when the incident beam is tangential to the cortical defect or the erosion is large (Wakefield 1999).

A role for US in the management of inflammatory arthritis is becoming established, especially with regard to early diagnosis and assessment prior to initiation of treatment

and in monitoring disease progression (Grassi 1993). In early RA, HRUS can detect joint cavity widening, synovial proliferation, free fluid, capsular thickening and tendon sheath widening (Grassi 1999b). US imaging of the metacarpophalangeal (MCP) joints in RA (Grassi 1993), allows MCP synovitis to be distinguished from other causes of regional swelling such as tenosynovitis and subcutaneous oedema. In obese patients particularly, US helps detect arthritis and tenosynovitis in joints such as the ankles, feet, MCP and wrists, which can be difficult to evaluate clinically (Koski 2000).

The quantitative aspect of joint assessment by HRUS offers opportunities for the measurement of responsiveness in therapeutic trials. Unsurprisingly, early studies found that US evidence of synovial thickening was more closely correlated with joint swelling rather than tenderness (Spiegel 1987). Storage of US images of joints allows subtle differences in synovial proliferation and effusion to be detected by later comparative examination. HRUS is more sensitive for the detection of erosions than plain radiographs. Wakefield et al. (Wakefield 2000) demonstrated 6.5 times as many erosions in the MCP joints within an early arthritis cohort using US compared with plain radiographs. Evidence for the pathological specificity of US erosions was indicated by MRI, with all the additional lesions on US also being demonstrated on MRI. Corresponding abnormalities were found on retrospective review of plain radiographs in 82%, previously labelled as peri-articular bone cysts. Most US erosions were small and located in the metacarpal (MC) heads. That US detected more and smaller erosions when compared with conventional radiography is not surprising considering its multi-planar capabilities.

Backhaus and co-workers performed a comprehensive study comparing multiple imaging methods, that included conventional radiography, MRI, US and 3-phase bone scintigraphy, to determine the optimal imaging method for identifying early erosions and acute inflammatory joint changes in erosive and non-erosive rheumatic disease (Backhaus 1999). All three of the latter methods of imaging were more sensitive than plain radiography in detecting inflammatory arthritis, US being best for synovitis, and MRI for erosions. The latter observations are consistent with previous studies showing that MRI is more sensitive than US in detecting erosions (Wakefield 1997, Szkudlarek 1999). MRI was found to detect more erosions than plain radiography in early arthritis of the finger joints (Klarlund 2000a). The specificity of MRI findings remains to be determined in longitudinal studies. While, in principle, histopathology is the desired 'gold standard', there are, for most locations, significant practical barriers to the acquisitions of suitable samples.

Higher frequency transducers and high resolution US machines are now widely available and avoid the need for an acoustic stand-off gel pad to enable better quality images of superficial structures (Chhem 1994, Hashimoto 1999). Transducers with frequencies of between 13 to 20MHz are now recommended for assessment of synovitis of the hand (Grassi 1999b). Grassi et al. (Grassi 2001b) compared US and radiography in early RA, and performed selected US examinations of only the second MCP and fifth metatarsophalangeal (MTP) joints. Both are locations where erosions appear early. US was more sensitive in detecting small erosions in areas not revealed adequately by standard radiographic views. Erosive changes documented on US correlated with cystic areas of bony resorption and low bone density on radiographs. In this sense US and radiographs correlate, with US providing certainty for lesions for

which radiographic appearances are equivocal. Thus, high frequency transducers allow safe, quick, inexpensive and accurate identification of small bone erosions.

Nearly half of all RA patients have shoulder involvement in the first few years and arthritis of this joint is often unrecognised (Naredo 2002). US has been found to be sensitive in early detection of bursitis, biceps tendon changes, rotator cuff tears and synovitis about the shoulder, as confirmed by histology of operative biopsy specimens (Alasaarela 1998a). There is evidence that both MRI and US detect more humeral head erosions than either CT or plain radiography (Alasaarela 1998b).

A review of recent publications revealed a relationship between damage on plain radiographs and functional disability both of which increased with increasing duration of RA disease (van der Heijde 2001). The question remains as to whether documentation of small erosions or synovitis on US in early RA predicts later radiographic damage in the affected joints, and therefore worse functional outcome. Further longitudinal studies to validate US and evaluate the relationship between sonographic findings and other imaging techniques are required.

US has a special place for imaging tendons in rheumatology, as it is more sensitive than MRI for detection of tenosynovitis (Backhaus 1999) and complete tendon ruptures in the hand (Swen 2000). Up to 64% of RA patients have finger tenosynovitis, which may be complicated by rupture with major functional consequences (Swen 2000). Partial tears are difficult to detect clinically but the evidence to date suggests that US is not sufficiently sensitive to detect all partial tears of the finger extensor tendons in RA that can be revealed surgically (Swen 2000). However, with advances in higher frequency

transducers and image acquisition software, HRUS should become more sensitive. The presence of ET is RA is a neglected aspect of clinical assessment and it is uncertain to what extent the tenosynovitis in EA has prognostic value. Longitudinal studies into the significance of ET of the fingers revealed by HRUS are clearly warranted.

1.2.3 US in early undifferentiated polyarthritis

Early treatment of RA is important as radiographic damage can occur within a few months of onset. However, it can be difficult to differentiate RA from other types of arthritis early in the course of the disease. EA has variously been defined as up to one to three years of symptoms and termed "undifferentiated" if the rheumatologist's diagnosis was uncertain (Saraux 2001, Jansen 2002, Machold 2002). In one study, 55% of undifferentiated arthritis was diagnosed as RA one year later, with 39% remaining undifferentiated (Machold 2002). In a study of very EA by Machold et al (Machold 2002), 90% of the RA group had hand and wrist involvement in the RA compared with 60% in the non-RA group. Given that the finger joints were involved early, prompt assessment of these target joints is important for diagnostic purposes (Szkudlarek 2006). An increase in yield with inclusion of PD of the ulnar styloid region (Kiris 2006) suggests that this region of the wrist is important in assessment of RA disease activity, especially in the early stages of the disease.

Previous studies have shown RF alone (van Zeben 1993, Wolfe 1993, Gonzalez-Lopez 1999, Green 1999) or in combination with a high erythrocyte sedimentation rate (ESR) (Tunn 1993) is associated with increased likelihood of disease persistence. In established disease, an increased C-reactive protein (CRP) is known to be a marker of poor prognosis, but in disease of less than 3 months' duration, CRP was not predictive

of disease outcome (Tunn 1993). Another study in palindromic rheumatism, a pattern of episodic arthritis that can be precursor to RA, found that older age, hand involvement, female gender, longer disease duration and presence of the HLADR β chain polymorphisms known collectively as the shared epitope also predicted development of RA (Gonzalez-Lopez 1999) .

In a study in Leiden of patients with RA of less than five years duration, predictors of outcome (including disease severity and activity, functional impairment and radiographic abnormalities) were determined by univariate analysis (van Zeben 1993). Factors identified included the number of swollen joints, the functional questionnaire score (Health Assessment Questionnaire, or HAQ), radiographic scores and a positive IgM-RF. The best combination for predicting outcomes accurately was the number of swollen joints, IgM-RF and the erosion score (van Zeben 1993).

A French study of early RA (duration less than one year) which sought predictors of remission (disease activity score or DAS less than 1.6) at three and five years (Gossec 2004), showed inverse correlations between remission and baseline DAS, joint count (Ritchie) scores, CRP level, RF status, HAQ score, duration of morning stiffness and baseline total radiographic scores. After logistic regression analysis, low DAS or joint score, duration of morning stiffness and total radiographic score survived as independent correlates. The laboratory variables ESR, CRP and anti-CCP antibodies were not correlates after adjustment for the above factors.

Clinical symmetry of disease is part of the ACR classification criteria (Arnett 1988), and is considered a predictor of disease persistence. Green et al. (Green 1999) found

symmetrical MCP joint involvement at presentation was associated with persistent disease at six months in 94% of patients with early mild synovitis, but was not linked to poorer prognosis in established disease. This association was only applicable in patients with disease of at least three months on presentation.

Short disease duration at presentation (12 weeks or less) was the only significant predictor of clinical remission, defined as absence of signs and symptoms off treatment at 6 months, with five fold greater likelihood of remission (Green 1999). The mean disease duration at presentation was 20 weeks for persistent disease and 10 weeks for those in remission. In an Austrian study involving a very early arthritis clinic setting (Machold 2002), those with RA took twice as long to be diagnosed or seek medical attention as those with other rheumatologic diagnoses (8 weeks compared to 4 weeks median disease duration). More acute onset disease resulted in earlier referral.

Jansen et al. (Jansen 2002) determined prognostic markers for progression of undifferentiated polyarthritis (UPA) in 77 patients with polyarthritis or oligoarthritis (at least two affected joints) with clinical synovitis of recent onset (less than three years duration, median 3.5 months). Factors predictive of radiographic progression and functional impairment were age, extent of hand synovitis and DAS at baseline. The progressive UPA group (defined as a total modified Sharp score at one year of at least ten and progression of at least four) had significantly higher levels of the above factors compared with the less progressive UPA group. About 80% of the progressive UPA group were receiving treatment at their one year follow-up (usually hydroxychloroquine, a weak agent), compared to 96% of the RA group (with more efficacious DMARDs, such as methotrexate or sulfasalazine).

A recent study from the Netherlands has examined potential predictors of remission, and found that a good response to RA treatment during the first year resulted in subjects being significantly more likely to achieve remission (Verstappen 2005). Other predictors of remission included absence of RF, lower joint score and less pain. Tailoring treatment to the individual and aiming for a rapid response by introducing more effective treatments early can thus be justified.

ACR classification criteria have low sensitivity for early RA, with around half of the RA patients typically not meeting criteria at presentation (Machold 2002). If RA was considered likely in spite of failure to fulfil ACR criteria, the most common pattern was hand polyarthritis with a negative RF. In one such group of patients, RF was positive in 47% of RA patients at baseline (compared with 12% of non-RA patients) which increased in frequency with increasing duration of disease. CRP and ESR values were similar in the two groups (Machold 2002). Radiographic erosions were seen in 13% of RA patients at baseline, increasing to 28% with erosions after one year. The odds ratio for new erosions if the RF was positive in the first year of disease was 9.7.

HRUS can assist prediction of progression of inflammatory joint disease to RA by determining the location of the inflammation, either intra-synovial involving the joint cavity and tendon sheaths or extra-synovial with changes adjacent to the joint capsule (McGonagle 1999b). In poor prognosis patients, 77% had synovial soft tissue enhancement with contrast on MRI and 23% had capsular enhancement, compared with 13% and 88% respectively in good prognosis patients. Intra-synovial involvement was associated with a worse prognosis with insidious onset, whilst capsular location was linked to an acute onset disease with good prognosis. At six months, 95% of poor

prognosis patients were being treated with DMARDs compared with none in the good prognosis group.

1.3 Detection of sub-clinical synovitis using HRUS

Joint damage as shown by either US or MRI can progress in spite of suppression of clinically evident synovitis achieved with DMARD therapy (McQueen 1999, Backhaus 2002). This disjunction may be due to persistence of synovitis which is not obvious clinically. In two studies in established RA, synovial tissue of unaffected knees demonstrated synovial lining layer hyperplasia and macrophage infiltration (Soden 1989, Kraan 1998). Furthermore, an EA study of clinically unaffected knee joints revealed 55% had inflammation on synovial specimens with increased vascularity (Pando 2000). US synovitis correlated with MRI synovitis at the knee (Ostergaard 1995a) and with synovial inflammation seen at knee arthroscopy (Fiocco 1996). US thus provides an opportunity to non-invasively detect synovitis that may not be evident clinically.

Wakefield and colleagues (Wakefield 2004c) demonstrated this US imaging capability in patients with early inflammatory arthritis (including RA, reactive arthritis, psoriatic arthritis and undifferentiated arthritis) of less than 12 months' duration. Although using an US machine (ATL HDI 3000) that lacks the resolution achieved with current instruments, they were able to distinguish abnormally hypoechoic areas within joints, consistent with synovitis and effusion, from the normal appearances of the hyperechoic intra-articular fat pad, which becomes indistinct when synovitis is present. The diagnosis of clinical synovitis was reached by consensus, and synovitis was found in 13% of all joints examined. The mean number of clinically swollen joints per patient

was two, compared with the mean number of US synovitis joints per patient of five. In joints with clinical synovitis, US synovitis was found in 79%. In a proportion of the remaining clinically affected joints US evidence of peri-articular tenosynovitis was found in 6.5% and US findings were equivocal in a further 6%. Unexplained clinical swelling with normal US findings was seen in 8% of joints.

Synovitis was found by US in 33% of joints which were tender but not deemed to be swollen on clinical examination, and in 13% of joints assessed as normal on clinical examination. US-evident sub-clinical synovitis was most often seen in MTP joints (79%) and to a lesser extent in MCP joints (16%). Overall 20% of joints, distributed among 64% of patients, who were apparently unaffected on clinical examination, had US evidence of synovitis. 58% of patients assessed clinically as having monoarthritis had US evidence of oligoarthritis (35%) or polyarthritis (23%), and a third of patients assessed clinically as having oligoarthritis could be reclassified as having polyarticular (6 or more joints) disease after US. This sub-clinical disease burden may contribute to the high prevalence of erosions at baseline in RA. This study highlights the high prevalence of sub-clinical synovitis in both painful non-swollen and asymptomatic joints, and thereby draws attention to the relative insensitivity of clinical examination for detection of synovitis. With regard to specificity, US findings have been shown to correlate better with clinically evident joint swelling and blood markers of inflammation than with joint tenderness and patient-assessed functional impairment (Naredo 2005a).

In a study of established RA patients (Naredo 2005a), semi-quantitative scoring of swollen joints 1-3 (swollen joint index) in 60 joints was compared with an US

examination performed on the same day by a rheumatologist blinded to the clinical findings. US detected more effusions and synovitis than clinical examination by a factor of 1.3. Naranjo et al (Naranjo 2002) also demonstrated that in the shoulder, clinical examination was less sensitive compared to US findings, with 44% of shoulders deemed normal on clinical examination showing US lesions. Of the shoulders with normal radiographs, 61% had abnormal US findings, confirming that radiographs are less sensitive than US for detecting soft tissue lesions.

In knee joints in RA, US was superior to clinical examination in detecting joint effusion, suprapatellar bursitis and popliteal cysts (Kane 2003). Clinical examination detected only 59% of ultrasonographically evident knee joint effusions. US of the knee has also been shown to be more reproducible than clinical examination for the presence or absence of joint effusion with excellent agreement between investigators for US findings (Hauzeur 1999). There are therefore significant limitations in monitoring inflammatory knee joint activity in RA by clinical examination. Reasons why synovial effusions may be obscured on clinical examination include soft tissue thickening due to obesity, fat pad hypertrophy, oedema associated with venous insufficiency and varicose veins. By allowing a non-invasive view of deeper tissues, US can obviate these difficulties.

A recent study in 40 patients with established RA by Rees et al. (Rees 2006) compared usual clinical signs of synovitis (joint tenderness and swelling) with US synovitis, PD sonography and post-contrast images with the vascular contrast agent Sono-Vue. A single MCP or PIP joint per subject was chosen as unambiguous for one of four possible findings (non-tender and non-swollen, tender only, swollen only or swollen

and tender). Joints with bony swelling were not included. Using stored images, two musculoskeletal sonographers scored the joints for synovitis, erosions and PD positivity on a semi-quantitative scale of 0-3 using consensus opinion. Normal was considered to be synovial thickness less than 1mm and a score of 0-1 on PD assessment.

Clinically swollen MCP and PIP joints were always confirmed by US synovitis. Summary scores of US synovial thickness were not significantly different statistically between the four groups although there was a trend towards higher median values in the groups with clinically evident swelling. The median PD score rose in all but the clinically normal joints after IV contrast was given. In tender only joints, pre-contrast PD scores were all 0-1 (normal) and no significant change was seen post-contrast, suggesting that "tender only" joints do not have increased vascularity (Rees 2006). The lack of clear discrimination between groups with regard to synovitis score is likely to be contributed to by the imprecision of the semi-quantitative scale used. However, the findings indicate that US is a sensitive modality for confirming the presence of synovitis that is evident clinically. As all subjects had RA, the US finding of synovitis in clinically normal joints does not necessarily imply lack of specificity, as all joints analysed were from subjects with RA and even overtly swollen joints may be non-tender. Thus, the findings are consistent with the hypothesis that US is a more sensitive means than clinical examination for detecting synovitis in RA. The findings also invite speculation that more quantitative parametric assessment methods may be more discriminatory.

The status of US as a means for detecting synovial thickening is also informed by the findings of Wakefield (Wakefield 2004c) who confirmed synovitis in 79% of joints

with clinically evident swelling from a group of patients with early untreated oligoarthritis. There was also US evidence of synovial thickening in 33% of joints that were tender but deemed to be without soft tissue swelling on clinical examination. In a study by Szkudlarek and co-workers on subjects with established and early RA, US detected 1.6 times more synovitis than clinical detection of swelling (Szkudlarek 2006), with 19% of clinically non-swollen joints having US evidence of synovitis or effusion. That 96% of clinically swollen joints showed confirmatory US evidence of inflammation corroborates the high sensitivity of US for confirming clinically evident synovial inflammation. Fournie et al (Fournie 2006) found US evidence of synovitis 100% and tenosynovitis in 44% of 25 fingers showing clinical evidence of soft tissue swelling in RA, again confirming the sensitivity of this method.

In the study of Rees and co-workers, there was a 30% increase in PD positivity in swollen joints with contrast (Rees 2006). Other studies have shown that not all clinically swollen joints have evidence of US synovitis (Wakefield 2004c, Naredo 2005a) and a swollen joint may be due to synovitis, but also other abnormalities such as joint effusion alone, tenosynovitis, thickening of the joint capsule or periarticular structures or bursitis (Ribbens 2003). A recent established RA study found synovitis in 30% of clinically non-swollen joints (including wrists, MCP and PIP joints) with sub-clinical synovitis in 41% of the MCP joints (Ribbens 2003). Using clinical examination as the standard of reference (although to date, there are no studies to validate clinical examination for reproducibility or sensitivity for synovitis), US sensitivity and specificity for the MCP joints were 73% and 41% respectively. If an MCP joint was clinically swollen at baseline, then US positivity for synovitis was twice as high compared with non-swollen MCP joints.

Soft tissue swelling in an RA joint is not necessarily associated with increased synovial vascularity and the presence of the latter is evidence of hyperaemia, one of the cardinal features of inflammation. The distinction between active synovitis with hyperaemia and residual soft tissue swelling from prior synovitis is potentially important. In this regard, the use of US with PD in the clinic to assess disease activity in RA joints may add important information to the clinical assessment. It has been suggested that PD evidence of synovial hyperaemia may be predictive of joint damage (Taylor 2004).

1.4 Correlation with traditional markers of inflammation

In established RA, CRP has been shown to correlate with the number of clinically swollen joints (Ribbens 2003, Naredo 2005a), but cumulative US-detected synovial thickness and the number of joints with synovitis correlated with ESR, not CRP (Ribbens 2003). Conversely, a high correlation of US joint counts and indices of effusion, synovitis and PD has been reported with CRP, with a moderate correlation with ESR (Naredo 2005a). These studies differ in methodologies used, with the study by Naredo et al. (Naredo 2005a) including 94 RA patients with assessment of 60 joints each clinically and by US in a cross-sectional approach. This study also included semi-quantitative clinical and ultrasonographic assessment of involvement by using a grading system. In contrast, Ribbens and co-workers (Ribbens 2003) presented a small longitudinal treatment response study involving only 11 active RA patients with 22 hand and wrist joints each. An US positive joint was defined as synovial thickness of at least 1mm. The more comprehensive study by Naredo was able to show moderate to high correlation of US findings with ESR and CRP. By contrast, Ribbens and co-workers, despite the positive correlation of clinically swollen joints with CRP, did not find a correlation between CRP and US synovitis. This discrepancy is difficult to

explain, as US has been shown generally to be a more sensitive measure of inflammatory joint change than clinical examination. The small number of joints assessed and the quantitative approach used may not be representative of the burden of disease clinically or ultrasonographically when compared to the serological inflammatory markers.

US did not correlate with DAS28 or functional results in the study by Naredo and co-workers (Naredo 2005a). This has been confirmed in other studies of RA (Lerch 2003, Scheel 2005) that revealed no significant correlation between US grades of inflammatory or erosive changes and DAS, ESR or CRP. However, the cross-sectional design of the studies is less meaningful than that of a longitudinal study in assessing the correlation with ESR, CRP or disease activity scores, values of which can fluctuate.

Makinen et al. (Makinen 2005) demonstrated that ESR was a poor predictor of remission in early RA, whereas the absence of joint pain increased the likelihood of fulfilling ACR criteria for remission. Furthermore, disease duration appears to influence the association between outcome and inflammatory markers. Welsing et al. (Welsing 2004) found that radiological progression was not linear in patients with RA, but varied with inflammatory disease activity. Greatest fluctuations in disease activity were associated with greater radiographic progression, with RF an independent contributing factor.

1.5 Doppler Studies in RA

1.5.1 Principles of PD

Martinoli et al. (Martinoli 1998) recently reviewed the applications of PD. Colour Doppler (CDUS) depicts local flow by encoding an estimate of the mean Doppler frequency shift at a particular position in colour, determined by the velocity and direction of flow of the red blood cells. In contrast, PD encodes the amplitude of the power spectral density or energy in the Doppler signal in colour, which is dependent on the amount of blood present. It is not reliant on direction or velocity of flow. Advantages over CDUS include greater sensitivity to low flow in smaller vessels and better vascular detailing. There is no flow signal in simple effusions, compared with the presence of signal in synovium adjacent to joint effusions associated with a component of synovial proliferation (Newman 1996).

1.5.2 PD in assessment of disease activity

Before cartilage and bone destruction is seen, formation of vascular, locally invasive, proliferative synovial tissue known as pannus occurs (Hau 1999). Angioneogenesis, or new blood vessel formation, in hypervascularised pannus is crucial for its invasive and destructive behaviour. These new blood vessels are visualised in early RA by arthroscopy of the synovium (Taylor 2005). Hau et al (Hau 1999) found that there was a significant difference between healthy and RA patients with respect to the presence of pannus and its vascularization in RA finger joints. Clinically, it is difficult to determine whether a swollen joint has active synovitis with associated hypervascularity or mere residual synovial thickening from prior inflammation. US detection of synovial thickening without use of PD does not necessarily correlate with clinical disease

activity assessments as thickened synovium is not always actively inflamed and may be persistent tissue thickening, blood clot, fibrin, complex effusion or tissue debris. Disease activity can be inferred from changes in the perfusion signal using PD, given that normal synovial membrane does not normally display a vascular signal (Gibbon 1999). PD sonography is thus able to differentiate between vascularised synovium and non-inflamed synovial swelling. The former correlates with synovitis on MRI defined by gadolinium enhancement (Szkudlarek 2001, Terslev 2003c).

Doppler technique has been used in several studies for evaluating inflammatory changes in the synovial membrane. Qvistgaard and co-workers (Qvistgaard 2001) utilised CDUS and spectral Doppler, with quantitative estimates of the degree of vascularisation of the synovial membrane (amount of tissue perfusion) calculated using stored images. The estimated vascular fraction was shown to correlate moderately with ESR and an index of tissue perfusion with both the ESR and the HAQ score. However, there was no significant correlation between the degree of vascularisation and clinical assessments such as VAS pain, patient or physician global assessment scores. Szkudlarek et al. (Szkudlarek 2001) studied 15 patients with active RA and assessed PD flow signal (present or absent) in 54 MCP joints. PD only weakly correlated with clinical assessment of MCP joint swelling/tenderness. These studies suggest that the presence or amount of synovial membrane inflammation does not correlate well with clinically detected swelling, perhaps due to non-inflamed synovial thickening present in parts of the synovial membrane. The addition of US to clinical trials should improve the disease activity assessment as discussed previously.

The ability of PD to assess overall disease activity in established RA patients was evaluated using a modified synovitis activity index and ACR remission criteria as the reference standards (Kiris 2006). Swollen and tender joints were considered active whereas if joints were swollen alone or non-swollen, then they were described as inactive. 21% of all MCP joints were PD positive affecting 54% of patients. This compares with 86% of all MCP joints being both clinically swollen and tender. There was a significant correlation between greater PD and a lower mean resistive index (a measure of diagnostic blood flow). Using the ACR remission criteria, PD was positive in 57% of active joints. Only 50% of PD positive MCP joints were 'active' clinically. The authors speculate that in established RA, joints may remain tender or swollen as a result of prolonged inflammatory processes that are inactive. Swelling and tenderness may be due to synovial hypertrophy, increased thickness of the joint capsule, tenosynovitis or bursitis, fibrotic or regressed pannus or degenerative changes rather than the inflammatory RA process and may not reflect actual disease activity. This may explain the significant number of swollen and/or tender joints that did not have flow signal. Overall, PD examination complemented the clinical synovitis assessment and could be used to monitor disease activity.

Abnormal perfusion in the synovial membrane can also be quantified using spectral Doppler US with the resistive index (RI) calculated automatically (represents the numerical value for the amount of diastolic blood flow). Preliminary data from Varsamidis et al. (Varsamidis 2005) in established RA showed that those with active disease at one year of follow-up had lower RI values than those in clinical remission or in the control group. Lower RI was a risk factor for relapse in those already in remission. Non-inflamed joints did not show any increased uptake on PD before or

after Levovist contrast was given in a preliminary study by Magarelli et al. (Magarelli 2001).

1.5.3 Correlation of PD with clinical and US findings

The relationship of PD findings to clinical examination and US results has been investigated in a number of studies. In a small RA study, 34% of MCP joints were PD positive compared with clinical swelling in 39% (Weidekamm 2003), a satisfactory correlation relative to the limitations of the methods used and the scale of the study. In untreated established RA, synovial measurements were taken at a single location with US positive joints defined as synovial thickness greater than 1mm. PD positivity was defined as detection of a vascular signal (Kaye 2001). Increased synovial thickness was found in 60% of all MCP joints with 34% of these being PD positive (the overall proportion of PD positive MCP joints was about 20%). If PD was positive, there was significantly greater synovial thickness. Further studies are required to examine whether identification of a vascular signal by PD positivity is likely to identify a more aggressive synovitis.

Quantification of PD can help in assessing response to therapeutic intervention. A decrease in PD signal in follow-up studies of treated joints is an indicator of a good response. In RA patients following anti-inflammatory treatment, synovial vascularity decreased with an associated significant decrease in tissue perfusion (Terslev 2003a, Terslev 2003b). PD is a potential method for early assessment of response to therapy, especially with biological agents such as TNF inhibitors and steroids, agents which are rapidly effective. PD could also be used to look at early RA patients to identify those who may have more aggressive disease and are at risk of accelerated or rapidly

progressive joint damage in order to target them for early aggressive intervention (such as with TNF blockers).

1.5.4 PD and erosive changes

Progressive bone damage and the resultant disability in RA are thought to be directly related to synovitis in a given joint (Conaghan 2003), with synovial thickness and vascularity able to predict erosive progression in RA patients on methotrexate (Taylor 2004). In another study, a strong correlation was shown between the US lesion PD severity grade and the Larsen radiographic erosion score (Weidekamm 2003) . Hence HRUS and in particular the Doppler analysis may be used as a complement to radiographic evaluation for assessment of joint damage.

1.5.5 PD vascularity and histologic synovitis

Results from patients undergoing knee arthroplasty for RA or OA demonstrated good correlation between prior PD grade and histopathologic findings in synovial tissue specimens taken at operation (Walther 2001). Synovial thickness of the suprapatellar recess measured by US correlated well with both the PD signal and vascularity in the tissue section. This correlation is not unexpected as tissue swelling and erythema are both intrinsic aspects of inflammation. By contrast, results with CDUS for knee joint synovitis (Schmidt 2000) failed to show a correlation between the number of intra-articular flow signals and the number of vessels on histopathology. This apparent difference in results may be explained by the differing methodologies used in the two studies. PD, which reflects the movement of blood cells within a vessel, does not allow a direct measurement of vascularity of the synovium unlike CDUS, and the number of red-yellow pixels was used as a representative measure of blood flow (Walther 2001).

The specimen of synovial tissue from the suprapatellar recess was taken by the surgeon at exactly the site where PD was initially performed in Walther's study (Walther 2001). The best correlation was found between PD and histologic findings when the PD signal and the vascularity of synovial tissue specimens were graded semi-quantitatively (1-4) ranging from normal to marked hyperaemia.

Koski and colleagues also examined the sensitivity of PD for detecting synovitis using histopathology as the gold standard, and found PD positivity in 83% of histologically defined active synovitis (Koski 2006a). Seven histologic parameters of the synovial samples were determined and each graded semi-quantitatively according to the amount of each feature. Specifically, these parameters were multiplication of the synovial lining, villous hypertrophy of the synovial surface, surface fibrin deposition, sub synovial infiltration of polymorphonuclear or mononuclear leucocytes (considered evidence of active synovitis for this study), proliferation of blood vessels and fibrosis. These criteria are important to understanding differences between PD and histological findings as PD detects certain patterns of hypervascularity which are not the sole defining features of active synovitis. Furthermore, vascular perfusion is a dynamic process that may be more labile than other aspects of inflammation such as cellular exudation. These theoretical considerations and the data cited above indicate that while PD is positive in joints with synovitis, it cannot be used to exclude the possibility of active synovitis.

1.5.6 PD compared to MRI vascularity

In order to further validate PD, comparisons with another imaging modality such as MRI have been performed. In a study by Magarelli and co-workers, MRI with contrast

was consistent with PD results (Magarelli 2001). There was also a very close relationship between the presence of a PD signal and the rate of early synovial enhancement on dynamic gadolinium-enhanced MRI of active MCP joints in RA in another study, providing further validation for PD synovial vascular signal as an indication of the inflammatory process in RA (Szkudlarek 2001). US contrast agent can be used in the setting of PD. There are certainly differences in the properties of MRI and US contrast agents, with MRI gadolinium rapidly diffusing from the capillaries in the inflammatory tissue into the interstitial space, whereas US contrast agent remains in vessels (Wamser 2003). The extra cost and invasiveness of the US contrast agent needs to be considered when deciding on its use as part of the US examination. As a cost-effective alternative to dynamic MRI with intravenous contrast agent, PD represents a readily available and easy to handle option.

1.5.7 Limitations of PD

Potential disadvantages of PD include sensitivity to tissue movement or flash artefact, enhancing the Doppler effect (Taylor 2005). The lower pulse repetition frequency (PRF) settings used in some studies could predispose to flash artefact, however use of pulsed spectral Doppler to confirm the presence of blood vessels is useful in uncertain images. This problem can therefore be corrected by decreasing the gain, increasing the PRF or adjusting persistence. Temperature fluctuations may also affect the signal, and it is important to keep constant temperatures in the room and delay scanning by at least ten minutes if coming in from outdoors. Other issues to consider include the effects of blood pressure, heart rate and medications (Walther 2001). Excessive transducer pressure may occlude vessels and reduce the PD signal (Taylor 2005). Although PD may be positive in 11-18% of normal joints, grey scale changes of synovitis and other

pathological changes are not usually present (Terslev 2004). Newer US machines have higher Doppler sensitivity, and it will be important to distinguish normal from pathological synovial flow.

Finally, there are potential problems with the reproducibility of PD, with results affected by operator experience and training, the quality of the US machine and processing (Wakefield 2003). Significant inter- and intra-observer variability has been reported for PD and reliability of the US findings using PD depends upon the quality of the US machine, the settings chosen, scanning technique and the scoring methods used (Grassi 2003b). A recent study by Koski and co-workers used dynamic image assessment with video clips to assess reliability in interpretation of US (Koski 2006b). The intra- and inter-reader agreements on detecting and scoring (semi-quantitative grading) a Doppler signal were moderate to good. Further studies are required to standardise PD assessment of joints.

1.5.8 Use of US contrast agents with PD

US contrast agents increase the sensitivity of Doppler examination by using microbubbles to enhance the scattering reflection from blood (Terslev 2005). Pre-contrast, 18% of MCP joints had colour activity in 11 healthy subjects with over 50% Doppler activity after one of two contrast agents. Vessels supplying non-inflamed joints have low perfusion compared with high perfusion in inflamed joints. The post-contrast Doppler signals seen in this study but not in previous ones may be a result of higher quality equipment with high end Doppler sensitivity, displaying vessels even in normal resting joints. High end Doppler will detect both high and low perfusion vessels, and since contrast enhances signals from all vessels, including those with low perfusion,

there is an increase in the number of normal vessels detected. To avoid false positives, cut-off levels for the threshold between normal and pathological activity, individualised for equipment quality, settings used and whether contrast is used, need to be determined.

The use of contrast renders US invasive, with potential for side effects as well as increased costs. Limitations of US contrast include a vascular blooming artefact (dramatic early enhancement after injection of contrast), low PRF being sensitive to patient movement, increasing background noise and a time limit for microbubble stability of 15 minutes (Magarelli 2001). In EA, the small increases in synovial thickness are harder to identify and perfusion may only be slightly increased in these joints compared with normal. The use of either contrast or a high end Doppler US machine may be advantageous.

1.6 Detection of erosions

1.6.1 Comparison of different imaging modalities

Previous studies have compared different imaging modalities and their sensitivities in detecting erosions in early and established RA. In a small study of MCP and PIP joints in established RA (Scheel 2006), MRI showed three times as many baseline erosions compared with US (27% versus 9%), which was superior to plain radiographs by a factor of 2.3. At the 7 year follow-up, US detected more erosive change than MRI (49% compared with 32%), perhaps related to the greater resolution of the US machine at follow-up compared with the MRI unit. In another study, US was twice as sensitive as radiographs for erosions and MRI 1.6 times more sensitive when compared with US

(Dohn 2006). US is less sensitive for detecting minute erosions than MRI and less reliable for detecting deeper erosions with only a narrow connection to the joint surface (Backhaus 2002). Additionally, joints with the poorest access on US, such as the third and fourth MCP joints, do not perform well for erosion detection in comparison to MRI (Szkudlarek 2006).

1.6.2 Location of erosions

Radiographically evident erosive changes in small joints have been shown to correlate well with damage in other RA joints and to be subject to progressive damage (Scott 1986). Therefore, one can use radiographic changes in small joints as an indicator of overall propensity to damage. Metatarsophalangeal (MTP) joints may show more damage and earlier erosions than finger joints (van der Heijde 1995). Plant et al. (Plant 1998) followed early pre-erosive RA patients over eight years using serial radiographs scored by Sharp's method, and confirmed that the feet showed the most radiographic progression in the early stages.

In the hands, erosions are most often found at the MCP joints, mainly involving the metacarpal head (Backhaus 2002). The radial aspect of the second MCP joint is the most common location for radiographically occult bone erosions (Filippucci 2006). US has the highest sensitivity for bone erosions at the easily accessible joints such as the second and fifth MCP and PIP joints (Wakefield 2000, Szkudlarek 2006). This was confirmed in a recent study demonstrating improved sensitivity of US in erosion detection when considering the easily accessible MCP and PIP joints only (Dohn 2006). US detected more bone erosions at the PIP joints than MRI in RA, with most at the second and third PIP joints (Szkudlarek 2006). In contrast, Backhaus and co-

workers showed no superiority of US for PIP joint erosions (Backhaus 1999). An explanation for this apparent inconsistency is that the Backhaus study used a lower frequency transducer for their US machine as well as a standoff pad (lower overall resolution) and compared their images to 1mm thick MRI slices (Backhaus 1999). In comparison, Szkudlarek et al. used 3mm thick slices on MRI, providing a lower spatial resolution suboptimal for the smaller PIP joints (Szkudlarek 2006).

1.6.3 Specificity of erosive changes

In order to determine the specificity of US erosions, healthy subjects have been examined. In a study of 102 healthy subjects by Schmidt et al. (Schmidt 2004), no US erosions were detected in MCP or PIP joints, therefore erosions in early arthritis patients are thought to be real. Conversely, about 4% of all MCP joints of healthy controls had erosions detected on MRI compared with none on US and one on radiography. Therefore there is concern regarding the specificity of the erosions found on MRI and radiography as they were seen in healthy subjects. Despite this, using MRI as a reference method for erosions, the sensitivity of US was 59% and specificity 98%, compared to plain radiographs with 42% sensitivity and 99% specificity (Szkudlarek 2006). All patients with erosive changes on MRI were also positive for erosions on US. In a small study by Taouli et al. (Taouli 2004) in stable established RA, cross-sectional grading of joint space narrowing, erosions and synovitis on MRI was compared with plain radiograph findings based on the Sharp-Genant score. There was good to excellent inter-observer agreement between two trained assessors with regard to MRI scores, and no significant difference between low and high field strength MRI devices in scoring or with radiographs.

The definition of US erosions can affect the results of studies. When an US erosion was defined as the presence of irregularities of the bone surface next to the joint seen in 2 planes, all 4 healthy controls in one study had erosion-like changes on US and not MRI, CT scan or radiographs (Dohn 2006). This is in contrast to other US studies in RA which in addition to the bony irregularities have required discontinuity of the cortical bone in 2 planes as part of the definition for erosions (Wakefield 2005). In a French study of healthy subjects and cadaveric specimens of the MCP joints, US revealed 37% had small well defined bone defects at the dorsal metacarpal head (Boutry 2004) with no cortical break, seen particularly at the second and fifth metacarpal bones. At anatomical inspection, this depression was filled with the dorsal synovial recess, and may be a potential site for erosive changes as synovium filled the depression. Care should be taken to avoid misinterpretation of this dorsal metacarpal head bone defect or the anatomical neck of the metacarpal bone as erosive change (Filippucci 2006).

1.6.4 Utility of reference standards for erosions

Recent comparison with computerised tomography (CT) scanning has provided important validation of US and MRI erosions in RA patients (Dohn 2006). Use of CT imaging in rheumatology is limited given the need for ionising radiation and also inferior visualisation of soft tissue changes such as synovitis (Roemer 2005), but CT is useful for bony pathology in any imaging plane with excellent resolution to 0.5mm. CT with multi-planar reconstruction allows three-dimensional (3D) visualisation of joints compared with 2D for radiographs. High resolution visualisation of calcified tissues and hence any destructive change such as erosions makes CT the standard reference for detecting bone erosions in RA. With CT as the reference standard (Dohn 2006), plain radiographs were 19% sensitive, 100% specific and 81% accurate. US sensitivity was

42%, specificity 91% and accuracy 80%, with MRI sensitivity 68%, specificity 96% and accuracy 89%. For plain radiographic occult erosions evident on CT, results for US and MRI were US erosions sensitivity 30%, specificity 92% and accuracy 80% and MRI erosions sensitivity 65%, specificity 96% and 90% accuracy. High specificity suggests that these erosions are true erosive changes on US and MRI. Therefore, bone erosions detected by MRI and US represent loss of calcified tissue with cortical destruction and can be considered true erosions.

1.6.5 Outcome of erosions and predictors of radiographic damage

Several studies have examined the outcome of MRI erosions not initially visible on plain radiographs. A lag time has been shown between the appearance of erosions on MRI and emergence on plain radiographs about 6-12 months later in the hand and wrist (Taouli 2004). In the established RA study by Scheel and co-workers, 41% of initial MRI erosions were evident on radiographs seven years later (Scheel 2006). In early RA, Ostergaard et al. found that when erosions were visualised on MRI at baseline, there was at least a four fold increase in the risk of radiographic erosion progression in those bones at five years of follow-up (Ostergaard 2003).

If one considers radiographically occult erosions on MRI or US that do not progress over two to three years to radiographic lesions, there are two possible explanations for this observation. Firstly, the erosions may have healed with DMARDs in the interim and not have a chance to appear later on plain radiographs. Alternatively, the erosions may be non-specific and not representative of true early erosive changes (van der Heijde 2003). Ostergaard and co-workers (Ostergaard 2003) speculated that there were two possible explanations for the baseline MRI erosions in early RA that were not

detectable after five years follow-up on plain radiographs. Firstly, different tissue characteristics were represented by MRI signal in erosions compared with bone calcium loss on radiographs. Also, not all MRI erosions will increase in size (if treatment is given, or erosions not large enough in size to be detectable on radiographs).

Radiographic damage is a valid outcome marker as it has previously been shown to be related to functional capacity (Scott 2000, van der Heijde 2003). However, for patients in remission (Molenaar 2002), functional disability most closely correlates with pain, rather than radiographic damage. Presence of radiographic erosions is a predictor of radiographic progression and can justify DMARD therapy. Bone oedema is a precursor of MRI erosions, which in turn are able to predict radiographic erosions (Wakefield 2004b). Previous studies have shown that the relative proportions of active hyper-vascularised synovium and inactive non-vascularised synovial thickening on gadolinium-enhanced MRI reflect the degree of histologic angiogenesis and potential for progressive erosions (Dawes 1999).

Conaghan et al. (Conaghan 2003) found a close correlation between the degree of synovitis on MRI scoring and the number of new erosions in the MCP joints at one year, with no erosions developing in those joints without synovitis. Boers et al. (Boers 2001) demonstrated that suppression of clinical synovitis (that is, swollen and tender joints) was closely related to reduction of erosion progression in the hand joints on plain radiographs using the Sharp/Van der Heijde scoring system in early RA. With modern therapeutic strategies (eg. early combination DMARDs), many lesions may not increase in size or may heal. Therefore, baseline US and MRI erosions may never progress to visible radiographic erosions at follow-up.

1.7 Assessment of remission

There is a well known mismatch between clinical improvement in disease activity and continuing radiographic deterioration and damage (Boers 1997, Backhaus 2002). Backhaus et al. (Backhaus 2002) showed that clinical improvement correlated with regression of inflammatory soft tissue lesions such as synovitis and tenosynovitis on US and MRI, but not with bone erosions which increased at the 2 year follow-up. Boers et al (Boers 1997) were able to demonstrate that radiographic progression only moderately correlated with the extent of clinical swelling during their follow-up period. Mulherin et al found that despite significant improvement in all clinical and laboratory measures of disease activity, there was progression in articular destruction and radiological score (Mulherin 1996). In established RA after 7 years, there was significant reduction in synovitis on MRI and US and clinical improvement in tender and swollen joints, despite an increase in erosions (Scheel 2006).

A potential explanation for ongoing radiographic damage despite clinical improvement may be provided by recent US studies. Use of HRUS in the assessment of clinical remission in RA has revealed evidence of persistent sub-clinical synovitis (Karim 2001). These results have raised questions regarding the current management of clinical remission and modification of drug therapy to achieve a 'true' remission. US can be helpful in identifying those with smouldering but aggressive arthritis in finger joints, which may progress to increasing deformity, even if in apparent clinical remission. This would allow earlier intensification of DMARD therapy if appropriate. There are therefore three potential dimensions to remission; clinical (such as ACR or DAS28 criteria) with or without medical therapy, imaging-defined (US or MRI) and immunologic remission (normalisation of RF and anti-CCP antibodies). Large long

term double-blinded trials are required to determine if using US to monitor treatment response is feasible in the clinical setting.

1.8 Potential pitfalls of US diagnosis

Given its operator-dependency, care must be taken to avoid misinterpretation of US features due to technical reasons (Chhem 1994). Examples include anisotropy (refer to definitions, page 27) of tendons and bone surfaces that are specular (mirror-like) reflectors and can have the appearance of tendonitis or a tear if the US beam is not perpendicular to the reflector. Wakefield et al. reported that most of the radiographic erosions missed on US were in the region of the 4th MCP joint, which was anatomically more difficult to assess with the transducer (Wakefield 2000). Technical difficulties also existed when attempting to detect abnormalities in advanced RA with subluxation or severe finger deformities.

US is the most operator-dependent imaging modality and therefore adequate training is required (Roemer 2005). In Germany, 200 US examinations are required under the supervision of an expert tutor, with radiology programs having four one month blocks of hands-on practice, cases, lectures on physics and US technology and anatomy. Recently, Brown et al. (Brown 2005) developed, by consensus, definitions of basic requirements for training (knowledge, skills and selection of joints) and indications for applications of musculoskeletal HRUS in rheumatology. Appropriate indications for rheumatologists to perform HRUS included monitoring disease activity and progression, inflammatory arthritis (synovitis/tenosynovitis) bursitis, effusion and US-guided aspirations and injections. A basic knowledge of anatomy, pathology and US physics was recommended.

1.9 Comparison of US to MRI in RA

The main advantages of MRI over US are the relative lack of operator dependency, availability of standardised imaging protocols and the ability to thoroughly evaluate anatomical regions, including the bone marrow and deep soft tissues (Jacobson 1999). If no contrast is used with MRI (contrast prolongs the assessment time), it is difficult to differentiate between synovial fluid and thickened synovium reliably, as well as between these pathological features and cartilage on MRI. Limitations of MRI include its inability to directly visualise the bone cortex, instead utilising changes in sub cortical signals (bone marrow oedema or bony cysts) to detect lesions representing erosions (Wakefield 2000). When contrast is used for synovial enhancement, this is time-dependent and if there is no precise standardisation of the MRI protocol, its sensitivity for detecting synovial proliferation will be reduced by contrast shifting out into the synovial fluid (Fiocco 1996, Klauser 2002).

The specificity of MRI bone marrow oedema is uncertain, and may actually reflect both pre-erosive and non-erosive oedematous changes in subchondral bone (Alasaarela 1998b, Conaghan 2001). Klarlund et al. (Klarlund 2000a) found that most of their MRI erosions were not ever detected by radiography, so MRI may be highly sensitive, but not specific in the detection of erosions. McQueen et al (McQueen 2001) found that only 25% of MRI wrist erosions were seen on radiography one year later, perhaps due to healing, technical limitations of radiographs or false positive MRI lesions. However, overall MRI erosions have been found to have prognostic value in predicting radiographic outcome in early and late RA (Wakefield 2004b).

Advantages of HRUS include the ability to scan multiple joints in real time, no requirement for prolonged immobilisation and the ability for patients to see and

understand their particular joint problem. It is difficult with high resolution MRI to fully examine both hands simultaneously (Backhaus 1999), given the limited field of view with the coils used, and only one hand can be evaluated at a time if contrast is used (van der Heijde 2000). It is relatively expensive and too time-consuming for routine application (Manger 1995, Klarlund 2000a).

MRI has been validated with histopathology via mini-arthroscopy studies of knees and less often finger joints (Ostergaard 1997, Gaffney 1998, Ostendorf 2001). Synovial enhancement on MRI correlates with synovitis histologically, providing pathologic validation of MRI synovitis (Gaffney 1995). However given that it is expensive and requires a high level of training of the operators, it is more of a proof of concept than a feasible imaging method in routine clinical practice. MRI could be considered as a surrogate gold standard, especially when it is difficult to obtain histologic specimens, such as from finger joints.

1.9.1 Detection of synovitis and effusion

In early RA, 36% more synovitis was seen with US than MRI, with 76% agreement between MRI and US (Szkudlarek 2006). The ability of US to visualise more synovitis than the reference method of MRI may be explained by US synovitis positive joints including both active and inactive synovial thickening, compared with MRI only demonstrating active synovitis with gadolinium uptake. However, this is less likely to explain these differences in early RA, where excessive inactive synovial tissue is not usually present. The use of PD sonography can differentiate between active and inactive synovitis and can result in closer correlation between US and MRI synovitis. More baseline synovitis and/or effusion on US was reported compared with MRI in a

small study with established RA patients by Scheel et al. (Scheel 2006), possibly due to better detection of very small effusions in the PIP joints especially on US (83% compared with 63%). In a small study in established RA affecting shoulders, Wamser et al (Wamser 2003) found more effusion on US (96%) than MRI (71%) but more synovitis on MRI than US with an echo-enhancing contrast agent (92% compared with 50%).

When comparing US to MRI as a reference standard for finger joint synovitis, there was a sensitivity of 70% and specificity of 78% (Szkudlarek 2006). In the same study, grading of synovitis between US and MRI revealed moderate to good correlations for the second to fifth MCP and PIP joints (Szkudlarek 2006). There is a lack of studies investigating agreement between US and MRI measurements of synovial thickening. In assessment of synovitis, one of the potential difficulties with US is less efficient blinding of the sonographer compared with the MRI evaluator, with the former being able to visualise normal compared with swollen joints.

1.9.2 Assessment for tenosynovitis

US should be regarded as the gold standard (apart from surgical findings) for imaging tendons in rheumatology, as it is more sensitive than MRI for detecting tenosynovitis (Backhaus 1999) and complete tendon ruptures (Swen 2000).

1.10 Validation of US

The gold standard for validation of US findings is considered to be histopathologic specimens. Studies of tissue specimens from patients with chronic RA undergoing arthroplasty have shown tumour-like pannus tissue within erosions (Bromley 1984). In

early erosive RA, aspiration of bone erosions in finger joints was performed in those joints with clinically active synovitis as evidenced by clinical examination findings of swelling and tenderness (McGonagle 1999a). No features of pannus were seen in the tissues obtained and mostly necrotic bone or cellular debris was found, but this apparent inconsistency may be related to the small size of samples examined. Using strict criteria for quantification of effusion and synovial thickness by US in knee joint synovitis, Fiocco and co-workers were able to validate their US findings by correlation with clinical markers of inflammation and arthroscopic appearances at the time of synovectomy as the gold standard (Fiocco 1996).

In 1993, Grassi et al. (Grassi 1993) were the first to evaluate MCP joints in RA with high frequency transducers and described the joint cavity as the echoic inverted triangular structure located between the MC head and the base of the proximal phalanx. Wakefield et al. described this homogenous inverted triangular area in healthy subjects as an intra-articular fat pad filling the joint space (Wakefield 2005). More recently, this dorsal triangular structure, appearing homogenous and slightly echoic on US, appeared macroscopically at anatomical inspection as thick yellow tissue, and microscopically on histologic examination as consisting of vascularised connective tissue with a single synovial cell layer lining the articular surface (Boutry 2004).

1.11 Assessment of reliability

1.11.1 Reliability of US

Many studies do not evaluate reproducibility or reliability (Spiegel 1987, Grassi 1995, Alasaarela 1998b, Hau 1999, Swen 2000, Kane 2001, Naredo 2002, Rees 2006) or

assess this incompletely, considering either inter- or intra-observer reliability alone (Newman 1996, Backhaus 1999). Intra- and inter-observer reliability of US examination in Naredo's study were evaluated by using recorded images in a subset of patients on each machine (Naredo 2005a). Therefore images were not re-acquired but interpreted with regard to repeating the measurements to determine whether synovitis or effusion were present. Schmidt et al. (Schmidt 2004) repeated measurements using another physician sonographer but on recorded hard disc images with excellent inter-observer agreement. There was again no reproducibility data for acquisition of US images. Scheel et al. (Scheel 2005) also used stored US images to calculate synovitis measurements and to perform semi-quantitative grading. There was high concordance with inter-reader agreement kappa values of 0.88 for the MCP joints and 0.93 for the PIP joints. In Ribbens' study, intra- and inter-observer coefficients of variation (cv) were determined by scanning another 10 measurements of one of each joint in 10 participants with RA (Ribbens 2003). The intra-observer cv for MCP joints was 2.3% and inter-observer cv was 10.7%. In a small study of wrist RA and response to cryotherapy (Strunk 2006a), 2-dimensional (2-D) and 3-D PD sonography was performed under supervision of another investigator and representative images reviewed later by two blinded readers. Exact agreement proportion of 0.67 for the two observers was found with 0.65 for the readers.

Varsamidis et al. (Varsamidis 2005) in established RA patients found a mean cv of 4.5% for intra-observer measurement of RI based on 5 measurements in 20 examinations of the wrist joint. In Boutry's study in healthy controls, two independent musculoskeletal radiologists performed scanning on the same day with high inter-observer precision in identifying intra-articular and peri-articular structures (Boutry

2004). The cv's obtained were less than 5% for dorsal synovial recess measurements (considered very good inter-observer reliability). Standardisation of the position of the joint and subject, the insonation angle and pressure of the transducer on the skin are critical in the reliability of US findings (Grassi 2000).

One major disadvantage of US is operator dependency, particularly given previous studies have mainly assessed stored images qualitatively and reached consensus agreement as to the presence or not of pathological abnormalities (Grassi 1995, Newman 1996, Alasaarela 1997, Alasaarela 1998b, Klauser 2002). The use of consensus agreement does not address inter-observer reliability. Both intra- and inter-observer errors become more important when performing quantitative measurements. The magnitude of measurement errors of a specified distance in hip joints using US has been assessed (Balint 2001). It was possible to train a novice in a relatively short period of time to produce acceptable images of the hip with good inter-observer reproducibility. With well-defined anatomical landmarks and pre-determined criteria inter-observer variation was acceptable. In studies involving deeper structures, imaging was less reliable in obese subjects and therefore associated with an increased possibility of inter-observer variability (Balint 2001).

1.11.2 Reliability of PD

PD has been shown to have a large subjective component and does not always indicate increased vascularity of the tissue being examined, as artefacts may occur depending on machine settings (Grassi 2000), the observer and aspects of image processing (Cardinal 1996). Artefactual signals can be produced by strong stationary echoes, such as those from tendon fibrils and cortical bone. PD is sensitive to movement of the part scanned,

the transducer which is hand-held and thus subject to operator-related variability. Other influences are patient dependent, and include depth of the field of interest, blood pressure, heart rate and medication taken (Walther 2001). Therefore, caution should be exercised when interpreting PD results, given that many factors can contribute to difficulties with reproducibility.

Koski et al. (Koski 2006b) looked at inter- and intra-reader reliability of PD via video clips. Two rounds of video clips and physician assessments for inter and intra-observer reliability were performed (in differing order of the same subjects) after 3-4 months. Questions raised included the presence or not of Doppler signal and semi-quantitative grading of the PD signal (0-3). About 70% of readers could correctly classify whether the image came from the healthy or patient group in at least 70% of the videos. Intra-reader agreement was good to excellent and inter-reader agreement was moderate to good. Presence or absence of signal was more reliable than quantifying the amount of PD positivity which had moderate to good agreement only. Although lacking the image acquisition component of operator dependency, advantages of this video reading method were the large sample size, the readers were fully blinded to the person scanned and second rounds of reading could be easily organised and distributed to different countries and many readers. More definitions and training are required to improve PD US reproducibility.

1.11.3 Reliability of clinical examination

Inter-observer variability for clinical examination in Naredo's study was better for clinical tenderness (moderate to good agreement) than clinical swelling (poor to moderate) (Naredo 2005a). In an attempt to reduce variability, a group of Canadian

rheumatologists assessed joint tenderness in 68 joints in RA patients before and after 3 hours of discussion and patient examination. Percent variance between observers was 13.8% pre and 3.2% post standardisation, and 0% at 6 months. Agreement between assessors on the precise method of examining joints can reduce inter-observer differences and hence sample size required for clinical trials to detect clinically important differences (Klinkhoff 1988). Standardisation of detection of swelling and grading of severity of tenderness and swelling should also be considered, as even more variability is expected with an increase in the number of categories of assessment.

1.11.4 Reliability of MRI

When considering MRI erosions, especially of MCP joints, Goldbach-Mansky et al. (Goldbach-Mansky 2003) reported moderate agreement across multiple centres between readers and good agreements for single intra-reader and two inter-reader studies. Others have found good to excellent inter-observer agreement for MRI scoring of joint narrowing, erosions and synovitis (Taouli 2004).

1.12 Scoring systems in RA

1.12.1 Conventional radiographs and scoring systems

Conventional radiographs are a permanent record of the history of the disease and useful for ongoing evaluation of any damage (van der Heijde 1999). They are inexpensive and easily accessible, and can be randomised and blinded for objective scoring to test reliability between observers. Erosions and joint space narrowing are the radiographic abnormalities regarded as the most reliable and specific for RA. The most commonly used scoring systems in clinical trials are the Sharp and Larsen systems

(Sharp 1971, Larsen 1977) or their modifications (Sharp 1985, Larsen 1995). Problems with the currently available versions include inter- and intra-observer variability and lack of accepted radiographic protocols (Giovagnoni 1998). Also, these radiographic lesions represent irreversible osteochondral damage, which occurs later in the course of RA than the articular and peri-articular soft tissue changes visible by US and MRI. In contrast, these latter changes are potentially reversible, and more likely to respond to treatment. Although radiographs have their advantages, there are limitations especially in early RA.

1.12.2 US assessment systems

US assessment methods all involve an element of subjectivity. Examples of the different types of assessment include qualitative (eg. yes or no), semi-quantitative or scoring with categories (grading system), measurements (such as of synovial thickness) and use of an index (especially with regard to Doppler studies). Ostergaard et al. (Ostergaard 2005) reviewed published US systems for RA assessment with semi-quantitative or quantitative scoring. Most were small studies with Weidekamm's study having the most subjects, totaling 47 (Weidekamm 2003). Less than half (44%) had published reproducibility data.

Szkudlarek et al. expanded their four-grade semi-quantitative scoring system to evaluate joint effusion, synovial thickening, bone erosions and PD signal (Szkudlarek 2003), by introducing grade four as a hypoechoic area of synovial thickening bulging out of the joint and extending either side of the joint (Szkudlarek 2004). The authors assumed a single pathology with extension of synovitis from the intra-capsular region. As an example of the grading system used, synovitis was defined as a non-compressible

hypoechoic intra-capsular area with grades 0-1 considered normal or probably normal (0 = no synovial thickening, 1 = minimal synovial thickening filling the angle between the peri-articular bones, without bulging over the line linking the tops of the bones) and grades 2-4 pathological changes (2 = synovial thickening bulging over the line linking the tops of the periarticular bones without extension along the bone shaft, 3 = synovial thickening bulging over the line linking the tops of the periarticular bones and with extension to one of the bone shafts only).

Lerch et al. (Lerch 2003) developed a grading system for six stages of progressive development of synovitis and erosions (normal to capsular distension to synovitis, then increasing size of erosions). This system was shown to be highly reproducible in the elbow joint, with intra- and inter-observer reliability of 91% and 89% respectively. Weidakamm et al. (Weidekamm 2003) developed a semi-quantitative scoring system involving quantification of the severity of joint involvement on a four point scale, from no abnormalities to strong changes. Their clinical findings of swollen and tender joints and laboratory inflammatory markers significantly correlated with US scores.

At present, there is no widely accepted international grading or scoring system for US features such as synovitis and erosions. In previous studies, clinical inflammation was seen most frequently at the 2nd and 3rd MCP and PIP joints of the hands, with a slight predominance in the right (dominant) hand (Grassi 1993). Signs of early radiographically evident damage on conventional radiography were more equally distributed among the joints (Klarlund 2000a, Boers 2001). In contrast, another study in early RA found that the first radiographic erosions were asymmetrical (van der Heijde 1999), so only scoring the dominant hand, as studies have previously done

(Klarlund 2000a, Klarlund 2000b, Wakefield 2000), may lead to significant loss of information. US scoring systems at minimum should include bilateral hand assessment in RA. When new scoring systems are developed, the benefits of fully describing the methods, with clear, explicit definitions and illustrations of pathologies and grades, cannot be overestimated. Also, new systems need to be validated before being widely accepted.

1.13 Quantitative assessment with HRUS measurements

1.13.1 Requirements for US measurements

Ideally, US measurements should serve several purposes: classification, prognostication and following change over time (Molenaar 1999). The measurement should have pathological specificity and be able to discriminate between different clinical situations reliably. The method must be feasible with regard to the ease of application, time and costs. To be clinically useful, the measurements must be reproducible (van der Heijde 2003). The more joints that are assessed, the more reliable the scoring system, with increased sensitivity with regard to progression of abnormalities (van der Heijde 1999). However, it becomes time-consuming and impractical when too many joints are scored. The majority of RA patients have early involvement of their hands, wrists and feet (van der Heijde 1999, Ostergaard 2005) and these are the joints most often included in assessment systems. Previous studies have measured a variety of features, including pannus (Hau 1999), joint cavity width (Grassi 1993) and tendon sheath thickness (Grassi 1995) measured on longitudinal scans. Longitudinal views on US scans were the most informative in RA (Grassi 1993), particularly for measurements.

Components of measurement theory were elucidated in an article by Eberl et al (Eberl 1976) and included the following features:

(1) Economy: ease of performance

(2) Validity: the measurement really measures the parameter it is supposed to measure

(3) Objectivity: the degree of inter-observer agreement on the measurement

(4) Reliability: degree of agreement between different but comparable measures (repeatability, or test-retest)

(5) Sensitivity: responsiveness of the test to alterations in the observed object

If the test is already very reliable, then there is no need to perform repeated measurements with more than one observer all the time, as this is not practical in everyday clinical practice or efficient in research.

1.13.2 Maximising precision of measurements

When considering conventional radiographs, more precise measurements are obtainable if radiographs are read by more than one reader (van der Heijde 1999). Scores can be combined by calculating the average of the readings or by a consensus opinion, with either method able to reduce measurement error. For US, a second sonographer or observer blinded to the others findings is advisable in order to avoid false positive US abnormalities influenced by clinical examination findings (Backhaus 2001). To date, US measurements have not been well described in the literature nor standardised for comparisons between different centres.

1.13.3 Factors affecting US measurements

Various factors may affect US measurements, such as the amount of gel used, the angle of the transducer and potentially decreased reliability in obese subjects for imaging deeper structures such as the hip joint. Gender was one of the factors influencing measurements in Schmidt's study, with no significant effect of hand dominance nor body mass index (BMI) (Schmidt 2004). To avoid displacing joint effusions, minimal pressure with the transducer should be applied over fluid collections in small joints. For proper examination using PD, researchers recommended assuming a position of lowest intra-articular pressure which for the finger joints is resting on the bed with a slight degree of joint flexion (Filippucci 2006). Intra- and inter-observer errors become increasingly important with quantitative measurements. Balint et al. (Balint 2001) considered this issue by performing measurements at the hip joint, and found a relatively small amount of inter-observer error of under 11%. They also reported that a novice can be trained in a short period of time (3 hour course) to produce acceptable images of the hip and with relatively small inter-observer variation. When definitions of pathology and grading are precise, there should be little variability of the scoring or measurement system (Lerch 2003).

1.13.4 Development of standard reference values in healthy adults

Very recently, Boutry and colleagues published results from standardised scanning and measurements in healthy control and cadaveric hands performed to determine normal anatomical findings at the dominant MCP joints 2 to 5 (Boutry 2004). Dorsal and palmar longitudinal and transverse views were performed, with dorsal scans obtained at 15 degrees of palmar flexion and a small wooden pad placed to better examine the metacarpal (MC) head cartilage. Dorsal longitudinal US scans were obtained through

the extensor tendon with the US beam perpendicular to the major axis of the finger. US data were recorded from intra-articular and peri-articular structures, including the dorsal MC synovial recess and maximum synovial thickness over the dorsal MC head tubercle (which corresponded to the end of the MC head cartilage on anatomical sections). Also the maximal thickness through the dorsal triangular structure and the maximal depth of the MC head depression, a bone defect seen without an actual cortical break, were studied.

Normative reference values have been developed by Schmidt et al. (Schmidt 2004) in 102 healthy adults with the normal range of values defined as the mean $\pm$ 2 standard deviations for various joints. Diameters of tendons, bursae, cartilage, erosions, hypoechoic rims around tendons and at joints were measured using established standard US scans. The values developed will hopefully prevent misinterpreting normal fluid as anatomically abnormal. Analysis of receiver operating characteristics (ROC) curves could help to define more exact standard reference values to enable differentiation between normal and a well-defined disease such as RA.

1.13.5 Development of reference ranges in RA studies

Several studies have addressed the issue of measurements in both healthy control subjects and RA patients, with the development of reference ranges to distinguish between the two groups. In a small group of established RA patients with active erosive disease on methotrexate and enrolled in an open label study with infliximab, standardised MCP joint measurements were performed dorsally in the sagittal plane (Ribbens 2003). The thickness of the hypoechoic tissue between the hyperechoic extensor tendon and the cortical line of the MC neck was measured perpendicular to the

great axis at the point of greatest thickness without exerting any pressure. Similar measurements for the PIP joints were obtained over the dorsal surface of the proximal phalanx. Clinical synovitis was defined as any swollen joint (Ribbens 2003), and US synovitis, joint effusion or both were defined as hypoechoic or anechoic areas in appropriate locations. US positivity for synovitis was determined by scanning the joints of ten healthy age-matched controls with no arthritis and was defined as greater than 1mm (Ribbens 2003). The mean synovial thickness in healthy controls was 0.5mm with 0.2mm standard deviation (SD) so the upper limit of the normal range was 0.9mm.

In a recent study by Scheel et al. (Scheel 2005), scanning was performed from the palmar aspect in the neutral position, with measurements taken from a proximal site perpendicular to the bone surface at the diaphysis, at the point where most synovitis was visualised. A mean synovitis measurement of 0.81mm in the RA group at the MCP joints was reported compared with 0.25mm in the controls. The optimal cut-off for synovitis being present was 0.6mm for both the MCP and PIP joints using ROC curves. The measurements correlated well with a semi-quantitative grading system they developed as an extension of Szkudlarek's original assessment system.

1.13.6 Definitions of US synovitis using measurements

Joint cavity widening is the US hallmark of synovitis (Filippucci 2006) and is related to joint effusion or synovial proliferation. Grassi et al. (Grassi 1993) were the first to measure the "joint cavity width" which included the dorsal MC synovial recess as well as part of the triangular structure. They defined this joint cavity width as the distance between the ventral margin of the joint capsule and the top of the MC head. Objective criteria for synovitis were also proposed as an increase in the joint cavity width greater

than 2 SD above the mean control value. Backhaus et al. (Backhaus 1999) defined probable synovitis at the wrist as a bone-capsule distance of 3mm or greater and definite synovitis of at least 4mm. In addition, a difference between the two sides of at least 1mm was considered an indicator of probable and at least 2mm, definite synovitis of the wrist.

Positioning of the joints to be examined was described in detail in several studies. In the study by Rees et al. comparing clinical and US determined synovitis (Rees 2006), synovial thickness was measured in the dorsal transverse view of the MCP or PIP joints in 20 degrees of palmar flexion at three points, radial, mid-dorsal and ulnar and the mean was taken as an objective measure of synovitis. Mean synovial thickness of less than 1mm was considered normal. In Naredo's study, scans were obtained of the MCP and PIP joints in the dorsal longitudinal view with joints in extension, and the maximum distance from the articular bony margin to the joint capsule was defined as abnormal synovial thickening if greater than 2mm (Naredo 2005a).

1.13.7 Studies in elbow joint effusions using measurements

Detection of effusion of the elbow with US has been defined as a measurement of the anechoic space between the capitulum of the humerus and the joint capsule greater than 2mm, or if there is any anechoic space in the olecranon fossa. Agreement between clinical effusion and US examinations was fair (Luukkainen 2005). Rules to define elbow effusion seemed specific as none of the healthy control elbow joints fulfilled criteria for effusion. A previous study of cadaveric elbows (De Maeseneer 1998) compared radiographs, US and MRI after incremental injections of 1-15mL of saline

and found that MRI was the most sensitive (even 1mL of effusion detectable) followed by US (1-3mL effusion able to be identified) then plain radiographs.

1.13.8 Limitations of US measurements

Methodological statements such as "measurements of synovial thickness were performed" are not very informative, especially if one wishes to apply the same approach and to test its reproducibility. As an example, synovial thickness in the transverse plane was scored from 0-5 in a small study in early erosive RA, with the total score being the addition of individual joint scores (Taylor 2006). This methodology was not further defined or described. In RA, measurement using HRUS is still in its infancy, and needs continuing peer review to develop this form of assessment and scoring to its full potential.

1.14 MRI scoring systems

Semi-quantitative MRI scoring systems have been assessed (Klarlund 2000a), with synovial membrane hypertrophy scores having variable success in differentiating RA from non-RA patients and variable correlation with clinical signs of disease activity (Gaffney 1995, Ostergaard 1995b). Findings have not been correlated with surgical or histopathologic data. Preliminary guidelines for MRI evaluation of the hand and wrist in RA have been formulated along with specifications for imaging acquisition (Conaghan 2001). Lesions to be scored were more clearly defined; in particular erosions were diagnosed only if a cortical break was visible in at least one plane. Much more work is required in this area to standardise and validate MRI scoring methods.

1.15 HRUS in clinical practice

1.15.1 US-guided interventional studies

Variability of efficacy of intra-articular corticosteroid injections may be explained by lack of accuracy in placement. Jones et al. demonstrated only 52% accuracy in intra-articular placement of injections into various joints (Jones 1993). Reduction in joint inflammation was associated with greater accuracy of injection. Eustace et al. confirmed that accurately placed steroid injections in shoulder joints (using clinical landmarks and assessed by radiographs post-injection) performed better in terms of clinical measures and resulted in greater perceived maximum benefit (Eustace 1997), but again their overall accuracy rate was low at 37%. Correct placement of the needle tip is very important in order to ensure efficacy of the injection (Grassi 2001a) and to avoid unwanted effects, in particular direct contact with nerves, tendons, blood vessels and articular cartilage (Grassi 1998).

Musculoskeletal US permits exact needle placement for aspiration, injection and biopsies and can be used at the bedside (Cardinal 1998, Koski 2000, Sofka 2001). US guidance is useful for locating the most suitable area of synovial hypertrophy for diagnostic synovial biopsies of the wrist (van Vugt 1998). As there is no ionising radiation, it can be used safely for interventions in children and pregnant women. There have been excellent clinical response rates in US-guided injections of flexor tendon sheaths (Kane 2001) and small joints of the hands and wrists (van Vugt 1998). Used prior to joint aspiration, US can aid in detecting synovial folds or septations that may hinder successful aspiration (Manger 1995). Longitudinal randomised trials of US-guided injections with clinical outcome measures would be informative.

1.15.2 Assessment of treatment response using PD US

The aetiopathogenesis of early synovitis is thought to be hyperaemia caused by vasodilatation with angiogenesis having an important role in pannus formation and hence ongoing synovitis. Synovial perfusion can be imaged to assess and monitor disease activity by PD sonography. A very recent study utilised 3-dimensional (3-D) PD for spatial demonstration of the synovial blood vessels in inflamed RA joints (Strunk 2006b) and investigated changes in synovial vascularity in response to intra-articular steroid injection in various joints. After about one week, there was significant reduction in 2-D PD grading levels after the steroid injection, with 7 of 8 intra-articular 3-D blood vessel trees disappearing. This suggested that the effects of steroids on endothelial cells and synovial blood vessels are seen within a week, as effusion and joint swelling were still present but flow was almost completely gone in the region of interest.

Similar reduction in vascular signal was found in RA wrist joints on repeat PD US after application of local cryotherapy for 20 minutes (Strunk 2006a) and also in PD positive joints after TNF blocker treatment (Ribbens 2003) and intra-articular steroid injection into knee joints (Newman 1996). US assessment of synovitis activity, including PD of the MCP joints, improved significantly following either IV or oral steroid treatment in RA patients with hand synovitis (Stone 2001). These findings suggest that PD can be used as an outcome measure in RA, with reduction in synovial vascularity being more obvious with 3-D PD as it shows the whole blood vessel tree.

1.15.3 Correlation of US-assessed treatment with clinical response

In an open label trial of a TNF inhibitor, US after six weeks of therapy demonstrated significant improvement, according to an US threshold of more than 11% reduction in synovial thickness (based on the inter-observer coefficient of variation), in 86% of MCP joints and 60% of wrists (Ribbens 2003). Mean synovial thickness was responsive to change, with a decrease from a mean of 32mm to 16mm. Change in synovial thickness correlated with change in DAS22 from baseline and physician global assessment. Hau et al. (Hau 2002) studied patients with active erosive RA and demonstrated a rapid response in terms of disease activity reduction within eight days of treatment with etanercept, a biological TNF inhibitor. A gradual decrease in pannus vascularization in finger joints was seen with good correlation between US findings and clinical parameters. Hence a decrease in the size and vascularity of pannus on US appears to be a genuine clinical correlate of patient and physician global assessment in RA patients.

Evidence from previous studies has supported the pathological specificity of these results by demonstrating correlation between pannus vascularization and synovial biopsy findings after TNF blockade (Moreland 1997), and also in animal models after inhibition of vascularisation by drug treatment (Storgard 1999). Therefore, US can be helpful in making therapeutic decisions and allowing treatment to be modified earlier to prevent further damage. Longitudinal studies are required to determine if this method can be recommended for everyday clinical use.

1.16 Development of screening tests

1.16.1 Distribution of synovitis

Imaging studies on the distribution of synovitis in the finger joints are limited. In Szkudlarek's RA study (involving established and early RA patients), synovitis was localised to the dorsal and volar aspects in 53% of the MCP joints, to the dorsal aspect alone in 25% and volar aspect only in 18% (Szkudlarek 2006). For PIP joints, there was more volar involvement alone and combined volar and dorsal involvement (43% and 30% respectively), with dorsal alone in 19% of joints. In a small, predominantly established, RA population with an early subgroup, Scheel et al. (Scheel 2005) found that synovitis was predominantly located over the palmar proximal aspect of both MCP and PIP joints with only 14% found over the dorsum only. Distribution in the MCP and PIP joints was not distinguished. The authors recommended scanning only the volar aspect of the second to fourth MCP and PIP joints (discarding 14% not detected on dorsum alone). However, previous studies of MCP and PIP joints have reported that 25-30% of finger joint synovitis would be missed if only the volar aspect was examined, given also that MRI studies have shown a preponderance of radial synovitis at the MCP joints (Tan 2003). Also, results from an established RA population cannot be transferred to an early RA group, as the joints involved and distribution of the synovitis may differ.

1.16.2 Validation of US screening tests

Assessment of the most frequently involved joints in RA may allow easier and faster everyday use in clinical management and trials. Naredo et al (Naredo 2005a) examined 60 joints clinically and with US and then compared this to a screening exam with a 28

joint count (the same joints as those assessed by the EULAR DAS 28 tender and swollen joint scores) for clinical examination and US synovitis, effusion and PD. Scanning time was reduced by almost half (15 minutes compared with 20-30 minutes) with the abbreviated system of US assessment. A recent trial in established RA patients by the same authors validated this reduced joint US assessment approach (Naredo 2005b). Effusion and synovitis were seen in more than 30% of second and third MCP joints, with PD positivity in greater than 25%. There was a high correlation of the reduced joint count with the extended joint assessment, especially with the 12 joint count that included second and third MCP and PIP joints, wrists and knees. A similar correlation was demonstrated with clinical swelling and laboratory parameters of inflammatory activity (ESR and CRP), validating the use of reduced joint counts with the added advantage of one third of the scanning time (10 minutes duration). Longitudinal studies using Naredo's reduced joint count are awaited to demonstrate sensitivity to change.

1.16.3 Selection of joints for reduced joint count approach

Guidance regarding choice of MCP joints for a reduced joints assessment comes from previous studies in RA of varying duration, that have reported more severe lesions with semi-quantitative PD at MCP joints 2 and 3 (Weidekamm 2003). These lesions correlated with the most commonly swollen joints clinically. MCP 4 was less often affected than MCP joints 2, 3 and 5 in previous studies (Wakefield 2000, Scheel 2006). In established RA using MRI, a 'few joints' approach including dominant MCP joints 2-5 and the wrist was not significantly different from a 'many joints' approach (bilateral MCPs 2-5 and wrists and unilateral MTP joints 1-5) in terms of the numbers

of subjects with disease progression (Ejbjerg 2005). The "few joints" approach was less time-consuming and more feasible in clinical practice.

Highly selective use of joints for assessment my result in important clinical disease remaining undetected, given that synovitis has previously been shown to affect all joints approximately equally. In a small pilot study, the second and fifth MCP and fifth MTP joints were selected for their known early involvement in RA and their easy accessibility on US (Alarcon 2002). All erosions found on plain radiographs were also detected on US and MRI, with some detected on US not seen on MRI (maybe due to volume averaging with MRI and the superior axial resolution of US of less than 1mm). More studies are needed to further validate the use of reduced joint counts prior to any recommendations for adopting this approach in routine clinical practice.

1.17 Newer US techniques

1.17.1 Spatial compounding

Spatial compounding (SonoCT) has been used in US imaging to reduce artefacts by combining several overlapping scans of an object acquired by electronic beam steering from different view angles to form a compound image. This improves image quality, by reducing acoustic artefacts to reinforce real structural information (Entrekin 2001). SonoCT reduces anisotropy, and allows curved interfaces to be shown as more continuous. Limitations with SonoCT include a trade-off between improving image quality and minimizing image blurring. The resultant reduction in acoustic shadowing or enhancement may decrease the diagnostic information compared with conventional US.

1.17.2 Extended field of view imaging

With the use of higher frequency transducers, especially those with a small contact area, there is a limited field of view which makes it more difficult to appreciate the spatial relationships and size of lesions. Newer technology using an image-registration-based position-sensing technique which generates panoramic images in real-time allows extension of the field of view, (Lin 1999). This is useful for measuring and following up large lesions, displaying the full extent of abnormalities and showing their spatial relationships to adjacent structures on a single image (Adler 2000).

1.17.3 Tissue harmonic imaging

Tissue harmonic imaging (THI) may further improve the contrast between tissues as well as spatial resolution, and reduce side lobe and noise artefact (Winter 2001), by suppression of interfering signals from clutter and multi-angle scattering. A recent review of THI described the harmonic formation which occurs when the sinusoidal sound waveform is distorted to a saw-tooth appearance, which corresponds to a change in frequency components from the fundamental or first harmonic frequency to the second or other multiple frequencies (Hedrick 2005). THI uses detection of the harmonic frequencies created by nonlinear beam propagation through tissue. In interventional musculoskeletal procedures, improved localisation of the needle may be possible with THI and 3-D imaging, which are able to demonstrate better the extent of a lesion or disease and its effects on surrounding structures. It is now possible with multi-planar reformatting to visualise structures in previously non-accessible image planes (Adler 2000). This may also reduce some of the operator dependency in US, by allowing the examiner to review images from many scan angles. In combination with CDUS, information on volumes can be obtained, such as that of acute inflammatory

pannus tissue. Intra-articular US may also be able to demonstrate very early changes in cartilage, such as the surface fibrillatory changes of osteoarthritis (Adler 2000).

1.18 Attempts at standardisation of HRUS

One of the pitfalls of US is the need for an experienced operator. Lack of experience may lead to incorrect acquisition or interpretation of images (eg. mis-interpretation of normal anatomy). It is recognised that a long, steep learning curve in the acquisition of imaging skills is one of the major limitations of US (Chhem 1994, Gibbon 1996). Proper training with suitable supervision and continuing education is essential (Grassi 1998). Standardised criteria for the evaluation of musculoskeletal US findings in rheumatology are urgently needed, to allow meaningful follow-up comparisons to be made (Grassi 2000).

Recently, international guidelines for rheumatologic US examinations were proposed by Backhaus et al (Backhaus 2001). They suggested that high resolution equipment was essential for demonstrating superficial structures. Linear array transducers with a frequency of at least 7.5MHz are recommended as most musculoskeletal structures are linear or elongated in nature (Hashimoto 1999). It must be kept in mind that a perfect imaging protocol does not exist, as parameters for imaging are both site and disease specific (Erickson 1997). Flexibility in performing the US examination with sonographer-patient interaction is essential, and should not be limited to standardised protocols (Lin 2000). Imaging samples could be developed for international standardisation, to use as a training set and to assess inter-observer reproducibility at an international level.

In 2005, the first recommendations for musculoskeletal US by rheumatologists were published by Brown et al. (Brown 2005), based on expert consensus of best practice (involving 57 radiologists and rheumatologists). Using the Delphi process, areas considered included the indications, regions, knowledge and skills required. These recommendations are a positive step towards developing competent rheumatologist sonographers, and for the introduction of specific training and assessment procedures in the future.

1.19 Impact of HRUS on patient management

There are few studies assessing the impact of US on everyday patient management decisions. In an observational study by Karim et al (Karim 2001), using an older ATL HDI 3000 unit, diagnostic US and US-guided injections were performed in patients, many of whom had had a poor response to previous 'blind' steroid injections. Joints were examined for synovitis (especially of small joints), enthesitis and tenosynovitis. 53% of patients had a change in site specific diagnosis and the overall diagnosis changed in 5%. As a result, the management plan changed in 53% of patients. There may have been a component of selection bias given that the reasons for US referral included diagnostic uncertainty or failed injection. DMARDs were changed in 77% of patients due to detection of extensive sub clinical synovitis. A poor correlation between US and clinical detection of synovitis was demonstrated, suggesting that patients who had clinically stable disease activity were potentially being under treated with a risk of continued erosive damage.

Preliminary results from a small study in RA and spondyloarthritis in the ankle and foot show the impact of US on the management of chronic inflammatory disease through

modification of treatment plans and the resultant possibility of improved clinical outcomes (d'Agostino 2005). Clinicians reported at least one change in anticipated treatment plan for steroid injections in 82.5% of patients with more injections being abandoned than added. A prognostic impact of US was demonstrated by the greater improvement in physical function seen in the group with prior knowledge of US results before a local corticosteroid injection was given. Also at three months, patient assessment of the efficacy of the steroid injections was better in the prior knowledge group. Overall, there was a trend towards improved symptomatic benefit in the short-term with knowledge of US results. Further longitudinal studies are required to determine whether clinical outcome measures are improved by US intervention in diagnosis or management.

1.20 Future directions

The future of US in rheumatology has been described by Grassi and colleagues (Grassi 2003a) as being dependent on several factors, including standardisation of US assessment (measurement or scoring), a certification procedure for training new specialists and cooperative interaction with musculoskeletal radiologists (to share financial and clinical obligations). It may be preferable to monitor disease activity in order to titrate therapy to optimise reduction of synovitis rather than radiological progression, given that effective suppression of synovitis prevents bone damage. There may be a threshold of synovitis above which new bone damage becomes significantly more likely (Conaghan 2003).

Longitudinal prospective studies are urgently required to confirm the diagnostic and prognostic implications of US findings, in particular detection of smaller erosions and

sub clinical synovitis. Their validity for predicting radiographic progression and functional impairment needs further consideration. The benefits of interventional US need to be confirmed, particularly concerning outcomes of US-guided steroid injections to soft tissue and joints. Integration of SonoCT with other imaging modes has been suggested (Entrekin 2001). It could be combined with the technique of THI further improvement in image quality, or with extended field-of-view imaging to show both normal landmarks and pathological abnormalities in the same single image. Suppression of artefacts would also aid in improving the interpretation of 3-D US.

There are limited data on the clinical impact of US and its ability to improve prognostication in RA and mechanical disorders. In early polyarthritis, it remains to be resolved as to whether specific US or MRI abnormalities such as erosions and PD positivity should be included in diagnostic criteria for early RA, to help further distinguish these patients from those with self-limiting disease. Early data on intra-observer and inter-machine reliability and sensitivity to change of measurements (responsiveness) are appearing in the literature. Findings in healthy individuals need to be defined. Consensus definitions for key musculoskeletal US pathological findings were published recently and need further testing (Wakefield 2005). Further training opportunities and standardisation of imaging protocols to achieve better reliability are needed. The operator-dependent nature of US may diminish with more orderly execution of examinations and refinements in equipment. Assessment of the cost-effectiveness of musculoskeletal US are needed.

1.21 Conclusions

Musculoskeletal US is an extremely useful and versatile technique for assessing soft tissue abnormalities (Gibbon 1996, Grassi 1998), with a rapidly expanding role in diagnostic and therapeutic areas of rheumatology. US can aid in establishing disease aetiopathogenesis, earlier diagnosis, prediction of prognosis and monitoring disease activity. It can also assess response to newer therapies and help guide treatment decisions. More validation studies are required especially regarding the issue of inter-scanner variability and sensitivity to change of current scoring systems (Ostergaard 2005, Hunter 2006).

Detection of sub clinical synovitis with HRUS is likely to be clinically relevant. Joints may have synovial hypertrophy and increased vascularity that is undetectable clinically and this may be responsible for continued erosive damage despite clinical remission in RA. One of the most important clinical challenges is differentiating active from inactive synovitis in RA joints, which clinical signs have been unable to achieve. The use of US and PD in clinic to assess disease activity in RA joints may be a useful tool complementary to clinical examination and laboratory inflammatory markers. Use of US in the assessment of clinical remission in RA has revealed evidence of persistent sub-clinical synovitis (Karim 2001). US may be helpful in identifying those with smouldering but aggressive arthritis in finger joints, which may progress to increasing deformity, even if in apparent clinical remission. Disease activity can be inferred from changes in the perfusion signal using PD, given that normal synovial membrane does not normally have any vascular signal (Gibbon 1999).

In comparison to MRI, advantages of US include the ability to scan multiple joints in real time, being relatively inexpensive, having no requirement for prolonged immobilisation and the ability for patients to see and understand their particular joint problem. Given its operator-dependency, care must be taken to avoid misinterpretation of US features due to technical reasons (Chhem 1994). Adequate training is required.

At present, there is no widely accepted international grading or scoring system for US features such as synovitis and erosions. In RA, measurement using HRUS is still in its infancy, and needs continuing peer review to develop this form of assessment and scoring to its full potential. There is increasingly widespread use of US in early arthritis and other types of rheumatology clinics across Europe and the UK, with many issues yet to be resolved with regards to aspects such as validity and reproducibility. Longitudinal studies are needed to assess the prognostic implications of earlier findings (Keen 2005).

Recently, international guidelines for rheumatologic US examinations were proposed by Backhaus et al (Backhaus 2001). In 2005, the first recommendations for musculoskeletal US by rheumatologists were published by Brown et al (Brown 2005). These recommendations are a positive step towards developing competent rheumatologist sonographers, and for the introduction of specific training and assessment procedures in the future. The utility of musculoskeletal US is an exciting opportunity to make a real impact on diagnostic capabilities and therapeutic interventions in many areas of rheumatology.

This thesis was undertaken to explore applications of US with particular reference to the challenges of clinical assessment in early RA and patients with treatment-induced clinical remission.

CHAPTER 2

Reproducibility of Ultrasonographic Measurements

2.1 Background

The digital joints are among the first and most frequently affected in rheumatoid arthritis (RA) and damage to finger joints correlates with overall joint damage in RA (Drossaers-Bakker 2000). Furthermore, the metacarpophalangeal (MCP) joints are usually chosen for US assessment in early RA as their anatomy allows the most reproducible and interpretable documentation of synovitis and bone damage within the same joint (Conaghan 2003). Operator dependency with regard to the acquisition and real-time interpretation of images is considered one of the disadvantages of high resolution ultrasound (HRUS) (Canoso 2000, Wakefield 2004a, Wakefield 2004b). This is true of both qualitative assessment and quantitative measures of joint features (Balint 2001). There have been few studies on standardisation and reproducibility of MCP joint ultrasonography, especially intra- and inter-observer reproducibility (Keen 2005). These issues were addressed.

2.2 Aims

(1) To develop a standardised protocol for qualitative assessment and measurement of inflammatory changes in the MCP joints

(2) To assess the reproducibility of measurements obtained by this standardised protocol in subjects without evidence of inflammatory arthritis in order to establish normative data

(3) To document the acquisition of performance skills by a rheumatologist through assessment of variance over time and comparison of performance with that of experienced ultrasonographers

(4) In a sub study of obese subjects, to determine the extent to which increased adipose tissue may affect the measurements of synovial swelling

2.3 Hypotheses

(1) HRUS measurements of MCP joint parameters developed for the protocol have good intra- and inter-observer reproducibility

(2) A rheumatologist with limited US experience can learn and apply a standardised protocol reproducibly after a short period of time

(3) In obese subjects, the adipose tissue in the region of the intra-articular 'fat pad' can distort measurements of synovial thickness, thereby necessitating the development of separate reference ranges for obese subjects

2.4 Subjects

2.4.1 Selection

Subjects with no history or clinical evidence of inflammatory arthritis were recruited. Subjects included hospital and university staff and members of the general public who had responded to local poster advertisements. Telephone contact was made with volunteers to ascertain suitability for participation. Adults classified as obese, based on a body mass index (BMI) of 30 or more, were recruited from among volunteers for a Commonwealth Scientific and Industrial Research Organisation (CSIRO) Human

Nutrition trial. These subjects were invited to participate via correspondence from Dr Peter Clifton, the coordinator of the CSIRO trial.

2.4.2 Informed consent

All subjects gave written informed consent prior to clinical assessment and investigations. Additionally, a consent form was signed regarding the safety of US. This research was approved by the Research Ethics Committee at the Royal Adelaide Hospital. The study was conducted in accordance with the Declaration of Helsinki.

2.4.3 Inclusion Criteria

Volunteers without inflammatory arthritis and able to give informed consent were enrolled.

2.4.4 Exclusion Criteria

Volunteers with a history of inflammatory arthritis (including RA, psoriatic arthritis, reactive arthritis, systemic lupus erythematosus or crystal arthropathy) or clinical findings of swollen MCP joints were excluded. Also, subjects with any bony or other deformities from previous trauma or other aetiology that may have interfered with US access to the MCP joints were not enrolled.

2.5 Methodology

Blinded Reproducibility study

HRUS was performed using the Sonoline Antares Elegra US machine (Siemens, Issaquah, Washington) with a multi-frequency linear array transducer (13-5 MHz range) and a scanning frequency of 11.4MHz. Images were optimised by presetting the

dynamic range and persistence for all subjects. Individual US images were continually optimised by adjustment of focal zone, depth and TGC gain (refer definitions, page 27). Efforts were made to avoid anisotropy (refer definitions, page 27), especially of the extensor tendon. All of the MCP joints of both hands were assessed for

- synovial swelling, defined as an abnormally large or hypoechoic joint space that is non-compressible). 'Joint space' in this context refers to the triangular region with its apex at the projected intersection of the articulating surfaces of the head of the metacarpal and the base of the proximal phalanx and its base at the overlying joint capsule (or if the joint capsule is not visible, at the volar aspect of the overlying extensor tendon) when viewed ultrasonographically from the dorsal aspect
- joint effusion, defined as a compressible anechoic joint space
- extensor tenosynovitis (ET), defined by a hypoechoic area around the extensor tendon with or without an increase in the size of the tendon
- bony erosions (depressions of the intrinsically hyperechoic bone surface with irregular margins and discontinuity of the cortical bone in two planes)
- osteophytes (abnormal projections of the bone surface typically found at the osseocartilaginous junction)
- increased joint space vascularity as determined by PD sonography.

A standardised procedure was devised for this study. Both hands were assessed. The hand to be examined was placed in the neutral position with the fingers in extension on a foam block. Dorsal longitudinal US scans were obtained in line with the extensor tendon with the US beam perpendicular to the major (coronal) axis of the hand. Measurements were performed using the images as depicted in Figures 2.1-2.3 on

pages 102-104. The transducer was held steady to allow gel to be visualised above the skin surface on the US image, in order to avoid placing any pressure on the structures below. The intent was to avoid displacement of fluid or reduction of PD signal due to external pressure on the tissues. All findings were confirmed in two planes, longitudinal and transverse. At the end of the examination, pressure was applied with the transducer to assess for joint effusion.

Repeated measures were performed by one of two experienced musculoskeletal sonographers and the author, a rheumatologist with prior experience of about 50 US scans under the supervision of one of the experienced sonographers. Each of the first 50 subjects for this aspect of the study was assessed using the pre-defined US protocol repeated four times, twice by each of the individuals scanning (one sonographer and one rheumatologist). The intent was to assess intra-observer and inter-observer reproducibility, with each observer blinded to the other's results. A further 50 subjects were assessed according to the protocol by the author and/or one of the sonographers. Assessments by two observers were undertaken on the same day and thereby also provided data for assessment of inter-observer reproducibility.

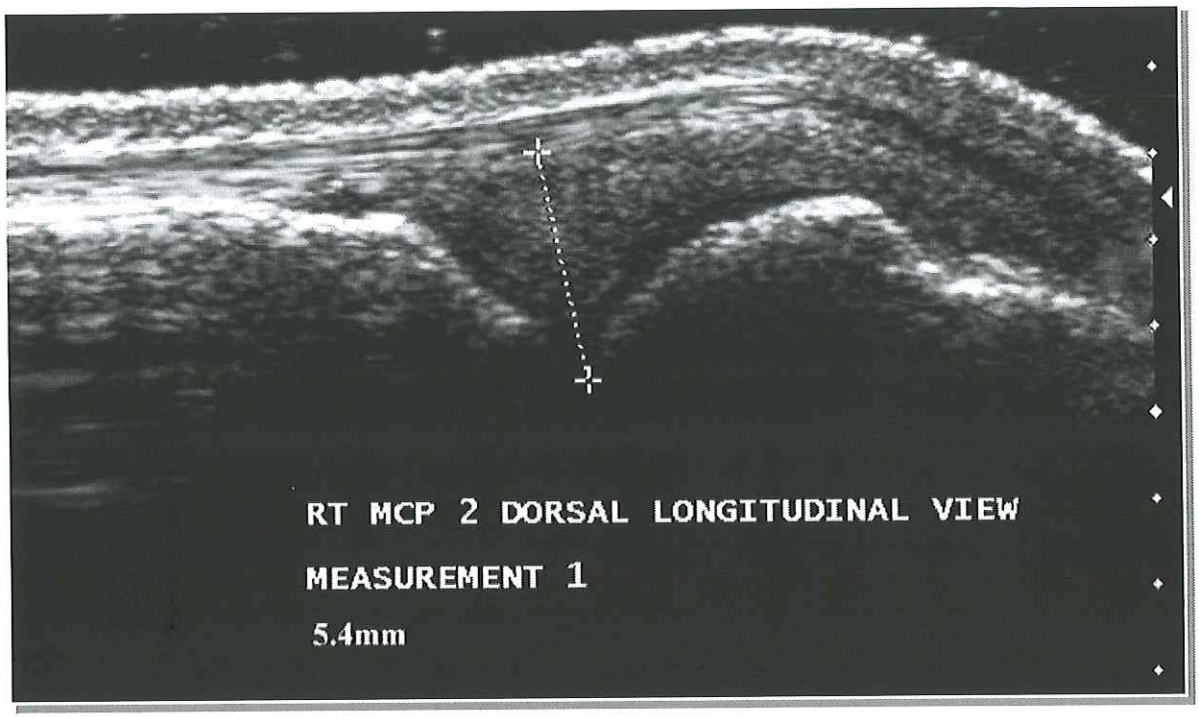


Fig 2.1 Measurement One (M1)

M1 is taken from the projected intersection of the bony outline of the metacarpal (MC) head and the base of the proximal phalanx upwards in a vertical line to bisect the intra-articular dorsal triangular structure. This triangular structure, called the intra-articular fat pad by previous authors (Wakefield 2005), appears homogeneous and slightly echoic on US. The measurement terminates at the volar surface of the overlying extensor tendon. This measure can be expected to increase in the presence of joint effusion, synovial proliferation or thickening of the joint capsule.

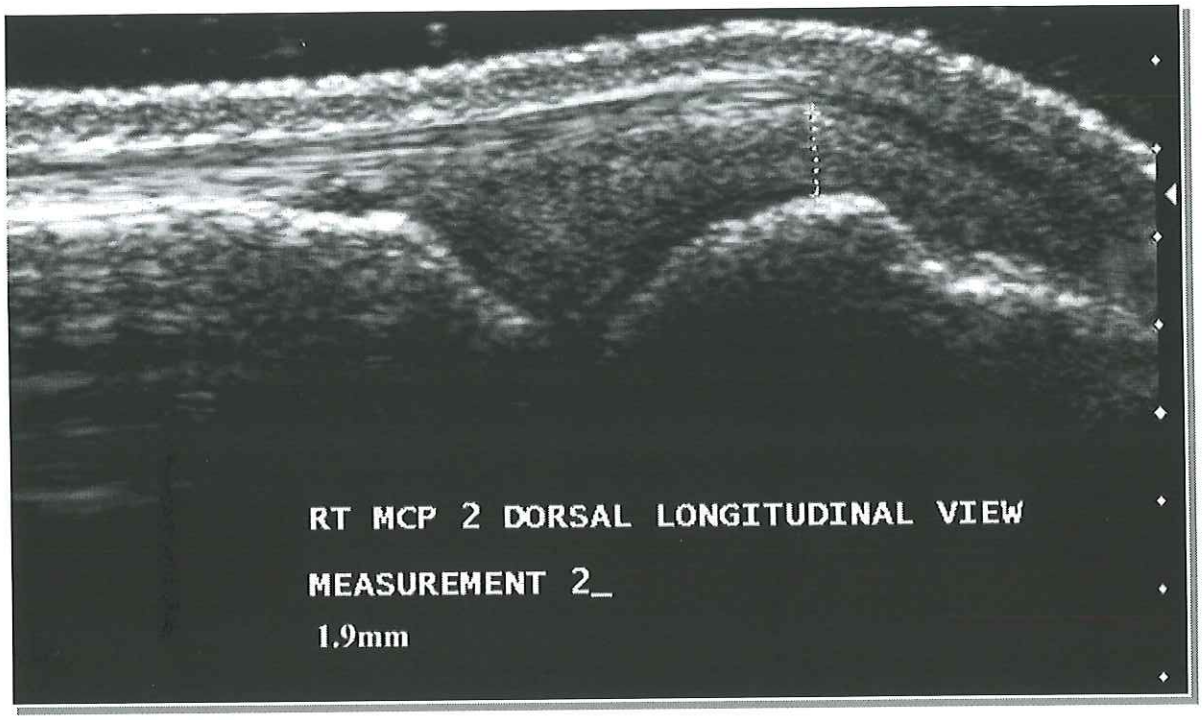


Fig 2.2 Measurement Two (M2)

M2 is taken from the highest point of the convexity of the MC head at the osseocartilaginous junction. The latter is defined by the limit of articular cartilage and its junction with the synovial lining which is juxtaposed to the bone surface before its reflection to become the inner lining of the flexible soft tissue sleeve which allows movement of the joint. M2 extends vertically to the volar surface of the overlying extensor tendon. This measure of synovial thickness passes through the proximal part of the triangular structure referred to above. Anatomically, it corresponded with the dorsal MC head tubercle (Boutry 2004), a common location for erosions of the MC head.

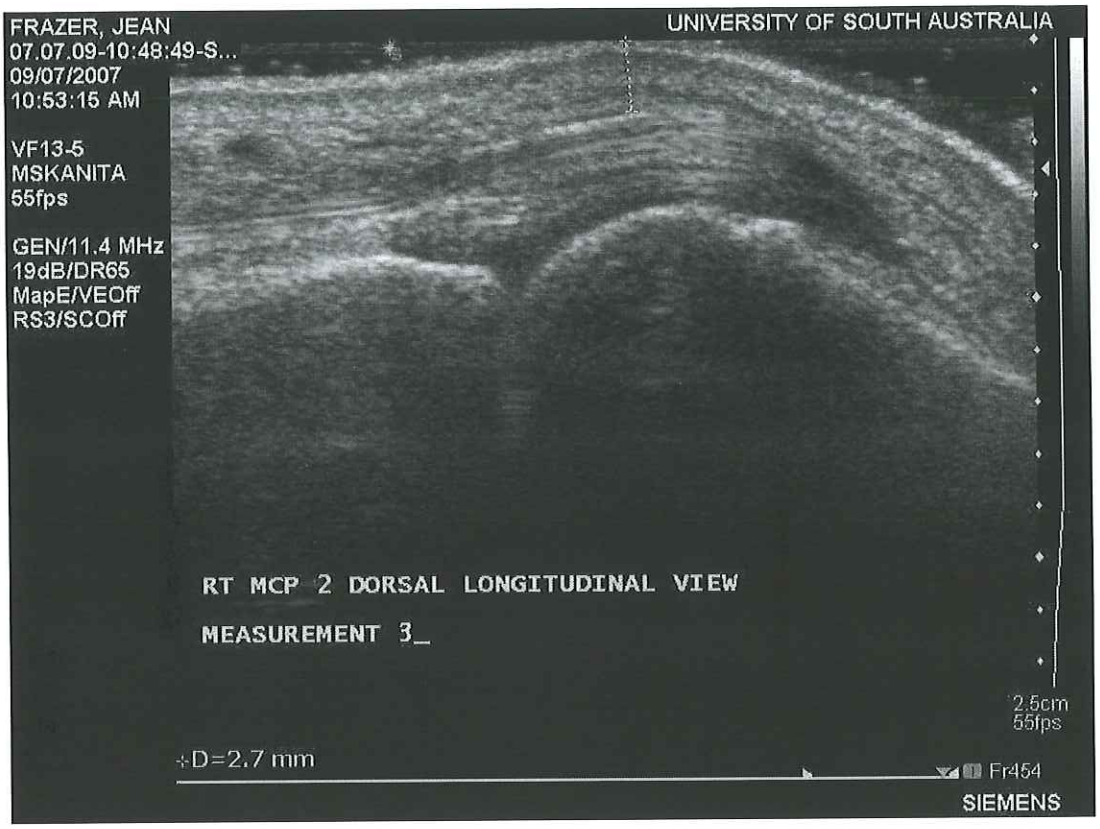


Fig 2.3 Measurement Three (M3)

M3 involves a projection of the line of M2 taken from the dorsal surface of the overlying ET to the overlying skin surface. This measure was designed to quantify subcutaneous swelling (including fluid and adipose tissue) that may contribute to the clinical appearance of MCP joint swelling.

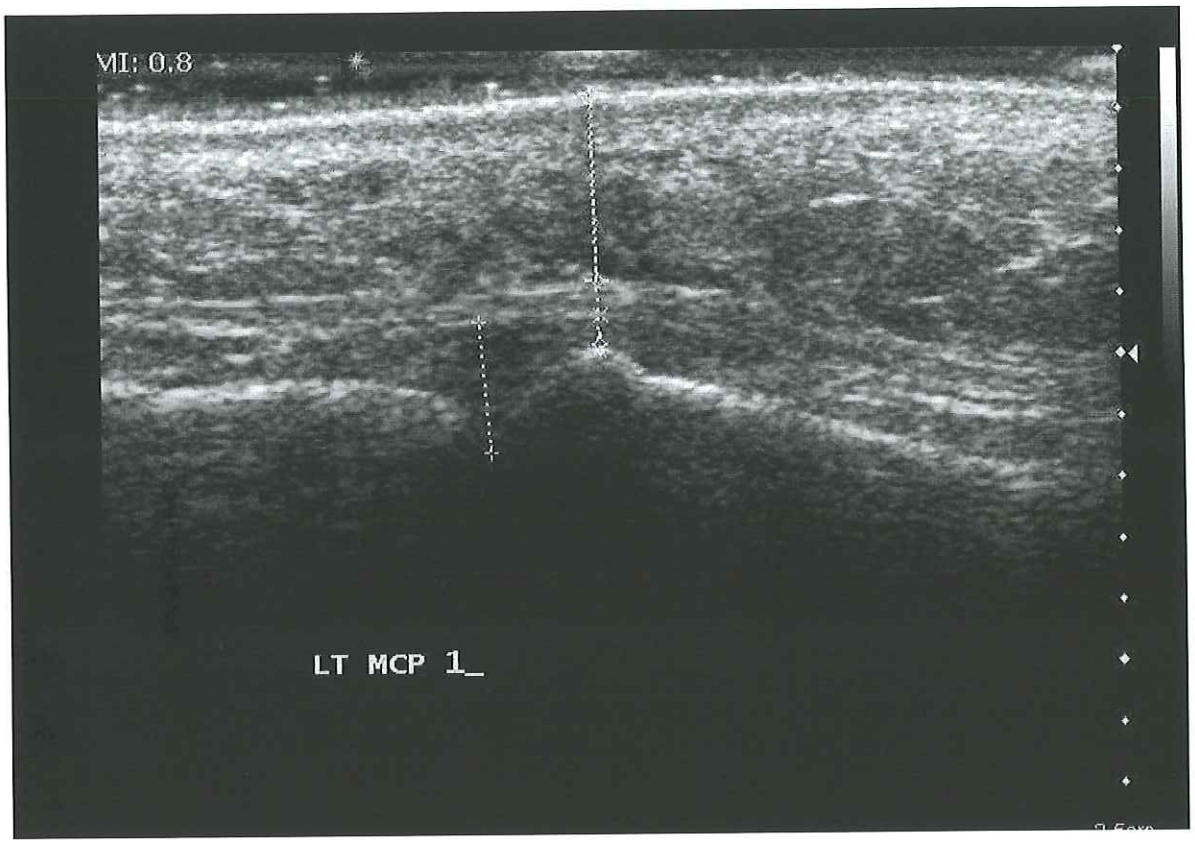


Fig 2.4 Example of abnormal Measurement Three (M3)

Subcutaneous swelling (including fluid and adipose tissue) that is contributing to the clinical appearance of MCP joint swelling, in a subject with a body mass index (BMI) of 40. Note that there is no significant influence of BMI on US measures of synovial swelling (M1 and M2).

2.6 Statistical analysis

The data were analysed using the Statistical Analysis System (SAS) Version 9.1 package (Cary, NC, USA) as well as PRISM and INSTAT (computerised statistical packages available locally). One way analysis of variance (ANOVA) was used to assess correlations with factors that may have influenced MCP joint measurements. These factors included body mass index (BMI), age, gender and handedness. Sub-categorisation was undertaken as follows:

- Level of BMI (kg/m^2)
    - 0-20 (underweight)
    - >20-25 (normal)
    - >25-30 (overweight)
    - >30 (obese)
- Dominance or handedness: dominant versus non-dominant
- Gender: male or female
- Age (years)
    - less than 35
    - 35-49 years
    - 50 years and above

A mixed model ANOVA was chosen in preference to a standard ANOVA as the analysis included repeated measurements on some subjects. The mixed model ANOVA has less stringent assumptions of independence of data than those of the standard ANOVA. The assumptions of independence required for the standard ANOVA render it inappropriate when repeated measures on individual subjects are included (ACITS).

The mixed model ANOVA also accounts for fixed effects (Lewicki), which are usually defined by the researcher (in this study, BMI, handedness, gender and age). Random effects are also accommodated (assuming the level of effects is randomly selected from the infinite population of possible levels). Examples of random effects are the selection of observers (one of three) or of subjects from the whole general population (an infinite number). The contribution of residual or unexplained effects, such as the relationship between the subject and the observer, can also be estimated. A statistically significant difference between the differing levels of a given factor was defined as $Pr > F$ less than 0.05. The larger the F value, the smaller the p value and the more likely the null hypothesis will be rejected (Motulsky).

Using the repeated measurements, intra- and inter-observer coefficients of variation (cv) were generated for each MCP joint using the mixed model ANOVA. The cv is the ratio of the standard deviation (SD) and the mean and is reported as a percentage. The lower the cv, the smaller was the scatter in the measurement data. Acceptability of cv values is context dependent. A cv of less than 10% is often considered acceptable for visual measurements. The data were used to generate reference ranges (mean and 2SD) for each MCP joint for subsequent testing in the patients with early arthritis (see Chapter 3).

The likelihood ratio test was used to determine whether there was a learning effect, as reflected by reduction in variance between observers when using the assessment protocol initially compared to later observations. The analysis compared data for the first 10 subjects studied with data for the remaining 90 subjects. A greater variance for

the initial studies relative to the remainder ($p<0.05$) was pre-defined as representing a learning effect.

To determine the optimal notional upper boundary for the normal range for US measurements, receiver operating characteristics (ROC) curves were constructed with the aim of differentiating RA participants from subjects without hand arthritis. ROC curves plot relationships between sensitivity and specificity for different boundary levels and were constructed using data for all subjects. The area under the curve (AUC) calculated provides a measure of the model's overall discriminatory capacity, from which the boundary values with higher sensitivity and specificity can be calculated for each MCP joint. The highest sum of sensitivity and specificity of all possible boundary values was chosen as optimal for differentiating RA from control participants. The ranges used in this study for interpreting AUC results and their ability to differentiate control from inflamed joints were 0.5-0.7 (poor), 0.7-0.8 (fair), 0.8-0.9 (good) and 0.9-1.0 (excellent).

2.7 Results

Of 100 control subjects with no history or examination findings of inflammatory arthritis, the median age was 42 years (range 17-71 years), 64% were female and the mean BMI was 27$\pm$4.9 SD.

2.7.1 Reproducibility

Using a mixed model ANOVA, the cv was less than 10% for all measurements, apart from M2 for MCP 5 which was 10.7% for inter-observer reproducibility. When considering intra-observer reproducibility, the cv was 0% for all but one MCP joint

(MCP 2 M2). Table 2.1 shows the cv results for each MCP joint, for the rheumatologist (Intra A) and the experienced sonographers (Intra B and C).

2.7.2 Learning effect

Using the likelihood ratio test to detect a difference in variance between early and later observations, a trend towards reduction was seen for most MCP joints, suggesting a small learning effect only (Table 2.2). The only reduction significant at the 0.05 level was for M1 at MCP1. This difference was as much attributable to absence of variance among later observations, than to an unusually high variance in the early observations.

2.7.3 Development of a reference range

Factors potentially influencing measurements were used to create sub-categories (eg. gender and age) for mixed model ANOVA of non-arthritic subjects (see Appendix A). Higher values were found in males and younger females. In some joints, there was a trend towards high values in the dominant hand, but this was not sufficient to warrant a sub-category of normative data with regard to hand dominance.

Increasing BMI was associated with increasing M3 with the highest values occurring in obese subjects (BMI > 30, mean BMI of 33.8). M3 can be expected to increase in the presence of increased amounts of subcutaneous adipose tissue or oedema. Increasing BMI showed a slight trend towards increased M1 and M2, but insufficient to impact on normative data (see Table 2.3). Thus adipose tissue appears to accumulate in the subcutaneous tissues, including those dorsal to the MCP joints, but not in the synovium. Accordingly, obesity may create an appearance of MCP joint swelling on

clinical evaluation but does not increase US measures of synovial swelling (M1 and M2).

Given the favourable reproducibility data, the mean reading of the four repeated measurements taken at each MCP joint for healthy subjects was used to construct the reference ranges with the upper limit of normal (ULN) being the mean plus 2 SD (Table 2.4). The median age for women of 42 years was used to dichotomise the healthy female subjects. Sensitivity and specificity values were based on Scenario one analysis as detailed below.

ROC analyses were performed and AUC values calculated (Table 2.5, Appendix B). Three groups were considered: RA US synovitis positive joints or RA US synovitis negative joints (from 50 RA patients described in Chapter 3) and control joints (non-RA), and three scenarios were formulated for analysis:

Scenario One: Healthy subject (control) MCP joints compared with RA US synovitis positive joints (excluding the RA US synovitis negative joints)

Scenario Two: Control MCP joints and RA joints with no US synovitis compared with RA US synovitis positive joints

Scenario Three: Control MCP joints compared to all RA MCP joints (with or without US synovitis)

There was little difference in AUC values between Scenario One (see Table 2.5) and Scenario Two, which as expected yielded AUC values more favourable than those for Scenario Three. The AUC values ranged from about 0.60 to 0.85 for all the MCP joints. These values represent poor to good ability to distinguish between controls and RA synovitis. M1 was fair to good at distinguishing RA synovitis from controls, with consistently higher AUCs than M2.

Table 2.1 Reproducibility using inter- and intra-observer cv

	Inter cv	Intra cv	Intra A	Intra B	Intra C
MCP 1 M1	3.0	0.0	0.0	2.5	2.4
MCP 1 M2	0.0	0.0	0.0	4.7	2.2
MCP 1 M3	7.5	0.0	0.0	0.0	1.5
MCP 2 M1	4.2	0.0	0.0	0.0	0.0
MCP 2 M2	7.0	2.2	2.8	0.0	0.0
MCP 2 M3	6.5	0.0	0.0	10.3	0.0
MCP 3 M1	1.6	0.0	0.0	0.0	0.0
MCP 3 M2	4.4	0.0	0.0	0.0	0.0
MCP 3 M3	5.4	0.0	0.0	4.4	0.0
MCP 4 M1	2.8	0.0	1.5	0.0	0.0
MCP 4 M2	4.8	0.0	0.0	0.0	0.0
MCP 4 M3	3.8	0.0	0.0	0.0	0.0
MCP 5 M1	4.3	0.0	0.0	0.0	1.3
MCP 5 M2	10.7	0.0	3.5	5.9	0.0
MCP 5 M3	9.7	0.0	0.0	0.0	0.0

Intra A = rheumatologist (n=100 subjects)
Intra B and C = sonographers (B n=22 subjects, C n=73 subjects)
M1 and M2 are measures of synovial swelling, M3 is a measure of subcutaneous thickness. These measures are described in Methods and depicted in Figure 2

Table 2.2 Inter-observer cv for M1 and M2: the first ten subjects compared to 90 subsequent subjects

	Inter cv First 10	Inter cv Rest of group (n=90)	p value
MCP 1 M1	7.9	0.0	*0.008*
MCP 1 M2	3.0	0.0	0.92
MCP 2 M1	2.8	4.5	0.38
MCP 2 M2	7.9	6.8	0.80
MCP 3 M1	2.0	1.5	0.86
MCP 3 M2	8.5	2.7	0.13
MCP 4 M1	1.4	3.0	0.56
MCP 4 M2	5.8	4.6	0.77
MCP 5 M1	6.7	3.4	0.12
MCP 5 M2	17.2	8.7	0.08

p value < 0.05 was significant

Table 2.3 Example of influence of BMI on US measurements

	M1	M2	M3
BMI	mean (mm)	mean (mm)	mean (mm)
0-20	5.49	1.68	1.49
>20 – 25	5.60	1.86	1.55
>25 – 30	5.63	2.00	1.63
>30	5.62	1.91	1.73
p value	0.98	0.72	*0.03*

Mixed model ANOVA, p value < 0.05 was considered significant

Table 2.4 Reference ranges based on normative data

MCP joint	Measurement	Subgroup	Mean + 2SD (mm)	Sensitivity	Specificity
1	M1	F>42 years	5.8	0.48	0.91
		Others	6.2	0.29	0.95
1	M2	All	2.0	0.14	0.93
2	M1	F>42 years	6.2	0.58	0.83
		Others	6.7	0.33	0.94
2	M2	F>42 years	2.6	0.31	0.88
		Others	2.8	0.18	0.96
3	M1	F>42 years	5.8	0.60	0.83
		Others	6.4	0.31	0.96
3	M2	F>42 years	2.5	0.42	0.84
		Others	2.9	0.11	0.99
4	M1	F>42 years	5.6	0.58	0.84
		Others	6.1	0.45	0.99
4	M2	F>42 years	2.5	0.26	0.87
		Others	2.9	0.08	0.97
5	M1	F>42 years	5.2	0.67	0.78
		Others	5.8	0.36	0.98
5	M2	F>42 years	2.0	0.31	0.73
		Others	2.7	0.06	0.96

2SD = two standard deviations from the mean
Others = female subjects 42 years and under and all male subjects

Table 2.5.1 ROC analysis AUC values for Scenario One: Joints from control subjects compared with US synovitis positive joints from RA subjects

	M1	M2
MCP 1 dominant	0.80	0.68
MCP 1 non-dominant	0.84	0.65
MCP 2 dominant	0.80	0.62
MCP 2 non-dominant	0.86	0.58
MCP 3 dominant	0.78	0.64
MCP 3 non-dominant	0.78	0.58
MCP 4 dominant	0.84	0.59
MCP 4 non-dominant	0.79	0.64
MCP 5 dominant	0.81	0.57
MCP 5 non-dominant	0.80	0.61

Table 2.5.2 ROC analysis AUC values for Scenario Two: Joints from control subjects plus US synovitis negative joints from RA subjects compared with US synovitis positive joints from RA subjects

	M1	M2
MCP 1 dominant	0.78	0.67
MCP 1 non-dominant	0.83	0.65
MCP 2 dominant	0.81	0.62
MCP 2 non-dominant	0.86	0.58
MCP 3 dominant	0.77	0.63
MCP 3 non-dominant	0.76	0.59
MCP 4 dominant	0.83	0.59
MCP 4 non-dominant	0.79	0.64
MCP 5 dominant	0.80	0.57
MCP 5 non-dominant	0.78	0.61

Table 2.5.3 ROC analysis AUC values for Scenario Three: Joints from control subjects compared with US synovitis positive and synovitis negative joints from RA subjects

	M1	M2
MCP 1 dominant	0.72	0.64
MCP 1 non-dominant	0.82	0.63
MCP 2 dominant	0.76	0.60
MCP 2 non-dominant	0.81	0.57
MCP 3 dominant	0.76	0.63
MCP 3 non-dominant	0.77	0.56
MCP 4 dominant	0.77	0.57
MCP 4 non-dominant	0.75	0.62
MCP 5 dominant	0.74	0.56
MCP 5 non-dominant	0.69	0.54

2.8 Discussion

Cvs for inter-observer reproducibility were less than 10% for all measures except M2 for MCP5 in the early assessments. The cv for intra-observer reproducibility was 0% for all but one MCP joint. A cv of 0% does not mean lack of variability but very little, as each cv is a best estimate, with some uncertainty around the estimate. There are no rules for determining how reliable various values are for cv, as the level of cv that is acceptable depends on the context. A small study of patients with active RA and hand joint synovitis provided the basis for a suggestion that the US threshold of response be defined as greater than an observed inter-observer cv of 11% (Ribbens 2003). In a study of healthy subjects, cvs of less than 5% were obtained for joint measurements and were considered very good inter-observer reliability (Boutry 2004).

Longitudinal views on US scans have been the most informative in RA (Grassi 1993), particularly for measurements. This was the orientation chosen for this study. The definition of synovitis or effusion of the MCP or PIP joints in Naredo's study (Naredo 2005a) was based on measurements performed in the dorsal longitudinal view with the joint in extension, which is similar to our standardised protocol. Their criterion for joint effusion or synovitis was a maximum distance from the articular bony margin to the joint capsule of greater than 2mm. The actual value of the measurements obtained was not reported nor was their correlation with other US, clinical or laboratory findings presented. There was no information on the reproducibility of their measurements and no data provided for normal controls.

Schmidt and co-workers undertook measurements on recorded hard disc images with excellent inter-observer agreement of 0.96 (Schmidt 2004). Scheel also used stored US images to calculate synovitis measurements and to perform semi-quantitative grading (Scheel 2005). There was high concordance with inter-reader agreement with kappa values of 0.88 for the MCP joints and 0.93 for the PIP joints. It is important to note that the use of saved images does not examine the operator dependency of US with regards to acquisition of images. In contrast, our study examined both aspects of operator dependency.

In a study by Ribbens and co-workers, intra- and inter-observer cvs were determined, with intra-observer cvs calculated from observations on three patients with discordance settled by consensus (Ribbens 2003). The intra-observer cv for MCP joints was 2.3% and the inter-observer cv was 10.7%, which are similar to those obtained in our study. In healthy controls, two musculoskeletal radiologists performed separate scans on the

same day and achieved a high degree of inter-observer concordance in identifying intra-articular and peri-articular structures (Boutry 2004). In Szkudlarek's study, there was a high level of agreement overall (79-91%) between an inexperienced rheumatologist and a radiologist for Us detection of joint erosions, synovitis, effusion and PD positivity using a semi-quantitative scale (Szkudlarek 2003).

Reproducibility of US findings may be improved by standardising the position of the joint and subject (Grassi 2000), which our study took into consideration. A study involving Canadian rheumatologists showed a decreased inter-observer variability from 13.8% to 3.2% after standardisation of the patient examination technique (Klinkhoff 1988). As a precursor to our study, this issue was considered and a consensus reached regarding the method of US examination of the MCP joints. This considered approach may have helped to reduce inter-observer variability.

In a report by Naredo et al., despite 20 hours of clinical joint examination in RA patients prior to the study to standardise the examiners, inter-observer agreement in clinical findings ranged from poor to excellent with better overall agreement for tenderness than for swelling (Naredo 2005a). At the MCP joints, mean kappa values were 0.61 for tenderness (good agreement) compared with 0.36 for swelling (poor). When contrasted with US studies, this study suggests that clinical observations may be less reliable than US observations.

Methods for US measurements have generally not been well described in the literature and this has militated against standardisation needed to allow corroboration of findings by investigators at different centres. Previous studies have measured a variety of

features, including pannus and tendon sheath thickness on longitudinal scans (Grassi 1995, Hau 1999). Hoving et al. measured synovial thickness in their early RA study and showed that joints positive for synovitis on US and MRI had a synovial thickness of greater than 3mm (Hoving 2004). However, the plane in which the measurements were taken, the position of the joint (flexion or extension) and the exact points between which measurements were taken were not described by the authors.

Grassi and co-workers were the first to evaluate the MCP joints in RA with high frequency transducers and also the first to measure what they termed "joint cavity width" (Grassi 1993). This was defined as the distance between the ventral margin of the joint capsule and the top of the MC head, with synovitis defined as an increase in this width greater than 2 SD above the mean control value (range of 2-2.8mm, mainly performed at MCP joints 2 and 3). Their definitions of synovitis and abnormal measurements were similar in location and methodology to M2. The measurements were almost identical to our study, with M2 ranging from 2.5-2.9mm for the MCP joints of the index and middle fingers in our study. As "joint cavity width" corresponds with M2, it differs from 'joint cavity widening', a term which has been applied to the measurement we have designated as M1.

A recent study by Boutry and co-workers utilised a very similar standardised protocol to our study (Boutry 2004). Measurements were performed in the dorsal longitudinal view through the extensor tendon with the US beam perpendicular to the major axis of the finger, exactly as in our protocol. Normal anatomical findings at the dominant MCP joints 2 to 5 were determined with the same US machine as in our study. The only slight difference in Boutry's study was the positioning of the hand, with the fingers in

15 degrees of palmar flexion and a small wooden pad placed beneath the hand to facilitate examination of the MC head cartilage. Measurements were clearly detailed, and included the dorsal MC synovial recess and the maximum synovial thickness over the dorsal MC head tubercle (Boutry 2004), which resembles M2 in our study. However, M2 in our study was taken to the volar surface of the overlying extensor tendon and therefore included some of the intra-articular "fat pad" (dorsal triangular structure) and connective tissue between the dorsal MC synovial recess and the volar extensor tendon. Additionally, the maximal thickness through the dorsal triangular structure was measured, with the point of origin being the most ventral point of the triangular pad that could be visualised. This resembles our M1, which was taken from the point of the projected intersection of the bony outlines of the MC head and the base of the proximal phalanx dorsally to bisect the dorsal triangular structure, terminating at the volar aspect of the overlying extensor tendon.

Using the mean healthy control values and 2SD above this value, the measurements in the study by Boutry and co-workers were lower than those of our study as expected based on the anatomical endpoints described. The maximal synovial thickness over the dorsal MC head tubercle closely approximated M2 in our study at all MCP joints (Table 2.6), performing better than the dorsal triangular structure measurement in comparison to M1. Not surprisingly, 'M1' in Boutry's study was 0.4-1.3mm lower than the lowest value of M1 in our study reference ranges, given that our point of origin at the projected intersection of the bony outlines of the MCP joint was more ventral than theirs at the most ventral point of the triangular structure. The most reliable measurement in Boutry's study was 'M1" of the dominant middle finger MCP joint, exactly as was the case in our study (cv of 1.1% and 1.6% respectively). Similarly, the

fifth MCP joint was the least reliable with a cv of 5% for 'M1' and 10.7% cv for M2 in our study. Compared to our study, there was a smaller younger healthy control group of 30 volunteers enrolled. Boutry and co-workers did not examine the potential influence of factors such as age, gender and BMI on their measurements and intra-observer reliability was not assessed. Hence, our study is novel in that factors influencing measurements were considered and if significant were retained as subcategories in the reference ranges.

There are advantages and disadvantages of the measurements developed for our study. Firstly, very detailed description of the anatomical points, between which the measurements were made, was provided, unlike previous studies. This resulted in excellent intra- and inter-observer reproducibility of the measurements in healthy control subjects. These measurements may be most useful in very early arthritis when synovial thickening is not clearly defined. Abnormal measurements may have prognostic implications, especially M1, if present at baseline assessment (to be addressed in Chapter 5). However, these measurements may be affected by the presence of osteophytes (potentially distorting M2), by erosions at the point where the M2 is taken (potentially increasing this measurement) and alteration in the position of the extensor tendon (such as rupture or ulnar deviation of the MCP joints). Nonetheless, these measurements should perform adequately in early arthritis, as these confounding changes are more likely to occur in advanced RA, when the diagnosis is secure.

2.8.1 Easy to learn technique with minimal learning effect

Our study has confirmed previous findings that a rheumatologist with limited US training can rapidly acquire skills and satisfactorily perform US of the hand in RA

when compared with an experienced radiologist (Szkudlarek 2003). Additionally, in Lerch's study, precise definitions of pathology and grading resulted in high reproducibility of measurements and acceptable images of the hip with relatively small inter-observer variation (Lerch 2003).

Table 2.6 Reference ranges compared to upper limit of normal in Boutry's* study

MCP joint	Measurement	Subgroup	Mean + 2SD (mm)	Mean+2SD (mm) (Boutry)
2	M1	F>42 years	6.2	5.8
		Rest	6.7	
2	M2	F>42 years	2.6	2.5
		Rest	2.8	
3	M1	F>42 years	5.8	4.8
		Rest	6.4	
3	M2	F>42 years	2.5	2.6
		Rest	2.9	
4	M1	F>42 years	5.6	4.3
		Rest	6.1	
4	M2	F>42 years	2.5	2.4
		Rest	2.9	
5	M1	F>42 years	5.2	4.7
		Rest	5.8	
5	M2	F>42 years	2.0	2.6
		Rest	2.7	

2SD = two standard deviations from the mean
Rest = female subjects 42 years and under and all male subjects
* Boutry's study reference (Boutry 2004)

2.8.2 Development of a reference range

In agreement with the present study, normative reference values for MCP joint measurements developed by Schmidt and co-workers were influenced by gender, but not hand dominance nor BMI (Schmidt 2004). We also examined the effect of age in females and observed higher synovial measures in younger subjects.

The reference ranges developed utilised the mean and two standard deviations (SD) as the upper limit of normal (ULN). It was not necessary to create a lower limit of normal as the aim was to determine if an MCP joint was abnormally enlarged. The significance of smaller than average MCP joint measurements is not known. Other studies have used either the same methodology with mean plus 2SD from healthy adults or analysis of receiver-operated characteristics (ROC) curves to help define more useful standard reference values for differentiation between normal and RA subjects (Schmidt 2004, Scheel 2005).

Inherent in every test is a divergent balance between sensitivity and specificity. By ROC analysis, M1 performed better than M2, being fair to good at distinguishing between controls and RA US synovitis positive joints (Scenario One). Scenario Three, comparing MCP joints of non-arthritic control subjects with those of RA subjects, was the poorest performer with regards to AUC values. This is to be expected as the scenario was distinguishing RA from non-RA subjects, not joints with and without synovitis, which is what the measurements aim to achieve. The mean and 2SD ULN was chosen as the higher specificity was thought to be of greater importance in an early arthritis group, where it is more important to avoid over-diagnosis of RA and consequent exposure to inappropriate DMARD therapy. This contrasts with needs for

measurement of response in clinical trials where the diagnosis is secure and sensitivity to change is paramount. For sequential measures in clinical trials, significant differences should be based on smallest detectable differences based on intra- and inter-observer variability, not on ROC analysis.

2.8.3 Obesity sub study

This sub study demonstrated that swelling seen about the MCP joints of obese subjects is explained by increased thickness of subcutaneous tissue, presumably due to fat deposition or subcutaneous oedema without an increase in synovial measures. The initial concern when developing the measurements was that excessive adipose tissue in the MCP joints may affect results. The lack of influence of obesity on M1, which is taken through the dorsal triangular structure (previously thought to be an intra-articular fat pad (Wakefield 2005)) is consistent with the histological findings in Boutry's study that this structure does not contain significant quantities of fat. M3 can be performed to confirm a clinical impression of obesity as the dominant contributor to apparent swelling of MCP joints.

2.9 Conclusions

The measurements used proved reliable, with excellent intra- and inter-observer reproducibility in control subjects. A reference range based on normative data was developed for testing in the early arthritis setting in Chapter 3. The standardised technique was easy to learn and apply, with rapid acquisition of US skills by a rheumatologist. In the next chapter, the sensitivity and specificity of measurements when compared to clinical and qualitative US findings will be presented.

CHAPTER 3

Ultrasonography in early arthritis

3.1 Background

Current criteria for the diagnosis of RA are not designed to detect early disease, and perform poorly at the first visit in predicting the subsequent development of RA in patients with early arthritis (Arnett 1988). Ultrasonography (US) has a role in the management of inflammatory arthritis, especially in early diagnosis and assessment prior to initiation of therapy, and in monitoring disease progression (Grassi 1993). Joints can have synovial hypertrophy and increased vascularity that is undetectable clinically, which may have implications for management decisions. The presence of sub-clinical synovitis, detectable by US, may be responsible for continuing erosive damage on plain radiographs despite clinical improvement (McQueen 1999, Backhaus 2002).

Imaging studies on the distribution of synovitis in the finger joints are limited. In Szkudlarek's study in early and established RA (median disease duration 5 years, range 0-20 years), dorsal synovitis was shown in 78% of the MCP joints (Szkudlarek 2006). This contrasts with Scheel's predominantly established RA group (Scheel 2005), in which synovitis was mainly distributed over the palmar proximal aspect of both MCP and PIP joints with only 14% located over the dorsum alone. Recommendations for scanning only the volar aspect have been proposed, however up to 30% of finger joint synovitis could be missed if only the volar aspect was examined (Tan 2003). Also, results from an established RA population such as that of Scheel and co-workers

(Scheel 2005) cannot be transferred to an early RA group, as the joints involved and distribution of the synovitis can differ according to disease duration.

3.2 Aims

(1) To compare clinical and US findings in patients with early RA

(2) To develop sensitive and specific US criteria that may be useful in defining early RA in subjects presenting with joint pain

(3) To study the distribution of synovitis in the MCP joints in early RA

3.3 Hypotheses

(1) When considering the MCP joints, US is more sensitive for synovitis detection than clinical examination

(2) In early RA, US criteria developed in this study will be able to differentiate between early RA and non-RA control subjects

(3) The distribution of synovitis in early RA differs from that of established disease

3.4 Subjects

3.4.1 Selection

Subjects with recent onset inflammatory arthritis who met the revised American College of Rheumatology (ACR) criteria for RA (see Appendix C) (Arnett 1988) and had at least one tender and swollen MCP joint were recruited from the Early Arthritis (EA) Research Clinic at the Royal Adelaide Hospital (RAH). This is an ongoing early RA trial that commenced in 1999 examining the benefits of high and low dose fish oil in the setting of triple disease-modifying anti-rheumatic drugs (DMARDs) including

methotrexate, sulphasalazine and hydroxychloroquine, with dosage adjustments based on disease activity criteria for response and any side effects resulting from medication usage. This protocol was developed to ensure tight disease control with the aim being to prevent radiographic progression and functional impairment. Non-RA control subjects, as described in Chapter 2, were also included as a comparator group.

3.4.2 Inclusion Criteria

Subjects who agreed to have an US of the hands and were recently enrolled in the early RA trial were included in this study.

3.4.3 Exclusion Criteria

Subjects with self-limiting disease by the time the US was to be performed were excluded from the trial. In the absence of clinical swelling of the MCP joints, the subject was also excluded.

3.5 Methods

US was performed using the structured protocol as described in Chapter 2. Measurements were obtained once only as the reproducibility of M1 and M2 had already been assessed and confirmed in an earlier part of this study. Proforma recording of US features such as capsular distension with synovial proliferation, joint effusion, bone erosions, signs of tenosynovitis (flexor and extensor), osteophytes, PD positivity and M1 and M2 measurements was done.

Routine baseline clinical and laboratory assessments were performed, including calculation of disease activity using the Disease Activity Score (DAS) 28, based on the

number of tender and swollen joints out of a maximum of 28 joints, patient global assessment and the ESR as follows (Prevoo 1995):

$$DAS28T+S = 0.56 \times \sqrt{28T} + 0.28 \times \sqrt{28S} + 0.70 \times \ln ESR + 0.014 \times GH$$

28T = 28 joint count for tenderness, involving both shoulders, elbows, wrists and knees and all MCP and PIP joints

28S = 28 joint count for swelling, involving the same joints as above

lnESR = natural logarithm of Westergren's Erythrocyte Sedimentation Rate

GH = general health or patient's global score, where 0 is excellent and 100 is very poor

Serology included inflammatory markers (ESR, CRP), rheumatoid factor (RF) and anti-cyclic citrullinated peptide (CCP) antibody. RF IgM was measured by nephelometry (normal range less than 20kIU/L) and anti-CCP antibody IgG measured by enzyme-linked immunosorbent assay (ELISA) technique (normal less than 6μ/mL). MCP joints were considered swollen if there was either swelling alone or in combination with tenderness (clinical synovitis). Medications were recorded, in particular recent oral or injectable corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs) or DMARDs. Standard radiographs of the hands and feet (postero-anterior and antero-oblique views) were obtained at baseline and approximately one year later. The presence of bone erosions, joint space narrowing, soft tissue swelling and periarticular osteopenia were recorded.

3.5.1 Statistical analysis

The data were analysed using the SAS Version 9.1 package (Cary, NC, USA) as well as PRISM and INSTAT. Odds ratio was utilised to assess for any significant difference in the association of US findings, such as synovitis, tenosynovitis and PD positivity, with the early RA group compared with controls. Descriptive statistics using chi square or Fisher's exact test as appropriate (with significance if $p< 0.05$) were also employed to compare findings such as US abnormalities in clinically swollen and in non-swollen joints. Sensitivity, specificity, accuracy, predictive values and their confidence intervals were calculated for US compared to clinical examination as the reference standard as a cross-product ratio in two by two (2x2) contingency tables.

Spearman's rank correlation coefficient (a non-parametric test) was used to assess for any association between inflammatory markers and clinical and US findings of synovitis. The relationships between US measurements, qualitative US and PD results and also DAS28 assessment of disease activity at baseline were also assessed. Significant correlation was present if the null hypothesis was defined as no relationship. Hence, even a weak association will give a significant p value. The r value (correlation coefficient) is used to determine whether the correlation is weak, moderate or strong. A weak r value is generally considered as less than 0.4, greater than 0.4 and less than 0.7 is considered moderate and an r value greater than 0.7 is a strong correlation.

Kruskall Wallis nonparametric statistical testing was used to determine if different joint pathologies could be distinguished by the quantitative measurements M1 and M2. A non-parametric test was chosen as the values of M1 and M2 were not necessarily normally distributed, were unpaired and involved standard deviations which may have

differed significantly. RA patients were divided into two groups as follows and compared to the non-RA control group.

- Group 1 = RA active joints group, that is positive for the particular factor being considered (clinical swelling, US synovitis, US PD positivity)
- Group 2 = RA inactive joints group, that is negative for the pathological factor being studied
- Group 3 = the joints from the non-RA control group

3.6 Results

3.6.1 Baseline demographics of early RA patients

Fifty patients were enrolled from the RAH EA clinic with a median age of 55 years (range 20-82 years) and median disease duration of 4 months (2 to 12 months range). Table 3.1 shows their demographic data. The majority were females (78%). Seropositivity for RF and anti-CCP antibody was present in 38% and 52% respectively. About 39% of patients were on anti-inflammatory medications and 22% were taking corticosteroids either orally (6.1%) or had received a recent intramuscular steroid injection (20%, mean 3.6 weeks ago). Forty four percent had started DMARDs for a mean period of about three weeks prior to the US scan with most being on two agents. Considering their delayed onset of action, it is unlikely that there would have been any significant effect on US findings (with regards to immediate improvement and findings of milder disease on US compared with their initial clinical assessment). The mean DAS28 at baseline of 5.7 indicates a high level of disease activity (defined as a DAS28 score > 5.1). Radiographic evidence of erosive disease in the hands or feet was present

Table 3.1 Early RA group demographics (n=50)

Age (years), median (range)	55 (20-82)
Disease duration (months), median (range)	4 (range 2-12)
Females (%)	78
RF positive (%)	38
Anti-CCP antibody positive (%)	52
BMI, mean (SD)	26.8 (6.4)
Commenced DMARDs (%)	44
Corticosteroids (%)	22
NSAIDs (%)	39
Baseline DAS28 (mean)	5.7
Baseline radiographic erosions (%)	12

in 12% and about 2.5 times as many subjects had US features of erosive disease affecting their hands (30%).

3.6.2 US findings in early RA compared to the control group

In total, 500 MCP joints were examined in the early RA group, with 48% documented as having clinically evident joint swelling (synovitis), with a mean of 4.8 swollen MCP joints per patient. In comparison, the mean number of MCP joints with US synovial proliferation was 7.6 MCP joints. Figures 3.1-3.4 show the frequency of involvement of each MCP joint with various US features in the RA compared with the control group. US examination detected US-defined joint swelling (synovitis and/or effusion) in 378/500 (76%) of MCP joints from the RA group compared with 2.1% in the control group. US swelling of control MCP joints was mainly due to small joint effusions (1.6% of MCP joints) and only 0.6% were due to synovitis. The proportion of MCP

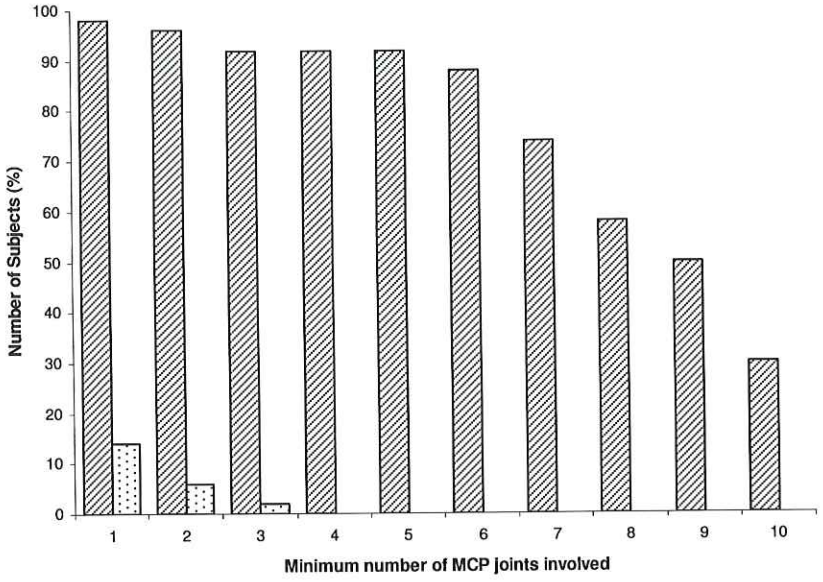
joints with abnormal M1 documented on US was 210/500 (42%) and abnormal M2 was 83/500 (16.6%). This compares with the control group, where by definition 2.5% of all MCP joints examined for M1 and M2 were abnormally increased given that the reference range was defined as the mean and 2SD above and below this (capturing 95% of normal values).

PD positivity was found in 27% of all MCP joints in the RA group and was absent in the controls. ET was seen as a component of joint swelling in 42% of MCP joints and again not found in the control group. Therefore PD positivity and ET appear to be specific for the early RA group as they were absent in controls. 0.5% of the control group showed erosive changes, possibly related to OA and erosive osteophytic changes. Table 3.2 summarises results in the RA compared to the control group. Odds ratios were calculated to show the amount of increased US abnormalities seen in the RA group MCP joints.

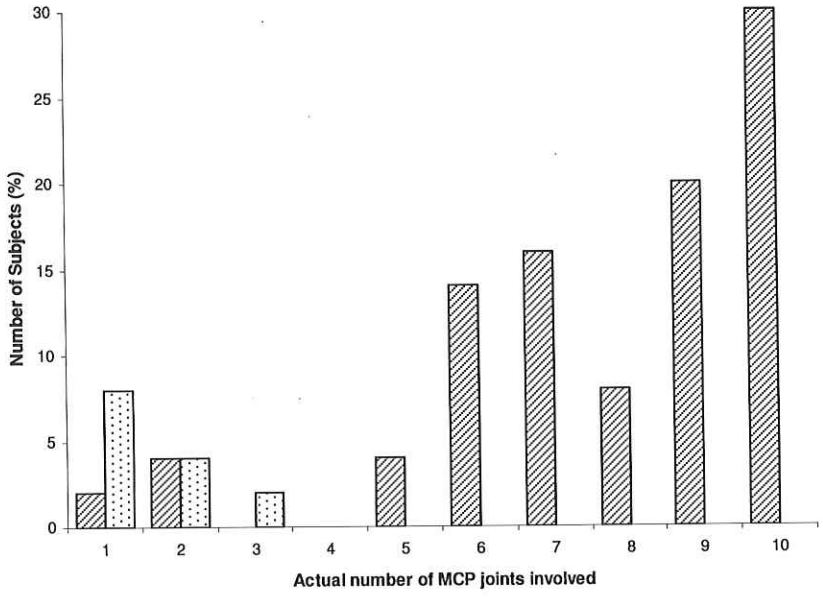
Table 3.2 Odds of association of US findings with early RA joints compared to controls

	Synovitis/ effusion	ET	PD positive	Abnormal M1	Abnormal M2
Early RA (n=500)	77%	42%	26.6%	42%	16.6%
Controls (n=1000)	2.1%	0%	0%	2.5%	2.5%
Odds Ratio	156.1	∞	∞	28.2	7.8
95% Confidence interval	96.6-252.2			18.3-43.6	4.9-12.3

M1 and M2 are measures of synovial swelling. These measures are described in the Methods section and depicted in Figure 2 of Chapter 2

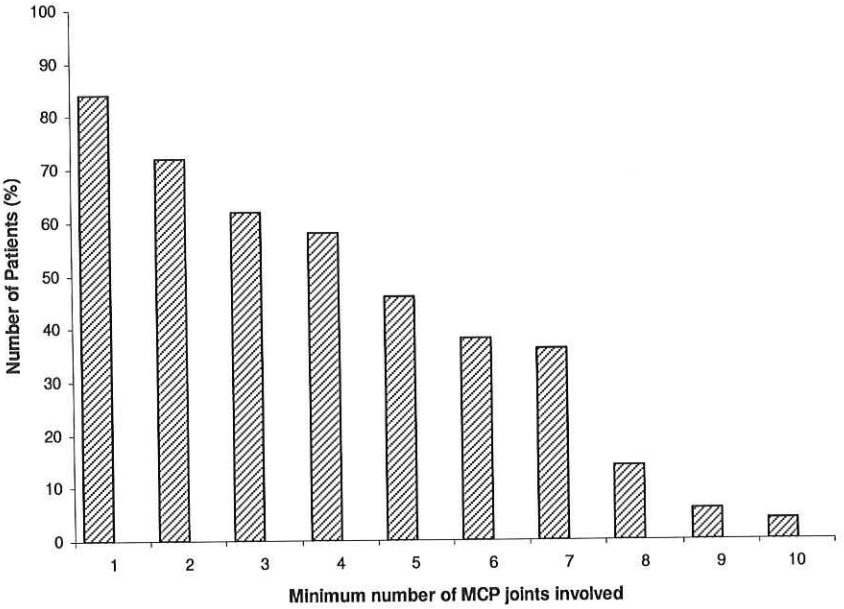


(a)

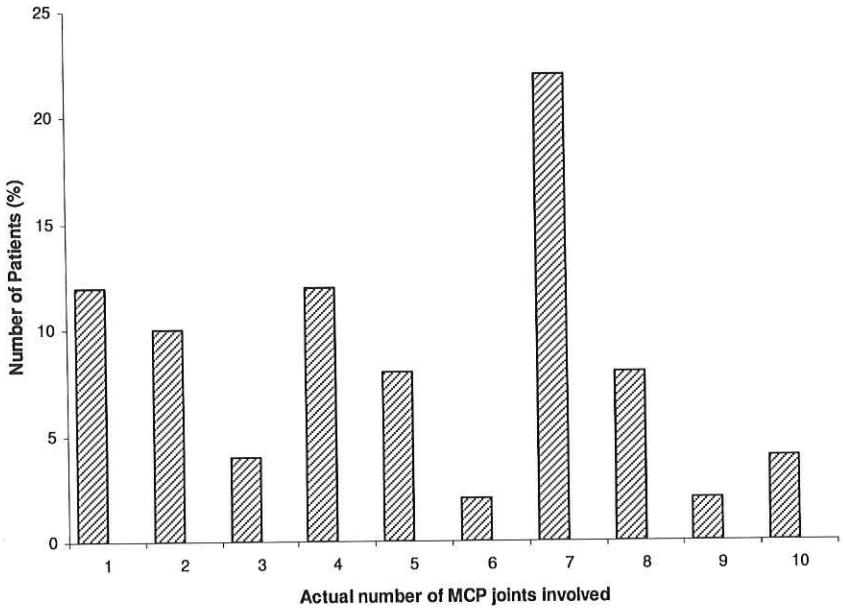


(b)

Fig 3.1 Frequency of US-detected synovitis/effusion: differences in the frequency of US-detected synovitis and/or effusion between the RA and control groups. (a) shows the percentage of subjects with a minimum number of MCP joints affected by synovitis/effusion. (b) shows the percentage of subjects with specific numbers of MCP joints involved with synovitis/effusion. Hatched columns represent the early RA patients, and spotted columns the control subjects.

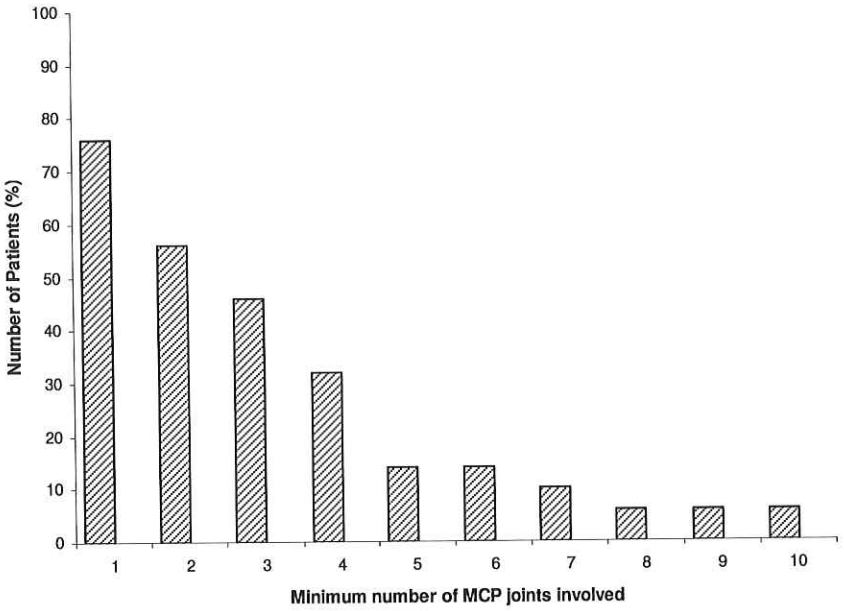


(a)

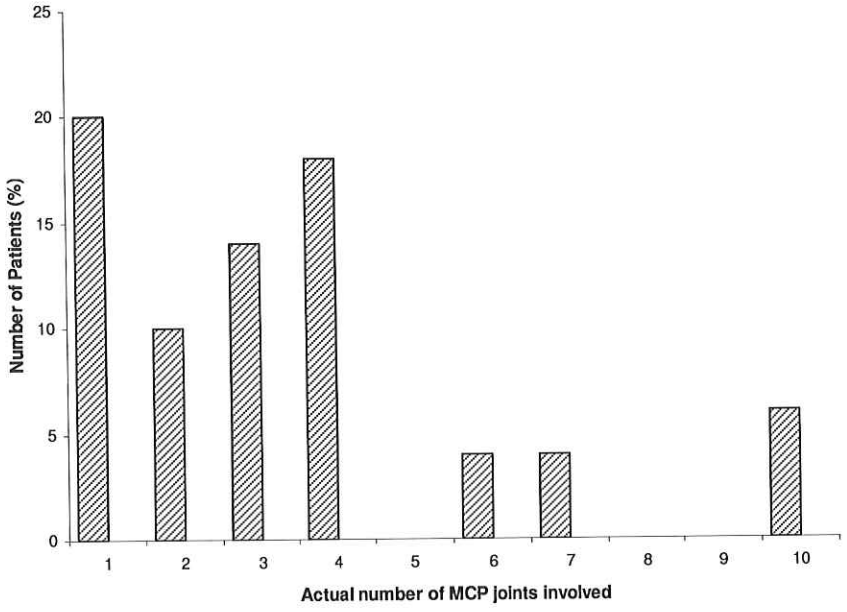


(b)

Fig 3.2 Frequency of US-detected extensor tenosynovitis (ET): early RA group. Note that ET was not detected in the control group. (a) shows the percent of subjects with a minimum number of MCP joints affected by ET. (b) shows the perçent of subjects with specific numbers of MCP joints involved with ET. Hatched columns represent the early arthritis patients.

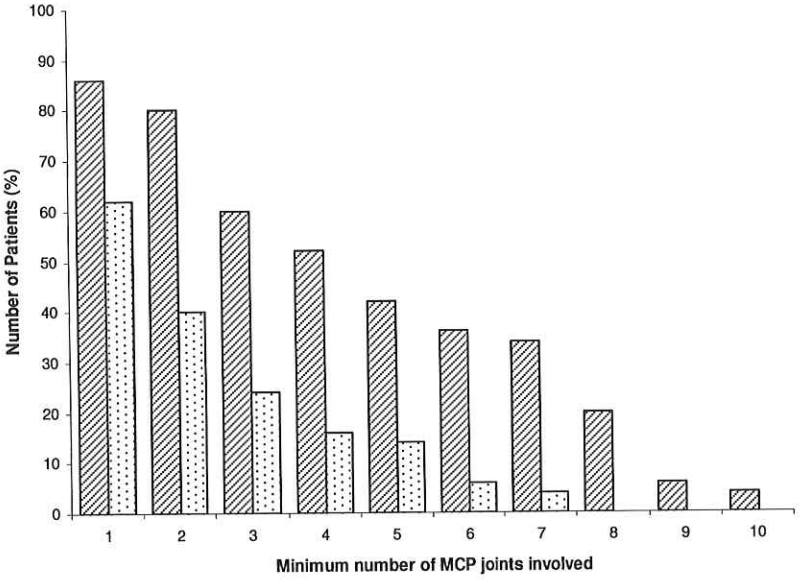


(a)

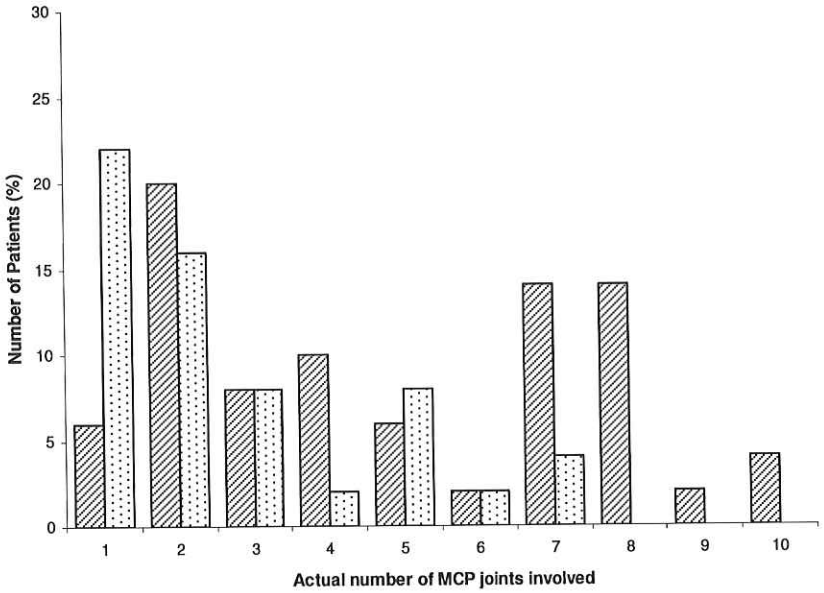


(b)

Fig 3.3 Frequency of power Doppler (PD) positivity: early RA group. Note that PD was not detected in the control group. (a) shows the percent of subjects with a minimum number of MCP joints affected by PD. (b) shows the percent of subjects with specific numbers of MCP joints involved with PD. Hatched columns represent the early arthritis patients.



(a)



(b)

Fig 3.4 Frequency of abnormal US measurements: early RA group only. (a) shows the percentage of subjects with a minimum number of MCP joints with abnormal M1 and M2. (b) shows the percent of subjects with specific numbers of MCP joints with abnormal M1 and M2. Hatched columns represent patients with abnormal M1 and spotted columns abnormal M2.

3.6.3 Profile of US features in early RA

The study showed overall how many early RA patients there were with features not seen in the control group. Of the 50 RA patients, 46 (92%) had at least 4 MCP joints with synovitis or effusion (Fig 3.1(a)). The maximum number of MCP joints with synovitis/effusion in controls was three joints. In those with RA with one to three MCP joints with synovitis or effusion, there was additionally one of the following two US features; ET or PD positivity in two of the remaining four RA patients. One patient had seven of ten MCP joints with ET and four of ten PD positive joints, whereas another had three of ten MCP joints with ET and no PD positive MCP joints. The other two patients with one to three MCP joints with synovitis or effusion did not have either ET or PD positivity. Therefore, the criteria developed to help identify the RA patients were as follows:

(1) Four or more MCP joints with synovitis or effusion OR

(2) One to three MCP joints with synovitis or effusion PLUS PD positivity and/or ET

Applying these criteria, there was a sensitivity of 96% and specificity of 100% of these features for early RA compared with the control group.

30% of patients had all ten MCP joints affected by synovitis or effusion (Fig 3.1(a)). Considering ET, the most common number of MCP joints involved was seven (Fig 3.2(b)). In comparison, over 60% of patients had one to four MCP joints with PD positivity (Fig 3.3(b)). Abnormal M1 was more evenly distributed than M2 with no greater than seven MCP joints with abnormal M2 seen (Fig 3.4).

3.6.4 Comparison of US and clinical synovitis

The data were analysed to determine the correlations between clinically determined joint swelling and US findings. 48% of the MCP joints of the early RA patients were swollen clinically and synovitis or effusion detected in 76% by US. This difference of 1.6 fold is even greater when one considers that clinical swelling of an MCP joint may also include a component of extensor or flexor tenosynovitis. When ET was included in the US findings, then the proportion of US positive joints rose to 81%, which is 1.7 fold more US positive than clinically swollen joints. Odds ratios for positive US findings relative to detection of swelling clinically are shown in Table 3.3 below.

Table 3.3 Odds for the presence of positive US findings in MCP joints relative to clinically swollen MCP joints

US feature	Odds ratio	95% CI	p value
Synovitis	2.91	1.87-4.52	<0.0001
PD positivity	4.97	3.18-7.76	<0.0001
Abnormal M1	1.66	1.16-2.38	0.006
Abnormal M2	1.50	0.93-2.42	0.11

p value of < 0.05 considered significant
CI = confidence interval
M1 and M2 are measures of synovial swelling. These measures are described in the Methods section and depicted in Figure 2 of Chapter 2

There was a trend to greater sensitivity of M2 which did not reach statistical significance (p=0.11). The accuracy of US synovitis when compared with clinical synovitis (swollen MCP joints) as a reference standard was 58% (Tables 3.4 and 3.5).

Table 3.4 Number of joints with and without US synovitis and/or effusion among joints with and without clinical swelling

	Clinical swelling	Clinically non-swollen
US synovitis/effusion present	207	173
US synovitis/effusion absent	35	85

Table 3.5 US synovitis and/or effusion compared to clinically detected swelling as the reference standard

	Results (%)	95% CI
Sensitivity	85.5	80.5-89.7
Specificity	33	27.3-39.0
PPV	54.5	49.3-59.5
NPV	70.8	61.8-78.8
Agreement	58.4	

PPV = positive predictive value
NPV = negative predictive value
CI = confidence interval
Agreement was defined as the sum of the true positive and true negative joints as a percentage of the total number of joints assessed (n=500)

When examined separately, MCP 2 and MCP 3 performed the best with agreement with clinical examination results of 75% and 80% respectively.

The correlation between US and clinical examination results in early RA was studied, using chi-square and Fisher's exact test where appropriate. The findings are detailed in Tables 3.6 and 3.7. Approximately 86% of all MCP joints that were clinically assessed as swollen had evidence of underlying US synovial proliferation. US detected synovitis

in 67% of MCP joints not thought to be clinically swollen, affecting 80% of the patients. Therefore, US was more sensitive for synovitis than clinical examination and detected a significant amount of sub-clinical synovitis. There was significantly more ET, PD positivity and abnormal M1 in clinically swollen compared with non-swollen joints. A trend towards a greater proportion of abnormal M2 in clinically swollen joints was shown (p=0.099).

Table 3.6 Clinico-ultrasonographic correlation in early RA (n=500)

	Synovitis/ Effusion (n=380)	ET (n=205)	PD positive (n=135)	Abnormal M1 (n=206)	Abnormal M2 (n=81)
Early RA					
Clinical swelling	85.5%	47.1%	42.1%	47.5%	19%
no clinical swelling	67.1%	35.3%	12.8%	35.3%	13.6%
p value	<0.0001	0.007	<0.0001	0.005	0.099

p values < 0.05 considered significant
M1 and M2 are measures of synovial swelling. These measures are described in the Methods section and depicted in Figure 2 of Chapter 2

Table 3.7 Clinico-ultrasonographic correlation in early RA (n=500)

	Any US qualitative* abnormality (n=404)	Any US quantitative^ abnormality (n=229)	Any US qualitative or quantitative abnormality (n=425)
Early RA			
Clinical swelling	90.5%	53.1%	93.8%
no clinical swelling	71.8%	39.0%	76.8%
p value	<0.0001	0.002	<0.0001

p values < 0.05 considered significant
* qualitative abnormalities on US included synovitis, joint effusion, ET and PD positivity
^ quantitative abnormalities on US included abnormal M1 and/or M2
M1 and M2 are measures of synovial swelling. These measures are described in the Methods section and depicted in Figure 2 of Chapter 2

Clinical swelling was compared with US qualitative and quantitative results, separately (Tables 3.8 (a) and (b) respectively) or together (Table 3.9), as the reference standard, given the greater sensitivity of US for detection of joint synovitis and/or effusion compared to clinical examination. Sensitivities for swelling detected by clinical examination ranged from 55% to 76% for US synovitis/effusion and PD positivity respectively as the reference standards, with specificities of 54% for abnormal M2 to 71% for US synovitis/effusion. Agreement between clinical swelling and US results was highest for US PD positivity (65%).

Table 3.8(a) Clinically detected swelling of joints compared to individual qualitative US abnormalities as the reference standard

	Synovitis/ Effusion (n=380)	ET (n=205)	PD positive (n=135)
Early RA			
Sensitivity	54.5 (49.3-59.5)	55.6 (48.5-62.6)	75.6 (67.4-82.5)
Specificity	70.8 (61.8-78.8)	56.6 (50.8-62.4)	61.6 (56.5-66.7)
PPV	85.5 (80.5-89.7)	47.1 (40.8-53.6)	42.2 (35.9-48.6)
NPV	33 (27.3-39)	64.7 (58.6-70.6)	87.2 (82.5-91)
Agreement	58.4%	56.2%	65.4%
Odds ratio (95% CI)	2.9 (1.9-4.5)	1.6 (1.1-2.3)	4.97 (3.18-7.76)
p value (Fisher's test)	<0.0001	0.008	<0.0001

Values are expressed as a percent (95% confidence interval)
Agreement was defined as the sum of the true positive and true negative joints as a percentage of the total number of joints assessed

Table 3.8(b) Clinically detected swelling of joints compared to abnormally increased US measurements as the reference standard

	Abnormal M1 (n=206)	Abnormal M2 (n=81)
Early RA		
Sensitivity	55.3 (48.3-62.2)	57 (45.9-67.6)
Specificity	56.9 (50.9-62.6)	53.6 (48.6-58.5)
PPV	47.7 (41.3-54.2)	20.3 (15.4-26)
NPV	64.1 (57.9-69.9)	85.7 (80.8-89.7)
Agreement	56.2%	54.2%
Odds ratio (95% CI)	1.6 (1.1-2.3)	1.5 (0.96-2.45)
p value (Fisher's test)	0.009	0.08

Values are expressed as a percent (95% confidence interval)
M1 and M2 are measures of synovial swelling. These measures are described in the Methods section and depicted in Figure 2 of Chapter 2
Agreement was defined as the sum of the true positive and true negative joints as a percentage of the total number of joints assessed

When considering combined US findings as the reference standard, clinical examination was more specific for qualitative (synovitis/effusion, ET, PD) than quantitative (abnormal M1/M2) US results (76% compared to 58%) with sensitivities of approximately 55% for all three combinations as shown in Table 3.9. PPVs were much higher for any combination with US qualitative abnormalities (over 90%) compared to only US measurements (53%).

Table 3.9 Clinically detected swelling of joints compared to US qualitative and quantitative abnormalities as the reference standard

	Any US qualitative* abnormality (n=404)	**Any US quantitative^ abnormality (n=229)**	**Any US qualitative or quantitative abnormality (n=425)**
Sensitivity	54 (49-58.9)	55.9 (49.3-62.4)	53.2 (48.4-57.9)
Specificity	76 (66.2-84.2)	58.3 (52.2-64.3)	80 (69.2-88.3)
PPV	90.5 (86.1-93.9)	53.1 (46.6-59.6)	93.8 (89.9-96.5)
NPV	28.2 (22.8-34.1)	61 (54.8-66.9)	23.2 (18.2-28.8)
Agreement	58.2%	57.2%	57.2%
Odds ratio (95% CI)	3.7 (2.2-6.2)	1.7 (1.2-2.5)	4.5 (2.5-8.3)

PPV = positive predictive value
NPV = negative predictive value
Values expressed as percent (95% confidence interval)
* qualitative abnormalities on US included synovitis, joint effusion, ET and PD positivity
^ quantitative abnormalities on US included abnormal M1 and/or M2
Agreement defined as the sum of the true positive and true negative joints as a percentage of the total number of joints assessed (n=500)

3.6.5 PD positivity and US qualitative abnormalities

If MCP joints with US synovitis, effusion or ET were considered, 35% were PD positive, compared with 14% PD positivity in MCP joints without these qualitative features (Table 3.10).

Table 3.10 Number of joints with and without US synovitis/effusion/ET among joints with and without PD positivity

	PD positive	PD negative
US synovitis/effusion/ET present	139	262
US synovitis/effusion/ET absent	14	85

Fisher's p value < 0.0001

3.6.6 Distinguishing between control and RA subjects

Next, the actual measurements of MCP joints in the RA active joints (clinically swollen, US synovitis positive, or PD positive) compared with the non-RA (healthy) control group joints were examined using nonparametric analyses (Kruskall Wallis for three variables).

When considering M1, significant differences were evident between joints of the RA active group (group 1) and the non-RA control group 3 (with p values all less than 0.001). Significantly larger measurements were typical of group 1 as shown in Tables 3.11 and 3.12.

Table 3.11 Measurement 1 and clinical and US results

	RA Active Joints^ (Gp 1)	RA Inactive Joints^ (Gp 2)	Non-RA Control Joints^ (Gp 3)	Gp 1 vs 2*	Gp 1 vs 3*	Gp 2 vs 3*
Clinical swelling	Yes (n=242)	No (n=258)	No (n=1000)			
MCP 1	5.8	5.5	4.8	NS	p<0.001	p<0.001
MCP 2	6.3	5.8	5.5	NS	p<0.001	p<0.05
MCP 3	6.0	5.4	5.1	NS	p<0.001	p<0.05
MCP 4	5.6	5.5	4.9	NS	p<0.001	p<0.001
MCP 5	5.3	5.1	4.6	NS	p<0.001	p<0.001
US synovitis/ effusion	Yes (n=380)	No (n=120)	No (n=1000)			
MCP 1	5.9	5.3	4.8	p<0.05	p<0.001	p<0.05
MCP 2	6.3	5.5	5.5	p<0.001	p<0.001	NS
MCP 3	5.9	5.6	5.1	NS	p<0.001	NS
MCP 4	5.6	5.0	4.9	p<0.01	p<0.001	NS
MCP 5	5.3	4.8	4.6	p<0.001	p<0.001	NS
PD positive	Yes (n=135)	No (n=365)	No (n=1000)			
MCP 1	6.0	5.3	4.8	p<0.05	p<0.001	p<0.001
MCP 2	6.3	6.1	5.5	NS	p<0.001	p<0.001
MCP 3	6.2	5.7	5.1	NS	p<0.001	p<0.001
MCP 4	5.6	5.5	4.9	NS	p<0.001	p<0.001
MCP 5	6.2	5.1	4.6	NS	p<0.001	p<0.001

^Values are median (mm)
*p values < 0.05 considered significant (Kruskall Wallis)
NS = non-significant

M1 could also distinguish RA inactive joints (group 2) from the non-RA group 3 despite being clinically non-swollen or US PD negative. However, M1 was unable to differentiate between RA US synovitis negative and non-RA joints (groups 2 and 3). That is, if there was no evidence of US synovitis, then it was difficult to differentiate an RA from non-RA MCP joint using M1. Also M1 of RA clinically swollen and PD positive joints was not significantly different from M1 of RA inactive joints (group 1 versus group 2, Table 3.11). M1 could distinguish synovitis positive from negative RA joints, except for MCP 3.

M2 was not as useful in distinguishing between the three groups, being unable to differentiate between the RA positive and negative groups, or the RA inactive and non-RA joints. M2 was helpful in distinguishing between RA synovitis positive and non-RA joints. However, when considering RA clinically swollen and PD positive MCP joints, there was no significant difference in M2 values when compared to the non-RA group (except MCP 1 for both, and MCP 3 for clinical swelling, Table 3.12). Hence overall, M1 performed better in distinguishing RA involved and uninvolved joints from control non-RA joints than M2.

Table 3.12 Measurement 2 and clinical and US results

	RA Active Joints^ (Gp 1)	RA Inactive Joints^ (Gp 2)	Non-RA Control Joints^ (Gp 3)	Gp 1 vs 2*	Gp 1 vs 3*	Gp 2 vs 3*
Clinical swelling	Yes (n=242)	No (n=258)	No (n=1000)			
MCP 1	1.6	1.4	1.2	NS	p<0.001	NS
MCP 2	2.0	2.0	1.9	NC	NC	NC
MCP 3	2.2	2.1	2.0	NS	p<0.01	NS
MCP 4	2.2	2.0	1.9	NS	NS	NS
MCP 5	1.9	1.5	1.5	NC	NC	NC
US synovitis/ effusion	Yes (n=380)	No (n=120)	No (n=1000)			
MCP 1	1.5	1.4	1.2	NS	p<0.001	NS
MCP 2	2.0	1.9	1.9	NS	p<0.05	NS
MCP 3	2.2	2.1	2.0	NS	p<0.01	NS
MCP 4	2.1	1.9	1.9	NS	p<0.01	NS
MCP 5	1.7	1.4	1.5	NC	NC	NC
PD positive	Yes (n=135)	No (n=365)	No (n=1000)			
MCP 1	1.7	1.4	1.2	p<0.05	p<0.001	NS
MCP 2	2.0	2.1	1.9	NS	NS	NS
MCP 3	2.1	2.2	2.0	NS	NS	p<0.05
MCP 4	2.1	2.1	1.9	NS	NS	P<0.05
MCP 5	1.7	1.6	1.5	NC	NC	NC

^Values are median (mm)
*p values < 0.05 considered significant (Kruskall Wallis)
NS = non-significant; NC = not calculated given Kruskall Wallis overall p value > 0.05

3.6.7 Relationship between US measurements, qualitative US and clinical findings

Using swelling on clinical examination (clinical synovitis) of the MCP joints as the reference standard, the sensitivity and specificity of abnormal US M1 and M2 could be determined. The sensitivity of US abnormal M1 overall was 48% and specificity was 65%. M1 performed best at the second MCP joint with a sensitivity of 56% and specificity of 80%. M2 performed much worse with regard to sensitivity in clinically swollen joints, with only 19% sensitivity, and 86% specificity. MCP 3 had the best sensitivity (24%) and specificity (90%).

When compared to qualitative US abnormalities, the sensitivity of abnormal M1 and M2 was low, with only 49% of MCP joints with US synovitis, effusion or ET (qualitatively abnormal US MCP joints) having an associated abnormal M1, and 24% of abnormal US MCP joints having an abnormal M2. On the other hand, using US qualitative inflammatory abnormalities as the reference standard, M1 and M2 were highly specific (84% and 91% respectively). Over 90% of all MCP joints with abnormally increased M1 or M2 had US evidence of synovial swelling or ET to explain the increased measurements. In detail, 92% of US abnormal M1 joints had associated US anatomical qualitative abnormalities ($p<0.0001$) and 91% of US abnormal M2 MCP joints were associated with US synovial swelling or ET ($p=0.002$). Additionally, in MCP joints with increased M1, 36% were associated with PD positivity compared with 24% in the normal M1 MCP joints ($p=0.002$ Fisher's exact test). In those with increased M2, there was 35% PD positivity compared to 26% in MCP joints with normal M2 values ($p=0.09$, non-significant).

3.6.8 Relationship between US findings and laboratory variables

Using Spearman's rank correlation test (to determine whether there was a significant association between the two nominal variables), there was a weak trend towards an association between the number of PD positive MCP joints and the level of ESR (p=0.054, Spearman's r=0.27). A non-significant trend toward association was also seen between US synovitis/effusion and ESR (p=0.058, r=0.27). There was also a trend towards an association between ESR and the number of clinically swollen MCP joints (p=0.06, r=0.27), but not between CRP and clinically swollen joints (p=0.97). CRP did not significantly correlate with any of the variables assessed, including US measurements and US qualitative abnormalities.

3.6.9 Relationship between disease activity and US and laboratory variables

Baseline DAS28 scores significantly correlated with the number of clinically swollen MCP joints and PD positive joints as well as weakly with the ESR level (p=0.03, r=0.32), but not CRP. The number of joints with PD positivity on US correlated significantly although weakly with the DAS28 (p=0.02, r=0.35), with the number of clinically swollen joints also being significantly associated with the DAS28 score (p=0.04, r=0.31).

3.6.10 Distribution of synovitis

The study examined whether synovitis was more prevalent on the volar or dorsal aspects of the MCP joints in early RA. Dorsal preponderance was seen at the MCP joints with 44% having dorsal involvement alone and 51% dorsal plus volar synovitis. Only 5% of MCP joints with synovitis had volar involvement alone.

The distribution of synovitis and erosions on the radial versus ulnar sides of the MCP joints was also studied. The radial aspect of the MCP joints was more often affected than the ulnar aspect. Anecdotally, if synovitis was unclear or uncertain on the dorsal longitudinal view, then the radial aspect helped to determine whether synovitis was present or not, especially for the second MCP joint and the PIP joints. PD assessment was carried out not only over the dorsal longitudinal view in line with the extensor tendon but also at angles to this medially and laterally as allowed by access to the joint due to transducer size. If PD was negative over the dorsal aspect, then scanning especially over the radial aspect of the second MCP joint often revealed PD positivity and also bony irregularity or early erosions.

3.6.11 Location of inflammation (intra- or extra-synovial)

When the 500 MCP joints of the early RA patients were considered, 146/500 (29%) MCP joints had evidence of abnormal M1 and normal M2. The majority of these joints had underlying US synovitis (88%), with only 12% without this association. To determine whether extra-synovial inflammation was an extension of involvement of the joint cavity with synovitis, the possibility of occurrence of abnormal M2 with normal M1 was explored. Sixteen of 500 MCP joints or 3% had abnormal M2 with normal M1, with 75% having associated US synovitis documented.

3.7 Discussion

3.7.1 Inflammatory arthritis compared with control group (specificity of US)

The baseline demographics of our participants were similar to other EA clinics, with just over a third of participants having RF (Harrison 1996) and a greater proportion

with anti-CCP antibody positivity. Bony erosions were found radiographically in 6.3% as assessed by the modified Sharp score. This compared with an EA study with median disease duration of less than 3 months and 60% self-limiting disease at 2 years in which 23% of subjects were RF positive and 15% had radiographic erosions of the hands and feet at baseline (Visser 2002). In another very early RA cohort, erosions were present in approximately 13% of baseline plain radiographs (Machold 2002). In the present study, all of the US findings were seen much more commonly in the early RA than the control group. 2.1% of control MCP joints had US evidence of synovitis or effusion, with 1.6% of all MCP joints in the control group having an effusion in the dorsal aspect of the joint. In a study by Boutry and co-workers of healthy controls, a comparable number (3%) of all MCP joints had a small amount of fluid in the dorsal or volar synovial recess (Boutry 2004).

3.7.2 Profile of US features in early RA

To differentiate between the early RA and control groups reliably, the study sought features not seen in the control group. ET and PD positivity were US features absent from the control group making them 100% specific for early RA relative to normal non-arthritic controls. These findings have not been reported previously. ET can be an important component of MCP joint swelling that is observed clinically, as the presence of ET alone was the major US feature of inflammatory arthritis that was seen in some participants. Additionally, 92% of all early RA patients had at least four MCP joints with synovitis or effusion, compared with none in the control group.

30% of the early RA patients had US features of erosive disease, compared with 0.5% of the control group. The definition of erosions on US is important, as the majority of

previous studies have defined erosions as having irregular margins and discontinuity of the cortical bone in 2 planes (Wakefield 2005), as they were in this study. However, if there is no requirement for a cortical break, erosion-like changes may be seen on US in healthy controls (Dohn 2006).

3.7.3 PD positivity and clinically evident joint swelling

One of the most important clinical challenges is to be able to differentiate active from inactive synovitis in RA joints, which may not be discernable on clinical assessment. Our rate of PD positivity in clinically swollen MCP joints of 42% was consistent with previous studies that have reported similar rates of 40-50% (Rees 2006). Up to 30% increase in PD positivity can be seen when intravenous (IV) contrast was employed (Rees 2006), however the disadvantages of IV contrast include increased assessment time, the invasiveness of IV access and the expense. Hence IV contrast was not utilised in our study.

The overall rate of PD positive MCP joints in the early RA group in this study was lower at 27% compared with 48.4% having clinical synovitis. A possible explanation for the excess in clinical synovitis compared to PD positivity is that clinical assessment of disease activity relies on synovial thickening which is not necessarily an indicator of active disease, as it may include inactive fibrous tissue, fibrinous aggregates, complex effusion or tissue debris (Hau 1999). Another small study of RA of varying disease duration reported similar results, with 34% of MCP joints being PD positive compared with clinical swelling in 39% (Weidekamm 2003). PD positivity may be lower in established RA due to chronic inactive synovial proliferation, such as in one established RA study with 20% PD positive MCP joints (Kaye 2001). Active synovitis is better

represented by the presence of positive PD, and US with PD in clinic can be a useful complement to clinical examination and laboratory inflammatory markers for assessment of disease activity in RA joints.

3.7.4 PD positivity and US synovial thickening

In the 500 MCP joints assessed in this study, 77% had US evidence of synovitis and/or effusion. Overall 27% of the MCP joints were PD positive, with 35% PD positivity if only MCP joints with US evidence of synovitis, effusion or ET were considered. This was comparable to a study in established RA by Kaye and co-workers (Kaye 2001), who reported increased synovial thickness (greater than 1mm) in 60% of all MCP joints, with 34% of these being PD positive. In contrast, approximately 14% of MCP joints without US demonstrated synovial thickening were PD positive in our study, therefore 2.5 times more PD positivity was seen in US abnormal MCP joints. PD positivity in joints without synovial thickening was not reported in the study by Kaye to allow for direct comparisons to be made. Overall, this suggests that in early disease, PD positivity may appear before or without synovial thickening, which may have a less distinctive appearance compared with in established RA.

3.7.5 PD positivity and US measurements

When the measurements in this study were considered, the mean M1 of the PD positive joints was 6.1mm compared with 5.6mm of PD negative joints, a highly significant difference statistically (Mann Whitney p value <0.0001). However, the mean values of M2 in PD positive compared with negative MCP joints were 1.99mm and 1.85mm, which was not quite significant (p=0.051). This was consistent with the findings in untreated established RA (Kaye 2001), in which there was significantly greater

synovial thickness in PD positive joints with a mean of 3mm compared with PD negative joints of 2.3mm (p=0.0002, unpaired t test). The exact location of measurements in Kaye's study (Kaye 2001) are not reported to allow direct comparison with either M1 or M2 from our study. Identification of a vascular signal by PD positivity is likely to identify more active synovitis (possibly associated with greater synovial thickness or pannus with the potential for progression to erosive damage). Longitudinal studies are required to clarify this issue further.

3.7.6 Sub-clinical synovitis

Sub-clinical synovitis has recently been recognised in RA and has been confirmed in early RA in this study. Our therapeutic approach is distinctive in that the aim has been rapid control of symptoms and achievement of remission using a standardised intensive regimen with combination DMARD therapy. US was performed at an early stage of disease, with a median duration of 4 months. Of the 45% of patients taking DMARDs at the time of the US, most were using only one DMARD for a period of one to two weeks (too early for a significant disease-modifying effect).

In this study, US detected more synovitis than clinical examination for swelling, with 76% of all MCP joints with US evidence of synovitis and/or effusion compared with 48% with clinically detected synovial thickening. These rates of detection of synovitis by US are higher than in previous early inflammatory arthritis studies in which US evidence of synovitis in joints examined was 52% and 27% respectively (Backhaus 1999, Wakefield 2004c). In the study of Wakefield and co-workers (Wakefield 2004c), which involved DMARD naïve patients with oligoarthritis of mean duration 18 weeks,

the rate of synovitis detected by US in MCP joints was 16% compared to 27% with US synovitis among all joints examined.

Our higher rates of US detection of synovitis may be due to the early timing of the US scans. Also, the studies by Backhaus and Wakefield both utilised US equipment of lower resolution than in our study, with one requiring a stand-off pad for better focussing (Backhaus 1999, Wakefield 2004c). The respective proportions of MCP joints with US and clinical synovitis cannot be determined from the data reported in either study since other joints are included in the datasets. Our results are consistent with the findings of Hau and co-workers who report pannus in 52-82% of RA joints scanned using high resolution US (Hau 1999).

The ratio of US synovitis to clinical swelling of 1.6 in our study was comparable to previous studies with similar ratios of 1.5-1.6 in early arthritis (Backhaus 1999, Wakefield 2004c, Szkudlarek 2006). By considering only the non-erosive shorter disease duration group of patients in the study by Backhaus, and using the definition of clinical synovitis of a swollen joint with or without tenderness, the ratio of US to clinical synovitis is 2.4 (Backhaus 1999). By comparison, in established RA, US has been shown to detect more effusion and synovitis than clinical examination by a lesser factor of 1.3 (Naredo 2005a).

Of clinically non-swollen MCP joints in our study, 67% had US evidence of synovitis and/or effusion affecting 80% of the early RA patients. This compares with Wakefield's study in early untreated oligoarthritis where overall, 33% of joints that were clinically non-swollen demonstrated US synovitis, affecting 64% of their subjects

(Wakefield 2004c). In Szkudlarek's study of early and established RA, only 19% of clinically non-swollen joints had US synovial inflammation (Szkudlarek 2006). In another established RA cohort, synovitis was found by US in 30% of clinically non-swollen joints (including wrists, MCP and PIP joints), with 41% sub-clinical synovitis affecting the MCP joints (Ribbens 2003). Lower rates of sub clinical synovitis detected by US in other studies may reflect the use of lower resolution US equipment or inclusion of established RA patients receiving treatment.

Using clinical examination as the standard of reference, the present study showed that the sensitivity and specificity of MCP joint US synovitis was 86% and 33% respectively. This confirms results of a study by Ribbens and co-workers in which sensitivity and specificity of US synovitis for the MCP joints was 73% and 41% respectively (Ribbens 2003). In Ribbens' study, if an MCP joint was clinically swollen at baseline, then US positivity for synovitis was twice as high compared to non-swollen MCP joints ($p<0.01$). In contrast, our rate was lower with 1.3 times the number of clinically swollen joints having US synovitis compared with non-swollen joints ($p<0.0001$). This can be explained by the greater amount of sub clinical synovitis expected in our early minimally treated RA patients, compared with treated erosive established RA patients (mean disease duration of 9 years) in Ribbens' study.

It is notable that there have been no studies to validate the reproducibility of clinical examination or its sensitivity for synovitis. In established RA, persistently swollen joints may be due to scar or pannus rather than active disease, and previous studies have designated swollen only joints as inactive (Kiris 2006). This is in contrast to the present study in early RA where swollen alone or swollen and tender MCP joints were

considered as having active synovitis. Given the amount of sub clinical synovitis detected, the use of US as the reference standard for inflammatory changes was also explored. PD appears to have clinical significance, with sensitivity, specificity and agreement with clinically detected swelling of 76%, 62% and 65% respectively when US PD positive joints were used as the reference. Specificity of clinical examination was improved to 76% when using combined qualitative US features with some loss of sensitivity and agreement. Similar results were obtained when comparing clinical swelling to US synovitis/effusion alone. Overall, sensitivity and specificity was low when considering US measurements as the reference standard, and combined M1 and M2 did not add much to the qualitative US variables. Considering the lower specificity of clinically-detected swelling for quantitative US abnormalities as the reference, it appears that there could be more use for US measurements in longitudinal assessment rather than for diagnostic purposes. This is explored in Chapter 5.

All of the above studies highlight the relative insensitivity of clinical examination for synovitis, and therefore the significant limitations of clinical assessment in monitoring disease activity in RA. Poor agreement between clinical and US findings may be explained by the presence of other factors such as excessive subcutaneous tissue or joint deformities including the osteophytes (bony outgrowths) of osteoarthritis. It is important also to consider that a clinically swollen MCP joint may not just be attributable to synovitis, but may include a component of flexor or extensor tenosynovitis, joint effusion, thickening of the joint capsule or bursitis (Ribbens 2003). If ET was included as US evidence of inflammatory change, then there was 1.7 times more US than clinical swelling in this study. About a third of various joints in

Wakefield's study that were positive for clinical synovitis but negative for US synovitis were explained by tenosynovitis (Wakefield 2004c).

The present study showed that about 15% of clinically swollen MCP joints had no corresponding US synovitis. However, 11% of these US negative results were positive for ET or PD or had abnormal US measurements or increased BMI with subcutaneous oedema and increased M3. Hence, clinical swelling with negative US was seen in less than 4% of MCP joints. This compares with Wakefield's early arthritis study, where 8% of clinically swollen joints were not explained by US findings (Wakefield 2004c).

There are currently no published longitudinal studies following untreated US-detected sub-clinical synovitis to determine the prognostic importance of this feature. This issue impacts on the definition of 'remission' in RA. Currently the aim is for clinical remission but increasingly it is being recognised with more sensitive imaging methods, that in spite of clinical remission, imaging remission is not present (that is, sub-clinical synovitis persists). The low sensitivity of clinical examination to ongoing inflammation may explain the deterioration of RA patients despite clinically adequate disease control, with progression of erosive changes despite minimal clinical evidence of disease activity. Thus the practical issue emerges as to how a low disease activity state defined by US but not evident on clinical examination should be managed to obviate potential vulnerability to progressive joint damage. Clearly, further studies will be needed to address this matter.

3.7.7 When should US measurements be performed?

Our results support the notion that quantitative US assessment in early RA is useful. The measurements could be done selectively in those subjects without obvious US evidence of synovitis or effusion or when anatomical structures are less well defined. US measurements can provide an objective measure of MCP joint swelling that is known to correlate with qualitative US abnormalities as reported and hence may be a marker of disease activity that is present but not obvious in the very early RA setting. An obvious potential application for US metrics is in the longitudinal evaluation of involved indicator joints in subjects with polyarthritis.

3.7.8 Correlation of inflammatory markers with US findings

Our study showed a weak trend towards an association between ESR and the number of PD positive MCP joints or with synovitis/effusion seen on US, which is consistent with previous results from an established RA study that showed ESR was significantly correlated with cumulative synovial thickness and the number of US synovitis positive joints (Ribbens 2003). Unsurprisingly, ESR also correlated with DAS28 levels in our study, given that ESR is used in the equation to calculate the DAS. CRP did not significantly correlate with any of the clinical or US variables assessed in our study. Previous studies in established RA revealed no significant correlation between US grades of inflammatory or erosive changes and DAS, ESR, CRP or functional assessments (Lerch 2003, Ribbens 2003, Scheel 2005).

There was a trend towards an association between ESR, but not CRP, and the number of clinically swollen MCP joints, contrasting with results from a recent study of established RA in which CRP did correlate with the number of swollen joints clinically

(Ribbens 2003). In our study, clinical disease activity appeared to be reflected in the number of PD positive joints with significant correlations between the DAS28 level and the number of PD positive MCP joints. A significant relationship between the number of clinically swollen MCP joints and the DAS28 is not unexpected, as swollen joints are part of the DAS equation.

3.7.9 Extensor tenosynovitis (ET) and its potential importance

ET as an entity is underestimated, is often not even considered in the clinical assessment of RA, nor is widely regarded as contributing to joint swelling. More than 80% of patients had at least one MCP joint with ET. This was slightly more common than in Hoving's study, where approximately 65% of all early RA subjects studied had tendon sheath thickening (Hoving 2004). In 42% of all MCP joints, ET was the only US feature of inflammatory disease, with no evidence of synovitis or effusion present. There are no studies to date examining the relationship between ET and the development of erosions in RA.

3.7.10 US compared to plain radiographic erosions

In the present study, there were approximately 2.5 times as many US compared with radiographic erosions at baseline. Wakefield and co-workers (Wakefield 2000) demonstrated 6.5 times as many erosions in the MCP joints of an early arthritis group using US than with plain radiographs. Some evidence of the pathological specificity of US erosions in our study was given by MRI (Chapter 4), with all the additional lesions on US able to be seen on MRI (100% specificity using MRI as the reference standard).

3.7.11 Documentation of synovitis distribution

When focussing on the finer details of involvement of the MCP joints with synovitis and erosions, the study demonstrated that the dorsal aspect of the MCP joints was more informative than the volar surface for detecting synovitis. In contrast, a previous study has suggested that fluid is more readily visible at the volar aspect of the MCP and PIP joints (Hoving 2004), and in those joints without synovitis on the dorsal aspect, it may be useful to examine further on the volar aspect. It was shown in this study that less information was available from volar assessment. That is, a very small proportion of MCP joints without dorsal synovitis had evidence of volar synovitis (about 5%) in early RA.

Scheel and co-workers suggested that in established RA, it may be reasonable to consider only performing volar US scans, as 86% of synovitis was detected at the palmar proximal MCP and PIP joints (Scheel 2005). However, it may not be appropriate to apply this methodology in the early RA setting, as synovitis may be more localised and sparse, with a different distribution of synovitis as shown in this study (localised mainly at the dorsal aspect of the MCP joints). In the author's opinion, given the time that it takes to examine the dorsal and volar aspects with little additional information being gained, it is more efficient in early RA to scan only the dorsal aspect initially for any abnormalities.

The distribution of synovitis and erosions on the radial or ulnar side of the MCP joints was also determined, and it was shown that in accord with previous MRI studies (Tan 2003), the radial aspect of the MCP joints was more often affected than the ulnar aspect, perhaps secondary to anatomical factors. In the present study, if power Doppler

was negative over the dorsal aspect, then scanning especially over the radial second MCP joint often revealed PD positivity and also irregularity or early erosions.

3.7.12 Intra- and extra-synovial involvement and measurements

Previous studies have shown that the extensor tendon overlying the MCP joint, especially at the MC head, can be displaced upwards by synovial swelling in the joint cavity, hence increasing M1. Our hypothesis was that as synovial proliferation extends proximally along the shaft of the MC bone, M2 would also be abnormally increased. This only holds true if there is one pathological process of synovial proliferation, originating in the intra-synovial space. However, an alternative explanation may be that there are two separate pathologies, both intra-synovial and extra-synovial.

To determine whether extra-synovial inflammation was an extension of involvement of the joint cavity with synovitis, we determined if there were any MCP joints with abnormal M2 alone. It was shown that 3% of MCP joints had abnormal M2 alone, with 75% having associated US synovitis documented. These findings suggest that in a small subset of MCP joints, extra-synovial involvement may occur alone, possibly as a separate discontinuous focus of inflammation. The possibility exists of distinct prognostic implications, as suggested by a previous MRI study, which showed that intra-synovial involvement was associated with a poorer prognosis compared with extra-synovial involvement (McGonagle 1999b).

3.8 Conclusions

The present study highlights the relative insensitivity of clinical examination for synovitis, and therefore its significant limitations in monitoring disease activity in RA.

ET is underestimated clinically and may be the only US feature of inflammatory disease in a significant proportion of MCP joints. PD positivity and ET were highly specific findings in early RA relative to normal controls. Thus criteria could be based on these findings and the number of MCP joints affected with synovial inflammation to distinguish between early RA and non-arthritic control groups. The dorsal aspect of the MCP joints was more informative than the volar surface for synovitis in early RA. Extra-synovial involvement alone (increased M2 and not M1) is an uncommon feature of early RA.

The next chapter examines the correlation between US and MRI findings, including the association between US and MRI measurements of synovial swelling, to further validate US results. In Chapter 5, we will consider whether US measurements are able to predict a poorer outcome, such as persistence of disease or progression of radiographic erosive changes and whether measurements are changed during DMARD treatment.

CHAPTER 4

Validation of HRUS with Magnetic Resonance Imaging (MRI)

4.1 Background

HRUS is able to detect sub clinical synovitis and two to six times more erosions than plain radiographs in early and established RA (Wakefield 2000, Dohn 2006, Scheel 2006). In contrast with magnetic resonance imaging (MRI), it is relatively inexpensive and does not involve ionising radiation. However, MRI also detects erosions earlier and is more sensitive for small erosions than US, with the ability to detect up to three times more erosions than US (Backhaus 2002, Scheel 2006). Comparisons of US to MRI with regards to the detection of synovitis and tenosynovitis have yielded somewhat variable findings (Backhaus 1999, Hoving 2004, Scheel 2006, Szkudlarek 2006) (see discussion section). Nonetheless, HRUS is likely to be a useful tool in the assessment of recent onset arthritis.

The question remains as to whether the detection of small erosions or synovitis by US predicts later radiographic damage in those joints, and hence worse functional outcome. Further longitudinal studies are required to validate US as a technique for detecting erosions and to evaluate the relationship between sonographic findings and other imaging modalities. Correlation between US and MRI findings with regard to bony erosions and histological evidence of erosions is technically difficult and was beyond the scope of the present investigations.

4.2 Aims

(1) To validate US findings in recent onset RA by comparison with MRI as the reference standard. Specifically, the study aimed to determine the sensitivity, specificity and accuracy of HRUS in the detection of synovitis, tenosynovitis, joint effusions and erosions.

(2) To validate the US measurement protocol presented in Chapter Two by comparison with corresponding MRI measurements.

4.3 Hypotheses

(1) In early RA, US is less sensitive for smaller erosions than MRI, but is superior for detection of synovitis, joint effusion and tenosynovitis (particularly in relation to the extensor tendon given its smaller size).

(2) Measurements performed by US and MRI correlate well

4.4 Participants

4.4.1 Selection

Patients from the early arthritis clinic as described in Chapter Three were invited to participate in the MRI sub study at Flinders Medical Centre, with MRI to be undertaken on the same day as their US examination. Their median age of subjects was 55 years (20-82), median disease duration 4 months (2-12), 78% were females, 38% RF positive and 52% anti-CCP positive. Disease activity was high (mean DAS28 of 5.7) and 12% radiographic erosions of the hands and feet were detected at baseline. 56% were DMARD-naïve.

4.4.2 Inclusion Criteria

Patients completed a screening questionnaire to assess MRI suitability (Appendix D). Those without contraindications to MRI (as described in the exclusion criteria) were recruited. An invitation was extended to subjects to contact the MRI department directly if there were any issues of concern or positive answers to any of the questions on the MRI safety screening form. Informed consent was obtained for the MRI procedure on the day of the MRI by Dr John Slavotinek, Director of MRI at the Flinders Medical Centre. This sub study was approved by the Royal Adelaide Hospital and Flinders Ethics Committees.

4.4.3 Exclusion Criteria

Patients were excluded if they had any contraindications to MRI, such as severe claustrophobia, metal foreign bodies (especially metal workers or welders with eye injuries caused by metal), neurostimulators, cochlear implants, artificial heart valves or clips, pacemakers, metallic clips (such as for brain aneurysms), implanted stimulation or drug infusion devices, implanted prostheses or artificial body parts, recent surgery with clips or wire sutures, embolisation coil, possibility of pregnancy, breastfeeding or previous reaction to CT scan contrast dye or asthma (increased potential for contrast dye reaction). If patients were not agreeable to the introduction of contrast dye for the MRI via intravenous (IV) access, they were also excluded.

4.5 Methodology

Observational validation study

4.5.1 Comparison with Magnetic Resonance Imaging

MRI was performed with a Phillips Intera Master 1.5 Tesla device (Best, Netherlands) at Flinders Medical Centre (Bedford Park, South Australia, Australia) with patients lying supine. The average acquisition time for the MRI scan was 40 minutes. Scans of the more severely clinically affected hand were directed at the second to fifth MCP joints using a dedicated MAI wrist coil. This procedure was chosen to save time and cost, as it was not possible to examine both hands simultaneously with high resolution contrast-enhanced MRI. Patients were examined with the following sequences:

- 2mm T1 weighted non-fat suppressed turbo spin-echo scans in coronal and axial planes and 2mm T2 weighted fat suppressed turbo spin-echo in the coronal plane
- Pre-gadolinium injection, fast field echo scan in the sagittal plane with 2mm thick slices at 1mm intervals
- IV bolus injection of gadolinium (Magnevist (dimeglumine gadopentetate), Schering AG, Germany) 15mL followed by normal saline 20mL via a pump
- Commencing 30 seconds prior to the gadolinium infusion, dynamic fat suppressed T1 weighted turbo spin-echo scans in the coronal plane at slice thickness 3mm every 9 seconds for 6 minutes
- Post gadolinium 3D T1 weighted fast field echo scans in the sagittal plane through the 2^{nd} to 5^{th} MCP joints with slice thickness of 1.6mm and 0.8mm spacing. Data from this sequence were reformatted to create images in the plane parallel to the extensor tendons for longitudinal measurements
- Lastly, T1 weighted turbo spin-echo coronal and axial non-fat suppressed images at intervals of 2mm were performed to examine contrast enhancement (synovitis)

Measurements were performed based on those developed in this study for US (see Chapter Two, pages 102-104). Briefly, the M1 measurement was taken from the midpoint of the MCP joint to the ventral surface of the extensor tendon proper. M2 was taken from the metacarpal head at the point where the articular cartilage terminated proximal to the ventral surface of the overlying extensor tendon. Scans were then graded according to the OMERACT RAMRI scoring system (Lassere 2003), with synovitis, erosions, bone defects and oedema scored. The presence of joint fluid and extensor or flexor tenosynovitis were recorded (not usually a formal part of the RAMRI scoring system).

4.6 Statistical analysis

The data were analysed using the SAS Version 9.1 package (Cary, NC, USA) as well as PRISM and INSTAT programs. Spearman's correlation, a nonparametric statistical method, was chosen as the data were not normally distributed. It was used to assess the relationship between US and MRI measurements. For the purposes of this study, a weak correlation was considered to be an r value of less than 0.4, a moderate correlation 0.4 to 0.7 and a good correlation of greater than 0.7. Sensitivity, specificity, accuracy, positive and negative predictive values (PPV and NPV respectively) with 95% confidence intervals (CI) of US for synovitis, erosions, tenosynovitis and joint effusion were determined using MRI as the reference standard.

4.7 Results

Among the 14 patients who underwent US followed by MRI on the same day, four had incomplete data. Of the latter, patient 3 had no measurements performed as no appropriate dynamic image was recorded by the radiographer in error (incomplete MRI

protocol performed). Patient 11 had significant movement when MCP five was being assessed and therefore there was uncertainty regarding the anatomical changes in this joint and no measurements were available for this region. Patient 12 refused IV contrast at the time of the MRI, therefore no reliable findings for pathological changes or measurements were available. Patient 13 also refused contrast on the day and could not stay immobile for long enough due to severely painful joints. Therefore, there were ten patients with complete data and eleven with sufficient data to assess the correlation between US and MRI measurements and to document other abnormalities.

In pooled data from all assessed MCP joints, MRI was more sensitive for the detection of erosions than US by a factor of 4.3. The odds ratio for detection of MRI erosions in the presence of US erosions was 25 (95% CI 1.2-523.6) with a significant p value using Fisher's exact test (p=0.01). Compared with MRI, US was almost equivalent for detection of synovitis (odds ratio of 1.07, 95% CI 0.10-11.44), and superior for extensor tenosynovitis (ET) with an odds ratio of 1.58 (95% CI 0.43-5.83). Flexor tenosynovitis (FT) was more commonly seen on MRI by a factor of 2.7 (odds ratio 21.0, 95% CI 1.1-387.1, p=0.004) and there were 1.6 times more joint effusions detected by MRI (odds ratio 0.33, 95% CI 0.04-3.02). In summary (Table 4.6), US detected more synovitis (by a factor of 1.2) and ET than MRI (sensitivities 91.4% and 64.3% respectively) but with low specificity (9.1% and 46.7% respectively) and was very insensitive for erosions, effusions and FT (23.1%, 7.7% and 37% respectively).

Accuracy of US varied between MCP joints 2-5. Overall US performed well at MCPs 4 and 5, but was most accurate at MCPs 2 and 3 for detection of synovitis when compared to MRI (100% and 82% respectively). MCP 2 was the most accurate for ET

(64%, Table 4.4(f)). When considering the MCP joints most accessible for US (MCP joints 2 and 5), the specificity of US for synovitis was doubled with the sensitivity and accuracy increased slightly from 91% and 72% to 94% and 77% respectively (Table 4.7). For detection of erosions, there was minimal improvement in sensitivity from 23% to 25% without loss of specificity (still 100%). There was a slight fall in accuracy from 80% to 76%, not likely to be clinically significant.

There was a significant correlation between US and MRI measurements, with a weak relationship shown using Spearman's rank correlation for M1 (r=0.32, p=0.046) and a moderate correlation for M2 (r=0.48, p=0.002). Therefore, M2 performed better than M1.

Table 4.1 HRUS compared to MRI for detection of erosions

Table 4.1(a) MCP 2 (n=14)

	MRI Y	MRI N
US Y	1	0
US N	5	8

Table 4.1(b) MCP 3 (n=13)

	MRI Y	MRI N
US Y	1	0
US N	3	9

Table 4.1(c) MCP 4 (n=12)

	MRI Y	MRI N
US Y	0	0
US N	1	11

Table 4.1(d) MCP 5 (n=11)

	MRI Y	MRI N
US Y	1	0
US N	1	9

Table 4.1(e) Pooled data MCP joints 2-5 for detection of erosions (n=50)

	MRI Y	MRI N
US Y	3	0
US N	10	37

Table 4.1(f) Performance of HRUS in detecting erosions defined by MRI

MCP	Sens (%)	Spec (%)	PPV (%)	NPV (%)	Agreement (%)
2	16.7	100	100	61.5	64.3
3	90	0	90	0	76.9
4*	-	-	-	-	91.7
5	50	100	100	90	90.9
Pooled 2-5	23.1	100	100	78.7	80

Sens= sensitivity; spec=specificity; PPV=positive predictive value; NPV=negative predictive value
* no US erosions shown at MCP 4, therefore unable to calculate results

MRI found 13:3 or 4.3 times more erosions when compared to US

Table 4.2 HRUS compared to MRI for detection of synovitis

Table 4.2(a) MCP 2 (n=11)

	MRI Y	MRI N
US Y	11	0
US N	0	0

Table 4.2(b) MCP 3 (n=11)

	MRI Y	MRI N
US Y	9	1
US N	1	0

Table 4.2(c) MCP 4 (n=13)

	MRI Y	MRI N
US Y	7	5
US N	1	0

Table 4.2(d) MCP 5 (n=11)

	MRI Y	MRI N
US Y	5	4
US N	1	1

Table 4.2(e) Pooled data MCP joints 2-5 for detection of synovitis (n=46)

	MRI Y	MRI N
US Y	32	10
US N	3	1

US found 42:35 or 1.2 times more synovitis than MRI

Table 4.2(f) Performance of HRUS in detecting synovitis defined by MRI

MCP	Sens (%)	Spec (%)	PPV (%)	NPV (%)	Agreement (%)
2*	-	-	-	-	100
3	90	0#	90	0	81.8
4	87.5	0#	58.3	0	53.8
5	83.3	20	55.6	50	54.5
Pooled 2-5	91.4	9.1	76.2	25	71.7

Sens= sensitivity; spec=specificity; PPV=positive predictive value; NPV=negative predictive value
* all MCP 2 joints had evidence of US and MRI synovitis, therefore unable to calculate sensitivity, specificity, PPV or NPV
# specificities of zero as no third or fourth MCP joints without synovitis on US and MRI in this subgroup

Table 4.3 HRUS compared to MRI for detection of joint effusion

Table 4.3(a) MCP 2 (n=12)

	MRI Y	MRI N
US Y	0	1
US N	7	4

Table 4.3(b) MCP 3 (n=12)

	MRI Y	MRI N
US Y	0	3
US N	2	7

Table 4.3(c) MCP 4 (n=12)

	MRI Y	MRI N
US Y	1	0
US N	1	10

Table 4.3(d) MCP 5 (n=12)

	MRI Y	MRI N
US Y	0	3
US N	2	7

Table 4.3(e) Pooled data MCP joints 2-5 for detection of joint effusion (n=48)

	MRI Y	MRI N
US Y	1	7
US N	12	28

MRI found 13:8 or 1.6 times more joint effusions when compared with US

Table 4.3(f) Performance of HRUS in detecting joint effusions defined by MRI

MCP	Sens (%)	Spec (%)	PPV (%)	NPV (%)	Agreement (%)
2	0	80	0	36.4	33.3
3	0	70	0	77.8	58.3
4	50	100	100	90.9	91.7
5	0	70	0	77.8	58.3
Pooled 2-5	7.7	80	12.5	70	60.4

Sens= sensitivity; spec=specificity; PPV=positive predictive value; NPV=negative predictive value

Table 4.4 HRUS compared to MRI for detection of extensor tenosynovitis (ET)

Table 4.4(a) MCP 2 (n=11)

	MRI Y	MRI N
US Y	5	1
US N	3	2

Table 4.4(b) MCP 3 (n=11)

	MRI Y	MRI N
US Y	2	6
US N	1	2

Table 4.4(c) MCP 4 (n=11)

	MRI Y	MRI N
US Y	1	5
US N	0	5

Table 4.4(d) MCP 5 (n=11)

	MRI Y	MRI N
US Y	1	4
US N	1	5

Table 4.4(e) Pooled data MCP joints 2-5 for detection of ET (n=44)

	MRI Y	MRI N
US Y	9	16
US N	5	14

US found 25:14 or 1.8 times more ET than MRI

Table 4.4(f) Performance of HRUS in detecting ET defined by MRI

MCP	Sens (%)	Spec (%)	PPV (%)	NPV (%)	Agreement (%)
2	62.5	66.7	83.3	40	63.6
3	66.7	25	25	66.7	36.4
4	100	50	16.7	100	54.5
5	50	55.6	20	83.3	54.5
Pooled 2-5	64.3	46.7	36	73.7	52.3

Sens= sensitivity; spec=specificity; PPV=positive predictive value; NPV=negative predictive value

Table 4.5 HRUS compared to MRI for detection of flexor tenosynovitis (FT)

Table 4.5(a) MCP 2 (n=11)

	MRI Y	MRI N
US Y	5	0
US N	6	0

Table 4.5(b) MCP 3 (n=11)

	MRI Y	MRI N
US Y	2	0
US N	5	4

Table 4.5(c) MCP 4 (n=11)

	MRI Y	MRI N
US Y	3	0
US N	2	6

Table 4.5(d) MCP 5 (n=11)

	MRI Y	MRI N
US Y	0	0
US N	4	7

Table 4.5(e) Pooled data MCP joints 2-5 for detection of FT (n=44)

	MRI Y	MRI N
US Y	10	0
US N	17	17

MRI found 27:10 or 2.7 times more FT than US

Table 4.5(e) Performance of HRUS in detecting FT as defined by MRI

MCP	Sens (%)	Spec (%)	PPV (%)	NPV (%)	Agreement (%)
2[#]	-	-	-	-	45.5
3	28.6	100	100	44.4	54.5
4	60	100	100	75	81.8
5*	-	-	-	-	63.6
Pooled 2-5	37	100	100	50	61.4

Sens= sensitivity; spec=specificity; PPV=positive predictive value; NPV=negative predictive value
[#] MRI FT at all MCP 2 joints, therefore only able to calculate accuracy of US results
* US no evidence of FT at any MCP 5 joints, therefore unable to calculate values

Table 4.6 Performance of HRUS in detecting pathological features defined by MRI in MCPs 2-5

Pathological Feature	Sensitivity	Specificity	Agreement	Odds ratio (95% CI)*
Erosions	23%	100%	80%	25 (1.2-523.6)^
Synovitis	91%	9%	72%	1.07 (0.10-11.44)
Joint effusion	8%	80%	60%	0.33 (0.04-3.02)
Extensor tenosynovitis	64%	47%	52%	1.58 (0.43-5.83)
Flexor tenosynovitis	37%	100%	61%	21 (1.1-387.1)^

* odds ratio of detecting with US an MRI-defined feature
^ Fisher's p values 0.01 and 0.004 respectively, considered significant

Table 4.7 Comparison of HRUS to MRI using MCPs 2 and 5 only

Pathological feature	Sensitivity	Specificity	Agreement
Erosions	25%	100%	76%
Synovitis	94%	20%	77%

4.8 Discussion

4.8.1 US compared with MRI for detection of erosions

This study confirmed the lower sensitivity of US in detecting bone erosions when compared to MRI in early RA. This is usually explained by the lack of access of US to certain aspects of joints compared with MRI, for example the ulnar and radial aspects of the third and fourth MCP joints. US is known to have the highest sensitivity for bone erosions at the easily accessible joints such as the 2nd and 5th MCP and PIP joints (Wakefield 2000, Szkudlarek 2006). This was confirmed in a recent study which demonstrated greater sensitivity of US in detection of erosions when considering the easily accessible MCP and PIP joints only (Dohn 2006). In another RA study by Szkudlarek and co-workers, erosions not seen on MRI were seen on US mainly at the second and fifth MCP joints (Szkudlarek 2006) . Similarly, erosions not seen on US were visualised at the third and fourth MCP joints on MRI, those with the poorest access on US. In contrast, there was minimal increase in sensitivity for both US detection of erosions and synovitis when considering MCP joints 2 and 5 only in this study. These latter findings may be explained by the observations of Szudlarek et al. that there were still bone surfaces not able to be accessed by US at the second and fifth MCP joints in spite of good access to the radial and ulnar aspects respectively.

Backhaus and colleagues (Backhaus 2002) found that US was less sensitive for detecting minute erosions than MRI and less reliable for detecting deeper erosions with only a narrow connection to the joint surface. An example of this from our study is shown in Figures 4.1(a) - 4.1(c) which clearly demonstrate a ventral erosion of the left fourth MCP joint at the MC head on MRI, without any irregularity or bone defect on the corresponding US image. This would have been scored as an erosion for the MRI and negative on the US.

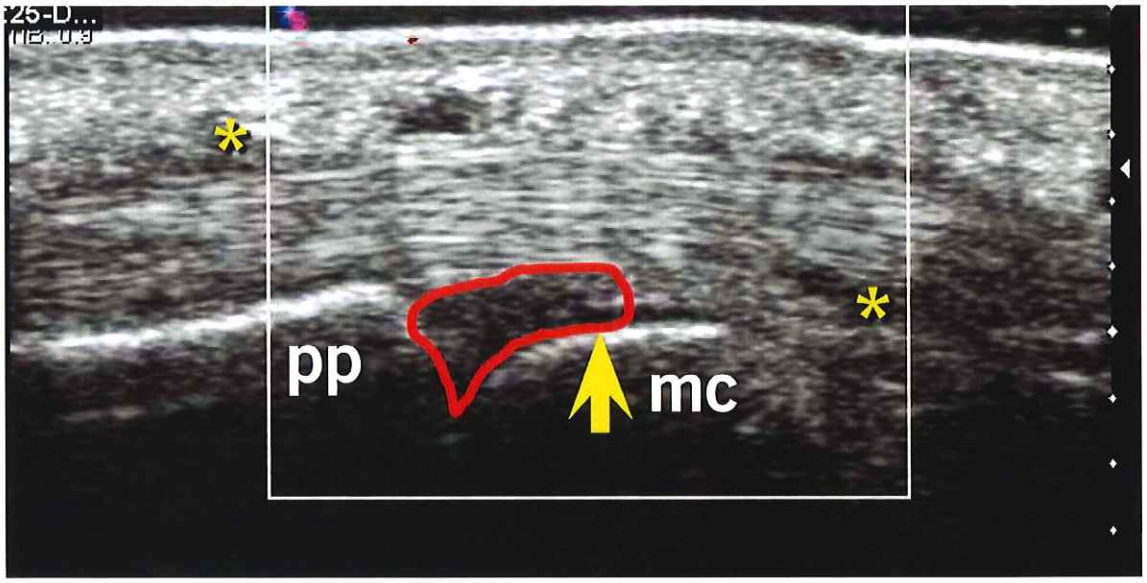


Figure 4.1(a) HRUS of volar left 4th MCP joint with * hypoechoic areas around flexor tendon representing tenosynovitis and arrow showing no erosion at the MC head

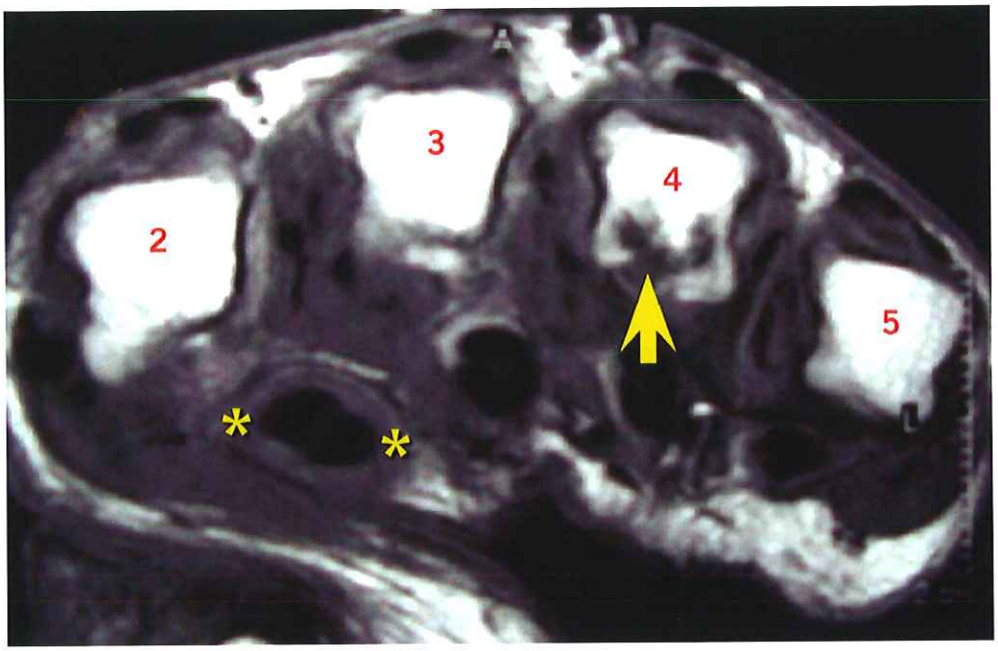


Figure 4.1(b) Pre-gadolinium MRI of corresponding left 4th MCP joint with bone defect on volar aspect of MC head (arrow) and FT (*)

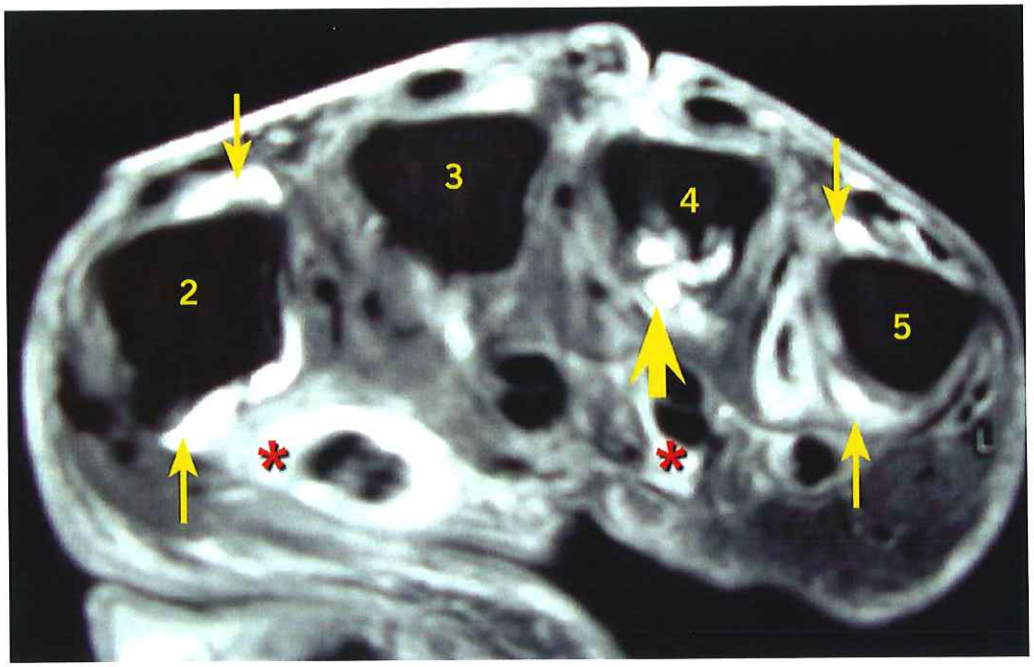


Figure 4.1(c) Post-gadolinium MRI of left 4th MCP joint clearly shows bone defect and erosion of volar aspect of MC head with gadolinium enhancement (thick arrow). Additionally, there is second and fourth finger FT (*) and synovitis of second and fifth MCP joints (thin arrows)

A previous study has examined imaging modalities for bone erosions and compared radiographs, MRI and US with high-resolution CT scans as the reference standard for imaging calcified tissue in which an erosion was defined as loss of calcified tissue with cortical destruction (Dohn 2006). Both US and MRI were highly specific and moderately sensitive in detecting bone erosions in comparison to CT scans for radiographically occult erosions (specificities 92% and 96% and sensitivities of 30% and 65% for US and MRI respectively).

When considering MRI as the reference method for erosions, this study demonstrated sensitivity and specificity of US to be 23% and 100% respectively. The sensitivity was lower than a previous RA study which found 59% sensitivity and 98% specificity of US erosions (Szkudlarek 2006). Given that there were no false positive US erosions, the study has shown that US is highly specific for erosions defined by MRI.

On the other hand, the significance of minute erosions detectable by MRI only may be quite different from that of obvious erosions on conventional radiographs or US, so it is yet to be established that it necessarily matters that US is less sensitive. Whilst MRI has the advantages over US of less operator dependency, availability of standardised imaging protocols and the ability to thoroughly evaluate anatomical regions, including the bone marrow and deep soft tissues (Jacobson 1999), the specificity of bone marrow oedema or bony cysts is uncertain. These features may actually be both pre-erosive and non-erosive oedematous changes in subchondral bone (Alasaarela 1998b, Conaghan 2001). Klarlund and co-workers (Klarlund 2000a) found that most of their MRI erosions did not develop into lesions that were detectable on plain radiographs. Thus while MRI may be highly sensitive, it may lack specificity in the detection of erosions.

McQueen and colleagues (McQueen 2001) found that only 25% of MRI wrist erosions were seen on radiographs one year later, perhaps due to healing, technical limitations of conventional radiographs (erosions too small to be detected) or false positive MRI lesions. Small breaches of cortical bone may not be erosive, and may be present in normal individuals due to nutrient vessels or interosseous entheses (Hoving 2004). Nonetheless, MRI erosions have been found to have prognostic value in predicting radiographic outcome in early and late RA (Wakefield 2004b).

Although US may be less sensitive in detecting erosions, it does have practical advantages over MRI, including the ability to scan multiple joints in real time, avoidance of prolonged immobilisation and intravenous contrast and the ability for subjects to see and understand their particular joint problem through shared dynamic real time observations. It is difficult with high resolution MRI to fully examine both hands simultaneously (Backhaus 1999), given the limited field of view with the coils used, and the constraint of only a single hand being imaged if contrast is used (van der Heijde 2000). A focussed examination needs to be performed with MRI as the region to be scanned has to be defined beforehand. It is relatively expensive and too time-consuming for large-scale application (Manger 1995, Klarlund 2000a), compared with US (although US documentation of all finger joints is also very time-consuming, so a "reduced joints" US assessment has been proposed as detailed in Chapter 6). Patients are less discomforted by US than MRI, because the latter requires immobilisation of the arm in a wrist coil. This issue was evident in the current study, where one patient was unable to remain immobile because positioning aggravated shoulder pain. Marked degradation of the MRI image quality may result from motion. One practical disadvantage of US is the need for the reader to be present in real-time as images

dynamically acquired are best interpreted at the time of US scanning, unlike MRI for which a technician acquires the images for later interpretation and scoring by one or, if necessary, more readers. On balance, the researchers consider it acceptable that some erosions are missed by US as long as those identified are real (100% specificity in this study).

4.8.2 US compared with MRI for detection of synovitis

US detected slightly more synovitis than MRI by a factor of 1.2, confirming the study by Backhaus and co-workers where synovitis was more prevalent on US than MRI by 1.15 times (Backhaus 1999). In another RA study, in which about 50% of patients had early disease, found 36% more synovitis with US than MRI (Szkudlarek 2006), with agreement for synovitis 76% compared with 72% in this study. In that study, MRI was also used as the reference standard and sensitivity of 70% and specificity of 78% were documented for inflammatory changes, defined as joint effusion and/or synovitis. This compares with a sensitivity of 91% and specificity of 9% for US synovitis compared to MRI in our study. The very low specificity for synovitis was due to the greater detection of synovitis with US than MRI. This has been reported before in a small study of established RA patients by Scheel and co-workers (Scheel 2006) in which more baseline synovitis and/or effusion was detected with US compared with MRI, possibly due to detection of very small fluid collections in the PIP joints on US (83% compared with 63% respectively). Conversely, another early RA study revealed that MRI was superior for synovitis with 1.7 times more at the joint level (Hoving 2004), when using slice thickness of 1mm or less. Our study used 2mm slices, which may explain the limited MRI sensitivity for synovitis compared to US.

The ability of US to visualise more synovitis than MRI may be explained by the inability of US to distinguish between active and fibrotic pannus (compared with MRI only showing active synovitis with gadolinium uptake). However, tissue fibrosis is not likely to explain these differences in early RA, although tissue oedema may contribute. PD sonography can differentiate between active synovitis and fibrotic pannus and may result in closer correlation between US and MRI synovitis. There may also be less efficient blinding of the sonographer compared with the MRI evaluator as scanning in real-time permits a visual comparison of normal with swollen joints.

It is important to consider that an IV injection of gadolinium is required for detecting synovitis on MRI (contrast enhancement), that this is invasive and it prolongs the assessment time compared to US. If no contrast is used with MRI, it is difficult to differentiate between synovial fluid and thickened synovium reliably (Figure 4.1(b)), or between these pathological features and the cartilage. Two of the 14 MRI participants refused IV contrast at the time of their MRI examination, thereby limiting the interpretation of these results. The use of contrast for synovial enhancement is time-dependent and its sensitivity for synovial proliferation will be reduced by contrast shifting out into the synovial fluid if the MRI protocol is not precisely standardised (Fiocco 1996, Klauser 2002).

A very recent development is the issue of nephrogenic systemic fibrosis (NSF), which may be triggered by the use of gadolinium-containing contrast agents in patients with renal impairment (Grobner 2006, Kuo 2007, Moreno-Romero 2007, Sadowski 2007). NSF is characterised primarily by red skin areas or plaques that develop to painful thickened skin, with potential systemic involvement of lungs, myocardium or striated

muscles (Mendoza 2006, Grobner 2007). Renal impairment should now be considered a relative contraindication for gadolinium use, especially if the creatinine clearance is less than 60mL/min/1.73m^2 (Sadowski 2007), and patients warned regarding the increased risk of NSF if contrast is used.

4.8.3 US compared with MRI for detection of ET

ET was identified 1.8 times more frequently on US compared with MRI. This may be explained by the lower spatial resolution of MRI with 3mm thick slices 1 mm apart compared with US (spatial resolution of 0.1-0.2mm with the machine used). MRI also has a larger field of view (10cm) compared with US, with which the transducer is in skin contact a few millimetres only from the superficial ET. Our results contrast with those of Backhaus and co-workers, who demonstrated twice as much ET on MRI as US (Backhaus 1999). However, their study utilised a lower resolution US machine (with an acoustic standoff for better focussing) compared with our instrument and MRI with slice thickness between 1 to 1.6mm. Only a few early RA studies have examined ET, an important component of MCP joint swelling in addition to synovitis and effusion that is often overlooked (Hoving 2004, Wakefield 2004c). US should be regarded as the gold standard (apart from surgical findings) for imaging tendons in rheumatology, as it is more sensitive than MRI for detecting tenosynovitis (Backhaus 1999) and complete tendon ruptures (Swen 2000). There was a high incidence of tendon sheath thickening on US and MRI in early RA in Hoving's study, affecting 65% of participants, with tenosynovitis being the only feature of active inflammatory disease in some patients (Hoving 2004). About a third of the various joints in Wakefield's study that were assessed clinically as having synovitis but negative for US synovitis were explained by tenosynovitis (Wakefield 2004c).

4.8.4 US compared with MRI for detecting joint effusions and FT

US was shown to be inferior to MRI in detecting joint effusions and FT. The low sensitivity for joint effusions may have been due to the relatively small number of effusions found in any joints with either MRI or US. This contrasts with previous studies in early RA where US detected more joint and tendon sheath effusions than MRI (Hoving 2004). The latter study included small effusions tracking into the synovial fold created by flexion of the MCP and PIP joints, which helped delineate the volar plate (Hoving 2004). In the present study, 20% of all MRI negative joints with US positivity for joint effusion, may perhaps be partially explained by inclusion of non-joint fluid detected on US. The study by Hoving and co-workers (Hoving 2004) detected more tendon abnormalities overall with MRI compared to US (affecting 67% compared with 39% of subjects respectively), when assessing tendon sheath and tendon thickening at the wrist joint only (flexor and extensor tendons). Another study in inflammatory arthritis including RA, psoriatic arthritis, autoimmune disease and undifferentiated oligoarthritis had similar findings especially in the non-erosive group, with 1.7 times more FT and three times more ET of the fingers on MRI than on US (Backhaus 1999). The excess of ET on MRI in that study may be explained by the use of an older US machine with lower resolution (7.5MHz linear array transducer with a standoff pad for better focussing) than the US machine that we used (11.4MHz frequency for scanning and no requirements for a standoff pad).

The OMERACT RAMRIS scoring system does not include tenosynovitis, tendonitis and joint effusion of the hand and wrist (Lassere 2003), although there has been concern as to whether assessment of disease activity, including synovitis, bone oedema

and tendon lesions, is sufficiently comprehensive without the tendon component in RAMRIS. However, the detailed three dimensional anatomical knowledge required, if assessment of tendons is included, is likely to be achieved by dedicated musculoskeletal radiologists only. This would limit its application in a more general setting for rheumatologists or radiologists, thus rendering it less feasible and practical (McQueen 2003).

4.8.5 US compared with MRI measurements

The quantitative analysis developed for use with US was compared with the MRI assessment to provide further validation of the US measurements. M2 correlated better than M1, which was to be expected as the points of reference for M2 are better defined anatomically on MRI: measurement of synovitis or synovial thickening from the highest point of the convexity of the MC head at the proximal margin of the articular cartilage to the volar surface of the ET. In contrast, M1 was measured from a theoretical intersection point of the bony outlines of the MC head and the proximal phalanx at the midpoint of the MCP joint, which is not a distinct location on MRI compared with the signal attenuation seen with US. Despite this, there was a significant though weak correlation of M1 on US and MRI.

4.9 Conclusions

HRUS findings were validated in a subset of patients with MRI as the reference method. The US measurements devised for the study were found to be significantly correlated with MRI measurements, especially M2. MRI was superior for detection of erosions, joint effusion and flexor tenosynovitis, whilst US demonstrated more ET and

slightly more synovitis than MRI. Each imaging modality has its benefits and disadvantages which have been considered in detail in this chapter.

At present, MRI is too expensive and time-consuming for routine diagnostic use. US is more practical and easily available to rheumatologists in an outpatient setting for detecting sub-clinical synovitis and erosions in early disease when most needed. More recently, dedicated low field MRI devices have reduced the cost of MRI, made siting easier and more flexible through reduced dimensions, involved less patient discomfort and reduced patient risk through reduced scanning times (Taouli 2004, Wakefield 2004b). For patients with claustrophobia, this is an advance as the extremity MRI allows them to place only their arm or leg into the machine. However there is limited anatomical coverage and lower image quality in comparison to high field strength MRI.

The next chapter considers potential baseline predictors of clinical and radiographic outcomes, including the value of the novel US measurements developed in Chapter 2.

CHAPTER 5

Predictors of outcome in early arthritis

5.1 Background

In recent onset arthritis, it is important to diagnose synovitis confidently when clinical signs may be equivocal so that DMARD therapy can be introduced early before joint damage has occurred. It is also important to determine among patients with more obvious synovitis, those findings that connote special risk for disease persistence and poor outcomes in terms of joint structure and function, so that more intensive treatment can be applied when appropriate. Early findings which correlate with disease persistence include symmetrical synovitis (Green 1999, Jansen 2002), increasing duration of disease (Green 1999, Machold 2002) RF and increased ESR (Tunn 1993, Wolfe 1993, Gonzalez-Lopez 1999, Green 1999, Jansen 2002). Predictors of radiographic progression in RA include increasing age, hand synovitis, higher baseline disease activity score (DAS) levels and RF (Jansen 2002).

For disease duration of less than 12 weeks, it has been reported that predictors show no association with important outcomes (Green 1999). There is uncertainty as to whether the presence of tenosynovitis in early arthritis has prognostic value, and longitudinal studies addressing this are required (Swen 2000).

5.2 Aims

(1) To study disease course in patients with recent onset RA (less than one year in duration) with regular examinations and standardised clinical, laboratory and radiographic measures

(2) To identify potential baseline clinical, laboratory, radiographic or US features in early RA that may predict outcomes, such as DAS28 remission, response to DMARD therapy, radiographically evident peri-articular erosions and changes in modified Sharp score

5.3 Hypotheses

(1) Predictors of poor outcomes in early RA are similar to those identified in established RA

(2) HRUS features in early RA, such as the degree of synovitis, ET or PD positivity, can add to information which improves prediction of outcome

5.4 Participants

5.4.1 Selection

Patients with recent onset RA (less than one year's duration) as previously described in detail in Chapter 3, who had undergone follow-up assessment six or more months later. Clinical, laboratory, radiographic and US findings were included in this sub study.

5.4.2 Inclusion Criteria

Early RA patients with matching baseline and follow-up data at one year sufficient to allow determination of remission and responder status according to DAS28 criteria, assessment for radiographic erosions and calculation of the van der Heijde (vDH) modification of the Sharp scores, were included.

5.4.3 Exclusion Criteria

Early RA patients with incomplete baseline or follow-up data at one year, with missing information resulting in the inability to calculate remission or responder status or radiographic outcomes, were excluded.

5.5 Methods

5.5.1 Predictors of outcome study

The following factors were examined for predictive value with regard to disease remission or response to DMARD treatment:

- Age
- Gender
- Duration of disease symptoms at the time of diagnosis
- Symmetrical MCP joint synovitis on clinical examination (defined as identical distribution of swelling of the MCP joints in each hand)
- Number of swollen MCP joints on clinical examination
- US symmetry (synovitis of at least MCP joints 2 and 3 bilaterally and both wrists)
- US evidence of erosions at baseline
- Aggregate of US features of synovitis, effusion, ET, PD positivity and abnormal M1 and M2
- Radiographic evidence of erosions at baseline
- ESR and CRP
- IgM-RF and anti-CCP antibodies
- Presence of HLA-DR4/DR1 RA susceptibility alleles ('shared epitope')

5.5.2 Measures of disease activity and joint damage

5.5.2.1 Clinical assessment of disease activity

EULAR criteria for response to therapy and remission were applied as follows (van Gestel 1996):

- Good response = DAS28 at endpoint ≤ 3.2 and improvement of > 1.2
- Moderate response = DAS28 endpoint ≤ 3.2 and improvement of > 0.6 and ≤ 1.2 OR DAS28 at endpoint > 3.2 and ≤ 5.1 and improvement > 0.6 OR DAS28 at endpoint of > 5.1 with improvement > 1.2
- Poor response = DAS28 at endpoint of > 5.1 and improvement of > 0.6 and ≤ 1.2 OR any endpoint with improvement from baseline of ≤ 0.6
- Remission = DAS28 < 2.6

Symmetry and extent of clinical evidence of MCP synovitis was documented for separate analyses.

5.5.2.2 Ultrasonography

Subjects had repeat US six to twelve months after their original US scans. Characteristics of MCP joint arthritis that were analysed included synovitis, joint effusion, ET, PD status and measurements.

5.5.2.3 Plain radiography

Radiographic assessment of the hands and feet was undertaken at baseline and one year. Using the vDH modified Sharp score (van der Heijde 2000), the erosion and total damage scores, and change in erosion/total score from baseline to one year (assessing

damage progression) were calculated. Radiographs were scored by readers blinded to patient identity but not chronological order, with disputed scores settled by consensus.

5.6 Statistical Analysis

The data were analysed using the Statistical Analysis System (SAS) Version 9.1 package (Cary, NC, USA) as well as PRISM and INSTAT programs, using nonparametric methods. The Wilcoxon signed rank test was used for comparing baseline mean MCP joints affected by various US abnormalities with endpoint results to assess for any significant difference in values at follow-up. This was undertaken to determine parameters that were sensitive to change.

Univariate analysis was performed using a log-binomial model in order to identify potentially important predictors of each of the outcomes of interest in early RA (the dependent variables); treatment response, remission among all patients and remission among responders according to the DAS28 level. An additional dependent variable considered was radiographic outcome assessed by radiographic erosion score at follow-up, total modified Sharp score (of the hands and feet) and damage progression scores (change from baseline to one year in the total modified Sharp score).

Multivariate analyses were performed using a log-binomial model, to identify relevant independent prognostic factors. Only those variables with a p value of less than 0.2 in the univariate analysis were included in this model, to exclude those with only a weak association with outcome. Multivariate analyses allow the effect of each variable to be combined, so that their individual effects are adjusted for those of all the other variables. Relative risks (RR) were calculated for significant predictors in the

multivariate analysis, as well as for those predictors in the univariate analysis when patient numbers were too few to perform a multivariate analysis. No adjustment was made for multiple comparisons. Positive and negative predictive values (PPV and NPV) were calculated to determine the proportion of the outcome accounted for by the significant prognostic factors identified on multivariate analyses. A p value of less than 0.05 was required for statistical significance.

5.7 Results

5.7.1 Factors responsive to change at follow-up

Data from 41 of a total of 50 patients who underwent follow-up assessment at least 6 months after baseline were available for analysis (median 9 months, range 6-23 months). Five of 46 participants (10.9%) were lost to follow-up, either failing to attend several appointments for US scans or uncontactable by telephone or mail. Two of the 41 participants followed up had incomplete baseline data (did not complete their patient global assessment) which prevented calculation of baseline DAS28, which is required to determine the treatment response by EULAR criteria. These two subjects were included in the analysis of DAS remission as this assessment is not reliant on the missing baseline data. Another subject did not have a follow-up ESR and therefore responder and remission status could not be determined.

Two characteristics of MCP joints were found to have significantly different mean values at baseline and follow-up (Wilcoxon signed rank test), viz the number of clinically swollen MCP joints and the number of PD positive MCP joints as shown in

Figure 5.1. There was no significant change in the number of MCP joints with US evidence of synovitis/effusion, ET, nor M1 and M2 at follow-up assessment.

Baseline demographic data have already been presented in Chapter 3 (Table 3.1 ***page 68***). In more detail, the baseline number of clinically swollen MCP joints was 244 of a total of 500 MCP joints assessed (49%) which reduced to 107 of 410 MCP joints at follow-up (26%). The mean number of clinically swollen MCP joints reduced from 4.8 to 2.6 joints per subject (p=0.0006). The baseline number of MCP joints with PD positivity was 133 of 500 joints (27%) compared with 48 of 410 MCP joints at follow-up (12%). The mean number of MCP joints with PD positivity was significantly reduced from 2.9 to 1.2 MCP joints per patient (p=0.0002). These results are shown in Table 5.1 and Figure 5.1.

Table 5.1 Total number of MCP joints affected at baseline and follow-up

Pathological Feature	**Baseline (n=500)**	**Follow-up (n=410)**
	No. MCP joints (%)	**No. MCP joints (%)**
Clinical swelling	244 (49)	107 (26)
US synovitis/effusion	385 (77)	285 (70)
US ET	210 (42)	177 (43)
US PD positivity	135 (27)	48 (12)
US abnormal M1	210 (42)	148 (36)
US abnormal M2	83 (17)	63 (15)

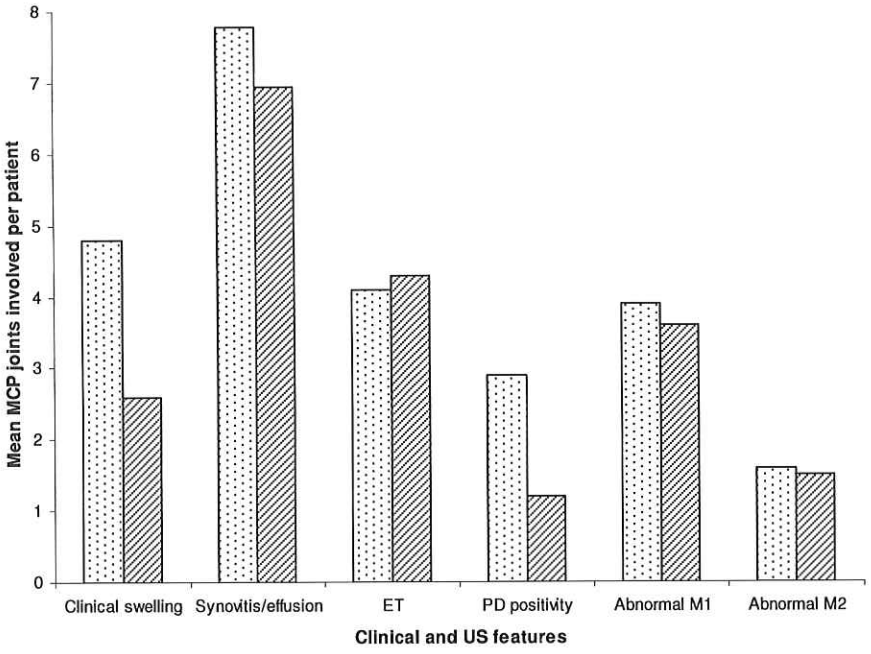


Fig 5.1 Longitudinal results in early RA patients (n=41), with the change in the mean number of MCP joints involved per patient. There was significant reduction in the number of MCP joints with clinical swelling and PD positivity between baseline (dotted columns) and follow-up (hatched columns) more than six months later (p=0.0006, 0.0002 respectively, Wilcoxon signed rank test).

Not unexpectedly, as all subjects received DMARD therapy, ESR decreased from a mean of 27.6±23.6mm/h SD at baseline to 15.7±18.1mm/h at follow-up (p=0.0002) and the mean CRP decreased from 17.2±38.5mg/l to 8.0±20.4mg/L (p<0.0001). These data indicate a significant systemic response to treatment.

5.7.2 Predictors of treatment response

In those with complete follow-up data, the proportion responding to DMARD treatment (good or moderate response by EULAR criteria) was 71.1%. No statistically significant baseline variables were found to predict response on univariate analyses (Table 5.2).

Table 5.2 Univariate analysis of potential predictive baseline factors of DAS28 treatment response at one year (n=37)

Variable	p value
Disease duration	0.95
Age	0.28
Gender	0.62
RF status	0.73
Anti-CCP antibody status	0.76
Shared epitope positivity	0.33
ESR	0.30
CRP	0.34
Number of MCP joints with:	
- clinical swelling	0.87
- US synovitis/effusion	0.87
- US ET	0.36
- US synovitis/effusion/ET	0.75
- US PD positivity	0.68
- abnormal M1	**0.15**
- abnormal M2	0.34
Radiographic erosions	0.89
US erosions	0.32
US symmetry	0.37
Clinical symmetry	0.29
DAS28	0.97

p value < 0.05 considered significant
Note that no multivariate analysis was performed as only one variable had a p value < 0.20

5.7.3 Predictors of disease persistence or lack of remission

In the 39 patients assessed, 12 (30%) were in remission at one year by EULAR DAS28 criteria. On univariate analysis, several factors yielded p values of less than 0.2 (Table 5.3). These included clinical symmetry (p=0.07), ESR (p=0.08), abnormal M1 (p=0.09), ET (p=0.12) and DAS28 baseline level (p=0.03). No patients with radiographic erosions at baseline were found among patients achieving remission. This suggested that presence of radiographic erosions may militate against remission. These above factors with a p value of less than 0.2 were entered into a multivariate analysis (Table 5.4). Significant predictors were ESR (p=0.007), clinical symmetry (p=0.02), and US total number of MCP joints with abnormal M1 (p=0.04).

The mean ESR of those in remission was half that of those with persistently active disease (mean 15.6 compared with 30.3 respectively). The RR or likelihood of remission for the ESR level was 0.96, with 3.96% reduction in remission rate for each unit increase in ESR. For the number of MCP joints with abnormal M1, the RR was 0.79 for remission, with every unit increase (involvement of an additional MCP joint with abnormal M1) associated with a 21.1% reduction in RR for remission. There was an exponential (log) reduction in RR of remission for every unit increase in these factors, excluding clinical symmetry. For example, there was about 69% reduction in likelihood of achieving remission if there were 5 MCP joints with abnormal M1 compared to none (calculated as 0.79^5). An example of applying these calculations is presented in Table 5.5. Overall, the greater the number of MCP joints with abnormal M1, the greater the likelihood of disease persistence at one year on DMARD therapy.

Table 5.3 Univariate analysis of potential predictive factors at baseline of DAS28 remission at one year (n=39)

Variable	p value
Disease duration	0.41
Age	0.62
Gender	0.52
RF status	0.72
Anti-CCP antibody status	0.56
Shared epitope positivity	0.97
ESR	**0.08**
CRP	0.43
Number of MCP joints with:	
- clinical swelling	0.59
- US synovitis/effusion	0.93
- US ET	**0.12**
- US synovitis/effusion/ET	0.74
- US PD positivity	0.73
- abnormal M1	**0.09**
- abnormal M2	0.41
US erosions	0.32
US symmetry	0.97
Clinical symmetry	**0.07**
DAS28	**0.03**

p value < 0.05 considered significant
Note that radiographic erosions were not included as a variable as no patients with radiographic erosions experienced remission

Table 5.4 Multivariate analysis of predictive factors at baseline of DAS28 remission at one year

Variable	RR estimate (95% CI)	RR Reduction for remission	p value
ESR	0.96 (0.93-0.99)	3.96%	0.007
Clinical symmetry	0.13 (0.02-0.76)	86.6%	0.02
Number of joints with abnormal M1	0.79 (0.63-0.99)	21.1%	0.04

p value < 0.05 considered significant

Table 5.5 Example of log reduction in RR of DAS28 remission using M1

Number*	RR reduction in the likelihood of remission	Remission rate at one year
Nil	0% RRR	50%
One	21% RRR	40%
Two	38% RRR	31%
Three	51% RRR	25%
Four	61% RRR	20%
Five	69% RRR	16%
Ten	91% RRR	5%

*represents the number of MCP joints with abnormal M1

For patients with symmetrical involvement of the MCP joints evident on clinical assessment, there was an 87% RR reduction in remission rate. That is, clinical symmetry increased the likelihood of disease persistence. One must use caution in interpreting these secondary analyses as they are descriptive only and at best hypothesis-generating. Accordingly, further studies are required to test the significance of the putative associations seen and described here.

A multivariate model including these three significant predictors resulted in a PPV of 0.73 (95% CI 0.39-0.94) and a NPV of 0.89 (95% CI 0.72-0.98) for remission. That is, 73% of those patients predicted by this model to achieve remission actually experienced remission. If the US variable total abnormal M1 was excluded, then there was a PPV of 0.56 (95% CI 0.21-0.86) and a NPV of 0.80 (95% CI 0.61-0.92). Hence this US variable abnormal M1 contributed an extra 17.2% predictive value for achieving remission in addition to clinical and laboratory variables in this model.

Potential predictors of remission were also examined in a sub-group analysis of 26 patients who responded to treatment, after exclusion of non-responders. From the univariate analysis (Table 5.6), the baseline factors in Table 5.7 were close to significance and RR estimates were calculated for these.

5.7.4 Predictors of radiographic erosions at one year (hands and feet)

At baseline, 12% (6/50) of patients had radiographic erosions of the hands and feet, compared to 21.2% (7/33) at one year. Potential predictors of radiographic erosions at follow-up were explored, notwithstanding the small sample size. On univariate analysis, abnormal M1, disease duration and ESR emerged as potential predictors of erosions identified using the vDH-SS scoring system (p values 0.07, 0.08 and 0.08 respectively). Baseline total modified Sharp score (p=0.18) also appeared to be potentially important. Using these four variables, the RR of radiographic erosions at follow-up for each was calculated (Table 5.8(a)). Results for erosions identified by a radiologist or rheumatologist review of the plain radiographs (more representative of clinical daily practice) were also presented (Table 5.8(b)). Again, the number of MCP joints with abnormal M1 appeared significant, as well as US erosions at baseline, ET

and age. Formal statistics using multivariate analyses were not done because of the small number of subjects with complete datasets.

Table 5.6 Univariate analysis of potential predictive factors of DAS28 remission in responders at one year (n=26)

Variable	p value
Disease duration	0.49
Age	0.85
Gender	0.41
RF status	0.85
Anti-CCP antibody status	0.24
Shared epitope positivity	0.50
ESR	**0.12**
CRP	0.57
Number of MCP joints with:	
- clinical swelling	0.68
- US synovitis/effusion	0.71
- US ET	**0.04**
- US synovitis/effusion/ET	0.75
- US PD positivity	0.71
- abnormal M1	0.23
- abnormal M2	0.86
US erosions	0.55
US symmetry	0.85
Clinical symmetry	**0.11**
DAS28	**0.02**

p value < 0.05 considered significant
Note that radiographic erosions were not included as a variable as no patients with radiographic erosions experienced remission

Table 5.7 Factors predictive of DAS28 remission in responders at one year (n=26)

Variable	RR estimate (95% CI)	p value*
ESR	0.97 (0.93-1.01)	0.12
Clinical symmetry	0.21 (0.03-1.41)	0.11
Number of MCP joints with US ET	0.84 (0.71-0.99)	**0.04**
DAS28 baseline	0.70 (0.52-0.94)	**0.02**

* p value < 0.05 was considered significant
RR estimates calculated using univariate analysis, with no multivariate model given the small number of patients

Table 5.8(a) Potential predictors of radiographic erosions at one year using vDH-SS (n=33)

Variable	RR estimate (95% CI)	p value*
ESR	1.02 (1.00-1.05)	0.08
Duration of disease at baseline	1.27 (0.97-1.67)	0.08
US abnormal M1	1.24 (0.99-1.55)	0.07
Baseline total modified Sharp score	1.08 (0.96-1.21)	0.18

*p<0.05 considered significant on univariate analysis

Table 5.8(b) Potential predictors of radiographic erosions at one year using radiologist report without formal scoring (n=33)

Variable	RR estimate (95% CI)	P value*
Age	1.05 (0.98-1.14)	0.16
US ET MCP joints	1.2 (0.96-1.5)	0.10
US abnormal M1	1.33 (1.02-1.74)	**0.04**
US erosions at baseline	4.6 (1.0-21.2)	0.05

*p<0.05 considered significant on univariate analysis

The data available for potential predictors of the total modified Sharp score (assessed using hand and feet radiographs) and change in total Sharp score were preliminary only. Taking into consideration the small sample size of 33 patients with follow-up radiographs scored so far, several potential predictive factors were identified (Table 5.9). Using univariate analysis, variables for predicting an increase in total Sharp score ('yes' or 'no' for progression in damage) included the number of MCP joints with abnormal M1 (p=0.197), symmetrical involvement of the MCP joints on clinical assessment (p=0.13) baseline total Sharp score (p=0.06).

With regards to the final total Sharp score at one year, factors identified using the Kruskall-Wallis test were symmetrical involvement of MCP joints on clinical assessment (p=0.06) and the presence of radiographic erosions at baseline (p=0.16). The mean final total Sharp score were 1.5 times as high in those with clinical symmetry compared to those with asymmetrical disease (18.2 and 12.0 respectively). Patients with radiographic erosions at baseline also had a higher mean final total Sharp score – 21.8 compared to 14.2 in those without erosions at baseline.

Table 5.9 Potential predictors of increase (progression) in total Sharp score at one year (n=29)

Variable	RR estimate (95% CI)	p value*
Number of MCP joints with:		
- US abnormal M2	0.43 (0.12-1.55)	0.197
Baseline total modified Sharp score	0.74 (0.55-1.01)	0.06
Clinical symmetry	0.21 (0.03-1.61)	0.13

*p<0.05 considered significant on univariate analysis

5.8 Discussion

5.8.1 Factors responsive to change with DMARD treatment

PD appears to be the parameter most responsive to change in early RA patients, as evidenced by reduced number of MCP joints with PD positivity on follow up. By contrast, the other US parameters of synovitis, effusion, ET, and measurements did not change significantly. This may be explained by the change from acute invasive hyperaemic synovium to less vascular but persistently thickened synovium. In the researcher's experience, the appearance of chronic synovitis is more homogeneous than in the acute state, in which hypoechoic areas representing synovial swelling appear heterogeneous. However, the synovial volume does not appear to diminish at follow-up and the measurements appear non-responsive to treatment. MRI studies have shown that synovial enhancement is a persistent finding, which is independent of disease duration or the treatment received (Ostergaard 1999, Hoving 2004). In the present study, a significant relationship was found between PD positivity and DAS28 disease. A trend towards an association between PD and ESR levels (but not with CRP) was seen. The relationship with the ESR contrasts with a previous study in which PD positivity in established RA did not correlate with inflammatory markers (Kiris 2006).

PD was found to be highly sensitive and specific when compared with dynamic MRI, suggesting that is a reliable method for assessing synovitis of the MCP joints (Szkudlarek 2001). Over 90% of this study's PD positive MCP joints had underlying US evidence of synovitis, ET or joint effusion, providing further validation for the PD findings. Koski and colleagues used histopathology as the gold standard to examine the validity of PD in detecting synovitis, and found 83% PD positivity in histologically

defined active synovitis (Koski 2006a). There was no statistically significant correlation between the amount of fluid, synovial proliferation or amount of PD signal and the overall histopathological score (Koski 2006a). Accordingly, dichotomous categorisation could be better than semi-quantitative grading of PD signal as is currently utilised in many studies.

The study by Koski and co-workers has certain limitations with regard to interpretation of hand findings in early RA. Their study involved multiple rheumatic diagnoses (eg. RA, monoarthritis and oligoarthritis). Their scans were mainly undertaken on knees and wrists. In addition the histologic analyses suffer from a lack of accepted and uniformly applied scoring system for synovitis. Indeed, criteria for histologic definition of active histological synovitis have not been established (the presence of neutrophils in the sub synovium is a candidate).

In summary, while a negative PD synovial signal does not exclude the possibility of active synovitis, a positive signal appears to be a good indicator of underlying active inflammation. Prospective studies with more patients to assess the prognostic value of PD findings are required. PD is an important area of ongoing clinical research and appears likely to remain a canonical aspect of the assessment of synovial inflammation by US.

5.8.2 Persistence of disease with DMARD treatment

In early RA, it is useful to identify patients, who by virtue of greater risk for loss of function and irreversible joint damage, warrant especially intensive treatment. In practice, the decision to offer DMARDs to individuals can depend upon whether the

disease is regarded as likely to be self-limiting or persistent without treatment. In the very early phase, it can be difficult to diagnose RA, with ACR criteria having limited value in predicting the subsequent development of RA in an early arthritis setting (Harrison 1998). About half of those with early RA did not meet ACR criteria at baseline (Saraux 2001). In an early RA study, there was 47% RF positivity of RA patients at baseline (compared with 12% of non-RA patients) which increased in prevalence with increasing duration of disease (Machold 2002).

5.8.2.1 Predictors of response to treatment

There were no significant predictors of response to DMARD treatment at one year identified, apart from a trend towards a reduced likelihood of response in those subjects with more MCP joints with abnormal M1 (p=0.15) on univariate analysis. In the responders in this study, potential predictors for remission were studied, with the only significant factors being the baseline DAS28 (p=0.02) and the number of MCP joints with ET on US (p=0.04). Again there was a trend towards both ESR and clinical symmetry as potential predictors of remission (p=0.12 and 0.11 respectively) but numbers of patients were inadequate to enter data into a multivariate model to determine independence of these factors. The addition of further follow-up data may provide sufficient power to determine if any other factors are predictors of the outcome variables.

5.8.2.2 Choice of remission criteria

In this study, the DAS28 remission cut-off was selected rather than the ACR remission criteria. Saraux et al. found that the ACR criteria when applied at the first visit in early arthritis of up to one year's duration were of limited value and specificity in predicting

the diagnosis of RA two years later (Saraux 2001). The DAS remission cut-off of 1.6 was previously shown to correspond strongly with the ARA preliminary remission criteria (Prevoo 1996), and a score of 2.4 or less with prevention of radiographic progression (van Gestel 1996). Also, the modified version of DAS that we used (DAS28) with less comprehensive joint counts has been shown to discriminate between high and low disease activity, validating the use of reduced joint counts for disease activity assessment (Prevoo 1995). When using the DAS28 criteria, remission is considered to lie at the lower end of the spectrum of inflammatory disease activity. A change of 0.6 represents a clinically relevant change in patients with mild disease activity, but for those with higher disease activity levels, a larger response of 1.2 is required for clinical relevance (Stucki 1996).

5.8.2.3 Remission rates in early arthritis

Using DAS28 criteria of less than 2.6, our rate of remission at one year on therapy of 29% was comparable to a 27% remission rate observed in an undifferentiated arthritis subgroup in a community-based early inflammatory polyarthritis study by Harrison and co-workers (Harrison 1996). In the latter study, the definition of remission was absence of clinically evident soft tissue swelling, and not requiring any DMARD or steroid treatment in the preceding three months. Therefore, their criteria were stricter than the DAS28, with which swollen joints do not necessarily exclude remission. In this study by Harrison, a subgroup classified subsequently as having RA at baseline achieved a much lower remission rate of 9.3% at one year. Another early RA study of patients treated for 2 years with DMARDs found that responders with a DAS of 2.4 or less did not have significant radiographic progression, with 36% of the total group being in remission at follow-up (Svensson 2000).

Tunn et al. found that over half of an early symmetrical arthritis group with disease of less than six months' duration were self-limiting at one year (Tunn 1993). Using a different approach, Prevoo et al found that about 10% of their early RA patients (duration less than one year) fulfilled the ACR remission criteria at least once during the first year of follow-up, with 25% fulfilling these criteria between Years 2 to 6 (Prevoo 1996). This latter study considered factors predictive of outcome measures assessed at one time-point (one year follow-up), rather than the presence of any periods of remission within the year. It is difficult to make comparisons with these studies due to different methodologies used.

5.8.2.4 Predictors of remission

Using multivariate analysis, independent predictor variables of remission at one year on treatment in our study were clinical symmetry (p=0.02), ESR (p=0.007) and number of MCP joints with abnormal M1 (p=0.04). By contrast, previous studies have found ESR to be a poor predictor of remission in early RA (Gossec 2004, Makinen 2005). Also, laboratory variables such as CRP and anti-CCP antibodies were not significantly independently correlated to DAS remission, unlike clinical markers of disease activity (morning stiffness, low DAS or joint score) and radiological joint scores (Gossec 2004). In previous studies, clinical symmetry has been recognised as a risk factor for disease persistence (Green 1999, Jansen 2002), as has increasing disease duration (Green 1999, Machold 2002) and a positive RF with or without an increased ESR (Tunn 1993, Wolfe 1993, Gonzalez-Lopez 1999, Green 1999, Jansen 2002). Our definition of clinical symmetry differs from previous studies in that we considered exactly the same pattern of involvement of the MCP joints with swelling as

representative of symmetry. Others have defined symmetrical arthritis as involvement of at least one of the joint groups bilaterally, such as MCP, MTP, PIP or DIP joints (Visser 2002). The use of ultrasonography in addition to clinical and laboratory tests in our study was shown to be of practical relevance, as exclusion of the significant US predictor variable total abnormal M1 resulted in a reduction in PPV of 17% for prediction of disease persistence using the multivariate model.

McGonagle and co-workers have suggested intra-synovial location of inflammation on MRI as a predictor of disease persistence (McGonagle 1999b). This was defined as gadolinium enhancement within the joint cavity and tendon sheaths in contrast to extra-synovial involvement with enhancement adjacent to the joint capsule. Abnormal M1 at the MCP joints in our study represents increased 'joint cavity' width due to synovial proliferation, joint effusion or thickening of the joint capsule. M2 incorporates the region between the MC head and the extensor tendon, including a small portion of the intra-articular triangular structure and the joint capsule. This measure captures intrasynovial and extrasynovial tissues described in McGonagle's paper. In the present study, an increase in M1 (or intra-synovial involvement) but not M2 was found to be an independent significant predictor of poor prognosis with less likelihood of remission. The limited numbers in the study do not allow an association with M2 to be discounted, but a stronger association with M1 seems more likely on the basis of this evidence.

In palindromic rheumatism, factors that have been identified as associated with a higher risk for the subsequent development of RA include older age, female gender, hand involvement, increasing disease duration and presence of the shared epitope (Gonzalez-Lopez 1999). Neither age, female gender nor the shared epitope were identified as

predictive factors for persistent disease activity in our study of early RA treated with intensive DMARD therapy. The baseline DAS28 level is known to be associated with radiographic progression and functional impairment in undifferentiated polyarthritis (Jansen 2002). Also, a low baseline DAS in early RA was an independent predictor of remission at three and five years (Gossec 2004). In our study, baseline DAS28 was identified as a potential predictive factor by univariate analysis (p=0.02), but this was not confirmed in the multivariate analysis.

Of interest, baseline radiographic and US erosions were not significant predictors of remission in the univariate analysis, despite previous workers noting the importance of baseline radiographic erosions in early arthritis as a predictor of persistent arthritis, with an odds ratio of 2.75 for persistent versus self-limiting arthritis (Visser 2002). The inability of baseline erosions to reach significance for remission prediction may be explained by the very low incidence of baseline radiographic erosions of 12% and US erosions of 24%. Also the limited number of observations makes potential type 2 errors unavoidable, especially in sub-group analyses.

Anti-CCP antibody, a specific marker for RA, performed better than RF as a potential predictor of remission in responders, although neither reached statistical significance. Previous studies have suggested that anti-CCP antibody is associated with a poorer prognosis with greater radiographic progression, functional disability and absence of clinical remission (Visser 2002, Bas 2003). RF was positive in only 40% of all of those with complete results and numbers may have been insufficient to reveal possible associations.

Factors that were not predictors of remission in this study but that were significant on multivariate analysis in another study in early inflammatory polyarthritis included male gender (3.9 OR for remission at 2 years) and less than six tender joints (OR 3.8), with absence of MCP joints swelling and less than five swollen joints (both with likelihood ratios or LR of 1.8) examples of other variables identified by the initial univariate analysis (Harrison 1996). Our study did not show a strong association with age or disease duration, unlike some studies (Wolfe 1985, Tunn 1993, Wolfe 1993) but in common with the study by Harrison and co-workers (Harrison 1996). Other parameters that were assessed included the shared epitope (genetic risk factor for poorer prognosis disease (Gough 1994, El-Gabalawy 1999, Combe 2001), which was not a significant predictor of remission nor response. However, it has been suggested that genetic typing, which is not easily available in everyday clinical practice, may not be of much value in the diagnostic evaluation of early inflammatory arthritis, with the presence of HLA DQ homozygosity not significantly increasing the discriminative value of previous models (Mottonen 1988, Visser 2002). Functional outcome using health assessment questionnaires (HAQ) could also have been assessed (van Zeben 1993).

When variables are identified in a multivariate analysis as predictors of outcome, it has been suggested that the final model should then be tested for its prediction ability in another sample (Harrison 1996), as has been performed in another early inflammatory polyarthritis study. Using a validation sample, the accuracy of their model was 73%, but although specificity was high (87%), sensitivity was low (25%) (Harrison 1996). Hence this model was not sensitive enough to be clinically useful. This additional testing could be performed with the variables in this study identified as independent predictors in the multivariate analysis.

5.8.3 Radiographic progression in early RA

5.8.3.1 Prediction of radiographic erosions at follow-up

When investigating potential predictors of radiographic erosions at one year follow-up using the vDH-SS erosion score, taking into consideration the small sample size, there were several factors that were identified. These included the number of MCP joints with abnormal M1, increasing duration of disease at baseline assessment, ESR and the baseline total modified Sharp score. The RR of radiographic erosions at follow-up for each potential predictor was calculated (Table 5.8(a)), with the highest RR shown for duration of disease and US abnormal M1 (1.27 and 1.24 respectively). This is descriptive only and formal statistics using a multivariate model were not performed given the small number of patients with complete data. If the formal radiologist report of the plain radiographic films was used to determine the presence of radiographic erosions at follow-up (Table 5.8(b)), then variables identified on univariate analysis were again US abnormal M1 (RR 1.33) and additionally increasing age, number of MCP joints with ET and US erosions at baseline (RR of 1.05,1.2 and 4.6 respectively).

5.8.3.2 Predictors of change in and final total modified Sharp score

The results for potential predictors of change in total modified Sharp score (of hand and feet radiographs) and final total Sharp score were preliminary only. Potential variables for predicting an increase in total score (radiographic progression) included a lesser number of MCP joints with abnormal M2, absence of symmetrical involvement of the MCP joints on clinical examination and a lower baseline total Sharp score. RF but not anti-CCP positivity was weakly suggestive (p=0.25 and 0.77 respectively). When considering the final total Sharp score at one year, potential predictive factors identified

were symmetrical involvement of the MCP joints (p=0.005) and the presence of radiographic erosions at baseline (p=0.11).

With regard to radiographic progression in RA, risk factors identified by previous researchers include increasing age, hand synovitis, higher baseline DAS levels and RF positivity, which were associated with earlier erosions (Jansen 2002). In an early RA study however, the rate of development of new erosions at two years was the same in RF positive or negative patients (Mottonen 1988). Inflammatory markers were raised in most patients at baseline with early arthritis and there was little difference between RA and non-RA patients seen in another study (Machold 2002). CRP may be a marker of poor prognosis in established disease but in very early disease (less than 3 months), CRP was not predictive of disease outcome (Tunn 1993). In other early RA studies (Mottonen 1988, Combe 2001) ESR was better at predicting radiographic damage at 2-3 years than CRP, with a significantly increased risk of radiographic progression (change in modified Sharp score) with an abnormal ESR but not CRP with an odds ratio of 3.44 (95% CI 1.39-8.5). The same study also confirmed IgM-RF positivity, HLA-DRB1*04 genotype and baseline erosion score or total Sharp score as predictors of radiographic progression and a high total Sharp score of more than 4 at follow-up (Combe 2001).

In a study by Mottonen and co-workers in early RA, there was a significantly increased number of joints with erosions at two years in those with flexor tenosynovitis of the hands (Mottonen 1988). Our study identified an increasing number of MCP joints with ET as a predictor in the univariate analysis of radiographic progression, only when considering the radiologist's report rather than using the Sharp scoring system. It

appears that tenosynovitis, whether flexor or extensor, may be a marker of a poorer outcome. Given that it is often difficult to differentiate between ET and MCP joint synovitis on clinical examination, US may contribute by defining ET as a separate entity. This information potentially could be used by clinicians to determine the intensity of DMARD treatment to apply in the quest for better outcomes, including reduced radiographic progression.

When considering MRI erosions at six months as the primary outcome variable in early RA in another Australian study, several baseline predictors were identified by univariate analysis (Hoving 2004). These included baseline MRI erosions ($p<0.001$), synovitis ($p=0.01$) and tendon sheath thickening ($p=0.056$), with radiographic and US erosions at baseline also increasing the likelihood of MRI erosions later. Age, CRP and tender joint count greater than 3 were the most important predictors of MRI erosions at six months in a multivariate model.

In early RA, there is no validated classification or diagnostic criteria set. Harrison and co-workers tested the ACR classification criteria in early inflammatory polyarthritis and found that about 50% were diagnosed as RA when referred to hospital, and 76% had persistent disease at three years (Harrison 1998). The overall sensitivity of the criteria was between 77-87% with poor specificities, resulting in poor discriminatory ability. Criteria that better differentiate RA from non-RA or even more importantly destructive possibly debilitating disease from benign entities within the early disease spectrum are needed. US promises to be a useful adjunct to assessment in search of this better discrimination. Very early DMARD treatment leads to higher responder rates, suggesting a therapeutic window of opportunity when the course of the disease can be

altered substantially. Anti-TNF agents may be useful in those with early poor prognosis RA as a recent study has shown reduction in MRI synovitis and erosions with the addition of early infliximab treatment to methotrexate monotherapy (Quinn 2005). Clearly, the putative advantage of bDMARDs needs to be assessed within the context of more effective, inexpensive combination DMARD therapy of the sort used in our study before recommendations regarding broader use can be made.

5.9 Conclusions

In early RA, two factors were identified that were the most responsive to DMARD treatment. These were the number of clinically swollen MCP joints and the number of MCP joints with PD positivity, with significant reduction in both parameters at assessment at follow-up six months or more later. Synovitis, ET and the US measurements did not change despite the improvement in other variables. This suggests persistence of synovial swelling in spite of resolution of increased blood flow.

Several factors have been identified that may be predictors of outcomes in treated early RA. Unsurprisingly, these baseline variables were similar for potentially predicting remission as for predicting treatment response. They included ESR, the number of MCP joints with abnormal M1 and clinical symmetry. Clinical symmetry was the best predictor with reduction in the remission rate by 87%. For radiographic erosions, factors identified were the number of MCP joints with abnormal M1 and the presence of baseline erosions on US. Baseline total modified Sharp score may be of importance in predicting radiographic progression.

Subject to further validation, the presence of one or more of these predictor variables may form the basis upon which treatment decisions can be made in early arthritis. These exploratory results thus contribute to the body of knowledge upon which more definitive studies can be based. Ultimately, predictive scores based on parameters of established predictive value could be used within algorithms for response contingent treatment regimens that take account of both individual risks and responsiveness.

5.10 Future Studies

For patients in clinical remission according to predefined criteria, studies could be performed to determine whether there is US evidence of persisting sub-clinical synovitis. Patients could then be followed to assess whether this contributes to predicting radiographic progression or functional impairment.

CHAPTER 6

Development and validation of a focussed US assessment tool

6.1 Background

In reports to date, investigators have chosen to study only the dominant hand or selected MCP or MTP joints for assessment of synovitis and erosions. These reports do not include broader data sets that provide information regarding the potential loss of information compared with an extended US joint examination.

6.2 Aims

(1) To develop and validate a "sentinel joints" US assessment in early RA with reduced joint count for synovitis, erosions, ET and PD positivity in quest of greater efficiency without loss of important information

(2) To review this study in the light of other published US assessment systems for detecting joint inflammation in recent onset PA and RA

6.3 Hypotheses

(1) A "sentinel joints" US assessment can provide sufficient information for diagnostic purposes and can be validated against an extended joint count assessment

6.4 Subjects

6.4.1 Selection

Subjects with recent onset inflammatory arthritis and at least one tender and swollen MCP joint were recruited from the Early Arthritis Research Clinic at the Royal Adelaide Hospital. Formal criteria for RA were fulfilled by these subjects (see selection criteria described in Chapter 3).

6.4.2 Inclusion Criteria

Subjects who agreed to have an US of the hands and were recently enrolled in the early RA trial were included in this study.

6.4.3 Exclusion Criteria

Any subjects with self-limiting disease prior to US or absence of clinical swelling of MCP joints (see exclusion criteria in Chapter 3).

6.5 Methodology

Observational study

6.5.1 Validation of the "sentinel joints" US examination

Given the time-consuming nature of this study's extended US protocol, which includes all MCP and PIP joints and the wrists (described in detail in Chapter Three), a focussed US examination with reduced joints was devised to determine whether a protocol focussing on selected joints could provide assistance in diagnosis and management of early RA, without significant loss of information. Based on the most commonly

affected MCP joints clinically and on US in previous studies (Grassi 1993, Weidekamm 2003) as well as from the clinical experience of the researchers, the "sentinel joints" US assessment of the MCP and wrist joints was developed.

6.5.2 Comparison with other US assessment systems for RA joint inflammation

The extended US joint count method was compared descriptively with five other published US assessment systems. Each involved scoring or measurement components as semi-quantitative or quantitative assessments respectively of synovitis.

6.5.3 Statistical analysis

The sensitivities of a "sentinel joints" US examination for detection of synovitis/effusion, ET, PD positivity and erosions were calculated when compared with the full US joint examination in identifying those subjects with disease affecting any of their MCP joints. The specificities of US synovitis/effusion and erosions were determined by comparing these results to MRI in a subset of patients.

6.6 Results

6.6.1 Development of the "sentinel joints" US assessment

In the RA subjects, over 66% of all MCP joints with clinical swelling were represented by MCP joints 2 and 3 as shown in Figure 6.1(a). Forty six percent of all joints showing US evidence of synovitis or effusion were captured by examination of MCP joints 2 and 3 in the two hands, equally affecting MCPs 2 and 3 (23% each). MCP 4 was the next most commonly involved with synovitis or effusion on US (20%) compared with

18% at MCP 1 and 16% at MCP 5 (Figure 6.1(b)). Overall, the dominant hand MCP joints were more commonly affected by synovitis/effusion than the non-dominant hand.

Additionally, as depicted in Figure 6.2(a), ET was most commonly detected by US at MCP joints 2 to 4, again affecting the dominant more than the non-dominant hand. The ET was most often seen over the third MCP joints (30%). Over half of the total amount of ET detected was represented by MCPs 2 and 3 in the two hands. PD positivity followed the same pattern with over 56% of all PD positive MCP joints distributed to the second and third MCP joints in the two hands (Figure 6.2(b)). Of the 28 MCP joints with erosions shown, 19 (68%) were found in MCP joints 2 or 3. MCP 2 was the most commonly involved joint accounting for 46.4% of all MCP joints with erosions.

Several versions of this US protocol were applied in the early RA patients and their comparative performances assessed as follows:

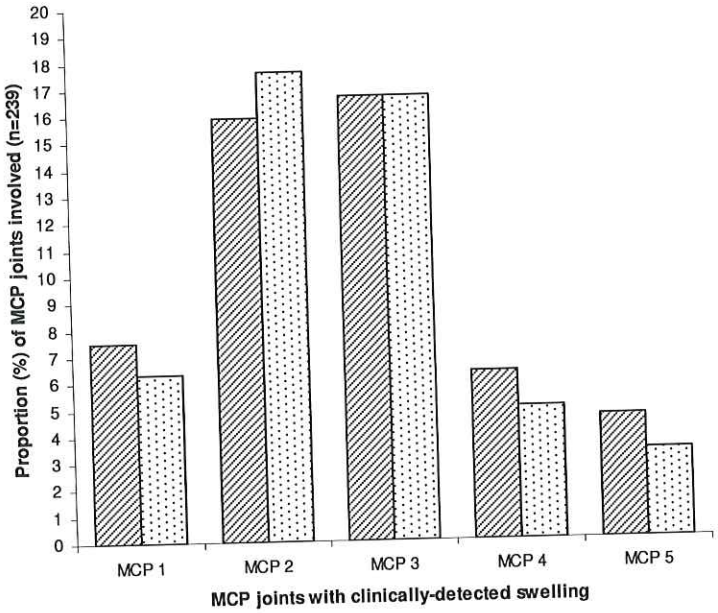
(1) Dominant hand MCP 2

(2) Dominant hand MCP 3

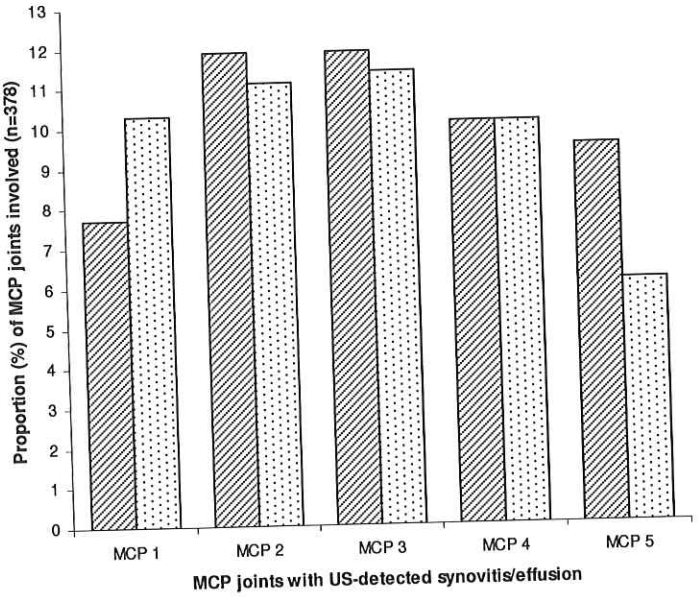
(3) Dominant hand MCP joints 2 and 3

(4) MCP joints 2 and 3 of both hands

(5) Combination (4) with the addition of both wrist joints

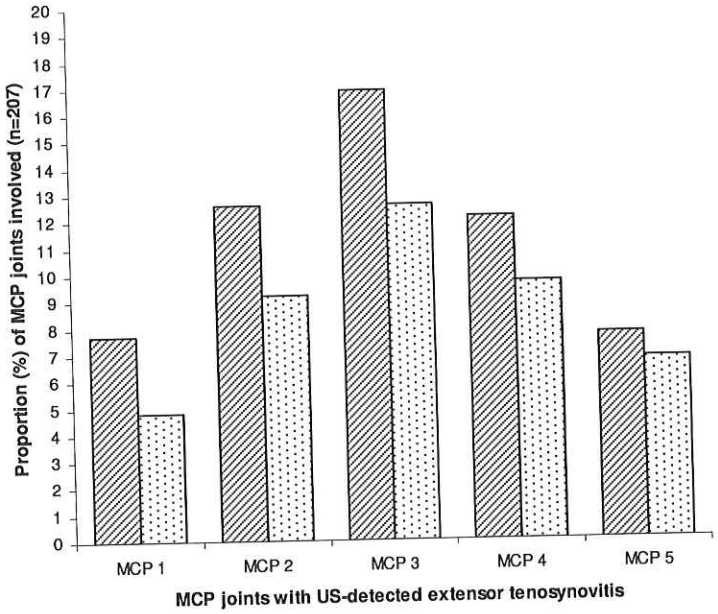


(a)

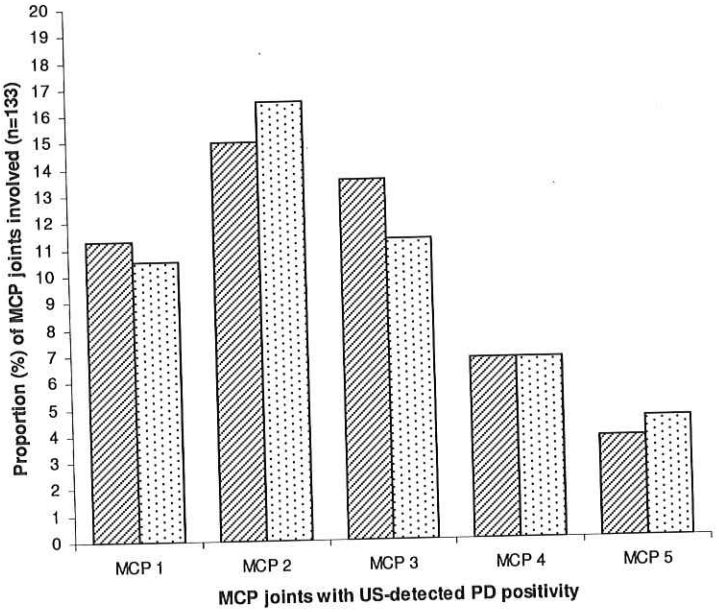


(b)

Fig 6.1 Proportion of individual MCP joints displaying US changes in early RA with (a) clinical swelling (n= 239 joints) and (b) US-detected synovitis/effusion (n=378 joints). The hatched columns represent the dominant hand and the spotted columns the non-dominant hand



(a)



(b)

Fig 6.2 Proportion of individual MCP joints in early RA with (a) US-detected extensor tenosynovitis (ET) and (b) PD positivity. The hatched columns represent the dominant hand and the spotted columns the non-dominant hand (n=50 subjects with 500 MCP joints)

6.6.2 Validation of the "sentinel joints" US examination

The sentinel joints chosen for limited US hand examination were MCP joints 2 and 3 of each hand. This combination of joints detected positive findings in one or more joints (including MCP, PIP or wrist joints) with sensitivities of 98% for synovitis/effusion, 93% for ET, 84% for PD positivity and 87% for erosions when compared to the extended US protocol. The comparison of differing combinations of MCP joints with or without the wrist joints for sensitivity at detecting one or more abnormal findings for the respective US parameters relative to the full US joint examination is detailed in Table 6.1. If both wrists were included among the sentinel joints, then sensitivities for the various US features were increased to 100% for synovitis and PD positivity, 98% for ET and 93% for erosions.

Table 6.1 Performance of candidate combinations of joints for "sentinel joints" US examination in early RA (n=50 subjects)*

Combinations of joint counts assessed	Synovitis/ effusion	ET	PD positivity	Erosions
Dominant hand MCP 2 only	90%	62%	55%	47%
Dominant hand MCP 3 only	90%	83%	50%	33%
Dominant hand MCPs 2 and 3	94%	86%	68%	67%
MCPs 2 and 3 of both hands	98%	95%	84%	87%
MCPs 2 and 3 of both hands plus wrists	100%	98%	100%	93%

* sensitivities of differing combinations of reduced joint counts at detecting one or more abnormal joints for specified parameters compared to detection by a full US protocol

Specificity was assessed by comparing the US results for MCP joints 2 and 3 with the available MRI data in a subset of 11 patients (for complete details of this group and the associated findings, refer to Chapter 4). There was 100% specificity at these MCP

joints for synovitis as well as erosions. Therefore, the "sentinel joints" US assessment tool developed in this study (bilateral MCP joints 2 and 3 with wrist joints) was highly sensitive and specific for synovitis in early RA.

6.6.3 Comparison with other US assessment systems for RA joint inflammation

Tables 6.2 (a) and (b) show the demographics, joints assessed, details of the measurement or scoring systems used, validation, reproducibility and longitudinal data in published US assessment systems in RA in comparison to this study.

Table 6.2(a) Comparison of US assessment systems for RA joint inflammation

Author	Year	No. pts	Mean duration (range)	Joints Assessed	Measurements
Ribbens *et al*	2003	11	9 yrs (2-31)	MCP, PIP	Synovial thickness
Szkudlarek *et al*	2003	30	5.5 yrs (0-20)	MCP, PIP, MTP	Not done
Szkudlarek *et al*	2004	30	2 yrs (0-20)	MCP, PIP, MTP	Not done
Taylor *et al*	2004	24	1.5 yrs	MCP	Not done
Scheel *et al*	2005	46	8.5 yrs	MCP, PIP	Max thickness
Lee *et al*	2007	50	0.4 yrs (0.2-1)	MCP	Joint cavity and synovial thickness

No. pts = number of patients studied

Table 6.2(b) Comparison of US assessment systems for RA joint inflammation

Author	Scoring system (semi-quantitative)	Comparison to MRI	Reprod Data	F-up Data
Ribbens *et al*	Not done	Not done	Yes	Yes
Szkudlarek *et al*	Grade 0-3 Localisation/extension	Not done	Yes	No
Szkudlarek *et al*	Grade 0-3	Yes (MTP joints) Localisation/extension	No	No
Taylor *et al*	Grade 0-5 thickness	Not done	No	Yes
Scheel *et al*	Grade 0-3 area	Yes (in 10)	Yes	No
Lee *et al*	Grade 0-3 Localisation/extension*	Yes (in 11)	Yes	Yes

* done but not reported in this thesis in detail
Reprod = reproducibility data
F-up = follow-up data, longitudinal results

6.7 Discussion

6.7.1 Development and validation of the "sentinel joints" US examination

The researchers in this study chose the MCP joints most frequently affected (with synovitis/effusion, ET and PD positivity) to develop a simplified screening protocol and applied this in the early RA setting to determine its sensitivity compared with an extended US standardised protocol (including all MCP joints and both wrists). The "sentinel joints" protocol was shown to be a highly sensitive tool using bilateral MCPs 2 and 3 for synovitis (98%), extensor tenosynovitis (95%), power Doppler positivity (84%) and erosions (87%). This increased when both wrists were included (sensitivities of 100%, 98%, 100% and 93% respectively). Assessment of specificities was limited to

the available data from MRI studies on the most severely clinically affected hand MCP joints in 11 patients, with US-detected synovitis proving highly specific (100%).

Naredo and colleagues (Naredo 2005b) recently have assessed several combinations of reduced joint counts and compared this to an extended 60 joint US assessment to determine its agreement with clinical and biological markers of inflammation. They showed that a reduced joint count of 12 including MCP 2 and 3, PIP 2 and 3 and wrists bilaterally with both knees was the best system with comparable information on disease activity of the patients. Scheel and co-workers also attempted to identify the optimal US assessment method from six joint combinations using ROC curve analysis (Scheel 2005). The combinations yielding the best results were MCPs 2 to 5 and PIPs 2 to 5, or the MCPs 2 to 4 and PIPs 2 to 4 (the second combination was recommended by the authors for assessing efficacy of treatment for synovitis).

The optimal "sentinel joints" US assessment method identified in this study was a less expensive and time-consuming tool for detecting sub clinical features of early RA than MRI or the extended US protocol.

6.7.2 Comparison with published US assessment systems for RA joint inflammation

The design of this study with regards to size, measurements, scoring, validation with MRI, reproducibility and longitudinal data was comparable to previous studies described in Tables 6.2 (a) and (b). These studies have been the subject of a recent editorial by Ostergaard and co-workers (Ostergaard 2005). The present study reports results on the greatest number of subjects (n=50) and focuses on early RA, not

established disease or a mixture of both, unlike most of the other studies (Ribbens 2003, Szkudlarek 2003, Szkudlarek 2004, Scheel 2005). Therefore, the results of this study can be applied with confidence in an early arthritis setting, unlike the findings of established RA studies. The advantages of our study are the inclusion of reproducibility and longitudinal data in a large number of early RA patients. There is only one other study that provides reproducibility data for measurements and longitudinal outcomes (Ribbens 2003). Less than half of published US assessment systems in RA of the finger, wrist or toe joints provide reproducibility data, which is crucial for validation of quantitative assessments (Ostergaard 2005). The present study also examined US in comparison to MRI.

6.8 Conclusions

A "sentinel joints" focussed US assessment was highly sensitive and specific in early RA for synovitis and other US findings when compared with an extended US assessment. The performance of this tool will be investigated in subjects with early polyarthralgia in the next chapter to further validate its usefulness. This study was comparable to and provided several advantages over previous US assessment systems for RA, since it includes reproducibility data and longitudinal observations in early disease.

CHAPTER 7

Early polyarthralgia

7.1 Background

Early initiation of treatment for RA is important as radiographic damage can be seen after only a few months of disease and even earlier with newer imaging modalities of HRUS and MRI. In the early stages, it may be difficult to differentiate RA from other types of arthritis (Saraux 2001, Machold 2002). Early arthritis has variably been defined as up to one to three years of symptoms and is called undifferentiated if the rheumatologist is uncertain of the diagnosis (Jansen 2002). In the setting of a suggestive history of inflammatory joint pains and polyarthralgia (PA) with subtle clinical signs, there may be difficulty in making a firm diagnosis of inflammatory polyarthritis and hence identifying the need for DMARD therapy. US can help identify sub-clinical synovitis in these difficult cases (Karim 2001).

7.2 Aims

(1) To compare clinical, laboratory and US features of subjects with early PA with those of an early RA group to evaluate variables that may influence probabilities for disease persistence and progression

(2) To validate a "sentinel joints" US assessment developed in Chapter 6 with reduced joint count for synovitis, erosions, ET and PD positivity in the PA group

7.3 Hypotheses

(1) Demographic data, clinical, laboratory and US features in early PA differ from those in early RA and can aid in distinguishing the two diagnoses

(2) A "sentinel joints" US assessment can provide sufficient information for diagnostic purposes and can be validated against an extended joint count assessment in early PA

7.4 Subjects

7.4.1 Selection

A group of subjects presenting to the Early Arthritis Clinic with recent onset joint pain, including the hands but without clinically evident signs of synovitis or blood abnormalities sufficient for a diagnosis of RA were selected.

7.4.2 Inclusion Criteria

Subjects with recent onset PA including hand involvement were enrolled into the early PA group and compared with another group with recent onset polyarthritis who fulfilled formal criteria for RA (see selection criteria described in Chapter Three).

7.4.3 Exclusion Criteria

Any subjects with prior or current diagnoses of a rheumatic inflammatory disease including RA or psoriatic arthritis.

7.5 Methodology

Observational study

7.5.1 Comparison of early PA to early RA

Clinical and laboratory assessments and an extended US examination were performed. Demographic data and US features documented in early PA were compared with those of the early RA group. This was an observational sub-study in which the utility of US was assessed as an aid to diagnosis and as a prognostic indicator in early PA.

7.5.2 Performance of "sentinel joints" US examination in early PA

Given the time-consuming nature of this study's extended US protocol, which includes all MCP and PIP joints and the wrists (described in detail in Chapter Three), a focussed US examination with reduced joints was devised in Chapter 6 and validated in the early RA group. Using the MCP joints most commonly affected by synovitis/effusion (as well as by ET, PD positivity and erosions) as the sentinel joints, the sensitivity of selected MCP joints in identifying those subjects with disease affecting any of their MCP joints was calculated in the PA group.

7.5.3 Statistical analysis

Given the small numbers of subjects in this sub study, results in each group were described and compared with each other. Sensitivities of a "sentinel joints" US examination in the PA group were determined as detailed in the Methods section.

7.6 Results

7.6.1 Comparison of early PA to early RA

A small group of 15 subjects with early PA was studied. The subjects were younger, with greater female preponderance, less RF and anti-CCP positivity and lower inflammatory markers (close to the upper limit of the normal range) than the early RA group of 50 patients (Table 6.1). Their mean disease duration at presentation was also longer than the RA group (11 compared with 5 months respectively). Despite not having a definitive diagnosis at the time of the US, 7% of subjects in the early PA group had evidence of US erosions compared with 24% in the early RA group.

Table 7.1 Demographics of early PA compared to the RA group

	Early PA (n=15)	Early RA (n=50)
Median age years (range)	45 (15-62)	55 (20-82)
Mean duration months (range)	10.8 (3.6-12)	4.8 (2.4-12)
Females (%)	93	78
RF positive (%)	27	38
Anti-CCP ab positive (%)	36	52
Mean ESR*	16	29
Mean CRP*	3.3	19.2
US erosions (%)	7	24

* the reference range for ESR was 0-15mm in the first hour and for CRP was less than 10mg/L

When comparing results of US of the MCP joints in the two groups, the pattern of joint involvement differed (Table 6.2). In the early PA group, 33% had limited arthritis (synovitis of 2-4 MCP joints) compared to 4% of the early RA group. Involvement of 5 or more MCP joints was found in 60% of PA and 92% of early RA subjects. There

were almost four fold more early RA subjects with PD positive joints (75% compared with 20%). 60% of MCP joints in PA subjects had US synovitis and/or effusion compared to 77% in the early RA group. Similar proportions of MCP joints had ET and abnormal measurements in each group. Few joints with PD positivity were found in the PA group with substantially more (27%) being found in the early RA group.

In addition, as a marker of clinical symmetry in the early PA group, 13.3% had bilateral clinically swollen wrist joints but no MCP joint swelling compared with 34% in the early RA group. Also US symmetry was less frequent in the PA group (33.3%) than in the early RA group (68.1%). Thus, both clinical and US symmetry were half as common in the PA group compared to the early RA group.

Table 7.2 Comparison of US findings in early PA and RA

	Early PA (n=15)	Early RA (n=50)
Participants (%) with:		
Synovitis of 2-4 MCP joints*	33	4
Synovitis of at least 5 MCP joints	60	92
Component of ET	93	83
Component of PD positivity	20	75
MCP joints (% of total) with:		
Synovitis/effusion	60	77
ET	43	42
PD positivity	4	27
Abnormal measurement 1	39	42
Abnormal measurement 2	23	17

* one subject each with early PA or early RA had no US synovitis in any of the MCP joints, and one early RA subject had synovitis in only one MCP joint

7.6.2 Performance of "sentinel joints" US examination in early PA

The sentinel joints chosen for limited US hand examination were MCP joints 2 and 3 of each hand. The performance of this tool with and without the wrist joints was assessed in the PA subjects (Table 7.3).

Table 7.3 Performance of candidate combinations of joints for "sentinel joints" US examination in early PA (n=15 subjects)

Combinations of joint counts assessed	Synovitis/ effusion	ET	PD Positivity	Erosions
MCPs 2 and 3 of both hands	93%	93%	18%	50%
MCPs 2 and 3 of both hands plus wrists	100%	100%	91%	100%

* sensitivities of differing combinations of reduced joint counts at detecting one or more abnormal joints for specified parameters compared to detection by a full US protocol

Of the 11 subjects with PD positivity and early PA, PD was present at the wrist joint only in 8/11 (73%) without MCP joints being involved. In one subject, PD positivity was seen only at the PIP joints. The 2 subjects with erosive disease showed erosions of the ulnar styloid, radio carpal joint or MCP 2.

7.7 Discussion

7.7.1 Comparison of PA to early RA: clinical and laboratory parameters

When dealing with patients with recent onset PA, a definitive diagnosis is often difficult in the setting of minimally raised inflammatory markers, fewer disease markers such as anti-CCP antibody and RF and lack of clinically swollen joints. There is also the challenge of deciding on the timing for introduction of pharmacological

therapy. Patients with early erosive changes have a poorer prognosis (Boers 2001). Ideally, early RA should be differentiated from self-limiting synovitis since there are risks associated with DMARDs prescribed for RA. Previous studies have reported differences in outcome between patients with RA and those with undifferentiated inflammatory polyarthritis (UIP), with remission rates at least twice as high in the UIP group (Nissila 1983, Wolfe 1993, Harrison 1996). If one is able to identify UIP compared with RA by recognising factors and patterns of disease seen commonly in each category, then this will help to target therapy for the individual.

The PA group in this study was characterised by younger females with less positive serology for RF and anti-CCP antibody, longer disease duration at presentation with fewer joints involved more often. Tunn and co-workers (Tunn 1993) found that it was difficult to distinguish between self-limiting and persistent symmetrical polyarthritis when utilising clinical and laboratory variables measured at a patient's first visit. In very early arthritis, previous researchers have reported rates of RF positivity of 47% at baseline in RA compared to 12% of non-RA (Machold 2002). This study confirmed more RF positivity (38% compared to 27%), higher inflammatory markers, higher median age and more polyarthritis in the RA group.

The duration of symptoms of PA at the time of US was longer in the early PA group with a mean disease course of about 11 months compared to 5 months in RA. This is in contrast to an Austrian very early arthritis study in which the median disease duration of RA was twice as long as non-RA, a group with more acute onset disease and hence earlier referral (Machold 2002). Our recent onset PA subjects gave a history of insidious symptom onset with uncertain rheumatologic diagnosis at the time of US.

Clinical symmetry has been recognised as a marker for disease persistence (Green 1999) and is part of the ACR classification criteria (Arnett 1988). In this study, about 2.5 times more patients in the early RA group had clinically symmetrical MCP joint involvement compared with bilateral symmetrical wrist joint swelling in the recent onset PA group. The wrist synovitis was used as an indicator of clinical symmetry in the PA group as there was no evidence of MCP joint swelling in any of these subjects. Additionally, US symmetry, defined as involvement of at least MCPs 2 and 3 bilaterally and both wrists, was twice as prevalent in the early RA group. Clinical symmetry was shown to be a marker of poorer prognosis with failure to achieve DAS28 remission in Chapter Five.

7.7.2 Comparison of PA to early RA: US parameters

US has been shown in this study to assist in differentiating recent onset PA from the true early RA group, with increased PD positivity seen in RA in almost four times the number of subjects and seven times the number of MCP joints. In a French study, Saraux and colleagues examined 270 early arthritis patients with disease duration of up to one year and reported that the ACR classification criteria (see Appendix C) when applied prospectively at baseline were not useful for predicting RA at the two year follow-up, if the rheumatologist opinion on diagnosis was excluded (Saraux 2001). The proportion of undifferentiated arthritis that evolved into RA at one to two years varied in previous studies from 36% to 55% (Saraux 2001, Machold 2002). The PA group in this study was characterised by subjects with fewer US erosions, synovitis and PD positivity, features not included in the ACR criteria for classifying RA.

Despite the absence of a diagnosis of RA, 7% of the PA group had evidence of US erosions affecting the MCP joints compared to 24% of RA patients. Given that DMARDs have been shown to slow radiographic progression (Boers 1997), early initiation of treatment is regarded as important (van der Heide 1996). Despite employing DMARD treatment early on in the course of RA, there may still be between 30% and 40% of patients with erosive disease at one year (Sharp 1991, Plant 1998, Machold 2002).

Jansen and co-workers identified several markers for radiographic progression and functional impairment in undifferentiated PA (Jansen 2002). The progressive PA group had significantly higher mean age, prevalence of hand synovitis and disease activity score (DAS) levels at baseline. The RA group had more arthritis affecting more than 3 joints, more symmetrical involvement, higher CRP and DAS28 and more RF positivity. Disease activity as reflected by PD positivity was almost four times as common in our early RA patients than in the PA group, and about 7 times the number of MCP joints were PD positive (27% versus 4%). This study has also reported a significant correlation with DAS28 level at baseline with the number of PD positive MCP joints (see Chapter 3).

About 95% of patients with RA would expect to be treated with DMARDs by 6-12 months of diagnosis, compared with none to 80% in an undifferentiated PA or good prognosis group (McGonagle 1999b, Jansen 2002). Hydroxychloroquine, an agent used in mild RA, was most commonly prescribed in the progressive PA group in Jansen's study (Jansen 2002), and was the medication most commonly used by rheumatologists after the US diagnosis of arthritis in the PA subjects in this study.

7.7.3 Performance of "sentinel joints" US examination in early PA

The "sentinel joints" US protocol developed in Chapter 6 was highly sensitive when compared with a full US examination for synovitis/effusion, ET, PD positivity and erosions in the early RA group. In PA subjects, the combination yielding the best result was MCPs 2 and 3 of both hands with the addition of both wrists. In particular, this performed much better when considering PD positivity (sensitivity of 91% with wrists compared to 18% without wrists) and was twice as sensitive for erosions. Caution must be exercised when interpreting the PD signal at the wrists, as previous investigators have shown that synovial vascularisation may be detected in healthy subjects using Doppler US, with up to 30% of wrist joints in healthy subjects showing a Doppler signal with a measurable resistive index (Terslev 2004). There is a need to distinguish normal from pathological synovial flow especially with the use of newer US machines with higher Doppler sensitivity, and the significance of the small amount of PD positivity shown at the dorsum of the wrists only in many of the PA subjects in the current study is uncertain. Despite this, the "sentinel joints" US examination can be applied in the early PA setting and is less expensive and time-consuming than the full US protocol.

7.8 Conclusions

In the challenging setting of PA, several factors have been identified that may help differentiate PA from early RA, in particular the presence of PD positivity. In the researchers' opinion, to avoid under-treatment of undifferentiated PA, treatment should be based on the severity of the disease based on US assessment as well as traditional clinical features rather than formal diagnostic categories that pre-date the advent of US. A "sentinel joints" focussed US assessment including MCPs 2 and 3 and the wrist

joints was highly sensitive in early PA for synovitis and other US findings when compared with an extended US assessment.

7.9 Future Studies

The researchers plan to examine the long term outcome of the PA subjects to identify those who evolve into established RA (defined as US erosions) and to determine factors that may predict this.

CHAPTER 8

Summary and Conclusions

8.1 Summary

Early rheumatoid arthritis (RA) is a diagnostic challenge and disease-modifying therapy (DMARD) used early results in best outcomes (Boers 1997). Conventional radiographs are relatively unhelpful for diagnosing early RA, thus there is a prospective role for high resolution ultrasound (US) in assessment of synovitis. This study has developed a standardised protocol for examining the metacarpophalangeal (MCP) joints in early RA. The novel US measurements of synovial inflammation devised were shown to be reliable with excellent intra- and inter-observer reproducibility. There was minimal learning effect observed, indicating that the technique could be learned promptly by a rheumatologist with limited prior US experience. The presence of increased adipose tissue in the MCP joints of obese subjects did not significantly influence measurements of synovial swelling. The US measurements were also validated by magnetic resonance imaging (MRI) with significant correlation between the two imaging modalities, particularly for M2.

The relative insensitivity of clinical examination for synovitis in the early RA setting was highlighted by this study, with US frequently revealing sub clinical synovitis in non-swollen MCP joints. Extensor tenosynovitis (ET) and power Doppler (PD) positivity were highly specific in early RA. The distribution of synovitis appeared to be localised predominantly to the dorsum of the MCP joints. Longitudinal data has shown that clinical swelling and PD positivity were the two factors most responsive to

DMARD treatment, with significant reduction in numbers of MCP joints with these features at follow-up.

The "sentinel joints" modified US assessment developed was shown to be sensitive and specific for synovitis, and highly sensitive for detection of ET, PD positivity and erosions at the MCP and wrist joints, when compared to a full standardised US protocol or MRI. This approach was applied successfully in subjects with early polyarthralgia (PA). This reduced count assessment was less time-consuming and thereby more cost-effective and hence more practical for routine diagnostic use. However MRI was superior for detection of erosions, joint effusion and flexor tenosynovitis. US demonstrated more ET and slightly more synovitis of the MCP joints than MRI.

Although CRP, RF, joint erosions and more recently anti-CCP antibody are recognised predictors of outcomes such as radiographic damage and functional impairment in established RA, they perform poorly as predictors of remission or response to treatment in early RA. This study showed that baseline variables predictive of disease persistence, despite DMARD treatment for one year, were clinical symmetry, abnormal measurements of a defined joint dimension (M1) and erythrocyte sedimentation rate (ESR). As regards radiographic progression, factors identified were an increasing number of MCP joints with abnormal M1 and the presence of US erosions at baseline.

In those subjects with early PA, several features were identified to aid in distinguishing undifferentiated polyarthritis from early RA. In the early PA group, these included longer disease duration, younger age, higher proportion of females, less positive

serology, slightly abnormal inflammatory markers, fewer involved joints as assessed by US, less PD positivity and US erosions at baseline.

8.2 Conclusions

In the light of the HRUS findings of this study, early RA needs to be redefined. US can provide objective data to support the clinical impressions of rheumatologists. The presence of increasing numbers of MCP joints with abnormal M1 or ET may suggest the need for more active treatment in early RA. If the additional information gained from US is shown to be of clinical significance in longitudinal studies (such as the prognostic importance of US-revealed sub-clinical synovitis), US may then be considered an important complementary tool in the early assessment of RA.

Appendix A

Factors significantly influencing measurements in a mixed model ANOVA (Refer Chapter 2)

MCP 1

MCP 1 Measurement 1

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sex*age	5	4.32461678	0.86492336	2.73	0.0304

Level of sex	Level of age	N	y Mean	y Std Dev
F	<35	12	4.86284722	0.65201576
F	35-49	18	4.51666667	0.44494712
F	50+	8	4.13125000	0.58554004
M	<35	7	5.07321429	0.45319632
M	35-49	4	4.75312500	0.96341272
M	50+	3	4.72083333	0.21734669

MCP 1 Measurement 2

dominant=Dominant

Mean	Std Dev
1.1544118	0.3843080

MCP 1 Measurement 2

dominant=Non-Dominant

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sex	1	0.37314054	0.37314054	2.77	0.1026

Level of sex	N	y Mean	y Std Dev
F	38	1.16776316	0.39838813
M	14	0.97678571	0.25915252

MCP 1 Measurement 3

dominant=Dominant

Source	DF	Type III SS	Mean Square	F Value	Pr > F
bmi	3	12.64689123	4.21563041	6.45	0.0009

Level of bmi	N	y Mean	y Std Dev
0-20	3	3.85833333	0.30138569
20-25	22	4.47045455	0.76042893
25-30	19	5.06973684	0.92891734
30+	7	5.74642857	0.68820851

MCP 1 Measurement 3

dominant=Non-Dominant

Source	DF	Type III SS	Mean Square	F Value	Pr > F
bmi	3	9.54637914	3.18212638	5.73	0.0020

Level of bmi	N	y Mean	y Std Dev
0-20	3	3.69166667	0.31655700
20-25	22	4.34886364	0.63823964
25-30	20	4.72500000	0.83732814
30+	7	5.47619048	0.87341694

MCP 2

MCP 2 Measurement 1

dominant=Dominant

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sex*age	5	7.67321142	1.53464228	5.20	0.0007

Level of sex	Level of age	N	y Mean	y Std Dev
F	<35	12	5.88333333	0.64845387
F	35-49	18	5.20833333	0.51277790
F	50+	8	4.97500000	0.50089206
M	<35	7	5.66071429	0.62995654
M	35-49	4	6.13750000	0.28025286
M	50+	3	5.85000000	0.22500000

MCP 2 Measurement 1

dominant=Non-Dominant

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sex	1	1.57822811	1.57822811	6.76	0.0122

Level of sex	N	y Mean	y Std Dev
F	38	5.24473684	0.48962747
M	14	5.63750000	0.46438027

MCP 2 Measurement 2

dominant=Dominant

Source	DF	Type III SS	Mean Square	F Value	Pr > F
age	2	2.11635559	1.05817779	5.15	0.0093

Level of age	N	y Mean	y Std Dev
<35	19	2.02675439	0.51039034
35-49	22	1.77727273	0.42872382
50+	11	1.47954545	0.38968227

MCP 2 Measurement 2

dominant=Non-Dominant

Source	DF	Type III SS	Mean Square	F Value	Pr > F
age	2	1.19994617	0.59997309	3.27	0.0463

Level of age	N	y Mean	y Std Dev
<35	19	1.81885965	0.45266565
35-49	22	1.70454545	0.43071344
50+	11	1.40681818	0.37351220

MCP 2 Measurement 3

dominant=Dominant

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sex*age*bmi	17	8.87820582	0.52224740	2.53	0.0103

Level of sex	Level of age	Level of bmi	N	y Mean	y Std Dev
F	<35	0-20	1	4.05000000	
F	<35	20-25	6	4.64166667	0.49311932
F	<35	25-30	2	4.32500000	1.09601551
F	<35	30+	3	4.57222222	0.19743728
F	35-49	0-20	1	3.62500000	
F	35-49	20-25	11	4.27954545	0.36976651
F	35-49	25-30	5	4.58000000	0.59513654
F	35-49	30+	1	4.45000000	
F	50+	20-25	1	3.47500000	
F	50+	25-30	5	4.18500000	0.17553490
F	50+	30+	2	4.25000000	0.35355339
M	<35	0-20	1	3.82500000	
M	<35	20-25	3	4.75000000	0.57662813
M	<35	25-30	3	5.40833333	0.51255081
M	35-49	20-25	1	4.75000000	
M	35-49	25-30	3	5.00833333	0.25041632
M	50+	25-30	2	4.13750000	0.40658640
M	50+	30+	1	5.62500000	

MCP 2 Measurement 3

dominant=Non-Dominant

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sex*age	5	3.48820758	0.69764152	3.39	0.0109

Level of sex	Level of age	N	y Mean	y Std Dev
F	<35	12	4.42986111	0.48521653
F	35-49	18	4.17638889	0.42499760
F	50+	8	3.99687500	0.43965033
M	<35	7	4.72500000	0.55018936
M	35-49	4	4.81875000	0.28750000
M	50+	3	4.40833333	0.44040701

MCP 3

MCP 3 Measurement 1

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sex	1	1.41643300	1.41643300	6.18	0.0163

Level of		y	
sex	N	Mean	Std Dev
F	38	4.90380639	0.48415944
M	14	5.27589286	0.46320021

MCP 3 Measurement 2

Source	DF	Type III SS	Mean Square	F Value	Pr > F
age	2	1.58049058	0.79024529	7.19	0.0018

Level of		y	
age	N	Mean	Std Dev
<35	19	2.05285088	0.33026964
35-49	22	1.85900974	0.36256617
50+	11	1.57727273	0.25768308

MCP 3 Measurement 3

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sex	1	2.65246458	2.65246458	13.51	0.0006

Level of		y	
sex	N	Mean	Std Dev
F	38	4.45153509	0.40125018
M	14	4.96071429	0.54479303

MCP 4

MCP 4 Measurement 1

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sex	1	3.39638431	3.39638431	12.70	0.0008

Level of sex	N	y Mean	y Std Dev
F	38	4.60953947	0.54230204
M	14	5.18571429	0.43756475

MCP 4 Measurement 2

dominant=Dominant

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sex*age	5	2.52251313	0.50450263	3.69	0.0068

Level of sex	Level of age	N	y Mean	y Std Dev
F	<35	12	2.02777778	0.43651705
F	35-49	18	1.71250000	0.35627257
F	50+	8	1.44062500	0.33698704
M	<35	7	2.10000000	0.32242570
M	35-49	4	1.97500000	0.33229003
M	50+	3	1.83333333	0.37610947

MCP 4 Measurement 2

dominant=Non-Dominant

Source	DF	Type III SS	Mean Square	F Value	Pr > F
age	2	1.15732065	0.57866033	3.19	0.0499

Level of age	N	y Mean	y Std Dev
<35	19	1.92850877	0.41885827
35-49	22	1.72045455	0.48209836
50+	11	1.52954545	0.29215111

MCP 4 Measurement 3

dominant=Dominant

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sex*bmi	7	8.66673478	1.23810497	4.00	0.0018

Level of sex	Level of bmi	N	y Mean	y Std Dev
F	0-20	2	4.11250000	0.30052038
F	20-25	18	4.33750000	0.48349600
F	25-30	12	4.35833333	0.51954234
F	30+	6	4.85000000	0.69749552
M	0-20	1	4.00000000	
M	20-25	4	4.73750000	0.20155644
M	25-30	8	5.13750000	0.75805201
M	30+	1	6.37500000	

MCP 4 Measurement 3

dominant=Non-Dominant

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sex*age*bmi	17	9.08617396	0.53448082	2.88	0.0042

Level of sex	Level of age	Level of bmi	N	y Mean	y Std Dev
F	<35	0-20	1	4.15000000	
F	<35	20-25	6	4.44166667	0.39422921
F	<35	25-30	2	4.37500000	0.77781746
F	<35	30+	3	5.03888889	0.57929155
F	35-49	0-20	1	3.47500000	
F	35-49	20-25	11	3.95909091	0.36763989
F	35-49	25-30	5	4.59500000	0.58105507
F	35-49	30+	1	4.00000000	
F	50+	20-25	1	3.75000000	
F	50+	25-30	5	4.16500000	0.32093613
F	50+	30+	2	4.28750000	0.12374369
M	<35	0-20	1	3.90000000	
M	<35	20-25	3	4.50833333	0.44744646
M	<35	25-30	3	5.14166667	0.26020825
M	35-49	20-25	1	4.70000000	
M	35-49	25-30	3	4.90000000	0.46703854
M	50+	25-30	2	4.07500000	0.38890873
M	50+	30+	1	5.27500000	

MCP 5

MCP 5 Measurement 1

dominant=Dominant

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sex*age	5	7.83218845	1.56643769	6.89	<.0001

Level of sex	Level of age	N	y Mean	y Std Dev
F	<35	12	4.76041667	0.56109252
F	35-49	18	4.26388889	0.48242816
F	50+	8	4.21875000	0.37648515
M	<35	7	5.11428571	0.35702974
M	35-49	4	5.35000000	0.59616832
M	50+	3	4.87500000	0.33071891

MCP 5 Measurement 1

dominant=Non-Dominant

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sex*age	5	6.93109715	1.38621943	6.22	0.0002

Level of sex	Level of age	N	y Mean	y Std Dev
F	<35	12	4.79930556	0.58280775
F	35-49	18	4.04305556	0.33942052
F	50+	8	4.37812500	0.53375983
M	<35	7	4.86071429	0.40999419
M	35-49	4	5.00000000	0.70975348
M	50+	3	4.65833333	0.14648663

MCP 5 Measurement 2

dominant=Dominant

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sex*age	5	2.67667697	0.53533539	2.75	0.0294

Level of sex	Level of age	N	y Mean	y Std Dev
F	<35	12	1.60208333	0.54098588
F	35-49	18	1.35000000	0.41841789
F	50+	8	1.16250000	0.25911939
M	<35	7	1.76071429	0.54636243
M	35-49	4	1.91250000	0.39817291
M	50+	3	1.30833333	0.07637626

MCP 5 Measurement 2

dominant=Non-Dominant

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sex*age	5	2.62525132	0.52505026	3.21	0.0143

Level of sex	Level of age	N	y Mean	y Std Dev
F	<35	12	1.57847222	0.50530592
F	35-49	18	1.20555556	0.30757060
F	50+	8	1.26875000	0.32175579
M	<35	7	1.69642857	0.52190129
M	35-49	4	1.80000000	0.45414755
M	50+	3	1.15833333	0.24281337

MCP 5 Measurement 3

dominant=Dominant

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sex*bmi	7	12.08951211	1.72707316	5.84	<.0001

Level of sex	Level of bmi	N	y Mean	y Std Dev
F	0-20	2	3.52500000	0.10606602
F	20-25	18	4.00277778	0.44307489
F	25-30	12	4.22916667	0.41021521
F	30+	6	4.36111111	0.45395382
M	0-20	1	4.12500000	
M	20-25	4	4.66875000	0.15326312
M	25-30	8	5.15000000	0.97952248
M	30+	1	6.02500000	

MCP 5 Measurement 3

dominant=Non-Dominant

Source	DF	Type III SS	Mean Square	F Value	Pr > F
sex	1	4.29961371	4.29961371	18.49	<.0001

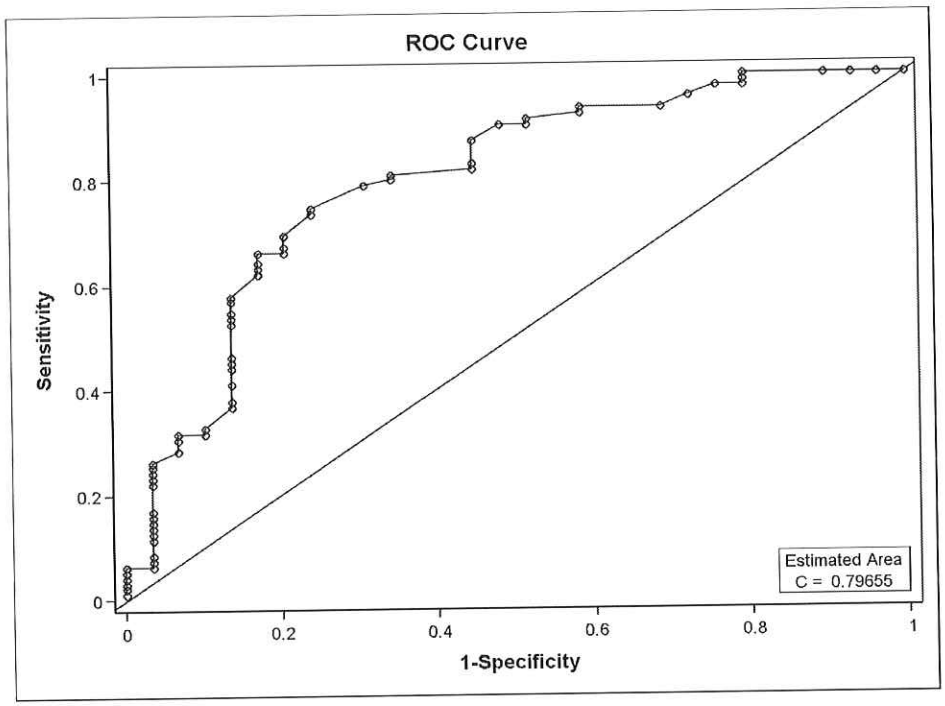
Level of sex	N	y Mean	y Std Dev
F	38	4.00350877	0.44273681
M	14	4.65178571	0.58024069

Appendix B

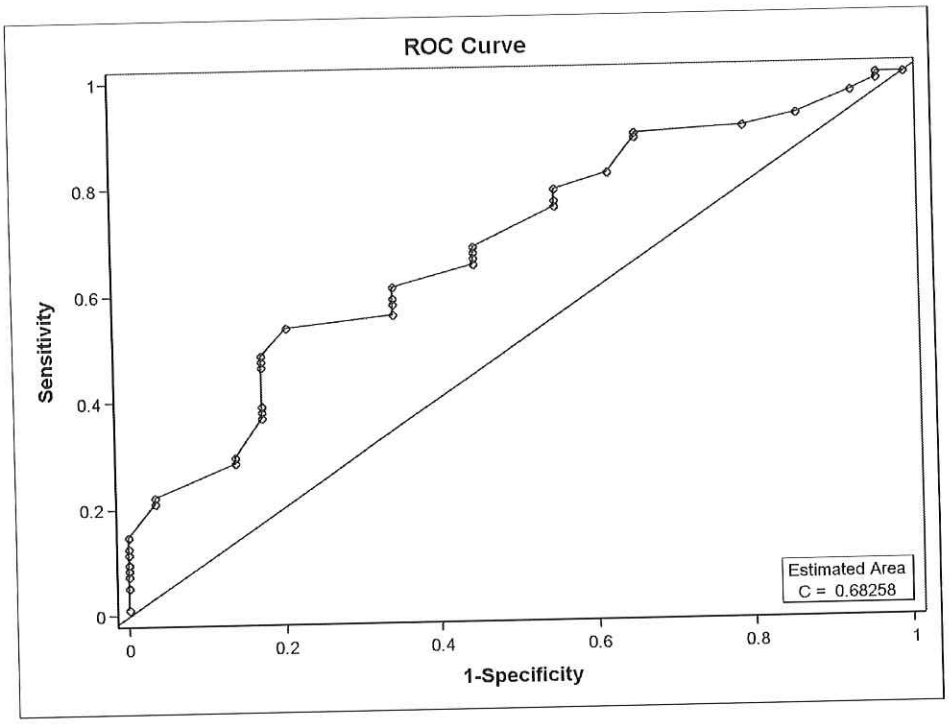
Example of ROC curves and AUC calculations

Scenario 1: Healthies vs. RA joints with 'yes' to synovitis

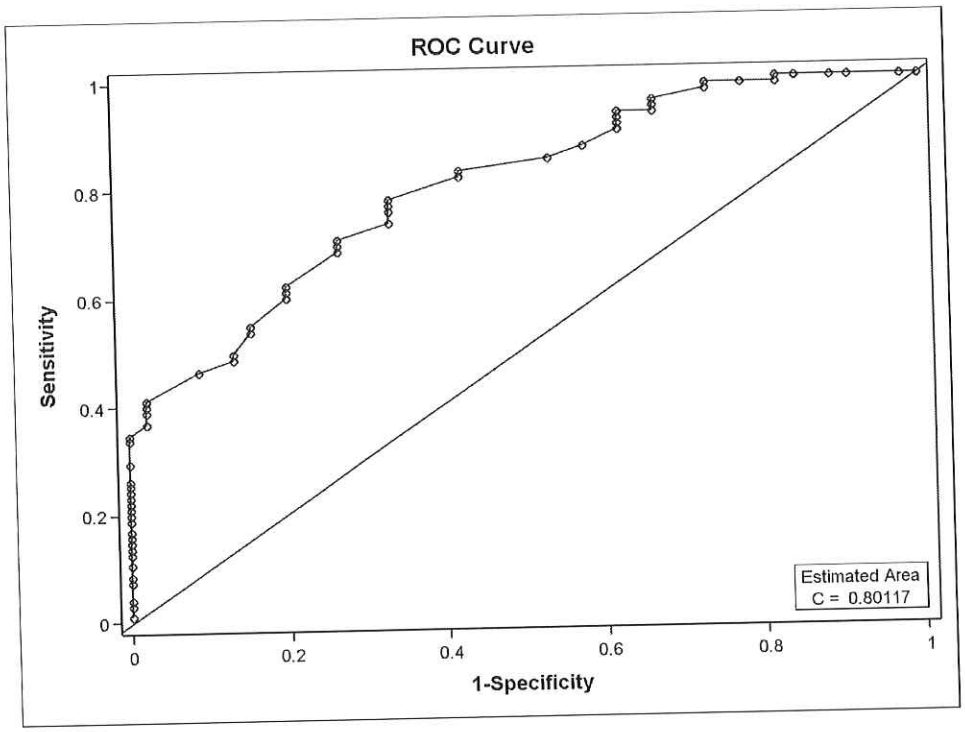
Dominant MCP1 M1



Dominant MCP1 M2



Dominant MCP2 M1



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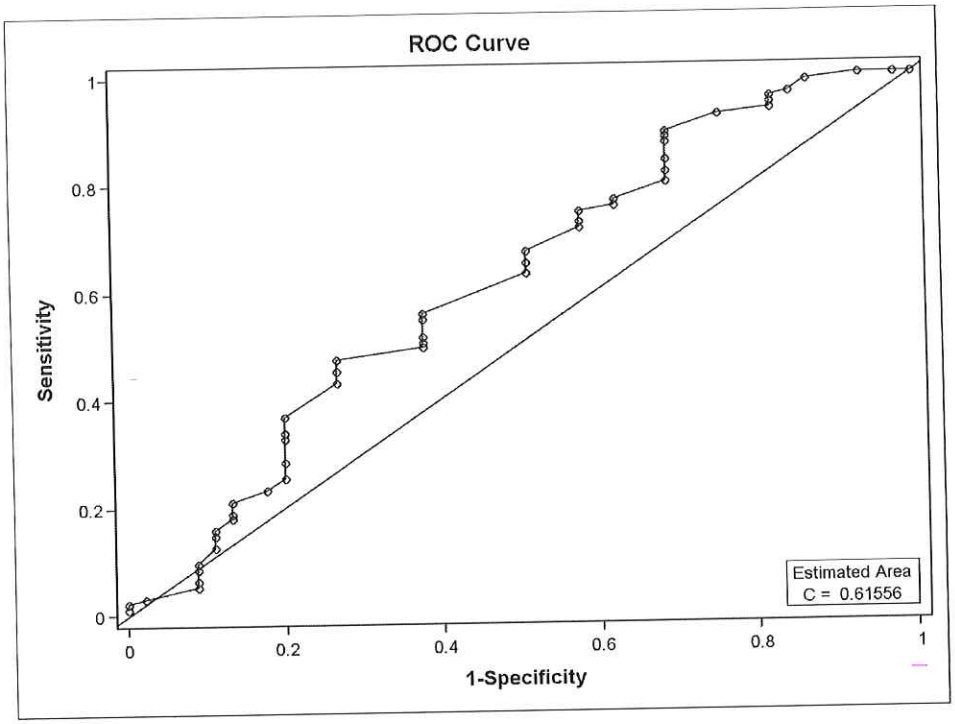
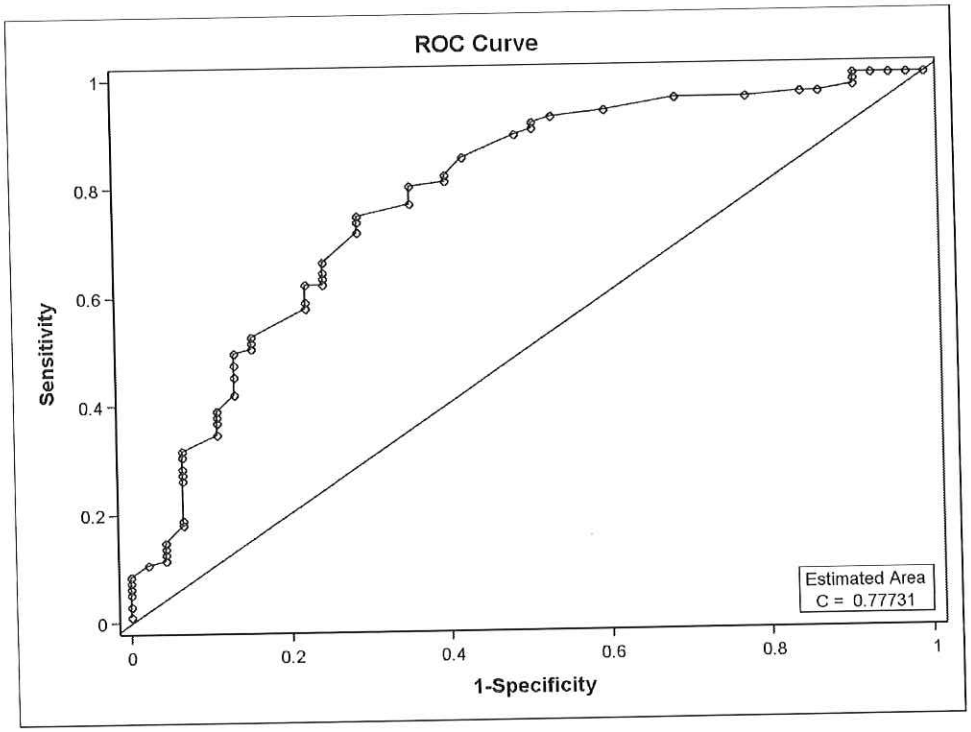


Dominant MCP3 M1



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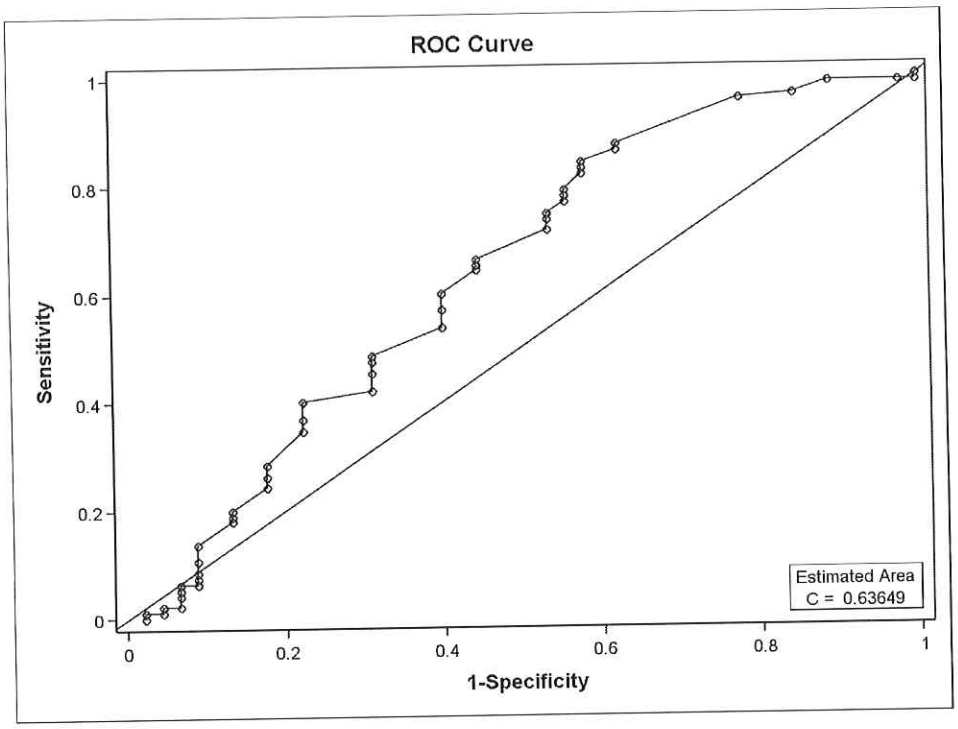
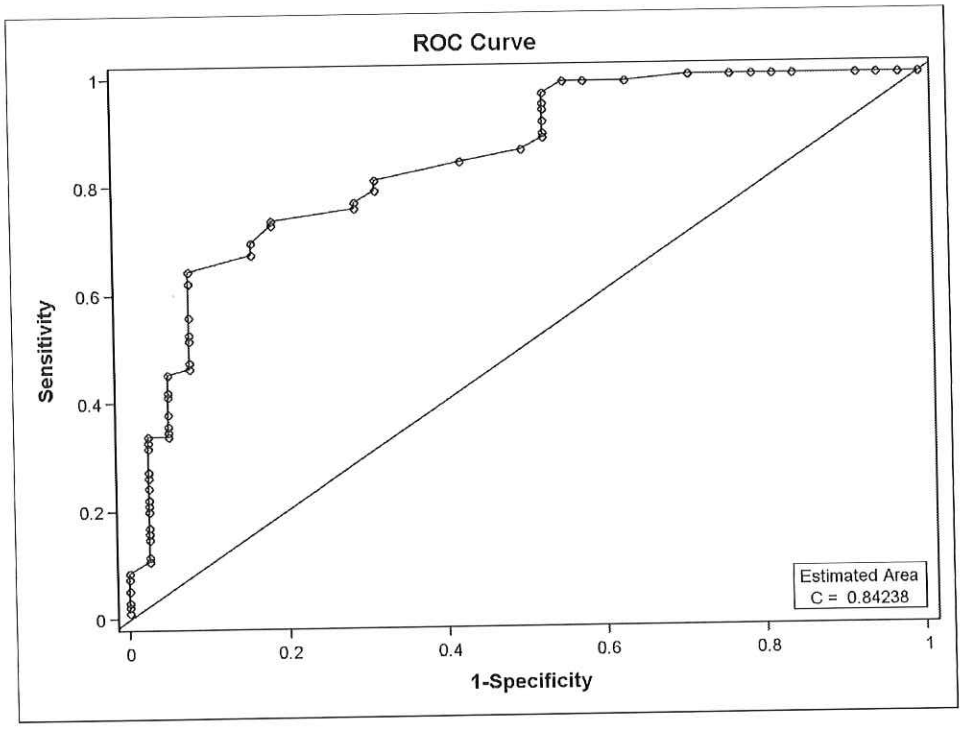
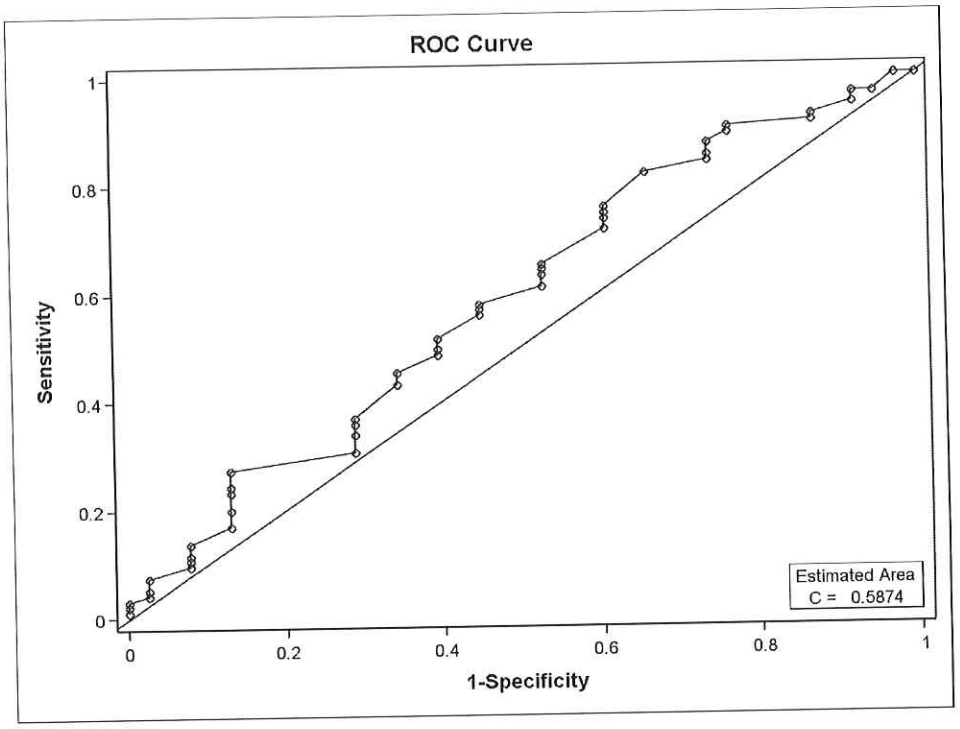


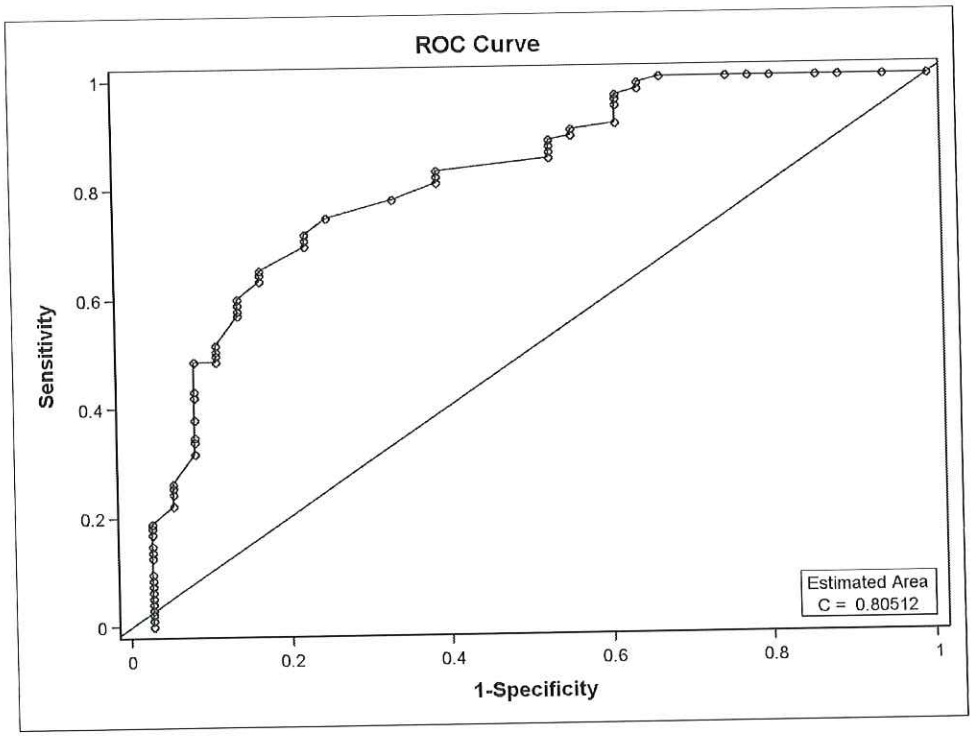
Dominant MCP4 M1



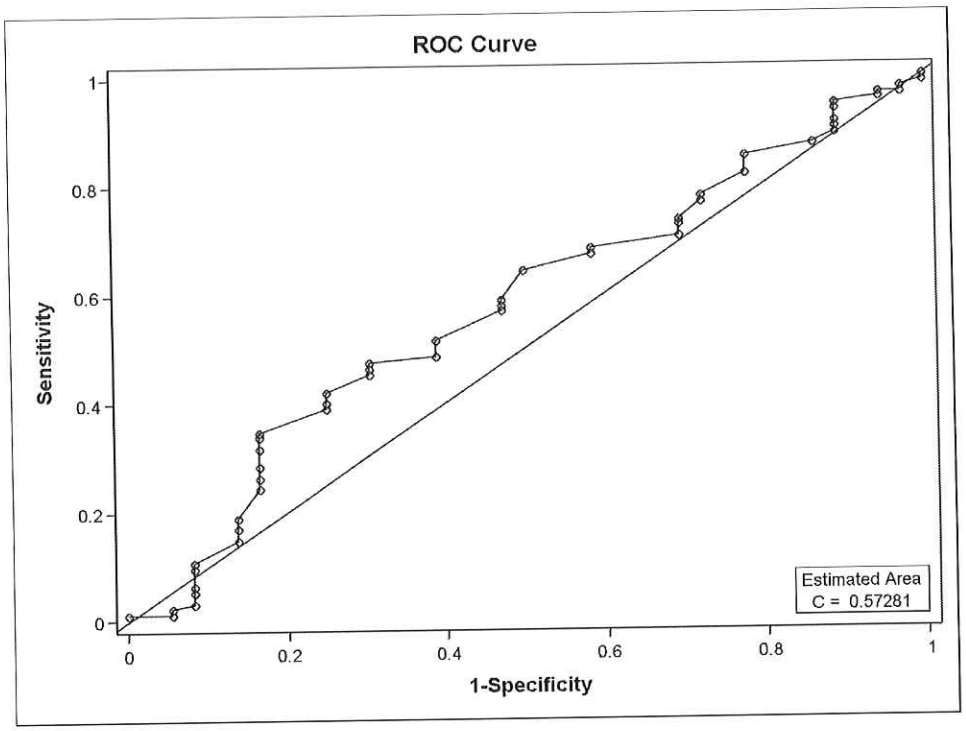
Dominant MCP4 M2



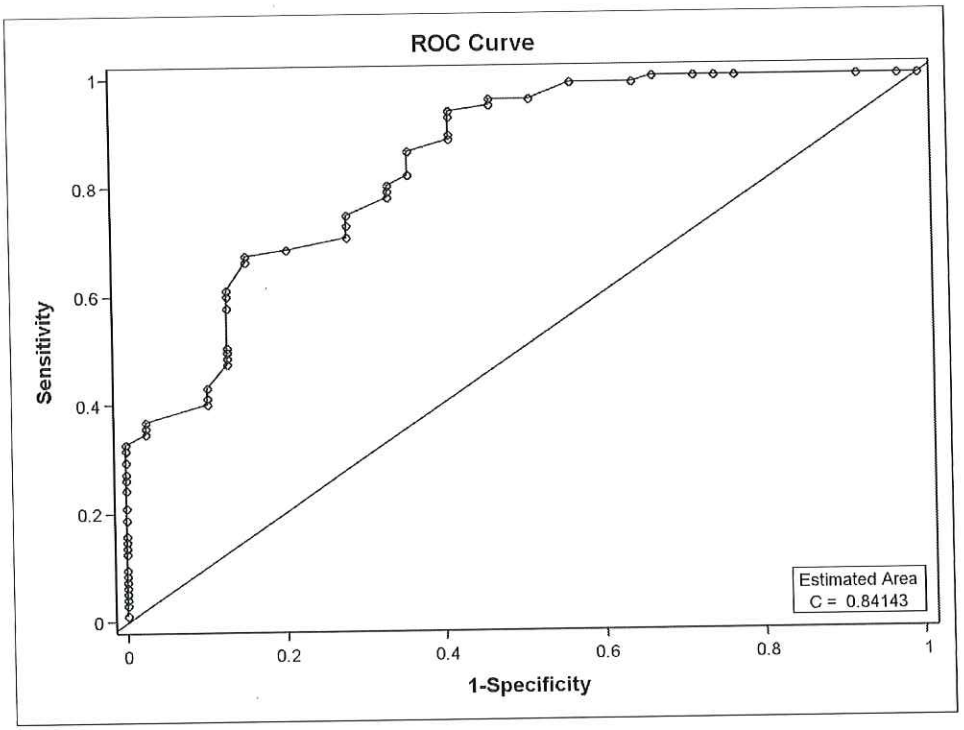
Dominant MCP5 M1



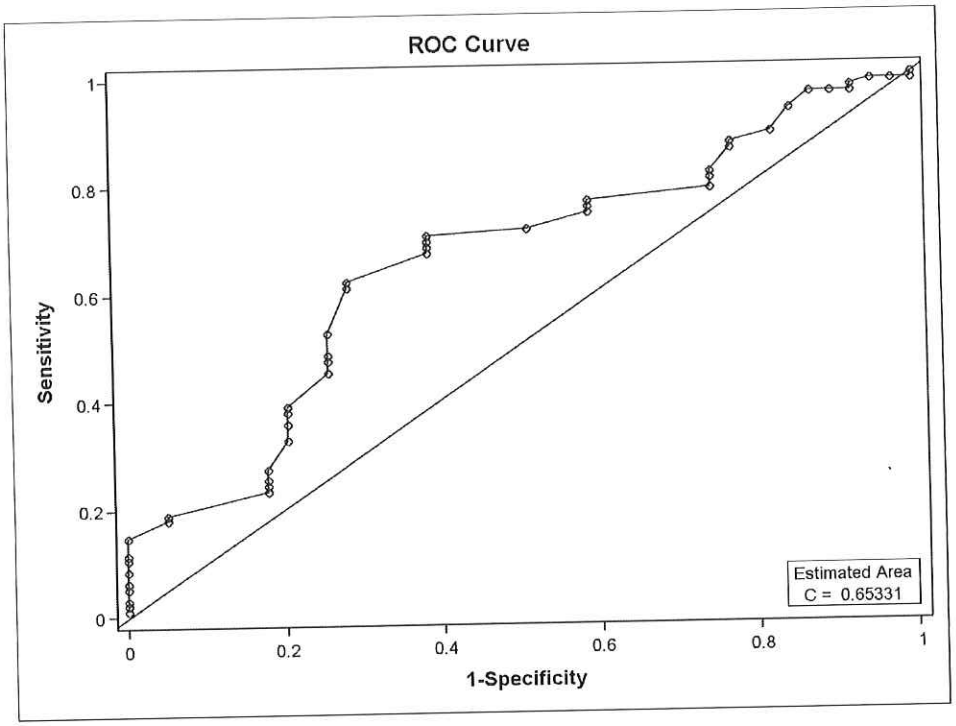
Dominant MCP5 M2



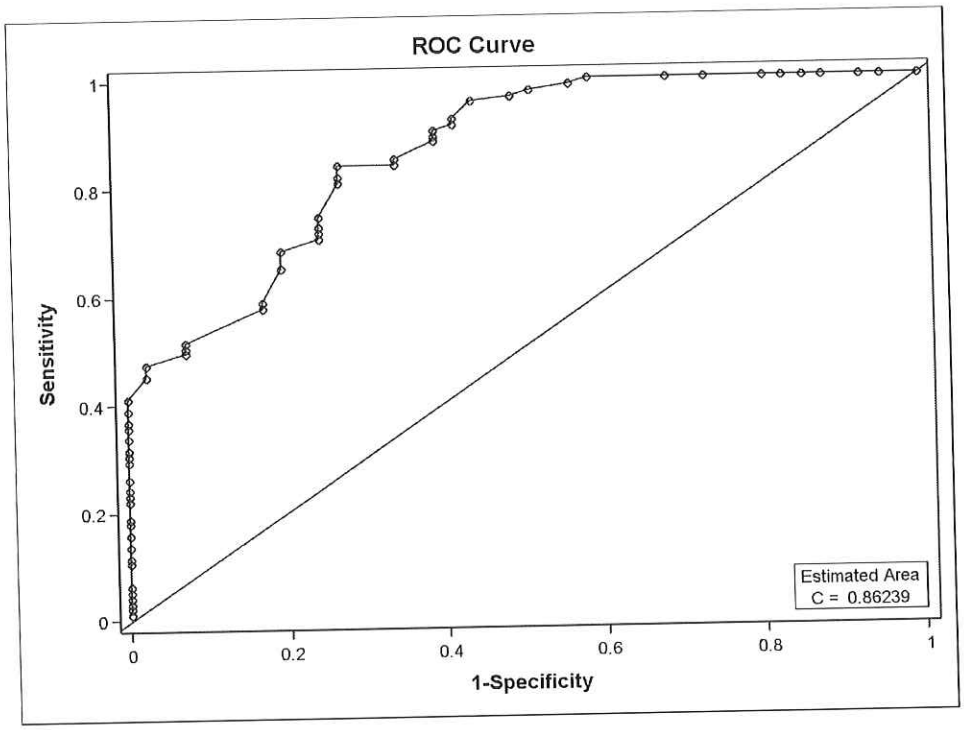
Non-dominant MCP1 M1



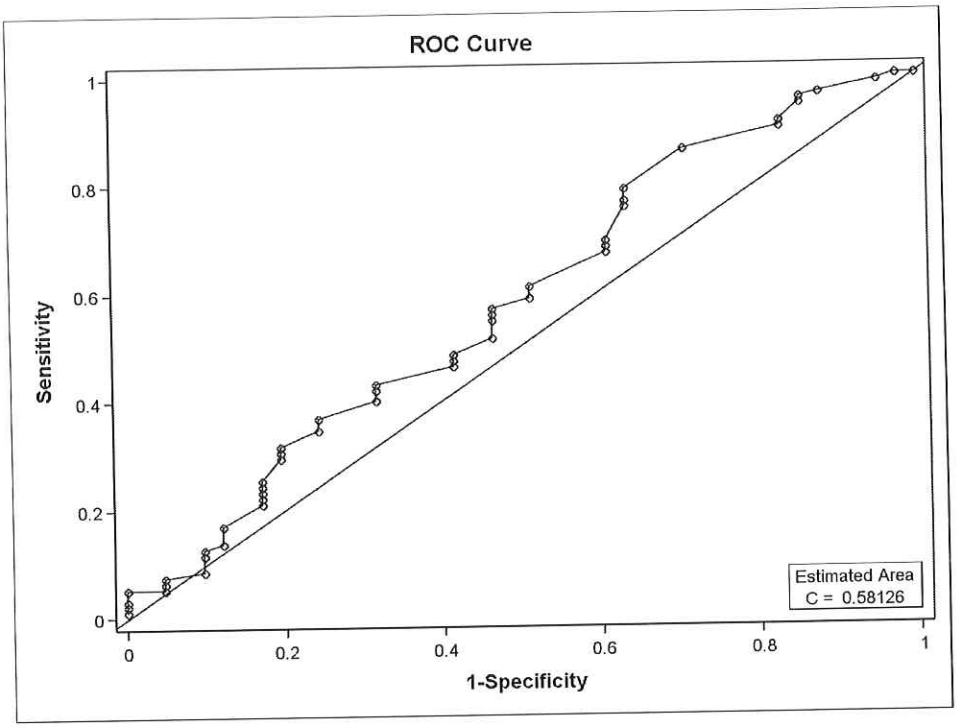
Non-dominant MCP1 M2



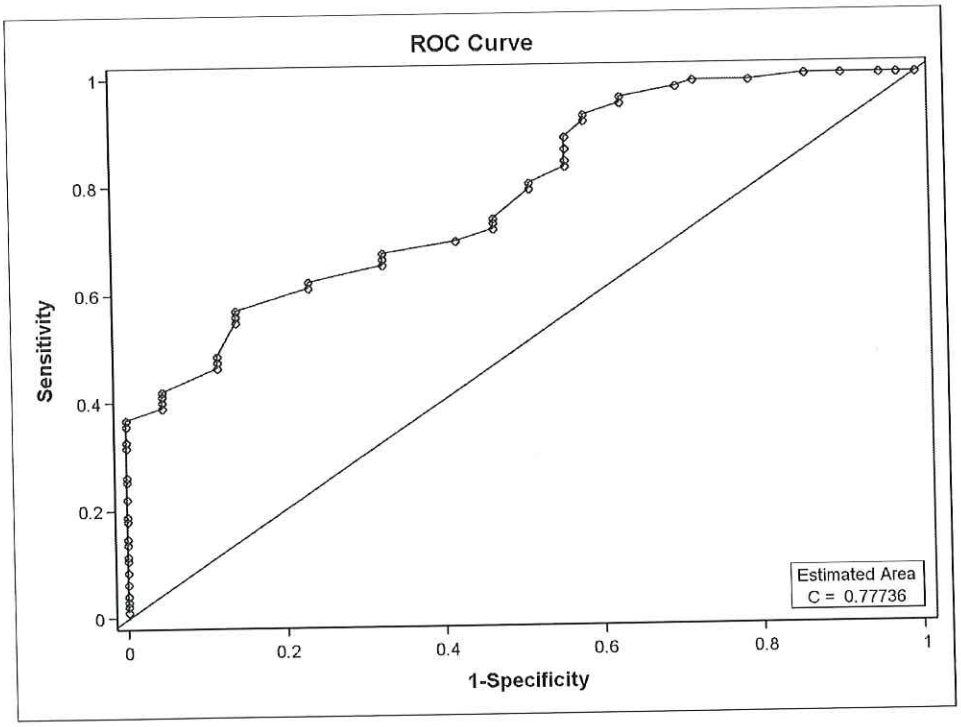
Non-dominant MCP2 M1



Non-dominant MCP2 M2



Non-dominant MCP3 M1



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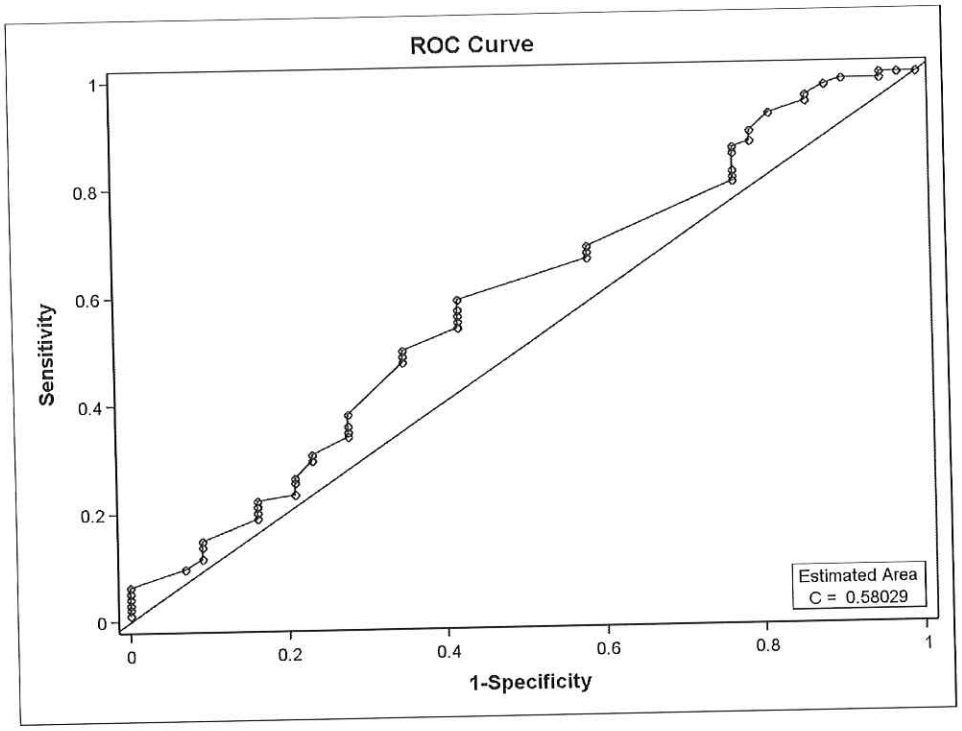
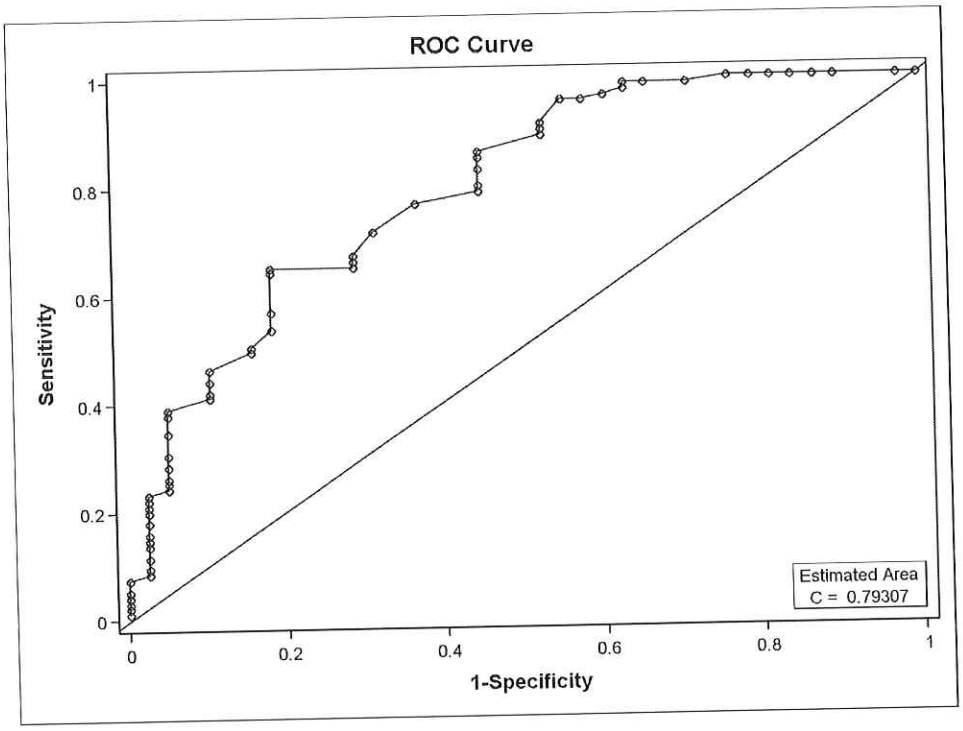


Non-dominant MCP4 M1



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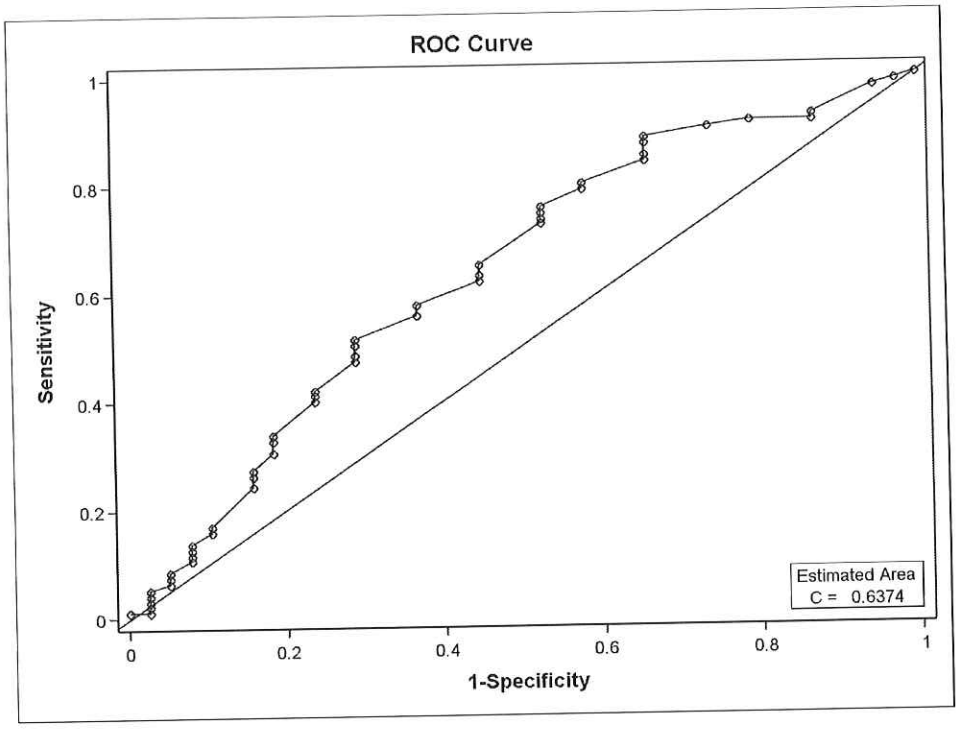
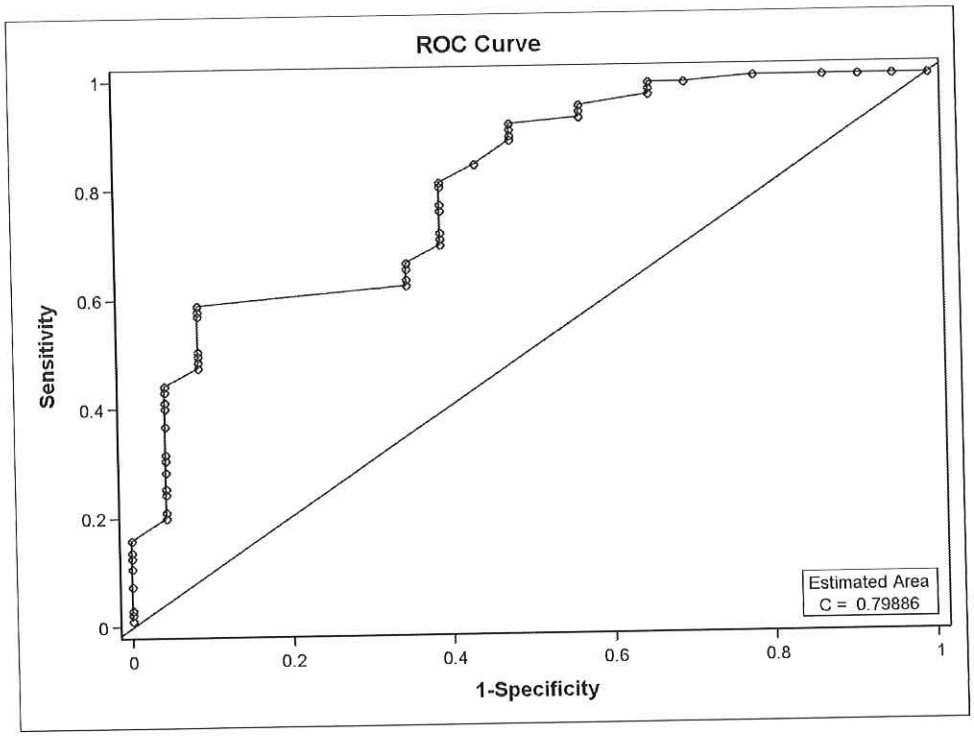
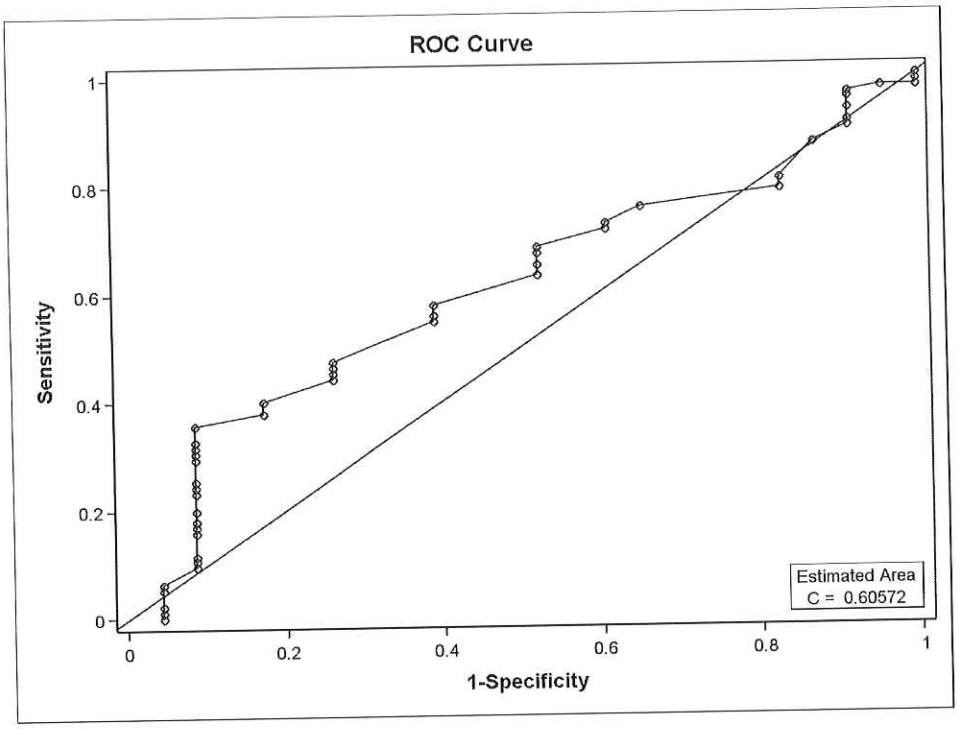


Non-dominant MCP5 M1



Non-dominant MCP5 M2



Appendix C

Revised 1987 American College of Rheumatology (ACR) criteria for diagnosing RA

Requires 4 or more of the following criteria for RA (Arnett 1988):

(1) Morning stiffness (duration at least one hour lasting at least 6 weeks)

(2) Arthritis of at least 3 joints* (soft tissue swelling at least 6 weeks)

(3) Arthritis of the hand joints (wrists, MCP, PIPs at least 6 weeks)

(4) Symmetrical arthritis* (at least one area, lasting at least 6 weeks)

(5) Rheumatoid nodules observed by physician

(6) Serum rheumatoid factor (RF) positive

(7) Radiographic changes (periarticular osteopenia or erosions of the hands)

* possible areas include MCPs, PIPs, wrist, elbow, knee, ankle or MTP joints

ACR responder criteria

For 20% improvement using ACR criteria (also known as ACR 20), at least 20% improvement in the first two variables and 3 out of 5 remaining variables is required (Felson 1995):

(1) Tender joint count

(2) Swollen joint count

(3) Acute phase reactant (ESR or CRP)

(4) Patient's pain (VAS 0-100mm scale)

(5) Patient's global assessment of disease activity (VAS)

(6) Physician's global assessment of disease activity (VAS)

(7) Physical disability (HAQ score)

ARA remission criteria

Five of more of the following criteria must be fulfilled for at least two consecutive months (Prevoo 1996):

- Duration of morning stiffness not exceeding 15 minutes
- No fatigue
- No joint pain (by history)
- No joint tenderness or pain on motion
- No soft tissue swelling in joints or tendon sheaths
- ESR: females < 30mm/h, males < 20mm/h

Appendix D

MRI Safety Screening Form (Flinders Medical Centre)

Patient Name:
Date of Birth: Weight:
Have you had a previous MRI scan?

In order to complete the examination safely we need to know the following information. Answer by ticking yes or no to each question.

Have you ever been a metal worker or welder?
Have you ever had an eye injury caused by metal?
Do you have, or have you ever had a pacemaker?
Do you have a neurostimulator?
Do you have a cochlear (inner ear) implant?
Do you have an artificial heart valve or clip?
Do you have a brain aneurysm clip?
Do you have any implanted stimulation or drug infusion devices?
Do you have an implanted prosthesis or artificial body part?
Is there a possibility you may be pregnant?
Are you breastfeeding?
Are you claustrophobic?
Have you ever had a reaction to CT contrast dye?

Do you have any surgical clips or wire sutures?
Do you have an embolisation coil?
Do you have an inferior vena cava (IVC) filter?
Do you have a brain shunt tube?
Do you have a joint replacement or prosthesis?
Do you have metal pins or screws in bone or soft tissue?
Do you have any wire sutures or metal mesh in or on your body?
Do you have any schrapnel, bullets or gun shots in your body?
Do you have a penile prosthesis?
Do you have a hearing aid?
Do you have an intra uterine device (IUD)?
Do you have any metallic foreign bodies?
Do you have tattoos around your eyes or elsewhere?
Do you have a removable dental device or dentures?
Have you had an operation in the last 6 weeks?
Do you have any allergies?
Have you had asthma?

If you have answered 'yes' to any of the above questions please phone before your scan.

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Addendum

Responses to Examiners Comments

(1) An issue which arose in the examination process was the comment that the terms 'real time' and 'high resolution' are obsolete in relation to contemporary ultrasonography. When the thesis was commenced in 2002, the terms 'real time' and 'high resolution' ultrasonography (HRUS) were in common usage (Erickson 1997, Wakefield 1997, van Vugt 1998, Szkudlarek 1999, Backhaus 1999, Hau 1999, Wakefield 2000). The descriptor 'real time' emphasises the use of US for dynamic evaluation of joints and raises the important issues of operator dependency of real-time acquisition and special aspects of interpretation of images (Manger 1995, Jacobson 1999, Wakefield 2004a, Wakefield 2004b). The term 'high resolution' highlights improvements in image definition which distinguish modern ultrasonography from the limitations of earlier instrumentation. Thus while the terms 'real time' and 'high resolution' may no longer be necessary, they provide a connotation that emphasizes advancement rather than obsolescence. Furthermore, these terms are still found in recent (European) literature (Alarcon 2002, Hau 2002, Weidekamm 2003).

The title including the term 'real time' has been left unchanged, as the issue of operator dependency in the rheumatology setting is an important topic addressed by this thesis. The author agrees that the term musculoskeletal US (MUS) or simply US could replace HRUS throughout the text, as appears in current US literature (Kane 2004, Conaghan 2005). This change was considered discretionary since, while the HR component of the initialism HRUS may now be superfluous, it does not alter meaning.

(2) Dynamic studies were performed to confirm the outline of the extensor tendon, particularly when this was not clearly defined, to determine the second measure points of M1 and M2 (add to p101).

(3) As mentioned on p167, MRI was used as the reference (not gold) standard for US findings, including erosions.

(4) It should be noted that US-defined synovitis was not confirmed histologically as part of this study, as the authors considered the technique of finger mini-arthroscopy (Ostendorf 2001) too invasive in early RA patients.

(5) Correction to p33 paragraph 2 should read: The American College of Rheumatology (ACR) criteria published in 1987 (Arnett 1988) are classification, not diagnostic, criteria for RA. The ACR criteria were developed to characterize a homogenous patient population for studies. Also p264 should read "ACR criteria for classifying RA".

(6) Addition to p101: The transducer was held steady to allow gel (dark area above the skin line) to be visualized…

(7) US and MRI were performed on the same day (see p164).

(8) Table 4.1(g) documents the site of erosions detected by MRI and US.

Table 4.1(g) Site of erosions detected by US compared with MRI as the reference standard

Patient Number	MRI (n=13)	US (n=3)
1	MC3R	MC3D
	MC4V	-
2	No erosions	No erosions
3	pp2R	MC2R
	MC3R	-
	MC5R	MC5R
4	MC2R	-
5	No erosions	No erosions
6	MC2R	-
7	MC3R	-
8	MC5U	-
9	No erosions	No erosions
10	MC2U	-
11	pp5U	-
12	MC2R	-
13	MC2R	-
14	No erosions	No erosions

D = dorsal; V = volar; R = radial; U = ulnar
MC = metacarpal head; pp = base of proximal phalanx
Numbers refer to the corresponding MCP joints 2-5

(9) As suggested, an US image (Figure 4.1 (d)) of erosive disease at the MCP joint is included.

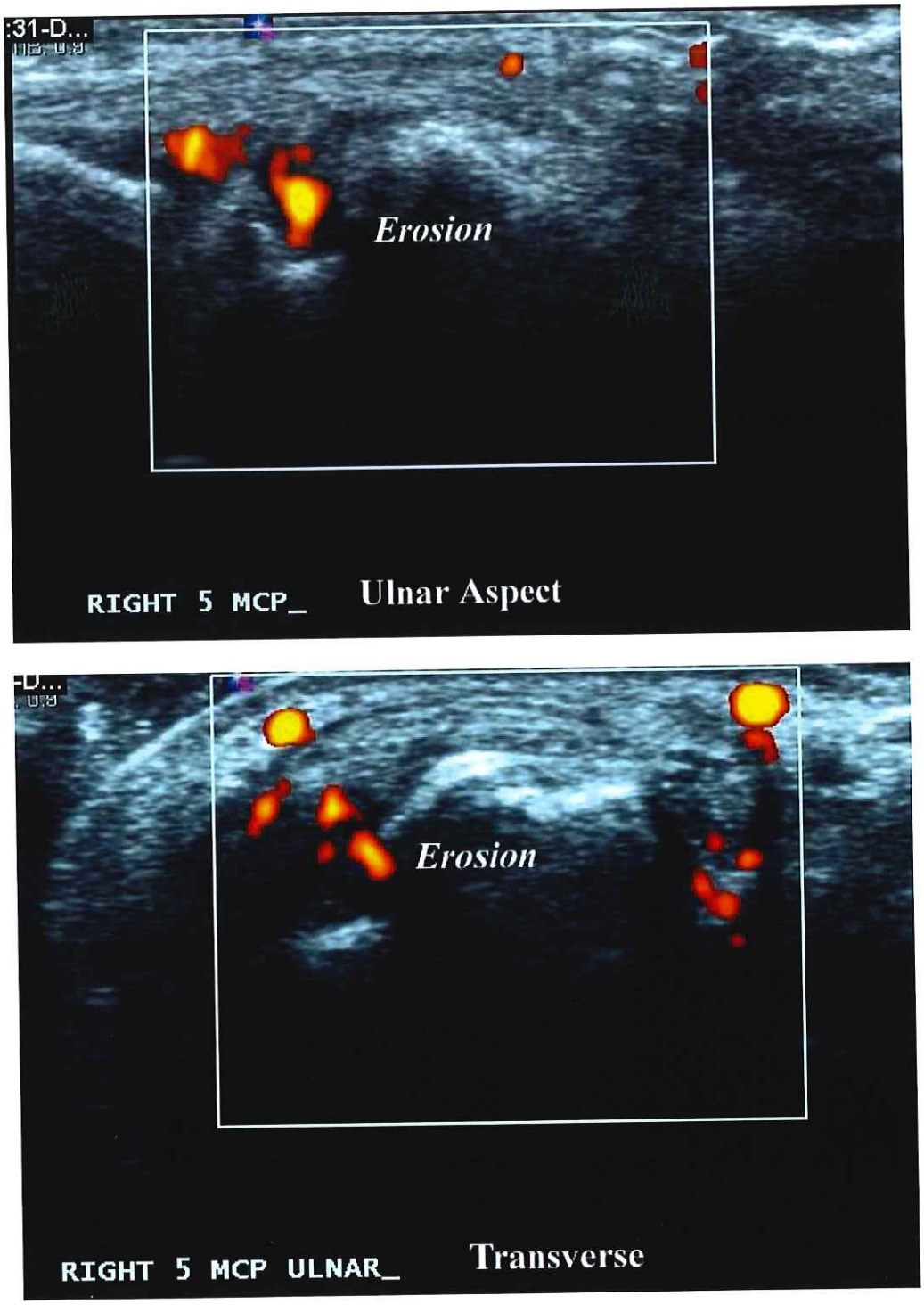

Figure 4.1(d) HRUS of dorsal right 5th MCP joint with longitudinal ulnar and transverse views showing cortical defect in 2 planes, consistent with bone erosion. PD positivity within the erosion suggests hypervascularised pannus eroding the bone.