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**THE ROLE OF X-RAY IMAGING AND
MUSCULOSKELETAL ULTRASOUND IN THE
DIAGNOSIS AND MANAGEMENT OF
RHEUMATOID ARTHRITIS**

HAMED REZAEI



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The role of X-ray imaging and musculoskeletal ultrasound in the diagnosis and management of rheumatoid arthritis

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Hamed Rezaei

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Principal Supervisor:

Professor Ronald van Vollenhoven
Karolinska Institutet
Department of medicine, Solna
Unit for clinical research therapy,
inflammatory diseases

Opponent:

Professor Maria Antonietta D'Agostino
Versailles Saint-Quentin en Yvelines University
Department of rheumatology
Ambroise Paré Hospital,
Boulogne-Billancourt, France

Co-supervisor(s):

Docent Anca Irinel Catrina
Karolinska Institutet
Department of medicine, Solna
Division of rheumatology

Examination Board:

Docent Ulla Lindqvist
University of Uppsala
Department of medicine
Division of rheumatology

Erik af Klint PhD, MD
Karolinska Institutet
Department of medicine, Solna
Division of rheumatology

Docent Örjan Smedby
University of Linköping
Department of Radiology and department of
Medical and Health Sciences

Saedis Saevarsdottir PhD, MD
Karolinska Institutet
Department of medicine, Solna
Division of rheumatology

Professor Ingiöld Hafström
Karolinska Institute
Department of medicine, Huddinge
Division of rheumatology

To Kevin & Alice

ABSTRACT

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease characterized by symmetric joint inflammation that often involves the small joints of the hands and feet, with progressive destruction, deformity, and disability of the joints. Small joints of the hands and feet are frequently the first to be involved in RA, which is why methods for assessment of these joints are of particular importance at the onset of RA and early stage of the disease. The results of this thesis have highlighted the role of conventional radiography, Digital X-ray radiogrammetry (DXR) and musculoskeletal ultrasound (MSUS) in the diagnosis and management of RA.

Paper I is based on the study about clinical and radiographic outcomes in patients with early RA who responded well to initial Methotrexate (MTX) monotherapy. Most early RA patients who achieved low disease activity after 3–4 months of MTX monotherapy continued to have low disease activity during 2 years follow-up. However, marked radiographic progression occurred in a proportion of patients, even despite sustained DAS28 remission.

Paper II aimed to evaluate whether a significant decrease of cortical bone mineral density (BMD) measured by DXR during the first year of RA correlated with radiographic progression after 2 years. The results indicated that patients with significant decrease of DXR-BMD had significantly greater risk for radiographic progression, compared with patients without. Evaluation of RA patients with significant decrease in DXR-BMD during the first year of the disease helps to identify patients with higher risk for radiographic progression later in the disease course. However, future studies should investigate whether decrease in DXR-BMD during the first 3 or 6 months of the disease could indicate the same results.

Paper III is based on a study about clinical predictors at the time of RA diagnosis for rapid radiographic progression (increase ≥ 5 units according to the Sharp score modified by van der Heijde after one year). The results from paper III indicated that baseline erosions, level of acute phase reactant and current smoking status were independent predictors for radiographic progression after 1 year. These results remained after further adjustment for treatment strategy. Three dimensional risk matrix including current smoking status, erosions and C-reactive protein showed a 12–63% risk gradient from patients carrying none compared with all predictors.

Paper IV aimed to assess the utility of MSUS in patients with suspected inflammatory arthritis, using a probabilistic approach. In this study, the proportion of patients with

maximal diagnostic certainty for inflammatory arthritis was increased significantly after performing MSUS. The similar significant increase was also observed for diagnostic certainty of RA. The findings from MSUS agreed with the final diagnosis in more than 95% of patients.

LIST OF SCIENTIFIC PAPERS

This thesis is based on four original papers. They are listed below and will be referred to in Roman numerals.

- I. **Rezaei, H**, Saevarsdottir S, Forslind K, Albertsson K, Wallin H, Bratt J, Ernestam S, Geborek P, Pettersson IF and van Vollenhoven RF.
In early rheumatoid arthritis, patients with a good initial response to methotrexate have excellent 2-year clinical outcomes, but radiological progression is not fully prevented: data from the methotrexate responders population in the SWEFOT trial.
Ann Rheum Dis. 2012 February; 71(2): 186-191

- II. **Rezaei, H**, Saevarsdottir S, Geborek P, Petersson IF, van Vollenhoven RF and Forslind K.
Evaluation of hand bone loss by digital X-ray radiogrammetry as a complement to clinical and radiographic assessment in early rheumatoid arthritis: results from the SWEFOT trial.
BMC Musculoskeletal Disord. 2013 March; 14: 79.

- III. Saevarsdottir, S., **Rezaei H**, Geborek P, Petersson IF, Ernestam S, Albertsson K, Forslind K and van Vollenhoven RF.
Current smoking status is a strong predictor of radiographic progression in early rheumatoid arthritis: results from the SWEFOT trial.
Ann Rheum Dis. 2014 April.

- IV. **Rezaei H**, Torp-Pedersen S, af Klint E, Backheden M, Kisten Y, Györi N and van Vollenhoven RF.
Diagnostic utility of musculoskeletal ultrasound in patients with suspected arthritis – a probabilistic approach.
Arthritis Research & Therapy. 2014 October 16:448

CONTENTS

1	Introduction	1
	1.1 Chronic arthritis.....	1
	1.2 Rheumatoid Arthritis.....	1
	1.2.1 Pathogenesis	1
	1.2.2 Clinical features and diagnosis	2
	1.2.3 Treatment.....	4
	1.2.4 Evaluation and outcomes of patients with RA.....	6
	1.2.5 Assessment of disease activity.....	7
	1.2.6 Radiographic progression in RA.....	7
	1.2.7 Conventional Radiography	8
	1.2.7.1 Sharp score modified by van der Heijde.....	9
	1.2.8 Radiographic progression and choice of treatment.....	10
	1.2.9 Smoking and radiographic progression in RA.....	12
	1.3 Digital X-ray radiogrammetry	12
	1.4 Musculoskeletal ultrasound	19
	1.4.1 The role of MSUS in inflammatory arthritis	19
	1.4.2 Diagnostic utility of MSUS in early inflammatory arthrits	24
	1.4.3 MSUS scoring system.....	25
2	Aim of the thesis.....	29
	2.1 General aim	29
	2.2 Specific aims	29
3	Materials and methods	30
	3.1 SWEFOT Trail (papers I-III).....	30
	3.2 Diagnostic utility of MSUS in patients with suspected arthritis (paper IV)	31
4	Results	33
	4.1 Paper I.....	33
	4.2 Paper II	35

4.3 Paper III.....	37
4.4 Paper IV.....	38
5 Discussion.....	41
5.1 Paper I.....	41
5.2 Paper II.....	43
5.3 Paper III.....	45
5.4 Paper IV.....	46
6 Conclusion.....	50
7 Future plans.....	51
8 Acknowledgements.....	53
9 References.....	55

LIST OF ABBREVIATIONS

ACPA	Anti Citrullinated Protein antibody
ACR	American College of Rheumatology
Anti-CCP	Anti-Cyclic Citrullinated Peptide
ART	Anti Rheumatic Therapy
BMD	Bone Mineral Density
CDAI	Clinical Disease Activity Index
CDUS	Color Doppler Ultrasound
CRP	C-reactive protein
CTLA	Cytotoxic T-Lymphocyte associated Antigen
DAS 28	Disease Activity Score based on 28 joints count
DMARD	Disease Modifying Anti Rheumatic Drug
DXA	Dual X-ray Absorptiometry
DXR	Digital X-ray Radiogrammetry
EULAR	European League Against Rheumatism
ESR	Erythrocyte Sedimentation Rate
FOI	Flouresnce Optical Imaging
GCs	Glucocorticosteroids
HAQ	Health Assessment questionnaire
HBL	Hand Bone Loss
HLA	Human Leukocyte Antigen
HCQ	Hydroxychloroquine
IL	Interleukin
INF	Infliximab
LOCF	Last Observation Carried Forward
MRI	Magnetic Resonance Imaging
MSUS	Musculoskeletal ultrasound
MTX	Methotrexate
NORD-STAR	Nordic Rheumatic Diseases Strategy Trials And Registries
NRI	Non-Responder Imputed
OMERACT	Outcome Measures in Rheumatology Clinical Trials
OPG	Osteoprotegerin
QTC	Quantitative Computed Tomography

QUS	Quantitative Ultrasound
RA	Rheumatoid Arthritis
RANK	Receptor activator of the NF- κ B
RF	Rheumatoid Factor
RRP	Rapid Radiographic Progression
SDAI	Simplified Disease Activity Index
SE	Share Epitope
SHS	Sharp score modified by van der Heijde
SRQ	Swedish Rheumatology Quality registry
SSZ	Sulfasalazine
SWEFOT	SWEdish PharmacOTherapy
TNF	Tumor Necrosis Factor
UIA	Undifferentiated Inflammatory arthritis
VAS	Visual Analogue Scale
VEGF	Vascular Endothelial Growth Factor

1 INTRODUCTION

1.1 CHRONIC ARTHRITIS

The word arthritis is derived from the Greek words for joint (arthrein) and inflammation (itis). The classic signs for arthritis are pain (dolor), heat (calor), swelling (tumor), redness (rubor) and decreased function (functio laesa). The joint inflammation is considered chronic if it lasts more than six weeks. In chronic arthritis, the anatomy of synovium undergoes changes including an increase in the number of lining cells, hyperplasia of the lining layer and hyperemia [1, 2]. This remodeling of synovial tissue results in the formation of “pannus” which is a continuous mass of synovial cells spreading out over and invading cartilage and subchondral bone [3, 4] leading to the destruction of joints.

1.2 RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is one of the most common systemic inflammatory disorders and affects 0.5-1 % of the general population [5]. The female/male ratio is about 2.5:1. The disease can occur at any age but it is most common between 40 and 70 years. The disease onset is mostly insidious and it sometimes takes several months before a confirmed diagnosis can be made [6]. The main symptoms of the disease are pain, stiffness and swelling of peripheral joints but other organs such as the lungs and blood vessels as well as the hematopoietic system can also be involved [7]. Synovial inflammation and aggressive tissue front called pannus invades and destroys articular structure locally [3]. Joint destruction because of synovitis can occur early and a proportion of patients develop bone erosion during the first 2 years of the disease [8].

1.2.1 Pathogenesis

The first concept of immune-reactivity of RA was the identification of rheumatoid factor (RF) that was observed first by Waaler in 1939 and later by Rose in 1948 [9]. The presence of RF predicts more aggressive and destructive course [3]. The primary potential pathogenesis of RF seems to be as an initiator of immune-complex mediation [10]. Complement fixation by immune-complex containing RF and other auto antibodies releases chemotactic mediators

such as C5a leading to the recruitment of inflammatory cells such as neutrophils to the inflammatory joints. T-cells are the dominant lymphocytes that infiltrate the rheumatoid synovium and CD4+ cells (Th2) predominate over CD8+ cells (Th1) in most of RA patients, leading to disturbed balance between T-cell derived cytokines. Other type of T-cells, such as Th17 cells can also play a critical role in pathogenesis of RA. The most important risk factor for RA is the presence of HLA-class II and particularly HLA-DRB 1 [11] and this observation lead to the shared epitope hypothesis several decades ago. According to this hypothesis, presence of a specific amino acid sequence in the protein molecule of DRB 1 (the shared epitope) facilitates presentation of atheritogenic peptides to T-cells [12]. Huizinga et al in 2005 showed that the share epitope (SE) alleles are only a risk factor for RA patients who are positive for anti-cyclic citrullinated peptide (anti-CCP) antibodies [13]. Anti-CCP antibodies are highly specific for RA and can be detected years before the first clinical manifestation of the disease [14]. Van der Helm et al later showed that the share epitope alleles were directly associated with the presence of anti-CCP antibodies and moreover correlated to the level of anti-CCP antibodies in RA patients [15]. None of the genetic risk factors by themselves is sufficient enough to cause rheumatoid arthritis. The most prominent gene-environment interaction in RA pathogenesis is smoking and several years of smoking seems to increase the risk for development of RA. The combination of HLA-DRB1 SE and smoking is a risk factor for anti-CCP positive RA but not anti-CCP negative RA [16].

1.2.2 Clinical features and diagnosis

The course of RA can vary extremely. Some patients may have very acute and severe disease onset with polyarthritis, fever and extra-articular manifestation whereas the insidious onset of the symptoms is most common. Joint symptoms include pain, stiffness and swelling whereas concomitant tenosynovitis and bursitis may be present from the beginning. Generalized symptoms such as low fever, weakness and weight loss might also be present. There is no pathognomonic symptom or sign for diagnosis. The American College of Rheumatology (ACR) classification criteria from 1987, table 1, [17] was designed to help rheumatologists to differentiate RA from other inflammatory arthritides. These criteria were originally created for research rather than diagnosis and the sensitivity of the ACR criteria is low during early stages of the disease [18]. Due to importance of and need for early diagnosis allowing early aggressive treatment [19] new classification criteria were created by ACR and European League against Rheumatism (EULAR) [20], table 2.

At least four of the following criteria:
1- Morning stiffness > 1 hour
2- Arthritis of at least 3 joints area
3- Arthritis of the hands joints
4- Symmetric arthritis
5- Rheumatoid nodules
6- Presence of rheumatoid factor
7- radiographic changes
<i>Criteria 1-4 must have been present for ≥ 6 weeks</i>

TABLE 1: ACR criteria for rheumatoid arthritis [17]

Target population	
1- have at least one joint with definite clinical synovitis	
2- with synovitis not better explained by another disease	
A score of at least 6/10 is needed for classification of a patient as having definite RA	
a- Joint involvement	Score
1 large joint	0
2-10 large joints	1
1-3 small joints (with or without involvement of large joints)	2
4-10 small joints (with or without involvement of large joints)	3
> 10 joints (at least 1 small joint)	5
b- Serology (at least one test result is needed)	
Negative RF and negative ACPA	0
Low positive RF or low positive ACPA	1
High positive RF or high positive ACPA	2
c- Acute phase reactants (at least one test result is needed)	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
d- Duration of symptoms	
< 6 weeks	0
≥ 6 weeks	1

TABLE 2: The 2010 EULAR/ACR classification criteria for rheumatoid arthritis [20]

The disease characteristic is recurrent inflammation of almost any synovial joint and typically small joints of the hands and feet. The chronic inflammation leads to different degrees of joint destruction and some radiographic changes occurs during the first years of the disease despite conventional treatment and low disease activity [21, 22].

1.2.3 Treatment

1.2.3.1 Disease Modifying Anti Rheumatic Drugs (DMARDs)

Initiating treatment with DMARDs in patients with early RA is recommended if there is no contraindication [23]. The most common used DMARDs are Methotrexate, Sulfasalazine, Leflunomide, Cyclosporin A and Hydroxychloroquine. The characteristics of these agents are slow onset of action, improved symptoms and signs of arthritis, improved functional status, protection against radiographic destruction in the bone and cartilage and improved acute phase response [24, 25]. Methotrexate (MTX) is the most frequently used DMARD in RA. MTX in high dosage blocks purine synthesis and has a cytotoxic effect. However at the low dosage which is used in RA, generalized cytotoxicity does not occur. MTX suppresses disease activity [26] and has a protective effect against joint destruction [27]. The common dosage used in RA patients is between 15 and 25 mg weekly. Folic acid supplement should be added in order to reduce liver toxicity. Many previous studies showed that RA patients treated with MTX had lower radiographic progression than patients with other DMARDs as an anti-rheumatic therapy [28-30] while some earlier studies showed that MTX did not slow radiographic progression in patients with established RA and more regular monitoring of disease activity was recommended [31, 32]. The precise mechanism of action of MTX in treating RA is not clear but it has been shown that MTX down regulates synovial inflammation by decreasing synovial macrophages [33]. Recently, Revu et al. showed that MTX decreases synovial cellularity as well as RANK expression (receptor activator of the NF- κ B) and RANKL/OPG (osteoprotegerin) ratio and might have a direct effect on bone metabolism in treatment of RA [34]. Data from clinical randomized trials showed that in RA patients who did not show adequate effects of MTX as a monotherapy, a combination of MTX, Sulfasalazine and hydroxychloroquine had a superior effect [35] and a similar result was noticed for the combination MTX and Cyclosporin A [36].

1.2.3.2 Glucocorticosteroids (GCs)

GCs were introduced in rheumatology by Hench and Kendall as early as 1948 and the first patient with RA was treated with GCs in the same year [37]. GCs are still used today with good efficacy. However, long term use of high dose GCs has been discovered to lead complications such as hypertension, diabetes and osteoporosis. Systemic administration of GCs decreases macrophage numbers and also the number of T-cells and B-cells, probably through down regulation of the expression of synovial chemotactic factors and adhesions molecules [38, 39]. Intra-articular GC treatment reduces rheumatoid inflammation by decreasing synovial cell infiltration and pro-inflammatory cytokine expression. Reduction of synovial T-cells, TNF, IL-1- β and VEGF (vascular endothelial growth factor) occur in association of with clinical effects [40]. Earlier randomized trials have shown that GCs in low dose have protective effects regarding radiographic progression in RA [41, 42].

1.2.3.3 Biological treatment

Several studies have reported the presence and local synthesis of many cytokines in inflammatory rheumatoid synovium [43-46]. Among these, TNF- α was first characterized as a factor that induces necrosis of tumor cells and subsequently been recognized to mediate numerous inflammatory and immune regulatory activities. In 1993, Elliot et al. presented a study in which 20 RA patients who were treated with monoclonal anti-TNF antibodies achieved significant clinical and laboratory improvement [47]. One year later, this pilot study was followed by a multi-center, randomised double-blind trial with the same anti-TNF monoclonal antibody. 73 patients with active RA were recruited and were randomised to low or high dose of active treatment compared to placebo. The result showed that blocking of TNF was highly effective in the treatment of therapy resistant established RA [48]. The efficacy of anti-TNF treatment has now been shown in many controlled trials [49-51]. In 2000, the use of MTX in combination with Infliximab was shown to be important in achieving radiographic results, even better than clinical results. Patients treated with Infliximab in combination with MTX achieved complete inhibition of radiographic progression at the group level [52]. Later studies supported the use of anti-TNF therapy in combination with MTX in RA patients, demonstrating lesser radiographic progression as compared to any agent alone. Breedveld et al in the PREMIER trial showed that RA patients treated with Adalimumab in combination with MTX had significantly less radiographic

progression, compared to patients in MTX or Adalimumab monotherapy arms [53]. Similar studies have now demonstrated the same result with other anti-TNF agents [49, 54, 55].

Besides TNF blocking, B-cells depletion using Rituximab has proved to be another successful therapeutic approach in RA patients. B-cells play an important role in immunopathogenesis of RA, such as autoantibody production and antigen presentation [56-58]. Rituximab is a chimeric monoclonal antibody directed against CD20 antigen expressed by B-cells. Repeated treatment with Rituximab has been shown to have sustained clinical response, good tolerability and safety in RA patients, however with somewhat reduced radiographic efficacy compared to anti TNF treatment [57, 59, 60].

The inhibition of T-cell activation has also been shown to be efficient in the treatment of both anti TNF naïve RA patients and those who had response failure to these drugs [61, 62]. Abatacept, a CTLA 4-Ig fusion protein down-regulates T-cell activation by inhibiting the CD80/96:CD28 co-stimulatory pathway that is required for full T-cell activation [63]. Kremer et al. showed in a 3 years open-label part of the AIM study [64] that Abatacept had a protective effect on radiographic progression in the majority of RA patients who remained on the treatment [65].

Anti IL-6 therapy (Tocilizumab) has been studied in several controlled trials and showed clinical efficacy in RA patients with response failure to prior anti-TNF agents, DMARDs or both [66, 67]. Tocilizumab is a humanized anti IL-6 receptor monoclonal antibody which binds to circulating soluble and membrane-expressed IL-6 receptor [68]. A recent study by Dougados et al showed that treatment with Tocilizumab as add-on or switching therapy in patients with MTX as a first treatment and with at least moderate disease activity improved both clinical and radiographic response. The majority of patients exhibited minimal radiographic progression at 52 weeks [69].

1.2.4 Evaluation and outcomes of patients with RA

In the assessment of RA, it is necessary to bear in mind that the disease has several facets that need to be captured. The three main areas of disease outcomes are disease activity, joint damage or radiographic destruction and functional impairment. At the same time, there is significant association between these elements and quality of life, co-morbidity and mortality [70]. Disease activity reflects different underlying variables that can fluctuate during the disease course spontaneously or upon treatment and it is reflected by using the core set of

measures. At the same time, radiological destruction and functional disability should be considered for assessment of disease outcomes and treatment decision is made since joint damage and a part of functional disability are permanent abnormalities and can no longer be improved.

1.2.5 Assessment of disease activity

As joint involvement is a fundamental hallmark for RA, it is therefore necessary to assess joint involvement regularly. In both the ACR and EULAR core sets of disease activity, the number of swollen and tender joints is included. Another reliable instrument is measuring acute phase reactant (ESR and CRP), the most frequently used biomarkers. These measurements should be done in conjunction with both clinical symptoms/signs assessment and patient self-assessment of global disease activity.

Disease activity score (DAS) was the first composite measurement developed to assess response to treatment (DMARDs) and also to compare RA patients in groups. DAS includes 44 swollen joint count, Ritchie articular index [71], ESR and visual analogue scale (VAS) for patient global self-assessment of disease activity [72]. DAS28 was introduced as a simplified version by Prevo et al. and includes 28 joint counts for tenderness and swelling, ESR and patient global self-assessment of disease activity [73]. DAS28 has also been modified to include CRP instead for ESR (DAS28-CRP) [74] or to exclude patient global assessment of disease activity (DAS28-3) [75]. Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI) are likely simpler instruments to measure disease activity by using reduced joint count and simple indices. They provide validated outcomes when assessing RA for disease activity and response to treatment [76]; however they have more stringency in defining remission [77, 78].

1.2.6 Radiographic progression in RA

As one of the goals of RA therapy is to prevent or retard joint damage as well as maintaining a good functional status, it is important to know how patients who respond well clinically to the treatment do at later follow-ups and, even more importantly, whether they progress radiographically or not. It is known that bone destruction during the disease course correlates with functional disability and decline in quality of life [79, 80] so one of the most important challenges in RA is to identify those patients who are likely to develop significant

radiographic progression. Several predictive factors for radiographic progression, including presence of anti-citrullinated protein antibodies (ACPA) and/or rheumatoid factor (RF), baseline level of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) and presence of bone erosions at the beginning of the disease have been identified before [81-83]. Accordingly, several studies have attempted to construct clinically useful risk matrices to predict so-called rapid radiographic progression (RRP), corresponding to an increase in the Sharp van der Hejde score (SHS) of ≥ 5 after 1 year and the performance of these matrices has been tested on both early and unselected RA population [84-88]. For patients who are likely to develop radiographic progression, it is possible that it is necessary to choose more potent therapies than MXT as a monotherapy or necessary to follow up them more regularly in the beginning of the disease as recommended by the EULAR guidelines which state that joint damage should be assessed by X-rays of the hands and the feet every 6–12 months during the first few years [89].

1.2.7 Conventional radiography

Conventional radiography has been the most common and one of the least expensive imaging modalities for the evaluation of patients with rheumatologic disorders. In RA, the radiographic assessment of the bone and cartilage includes:

- The presence or absence of bone loss or destruction
- Joint space narrowing
- Change in bone mineral density
- Subluxation, dislocation, ankylosis and complete luxation

Serial radiography can help us with staging, monitoring and assessment of treatment efficacy. Validated scoring methods of radiographic damages have been developed and are used mostly in clinical trials [90]. As conventional radiography is suitable to detect cortical bone damage, it is very useful for follow-up and monitoring of established RA. An important limitation of the method is the inability to detect early stages of inflammatory process [91, 92].

1.2.7.1 Sharp score modified by van der Heijde:

In 1971, John Sharp proposed a method for scoring of erosion and joint space narrowing in the hands [93] and the first description included 27 areas (all joints in the hands and carpus) scored for erosion and joint space narrowing. A new study in 1985 resulted in 17 areas read for erosion and 18 areas read for joint space narrowing in each hand [94]. The main limitation of Sharp score is that the feet are not included and as we know, joints in the feet are frequently involved in RA and even sometime before hands [8]. Because of this reason Sharp score from 1985 was modified by van der Heijde et al to include scoring of the feet and moreover one site for erosion and 3 sites for joint space narrowing were also excluded from the hands [95, 96].

Sharp score modified by van der Heijde (SHS) method is a combination of erosion and joint space narrowing score. The erosion score for one joint in the hands ranges from 0 to 5. The score of 1 is given if the erosion is small and erosion is scored 3 if it extends more than 50% over bone surface. Complete collapse of the bone is scored as 5. Joint space narrowing has a range between 0 and 4 and is combined with the score for (sub)luxation. A score of 3 is given if the joint space is decreased more than 50%. Bony ankylosis and complete luxation is scored as 4. Figure 1 demonstrates a description of scoring system and the sites of assessment in the hands. In the feet, the assessment is applied to the 10 metatarsophalangeal (MTP) and 2 interphalangeal (IP) joints as it is demonstrated in figure 2. The maximum erosion score in feet is 10 instead of 5 [95].

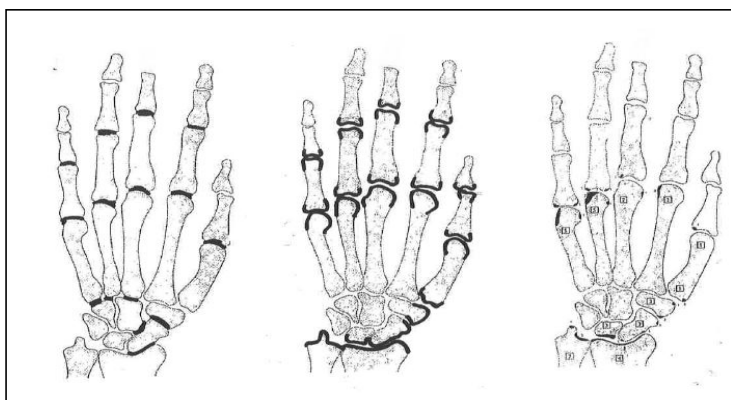


FIGURE 1: Sites of assessment and scoring system in the hands according to the Sharp score modified by van der Heijde. Left: Sites for assessment of joint space narrowing score, middle: Sites for assessment of erosion score, right: examples for erosion score.

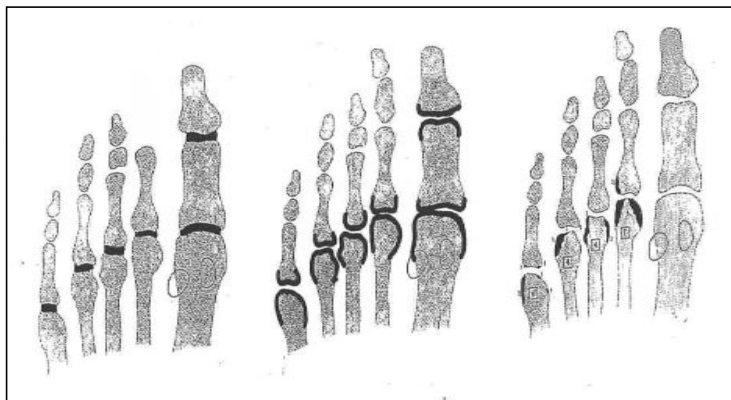


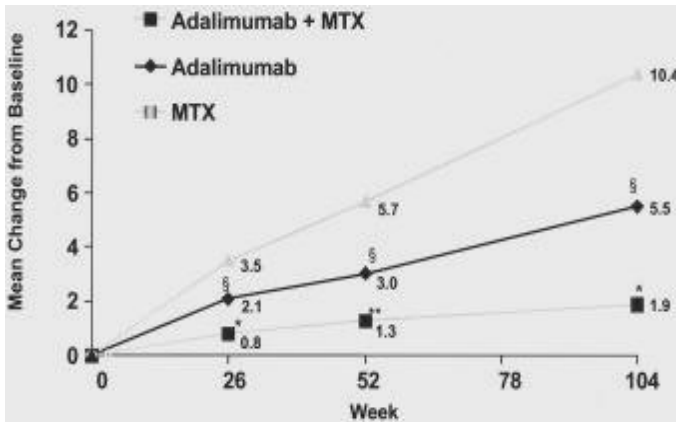
FIGURE 2: Sites and surface of assessment in the feet according to the Sharp score modified by van der Heijde. Left: Sites for assessment of joint space narrowing score, middle: Sites for assessment of erosion score, right: examples for erosion score.

The total erosion score of all joints in the hands is 160 points and in both feet is 120 points. The maximum score for joint space narrowing score in the hands is 120 and in the feet 48. It is important to note that the maximum erosion score in the joints of the feet is higher (10 instead of 5) and this may influence a total score of both hands and feet but on the other side, the total number of scored sites in the hands is greater and this counter-weighs the higher score for each joint in the feet.

1.2.8 Radiographic progression and choice of treatment

Although MTX is still the first line treatment of choice in RA according to the EULAR guidelines [97] several studies have shown that combination therapy with GCs, other DMARDs or biologic agents is superior to MTX as monotherapy, specially to prevent or retard radiographic progression [35, 42, 53, 98-100]. Svensson et al in 2005 showed that in patients with early RA, prednisone in low doses when added to initial DMARD retarded radiographic progression after 2 years [42]. In a multicenter, randomized double-blind clinical trial (PREMIER study), Breedveld et al showed that combination therapy with MTX and Adalimumab was superior to MTX monotherapy, regarding all outcomes measured. Radiographic progression was significantly lower in patients with combination treatment compared to those with MTX monotherapy and even Adalimumab as a monotherapy [53] as shown in figure 3. A similar result was presented by Emery et al in the randomized double-

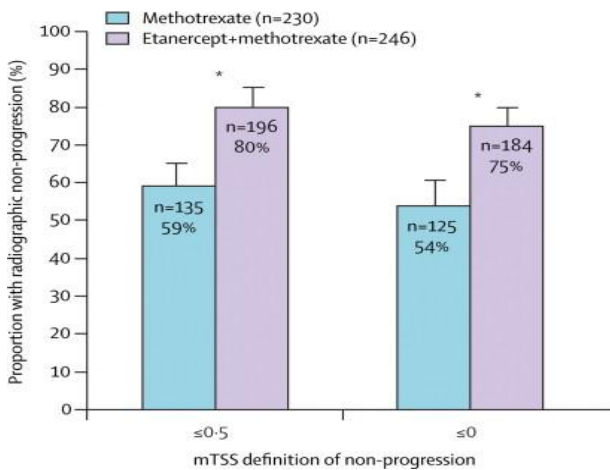
blind trial in 542 MTX naïve RA patients with moderate to high disease activity. 80% of patients who were treated with combination MTX and Etanercept had no radiographic progression (Delta SHS score < 0.5 point) after one year while this value for MTX monotherapy was 59%, figure 4.



Arthritis & Rheumatism

Volume 54, Issue 1, pages 26-37, 29 DEC 2005 DOI: 10.1002/art.21519
<http://onlinelibrary.wiley.com/doi/10.1002/art.21519/full#fig2>

FIGURE 3: Radiographic progression according to SHS score over 2 years in PREMIER trial



The Lancet, Volume 372, Issue 9636, 2008, 375 - 382

FIGURE 4: The proportion of patients with no radiographic progression in COMET trial.

*p= 0.0001

1.2.9 Smoking and radiographic progression in RA

It is known that RA patients who smoke have more severe disease and poor prognosis, compared to those who do not smoke. Smoking status at the time of diagnosis predicts higher disease activity with more prominent featuring of articular involvement from the disease onset, higher level of inflammation detected by acute phase reactant and more radiographic damage [101, 102]. Current smoker RA patients are less likely to respond to the treatment with DMARDs or biologic agents [103]. RA patients who are current smokers also have increased risk for developing severe extra-articular manifestation [104]. Current smoking at disease onset increased the risk for extra-articular manifestation 2.8 times more in current versus non-smokers and 4.1 times more in current versus never smokers. As mentioned previously, many predictive factors for radiographic progression have been identified before and several studies have attempted to construct clinically useful risk matrices to predict so-called rapid radiographic progression (RRP), however, none of these studies has evaluated whether smoking habits associate with RRP.

1.3 DIGITAL X-RAY RADIOGRAMMETRY

Bone mineral density (BMD) is calculated as bone mass divided by a projection area, figure 5. BMD is divided into cortical, trabecular and total bone mineral density. There are several non-invasive methods for the measurement of bone density status both axially and peripherally and considerable advances have been made during the last 3 decades. These methods include dual X-ray absorptiometry (DXA), quantitative computed tomography (QCT) quantitative ultrasound (QUS) and digital X-ray radiogrammetry (DXR) [105-107]. These quantitative bone measurements are demonstrated in details in table 3 [108].

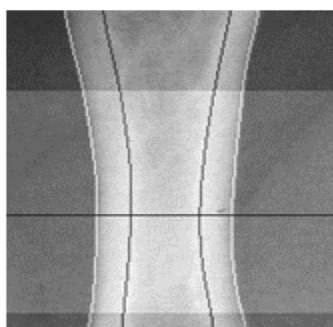


FIGURE 5: BMD = Bone mass / projection area. Larger bones have larger BMD

Method	Type of measurement
DXA	Total cortical and trabecular bone
DXR	Cortical bone only
QCT	Cortical and trabecular bone separately
QUS	Measurement that reflects bone quality

TABLE 3: Quantitative bone mineral measurement

Periarticular osteopenia is one of the earliest radiographic features of RA that can be detected by conventional radiography of the hands and feet [109, 110] and it reflects a reduction in BMD and may precede erosion and joint space narrowing [110]. Periarticular osteopenia may be caused by local release of inflammatory mediators and immobility [109, 111]. The sensitivity of conventional radiography regarding osteopenia is limited, as it can only be detected if the reduction of bone density is more than 35-50% [112, 113]. Quantitative measurement of hand bone loss that captures periarticular osteopenia has been proposed as a predictor or an outcome measurement in RA [114, 115]. For measurement of BMD in the hands in patients with early RA, DXR (a computerized version of an earlier technique of radiogrammetry as originally proposed by Barnett and Nordin [116]) has been shown to be superior to DXA [112]. Some previous studies have compared total bone loss measured by DXA and cortical bone loss measured by DXR in the hands of patients with RA [112, 117, 118].

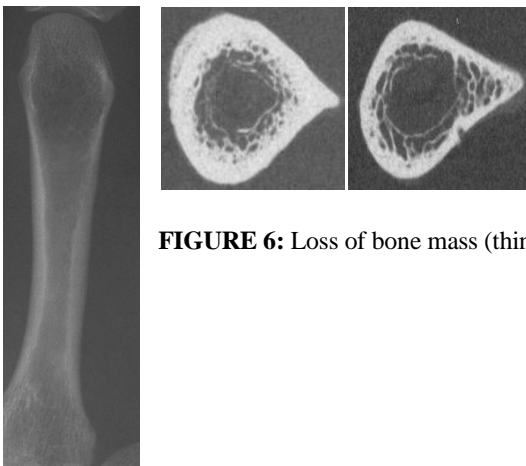


FIGURE 6: Loss of bone mass (thinning) in the cortical bone

The DXR technique measures cortical BMD in the diaphysis of 2nd, 3rd and 4th metacarpal bones through the conventional radiography of the hands. The measurement of the total and medullar width of the bone is used to quantify cortical BMD changes over time, figures 6 and 7 [109]. In recent years studies have been presented on ascertaining whether patients with RA exhibit inflammation-related osteopenia using DXR [109, 117, 119-121].

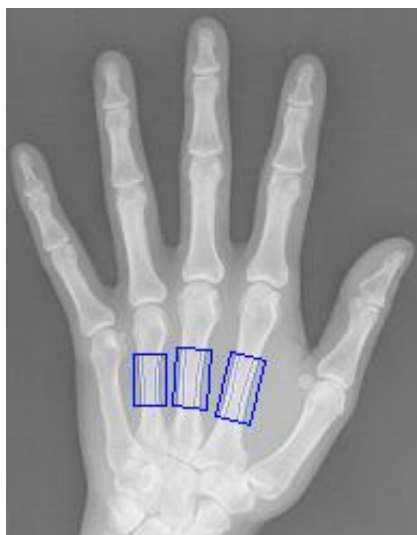


FIGURE 7: Digital X-ray Radiogrammetry, analysis of hand

Bottcher et al in 2005 showed that DXR estimated severity-dependent cortical BMD reduction in RA patients, independent of therapy with steroids. In 96 patients with RA, calculations of DXR-BMD, metacarpal index by DXR and BMD measurement of distal radius by QCT was performed. Correlation between DXR-BMD and metacarpal index versus QCT was significant, independent of steroids therapy. The highest correlation was observed between metacarpal index and total QCT. No significant association between DXR-BMD and cortical QCT was observed in patients without steroids intake. There was also shown to be a significant association between severity of RA and reduction of DXR-BMD and metacarpal index. So the results indicated a reduction of DXR parameters with an increase in the severity of RA [109].

Hoff et al in 2007 showed that hand bone loss (HBL) measured by DXA seems to occur only in the first 3 years of RA whereas DXR-BMD loss occurs both in the early and late stage of

the disease. DXR for measurement of cortical BMD and metacarpal index was performed in 215 RA patients; DXA was used to measure the whole hand BMD (both cortical and trabecular). Data for disease activity and anti-rheumatic treatment were also collected. RA patients with high disease activity during the early stages of their disease had more DXR-BMD loss than patients with low disease activity. This means disease activity independently predicted DXR-BMD reduction and not changes in DXA-BMD. A significant association between DXR-BMD and the metacarpal index was also observed [117].

The question that was investigated in later studies was whether HBL in early stages of RA could predict radiographic damage later in the disease course. A study by Hoff et al in 2009 showed that HBL as measured by DXR predicted later radiographic damage after 5 and 10 years. 136 patients with RA were followed for 10 years, radiographic damage was assessed by Sharp score modified by van der Heijde (SHS) and HBL was measured by DXR. A least significant change (LSC) of BMD (0.78% in the study of question) was used as a cut-off for hand bone loss. Patients with HBL at one year had higher median SHS-score at 5 and 10 years. In a linear regression model adjusted for clinical and laboratory data, HBL was an independent predictor for radiographic damage at 5 and 10 years [120].

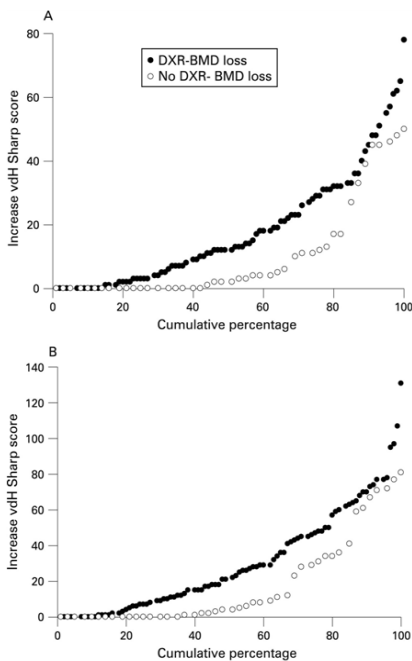


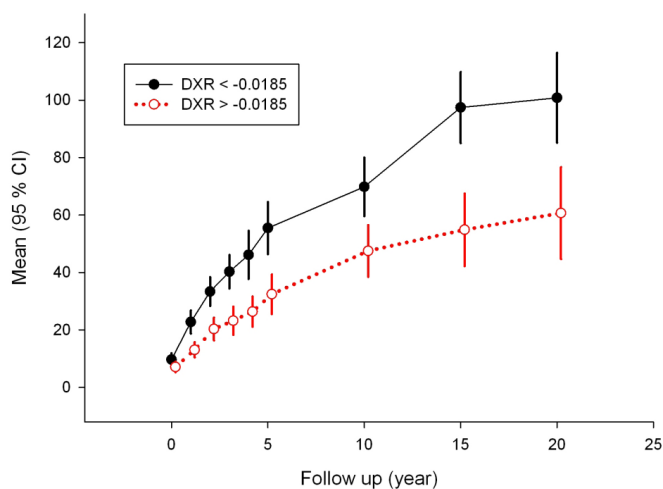
FIGURE 8: Change in SHS score at 5 years (A) and 10 years (B) in patients with RA stratified for HBL at 1 year [cut-off >LSC (0.78%)].

Hoff M et al. Ann Rheum Dis 2009;68:324-329

A similar study by Forslind et al showed the same results. In 166 patients with early RA, radiographic damage was scored according to the SHS at baseline, 1 and 2 years. BMD in the

diaphysis of 2nd, 3rd and 4th metacarpal bones was measured on a standard radiograph of the hand using DXR. The definition of HBL was change in BMD-DXR during the first year of more than 0.0048 g/cm² that was LSC used by Hoff et al [120]. Smallest detectable change was also used as the definition of radiographic progression (5.8 point according to the SHS). An interesting result in that study was that HBL was observed more often in patients without steroid therapy compared to those with steroid therapy (83% versus 44%, p=0.001). HBL during the first year was an independent predictor for radiographic damage at 1 and 2 years, using multiple logistic analyses [119].

Another similar study in 2011 also demonstrated that early BMD loss between two available radiographs (4-16 months), measured by DXR predicted radiographic progression according to the Larsen score [122] at 1 year and up to 20 years in the cohort of early RA patients. 183 patients with early RA were included between 1985 and 1989 in the south of Sweden. The definition of HBL was BMD reduction measured by DXR more than median for the group [121].

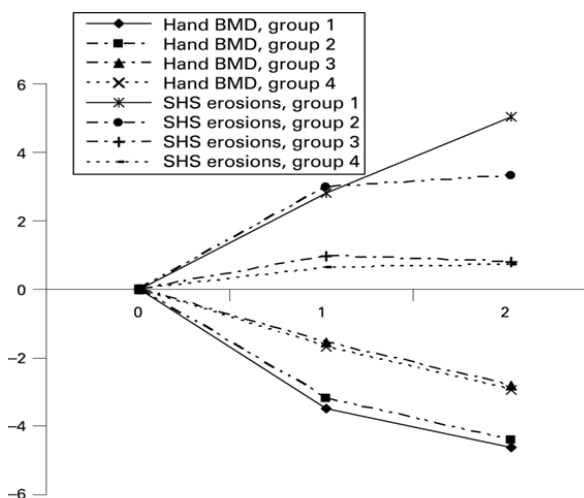


Kapetanovic et al. Arthritis Research & Therapy 2011, 13:R31

<http://arthritis-research.com/content/13/1/R31>

FIGURE 9: Radiographic progression according to the Larsen score over time after stratification according to the median (-0.0185 g/cm² per year) of early BMD measured by DXR.

Another potential application of DXR as a non-invasive imaging modality in RA is possibility to use it for treatment monitoring. In the BeSt study, 508 patients with early RA were included and were allocated to one of four therapies: Sequential monotherapy (group 1); step-up monotherapy (group 2); initial combination therapy with tapered high dose prednisone (group 3) and initial combination therapy with Infliximab (group 4). The disease activity was scored every 3 months according to DAS44 [99]. 218 of 508 patients with hand radiographs and DXA measurements of the hip and the lumbar spine at baseline, 1 and 2 years follow-up were included to investigate the effect of different anti-rheumatic therapies on BMD in the hands, hip and spine. BMD of the hands was measured by DXR. Patients with initial monotherapy had significantly more HBL than patients on initial combination therapy and progression in erosion score was independently associated with bone loss both in the hands and hip after 1 year. The study concluded that there were common pathways between radiographic progression and both HBL and generalized BMD loss [123].

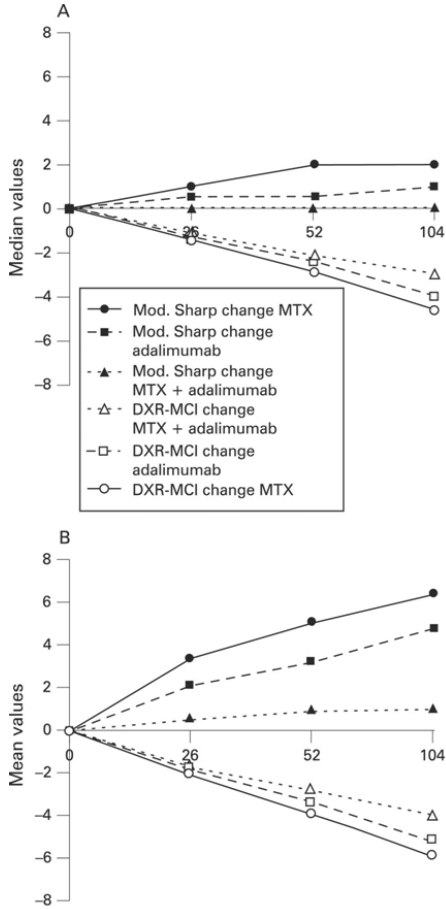


Güler-Yüksel M et al. Ann Rheum Dis 2009;68:330-336

FIGURE 10: The mean BMD loss and SHS erosion score in 4 treatment groups in the BeSt study.

In the PREMIER study, HBL was also less pronounced in patients with combination therapy and significant differences in HBL and radiographic progression were seen between combination therapy (Adalimumab + MTX) and MTX monotherapy at 12 and 24 months

follow-up as shown in figure 11 [124]. The key finding of the study was the role of anti-TNF treatment in combination with Methotrexate in bone protection; however the effect of combination therapy on HBL was not as great as for radiographic progression.



Hoff M et al. Ann Rheum Dis 2009;68:1171-1176

FIGURE 11: Change over 2 years in DXR metacarpal index and SHS score in 3 different therapy groups in PREMIER study

1.4 MUSCULOSKELETAL ULTRASOUND

Musculoskeletal ultrasound (MSUS) is being used increasingly in diagnosis and management of inflammatory arthritis in recent years. This change is driven by the need:

-To diagnose synovitis and other inflammatory conditions as early as possible.

-To monitor and follow-up the disease activity more accurately in order to achieve sustainable suppression of inflammation.

MSUS is a reliable, cost effective, patient friendly and safe imaging modality used as a complement to other diagnostic methods in rheumatology and it has been shown to be superior to clinical examination to identify synovitis [92, 125-128]. The validity of MSUS in detecting synovitis and other inflammatory pathologies in rheumatology has been shown in several studies [125, 127-130].

1.4.1 The role of MSUS in inflammatory arthritis:

In rheumatology, it seems to be necessary that imaging modalities should be available to provide immediate and accurate clinical information without compromising patient safety. MSUS is an imaging technique in this category [131] specifically in combination with the development of high-frequency transducers and the improvement of the software and hardware for ultrasound equipments. Table 4 shows a summary of the role of MSUS in inflammatory arthritis.

Summary of the role of MSUS in rheumatology
Detection and assessment of synovitis and other inflammatory conditions
Detection and evaluation of bone erosion
Ultrasound guided procedure
Remission assessment

Table 4: Application of MSUS for assessment and management of inflammatory arthritis

Early detection of synovitis and other inflammatory conditions in RA and other arthritic disorders seems to be the most important and fundamental application of MSUS in order to accurately diagnose, manage and follow-up the disease.

In 2005, OMERACT (Outcome Measures in Rheumatology Clinical Trials) and EULAR working groups on MSUS published an expert consensus on ultrasonographic definitions for methodological approaches in various inflammatory pathological processes as shown in table 5.

Pathology	Definition
Effusion	Abnormal hypoechoic or anechoic intra-articular material that can be displaced and compressed, but does not exhibit Doppler signals (figure 12)
Synovial hypertrophy	Abnormal hypoechoic intra-articular tissue that is non-displaceable and poorly compressible and which may exhibit Doppler signals (figure 13)
Tenosynovitis	Hypoechoic or anechoic thickened tissue with or without fluid within the tendon sheath with possible signs of Doppler signals, which is seen in two perpendicular planes (figure 14)
Bone erosion	An intra-articular discontinuity of the bone surface that is visible in two perpendicular planes (figure 15)

Table 5: Typical pathological findings detected by MSUS according to OMERACT [132]

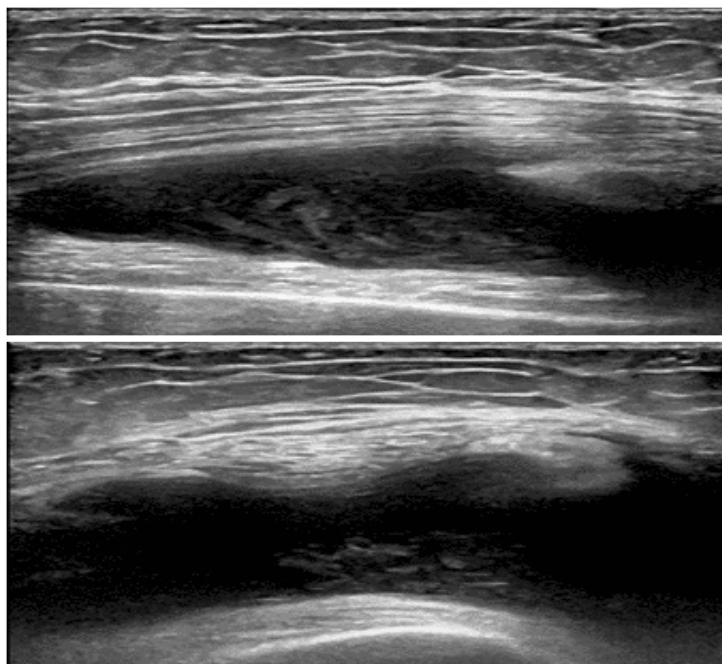


FIGURE 12: Scanning of the anterior knee on long- and short axis, showing effusion in the supra-patellar fossa (obtained by the author)

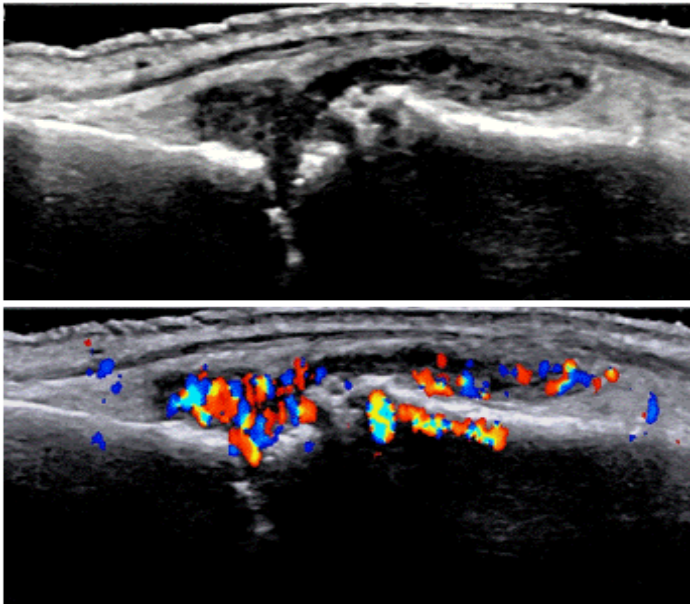


FIGURE 13: Dorsal longitudinal scanning of the 2nd MCP joint in a patient with RA, showing synovial hypertrophy with intra-articular hyperemia. (obtained by the author)

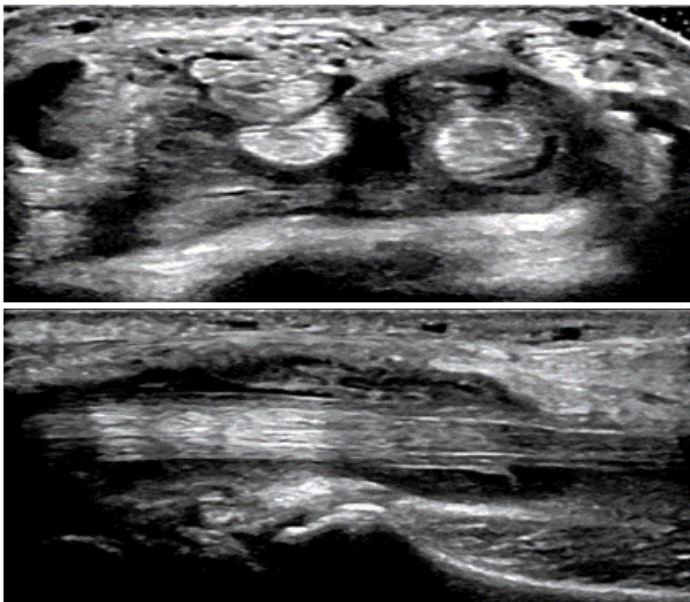


FIGURE 14: Volar transversal and longitudinal scanning of the wrist, showing tenosynovitis of flexor digitorum profundus tendons. (obtained by the author)

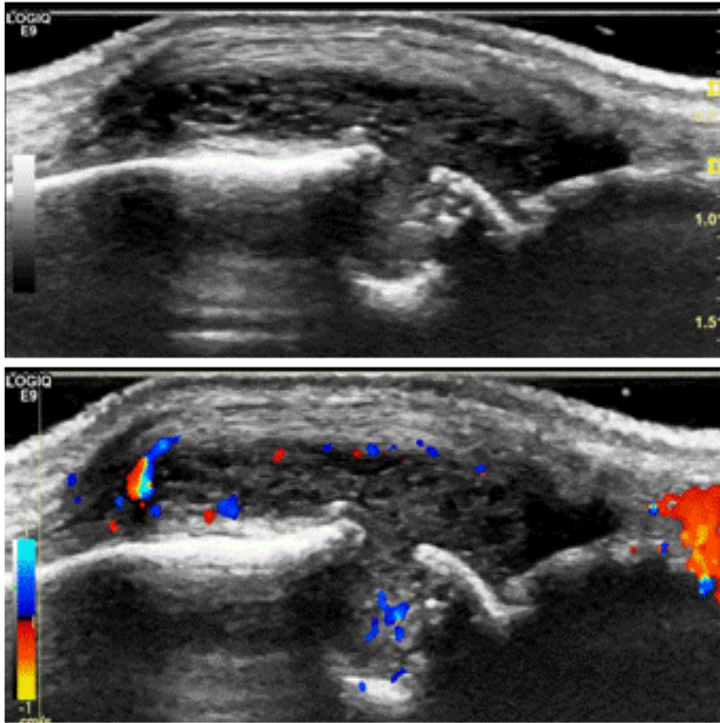


FIGURE 15: Radial longitudinal scanning of the 2nd MCP joint in a patient with RA. The images show erosion in the metacarpal head with active Doppler signals implying active erosive disease (obtained by the author).

As Kelly et al showed routine use of MSUS for patients with suspected inflammatory arthritis was associated with earlier diagnosis and earlier initiation of therapy in patients with RA as final diagnosis. In that study, 258 patients from four centers in the United Kingdom were included and divided into two groups, those who were diagnosed by MSUS versus those who were not. A significantly greater proportion of patients in the MSUS group received a final diagnosis at their first visit and a similar difference was observed for patients with a diagnosis of RA. Where patients had a diagnosis of RA, there was a significant difference in the time to diagnosis and time to initiation of therapy. That study showed that routine use of MSUS in newly referred patients was associated with earlier diagnosis and earlier DMARD initiation in patients with RA [133]. As is known, earlier diagnosis and treatment of RA leads to better outcomes. A study by van der Lindel et al showed that assessment in less than 12 weeks was associated with less joint destruction and a higher chance of achieving DMARD-free remission as compared with a longer delay in assessment [134].

Several previous studies have shown the usefulness of MSUS in early detection of synovitis, tenosynovitis and joint effusion in different anatomical sites. Backhaus et al showed in 1999 that MSUS was as sensitive as MRI for detecting synovitis in finger joints whereas MRI detected erosion more often. Synovitis in finger joints was detected by MSUS in all patients with (32 patients, 448 finger joints) and without (28 patients, 392 finger joints) radiographic signs of destructive arthritis [125].

Kane et al in 2003 showed that MSUS was more sensitive than clinical examination to detect effusion, supra-patellar bursitis and Baker's cysts in patients with RA. A total of 44 knees were examined in 130 sites both by MSUS and clinically. MSUS detected 61% of knee joint effusion whereas 36.4% of which were detected by clinical examination. The similar difference was also observed in detection of Baker's cysts and supra-patellar bursitis [135]. This indicates the confirmation of MSUS as a more sensitive and specific method to detect knee joint effusion. In another study that was conducted on 60 patients being examined for knee synovitis, MSUS was shown to be more accurate than clinical examination to detect synovitis in the knee. In that study, with the use of arthroscopy as a gold standard for detecting of knee synovitis, MSUS had a higher sensitivity (98% versus 85%), specificity (88% versus 25%), accuracy (97% versus 77%), positive predictive value (98% versus 88%), and negative predictive value (88% versus 20%) compared with clinical examination. At the same time, the Cohen kappa values for inter-observer and intra-observer reproducibility of MSUS for distinguishing between presence and absence of synovitis were 0.71 and 0.85, respectively ($P < 0.05$ for both). That study confirmed the validity of MSUS as a useful and reproducible modality for detection of synovitis in the knee [130].

The validity of MSUS to detect signs of synovitis and bone destruction in finger joints has also been assessed in previous published studies. In 2006, Szkudlarek et al performed a study on 40 RA patients and 20 healthy controls to investigate sensitivity and specificity of MSUS in detecting synovitis and erosions in MCP and PIP joints 2-5. MSUS was assessed in comparison with MRI as a gold standard. Agreement between MSUS and MRI regarding the presence or absence of synovitis was achieved in 76% of the examined finger joints. The sensitivity, specificity and accuracy of MSUS for detection of synovitis, compared with MRI as the reference, were 0.70, 0.78 and 0.76, respectively whereas these parameters for clinical examination were 0.40, 0.85 and 0.72, respectively. Similar results were shown for bone erosions, consistent with a study, performed by Wakefield et al in 2000 [136]. The conclusion of that study was that MSUS was more sensitive than clinical examination in assessing signs of inflammation, with only a slight loss of specificity [127]. A similar study with focus on

MTP joints also showed that MSUS was significantly more accurate than clinical examination for the detection of synovitis and more accurate than conventional radiography for the detecting of bone erosion. The sensitivity, specificity, and accuracy of MSUS for the detection of synovitis in MTP joints were 0.87, 0.74, and 0.79, while for clinical examination, the corresponding values were 0.43, 0.89, and 0.71 respectively [128].

1.4.2 Diagnostic utility of MSUS in early inflammatory arthritis:

Musculoskeletal complaints are exceedingly common in the population and a large proportion of patients with severe, refractory, or unclear joint symptoms are referred to rheumatology units for further diagnostic evaluation. The traditional evaluation of patients with joint symptoms primarily used to include medical history and physical examination, complemented by blood tests including rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA), synovial fluid examination, and radiography of affected joints [8, 20]. Although the traditional methods are well established, there are still a sizeable proportion of patients in this category who are not reliably diagnosed in the early stages of the disease. Thus more sensitive and accurate complementary methods seem to be needed. As mentioned, the validity of MSUS for detecting of synovitis has been confirmed by several studies before. However, quantitative analyses of the diagnostic utility of MSUS in patients with inflammatory arthritis in rheumatologic practice have been done in smaller groups of patients [137-139]. A study based on a retrospective analysis of clinical datasets from an early arthritis cohort in the United Kingdom showed that MSUS provided no additional discriminatory value to predict persistent inflammatory arthritis [140]. In that study, MSUS as a routine supplement in early arthritis patients did not add any substantial discriminatory value for predicting persistent inflammatory arthritis. Among 379 patients, seven clinical and serological variables had independent and significant associations with persistent arthritis. MSUS was performed on 16 peripheral joints in the hands and feet (wrist joints not included). A risk metric derived from 12 baseline clinical and serological parameters alone had an excellent discriminatory utility with respect to diagnosis of inflammatory arthritis (area under ROC curve 0.91; 95% CI 0.88 to 0.94). The discriminatory utility of a similar metric, which incorporated MSUS parameters, was not significantly superior (area under ROC curve 0.91; 95% CI 0.89 to 0.94). Neither did this approach identify any added value of MSUS over the use of routine clinical parameters in an algorithm for discriminating inflammatory arthritis patients whose outcome diagnosis was RA as shown in figure 16 [140].

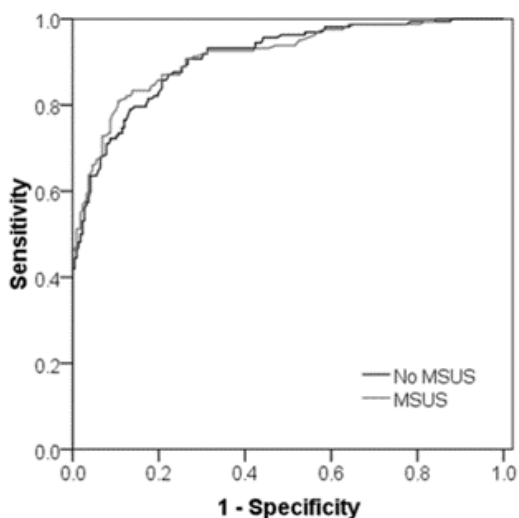


FIGURE 16: ROC curve for discriminatory utility of predictive metric for RA among patients with persistent IA.

Pratt et al. *Arthritis Research & Therapy* 2013 15:R118

Freestone et al in 2010 showed that combination of power Doppler ultrasound with conventional assessment in patients with seronegative inflammatory arthritis had a major impact on diagnostic certainty. 50 patients with inflammatory symptoms in the hands (stiffness > 1 hour with or without clinical synovitis) were recruited consecutively. All patients with positive ACPA and RF developed persistent inflammatory arthritis at 12 months. The diagnosis was obtained by a rheumatologist who was blinded to the MSUS results. MCP joints, both wrist and flexor tendons were scanned by MSUS. The likelihood of inflammatory arthritis in seronegative patients was 6% while adding clinical and radiographic information raised the probability to 30% and with certain MSUS findings this rose to 94%. That study addressed the diagnostic utility of MSUS in patients with early arthritis [139].

1.4.3 MSUS scoring systems:

Monitoring of disease activity in RA is provided by different clinical scoring systems [73, 76]. Some of these methods are used in clinical praxis and others for research purposes primarily to measure disease activity and to monitor response to treatment. However, clinical scoring systems have some limitations. Despite clinical remission, subclinical activity may sometimes be observed leading to radiographic progression [141, 142]. Therefore, more

sensitive methods seem to be needed to assess the disease activity and to evaluate response to therapy. During recent years, MSUS has become an important imaging modality in rheumatology serving this purpose. Thus, standardization of ultrasound results has become essential.

Ultrasound results in different joint areas can be scored binary (0/1), semi-quantitatively (0-3) or quantitatively in B-mode as well as in Doppler.

The first scoring system for erosions in RA was described by Wakefield et al in 2000 [136]. The measurement of erosion was as follow: normal: < 2 mm, small erosion: = 2 mm, moderate erosion: >2 <4 mm and large erosion > 4 mm. The Kappa value between two observers was at least 0.76 for present/absent erosions and most erosions were observed in the radial or ulnar aspects of MCP joints 2 to 5.

Szkudlarek et al described 4-grade scoring system for joint effusion, synovitis, bone erosions, and intra-articular power Doppler signals in 2003 [143]. Joint effusion was described as an intra-articular anechoic compressible area (0 = no effusion, 1 = minimal, 2 = moderate without distension of joint capsule and 3 = extensive amount of effusion with distension of joint capsule). He described synovitis as a hypoechoic intra-articular non-compressible area (0 = no synovial thickening, 1 = minimal without bulging over the line linking tops of the bones, 2 = synovial thickening with bulging over the line linking tops of the periarticular bones but without extension along the bone and 3 = synovial thickening with both bulging over the line linking tops of the periarticular bones and with extension to at least one of the bones). Szkudlarek et al described bone erosions in a different way compared to Wakefield et al. The definition of bone erosions was: 0 = normal regular bone surface, 1 = irregularity without defect formation, 2 = bone defect formation which is seen in 2 perpendicular planes and 3 = bone defect with extensive destruction. Intra-articular Doppler signals were defined as 0 = no signals in the synovium, 1 = single vessel signals, 2 = confluent signals in $\leq 50\%$ of synovial area and 3 = signals in $> 50\%$ of synovial area (figure 17).

Scheel et al introduced in 2005 a summary of ultrasonographic synovitis scoring systems suitable for evaluation of finger joint inflammation in RA [161]. The study was also a comparison of semi-quantitative MSUS scoring with quantitative MSUS measurements. Dorsal and palmar ultrasound scans were performed on the second to fifth MCP and PIP joints in 10 healthy controls and 46 RA patients with arthritis in the hands. Synovitis was standardized and scored semi-quantitatively and also compared with quantitative method. 10 patients underwent additional MRI of the hands and results were compared with both semi-

quantitative and quantitative ultrasound measurements. Grade of inflammation (effusion and synovial hypertrophy combined) was scored between 0 and 3 (no effusion or hypertrophy to extensive effusion or hypertrophy). In that scoring system, the grade of both effusion and synovial hypertrophy was measured and evaluated as described by Szkudlarek et al [143] but for simplification in clinical practice, both joint effusion and synovial hypertrophy were combined in one measurement and adapted to the scoring system as described above (figure 18).

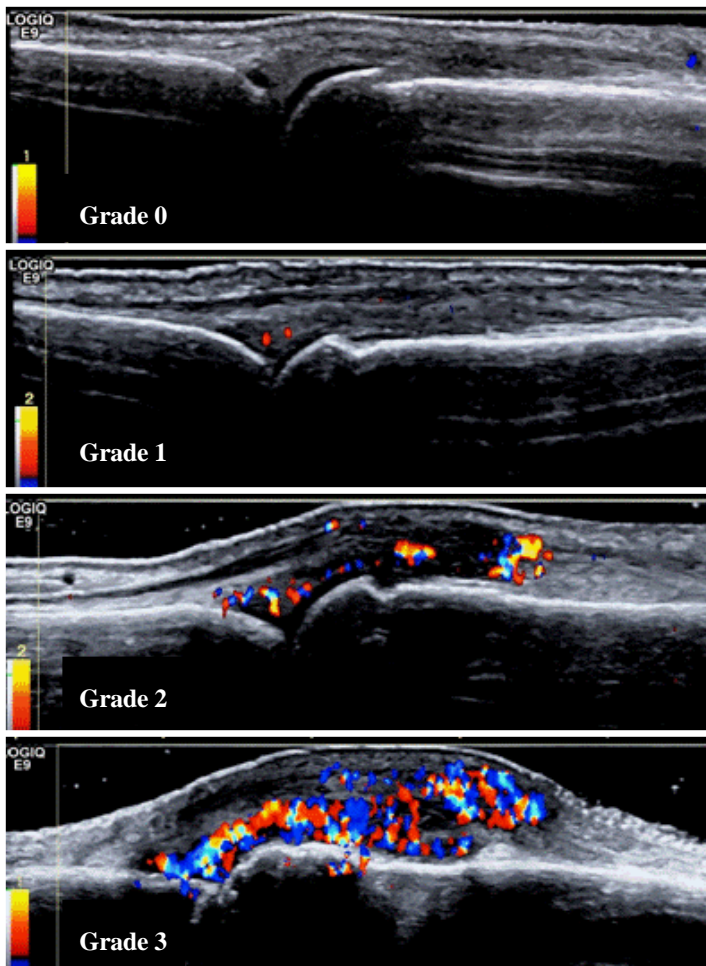


FIGURE 17: Dorsal longitudinal scanning of MCP joints in patients with RA, showing different grade of color Doppler signals (obtained by the author)

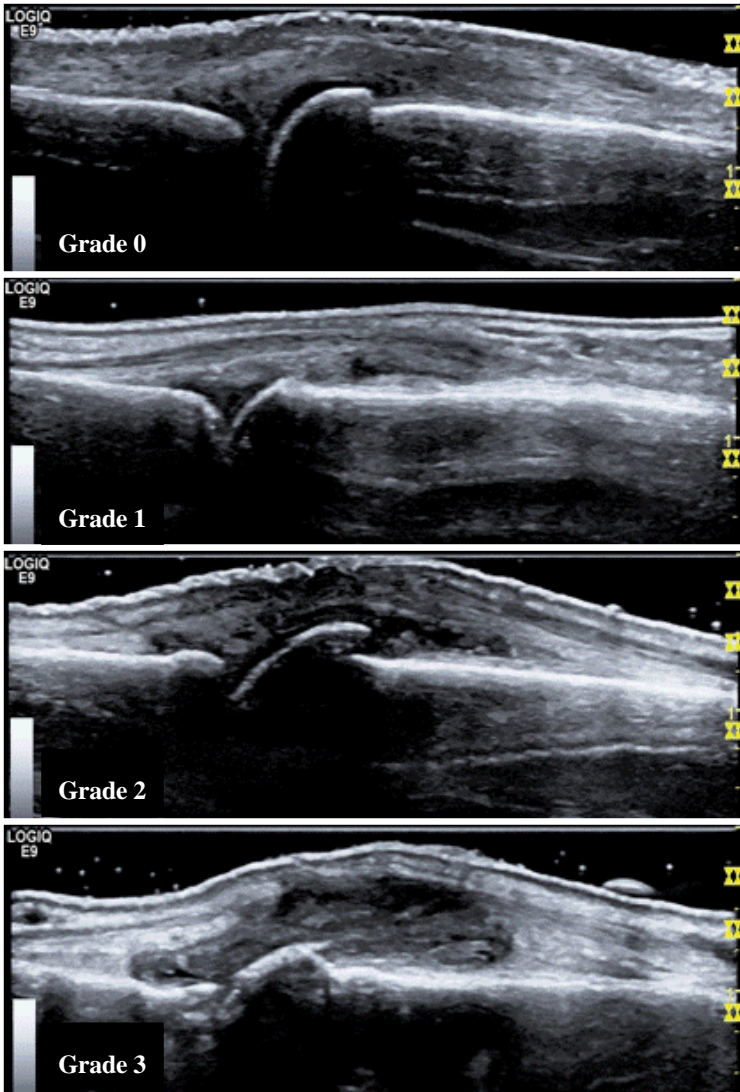


FIGURE 18: Dorsal Longitudinal scanning of MCP joints in RA patients, showing different grade of synovial hypertrophy/joint effusion (score 0-3) according to the scoring system by Scheel et al. (obtained by the author)

2 AIM OF THE THESIS

2.1 GENERAL AIM

The overall aim of this thesis was to study the role of three imaging modalities; conventional radiography, digital X-ray radiogrammetry and musculoskeletal ultrasound in diagnosis and management of rheumatoid arthritis.

2.2 SPECIFIC AIMS

1. To evaluate the clinical and radiological outcomes of early RA patients who initially responded well to MTX and follow up in regular care during the first 2 years of the disease course (study I).
2. To determine whether hand bone loss analyzed by DXR during first year correlated with radiographic progression, as measured by Sharp score modified by van der Heijde, after 2 years in early RA patients and to compare HBL and radiographic progression in the three treatment groups of the SWEFOT trial (study II).
3. To evaluate whether baseline predictors, such as smoking habits, are associated with rapid radiographic progression one year after diagnosis of RA in the SWEFOT trial (study III).
4. To assess the diagnostic impact of musculoskeletal ultrasound findings in patients referred for rheumatologic evaluation because of suspected arthritis (study IV).

3 MATERIALS AND METHODS

This thesis is based on four epidemiological clinical studies. The first 3 papers are based on the SWEFOT (SWEdish PharmacOTherapy) clinical trial and the last paper is an observational prospective study with focus on the role of musculoskeletal ultrasound in patients with suspected arthritis.

3.1 SWEFOT trial (paper I-III)

The SWEFOT trial was collaboration between 15 rheumatology units in Sweden between 2002 and 2008. Adult patients diagnosed with RA according to the revised ACR criteria [17] with symptom duration less than 12 months were included in the trial. They had no previous treatment with DMARDs, nor oral GCs or stable dosage of GCs for at least 4 weeks of, at most, 10 mg Prednisone or equivalent. Disease activity was measured by a rheumatologist using DAS28 [73]. A score of >3.2 was required to be included in the trial. The main exclusion criterion was contraindications to any trial drugs.

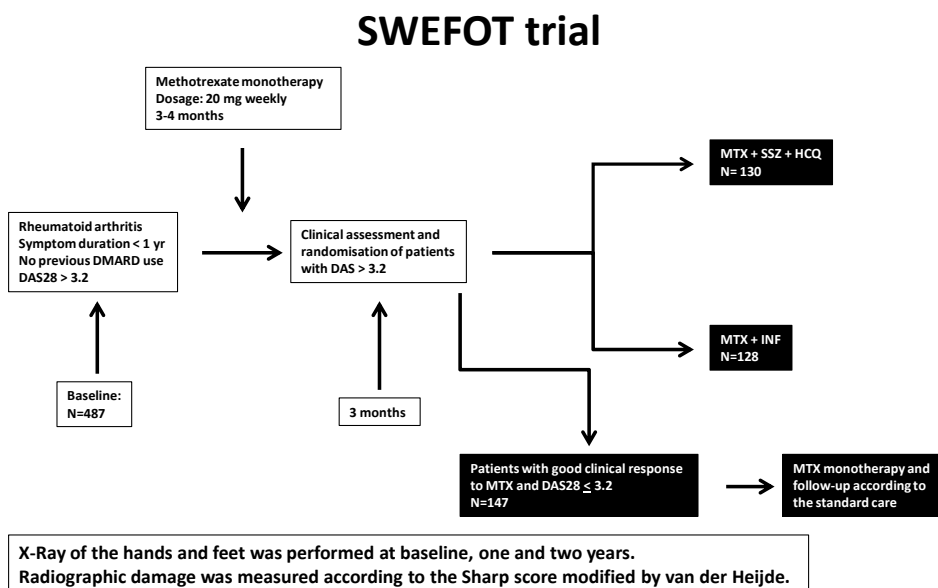


FIGURE 19: Schematic of the SWEFOT trial

After given informed consent and inclusion, all patients were treated with MTX at the initial dosage of 10 mg weekly. This dose was increased every 2 weeks by 5 mg increments up to 20 mg a week. Folic acid supplements in tablets of 5 mg were prescribed to be taken 1–6 times a week, but not on the day of intake of MTX. Liver enzymes and blood counts were monitored frequently at first and at wider intervals as time went by, in accordance with Swedish guidelines. Abnormalities in these measures could lead to dose adjustments, all based on well established clinical routines. Radiographs of hands and feet were obtained at baseline, 1 year, and 2 years in accordance with current practice guidelines in Sweden. Radiographic progression was evaluated according to the Sharp score modified by van der Heijde (SHS) by two certified readers. At 3-4 months follow-up, patients with an incomplete response ($DAS > 3.2$) to MTX monotherapy were randomized to two different treatment strategies as shown in figure 19. The patients who responded well to MTX monotherapy at the 3-4 months follow-up ($DAS_{28} \leq 3.2$) did not enter the randomization and were no longer, technically, part of the SWEFOT trial. These patients were followed in standard care.

3.2 Diagnostic utility of MSUS in patients with suspected arthritis (paper IV)

One hundred and three patients who had been referred to the early arthritis clinic at the Karolinska University Hospital by general practitioners were recruited consecutively between 2010 and 2013 in this study. All patients had suspected inflammatory arthritis but had no prior rheumatologic diagnosis. A first clinical assessment was performed by a rheumatologist, based on medical history, physical examination, and review of previously performed laboratory and/or radiological studies. The assessment was usually complemented by new blood tests including ACPA, RF and/or acute phase reactants. Radiographic assessment of the hands and feet was also performed. No MSUS assessment was done at the first visit. At this time point, the patients were invited to participate in the study and after informed consent was given, the rheumatologist completed the study case-report form (CRF) which included:

- Likelihood that the patient had inflammatory arthritis
- Likelihood that the patient had RA

In the pre-test assessment, the physician based likelihood on a five-point scale: Very likely (probability $\geq 80\%$), likely (≥ 60 and $< 80\%$), possible ($\geq 40\%$ and $< 60\%$), not likely but

possible ($\geq 20\%$ and $< 40\%$) and very unlikely ($< 20\%$). During one week after the first visit, MSUS evaluation was performed by one ultrasound specialist (the author) and the result subsequently was presented to the same rheumatologist for post-test assessment. Importantly, the MSUS findings including B-mode and color Doppler ultrasound (CDUS) was given descriptively as morphological and vascularisation data of the studied joints and not just positive or negative findings. The post-test evaluation was performed by the same rheumatologist based on clinical and MSUS finding on the same five-point scale. The final diagnosis and anti-rheumatic treatment that the patients had been given during a follow up of 1 to 4 years was studied at the end of the follow up time.

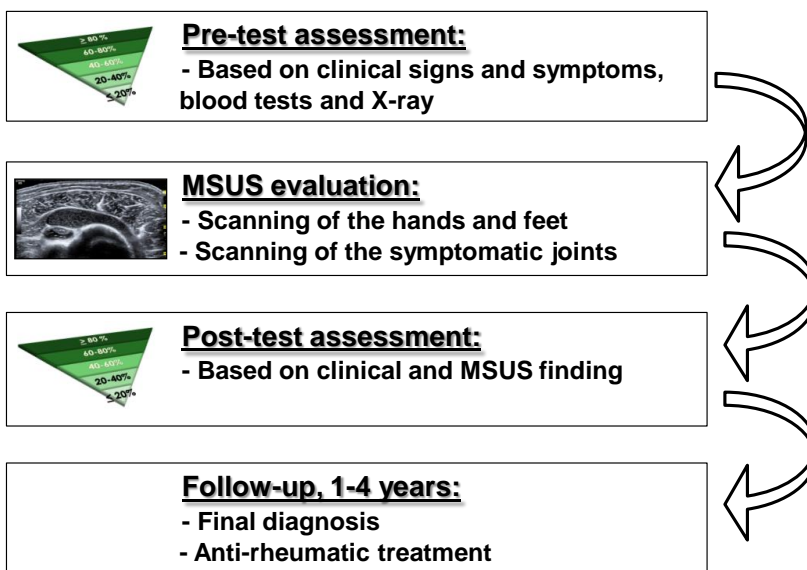


FIGURE 20: Schematic of the study IV

4 RESULTS

4.1 Paper I

In early rheumatoid arthritis, patients with a good initial response to methotrexate have excellent 2-year clinical outcomes, but radiological progression is not fully prevented: data from the methotrexate responders' population in the SWEFOT trial.

4.1.1 Characterization of the patients

147 patients of all 487 SWEFOT patients responded well to the initial monotherapy with MTX achieving DAS28 value of 3.2 or less at the 3 months follow-up visit. This group of patients received regular care and clinical and radiological data were collected up to 2 years. Complete 2 years' follow-up data was retrieved in as many as 110 out of these 147 patients. Baseline characteristics of this subgroup of patients did not differ from the whole group.

4.1.2 Clinical follow-up

Mean (SD) observed DAS28 values were 2.53 (1.02) and 2.25 (0.82) at 1 and 2 years, respectively ($p=0.03$). A LOCF (Last Observation Carried Forward) analysis for patients with missing data yielded mean DAS28 values of 2.50 (1.02) and 2.34 (0.85) at 1 and 2 years, respectively ($p=0.03$). The proportions of patients who achieved DAS28 remission after 1 and 2 years were 59.6% and 71.8%, respectively. 37.4% and 39.4% of patients achieved remission as defined by the SDAI and CDAI measures at 1 year follow-up visit. After 2 years, the proportions in SDAI/CDAI remission were 41.2% and 43.7%, respectively.

Responses	3 months (N=142)	12 months (N=114)	24 months (N=110)	3 months (NRI)	12 months (NRI)	24 months (NRI)
EULAR good response	95.1%	76.3%	85.5%	91.8% (135)	59.2% (87)	63.9% (94)
EULAR good or moderate response	95.2%	92.1%	97.3%	98.6% (140)	71.4% (105)	72.7% (107)
ACR20	89.6%	83.9%	86.4%	87.8% (129)	63.9% (94)	60.5% (89)
ACR 50	73.6%	70.5%	81.6%	72.1% (106)	53.7% (79)	57.1% (84)
ACR 70	35.4%	41.1%	47.6%	34.7% (51)	31.3% (46)	33.3% (49)

TABLE 6: EULAR and ACR responses at 3, 12 and 24 months, left section: based on available follow-up data; right section: Patients with missing data imputed as non-responders (NRI)

The vast majority of patients with complete follow-up data had good EULAR response at 1 and 2 years follow-up visit, as shown in table 6.

4.1.3 Radiographic follow-up

Table 7 demonstrates radiographic progression according to the SHS score during follow-up time (2 years) in all available patients at each visit and patients with complete radiographic data. As shown, the values are almost in the same level in both groups. The mean (SD) radiographic progression after 1 year (n=107) was 2.21 (4.15) and after 2 years (n=101) 3.90 (6.84) (p=0.0003). Progression was seen for both the erosion score and joint space narrowing score, with a mean increase at 2 years of 1.40 (4.11) and 2.50 (4.45), respectively, figure 21. The definition of no radiographic damage was 0 units according to the SHS score and 48.1% of patients had no radiographic damage at the baseline visit. This proportion decreased to 26.9% and 20.2% after 1 and 2 years, respectively (p<0.0001). No radiographic progression was observed in 51.4% and 38.6% of patients at 1 and 2-year follow-up, respectively (p<0.0001). A change of one to five units in the total SHS score was seen in 30.8% at 1 year and 31.7% at 2 years. Six patients had at least a 10 units increase in total SHS score at 1 year and 15 patients had a 10 units or greater increase in the SHS score after 2 years, of whom 11 patients were still on MTX monotherapy.

	All available patient at each follow-up visit				Patients with complete radiological data (n=91)		
	TS	ES	JSNS	N	TS	ES	JSNS
Baseline	3.78 (7.72)	1.74 (3.41)	2.05 (5.38)	131	3.88 (8.29)	1.79 (3.12)	2.10 (6.11)
1 Year	5.98 (8.66)	2.64 (4.06)	3.35 (5.99)	119	6.20 (9.21)	2.73 (4.16)	3.47 (6.50)
2 Years	7.87 (9.91)	3.24 (5.09)	4.61 (7.17)	114	7.95 (10.10)	3.34 (5.15)	4.60 (7.57)

TABLE 7: Radiological progression in all available patients at each follow-up visit (left) and patients with complete radiological data (right)

Regarding to the radiographic progression, no difference was observed between patients in DAS28 remission and other patients. Patients who received other anti-rheumatic treatment in combination with MTX or those who switched to other anti-rheumatic treatment during 2 years follow-up had numerically more radiographic progression compared to those with MTX monotherapy (p=0.06).

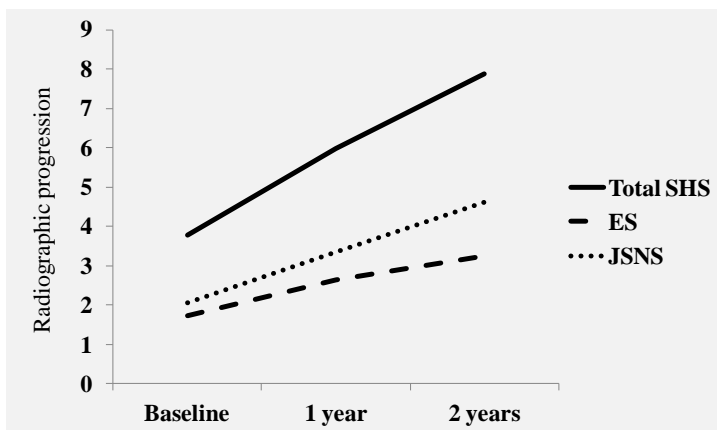


FIGURE 21: Radiological progression in all available patients at each follow-up visit. SHS: Sharp score modified by van der Heijde; ES: erosion score; JSNS: Joint space narrowing score.

4.2 Paper II

Evaluation of hand bone loss by digital X-ray radiogrammetry as a complement to clinical and radiographic assessment in early rheumatoid arthritis: results from the SWEFOT trial

4.2.1 Characterization of the patients:

159 patients of the SWEFOT trial, with same baseline characteristic as the whole group, had radiographs of the hands suitable for DXR analysis, at baseline and 1 year follow-up. The distribution of patients with different treatment strategies was almost equal as shown in figure 22.

MTX responders had lower baseline DAS28 and better functional status measured by HAQ [145] compared with randomized groups ($p < 0.05$ for both DAS28 and HAQ). Regarding to the radiographic damage according to the SHS score and bone mineral density (BMD), no differences were observed between the three groups at baseline. The definition of radiographic progression in this study was an increase more than 5 units according to the SHS score during 2 years. Hand bone loss was defined as DXR-BMD change rate ≥ 2.5 mg/cm²/month during 1 year. Patients with radiographic progression had higher

acute phase reactant (both CRP and ESR) at the baseline while patients with HBL had only higher CRP.

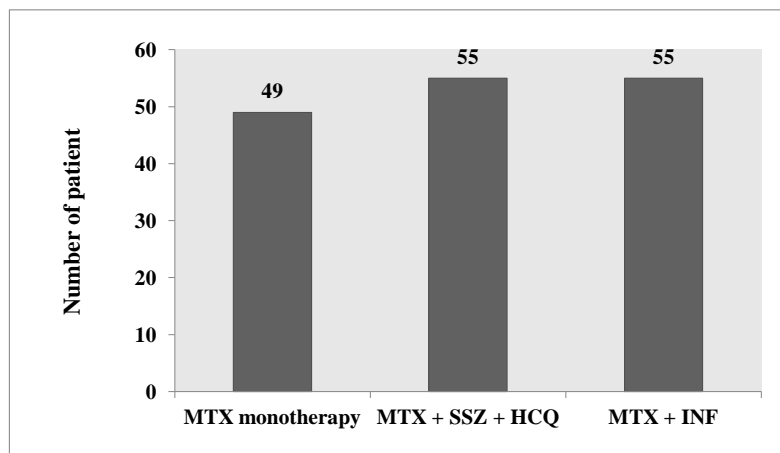


FIGURE 22: Distribution of patients in paper II with different anti-rheumatic therapies

4.2.2 Bone mineral density measured by DXR

BMD was measured by DXR at baseline and 1 year follow-up visit. Change in BMD was divided into normal ($< 0.25 \text{ mg/cm}^2$ per month), moderately (≥ 0.25 and $< 2.5 \text{ mg/cm}^2$ per month) and highly elevated ($> 2.5 \text{ mg/cm}^2$ per month). The definition of HBL was highly elevated BMD change. The proportion of patients with HBL was significantly lower in MTX monotherapy group compared to randomized groups ($p=0.01$).

4.2.3 Radiographic progression and hand bone loss

The sensitivity of DXR change during 1 year (cut-off $> 2.5 \text{ mg/cm}^2$ per month) to predict radiographic progression was low (26%) while the specificity was 89%. Patients with HBL during 1 year had significantly more radiographic progression after 2 years (Total SHS-score, Erosion and joint space narrowing score) compared to those without HBL. The number of patients with radiographic progression was 50 (14/44 in the monotherapy, 23/53 in triple therapy and 13/47 in MTX + INF group, respectively). When each therapy group was analyzed separately, only patients in triple therapy group had significant radiographic

progression when they had HBL. Patients with HBL had significantly greater risk of radiographic progression over 24 months (odds ratio 3.09, 95% CI =1.20–7.79, p =0.02). This was most marked and only statistically significant in the group of patients receiving triple therapy (odds ratio 4.15, 95% CI = 1.05–16–35, p = 0.04) and not in two other groups.

4.3 Paper III

Current smoking status is a strong predictor of radiographic progression in early rheumatoid arthritis: results from the SWEFOT trial

4.3.1 Characterization of the patients:

In this study, 311 of the 487 patients from the SWEFOT trial were included that is those with complete available radiographic data at the baseline and 1 year follow-up visit. Baseline characteristics of this sub-group did not differ from the whole SWEFOT population. Patients were grouped as current smokers versus non-smokers (pooling past-smoker and not-smoker). Radiographic progression was defined as an increase in total SHS-score of at least 5 points after one year, as previously described [84, 87, 146]. The proportion of patients with erosions at the baseline was 41% and the median (IQR) of SHS-score was 2 (0-6).

4.3.2 Association between radiographic progression and baseline parameters

Significant associations were observed between rapid radiographic progression (SHS-score \geq 5 points) and smoking status, erosions at the baseline, DAS28 and its inflammatory components (ESR, CRP). Table 8 demonstrates these associations.

	All patients	Patients in multivariate model	
	Unadjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI) *
Current smokers vs. Non-smokers	2.70 (1.50 to 4.87)	2.85 (1.57 to 5.16)	2.67 (1.44 to 4.95)
Erosions	2.38 (1.41 to 4.00)	2.43 (1.40 to 4.22)	2.28 (1.28 to 4.07)
DAS 28 (per unit increase)	1.36 (1.06 to 1.74)	1.30 (1.00 to 1.69)	1.37 (1.04 to 1.81)
CRP (<10, 10-35, >35 mg/dL)	1.66 (1.18 to 2.34)	1.68 (1.18 to 2.41)	1.52 (1.03 to 2.24)
ESR (<21, 21-50, > 50 mm/h)	1.59 (1.09 to 2.30)	1.68 (1.13 to 2.49)	1.67 (1.10 to 2.53)

TABLE 8: Significant association between radiographic progression during 1 year and some of the baseline characteristics in paper III (for the whole model and variable list see paper III).

*Adjusted for gender, symptom duration, current smoking, baseline erosions and HAQ

Since high co-linearity was observed for HAQ and DAS28 and its components, so only HAQ was kept in the model, and excluded when DAS28 and its components were analyzed. Further adjustment for treatment strategy did not change the associations between these significant predictors and radiographic progression. Using a cut-off of 5 units for radiographic progression according to the SHS-score, no significant association was observed for auto-antibody status. Based on 3-dimensional matrix including the main predictors, current smoking status, baseline erosion and CRP in tertiles, 63% of patients who had all 3 predictors developed radiographic progression after 1 year. This proportion for patients without these 3 baseline parameters was 12%. Separate analysis for ACPA positive and negative patients showed the lowest proportion of patients with radiographic progression in ACPA negative patients lacking all baseline predictors.

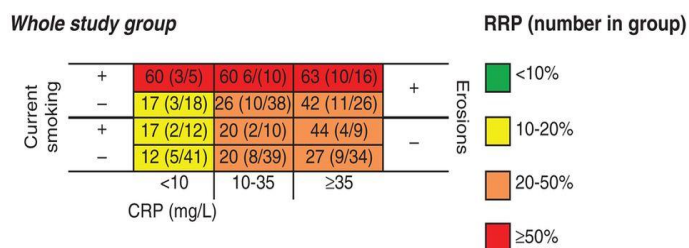


FIGURE 23: Risk matrix showing the proportion of SWEFOT patients in paper III who developed radiographic progression after 1 year.

4.4 Paper IV

Diagnostic utility of musculoskeletal ultrasound in patients with suspected arthritis – a probabilistic approach

4.4.1 Characterization of the patients:

One hundred and three patients with a mean age (SD) of 50 (16.4) years were included consecutively in this study between 2010 and 2013. All patients had suspected inflammatory arthritis but had no prior rheumatologic diagnosis. The proportion of patients with ACPA and RF positivity was 29% and 34%, respectively. The mean (SD) symptom duration was 8.5 (3.8) months. 76 (73.8%) of patients were female. Figure 24 demonstrates the proportion of patients with different final diagnosis at the end of the follow-up time (1-4 years).

At the end of follow-up, 53.4% of the original cohort (55/103) had been treated with anti-rheumatic therapy including DMARDs, corticosteroids and biologics. 35 were treated with MTX and 14 had other DMARDs. 18 patients were treated with biologics as a monotherapy or in combination with DMARDs.

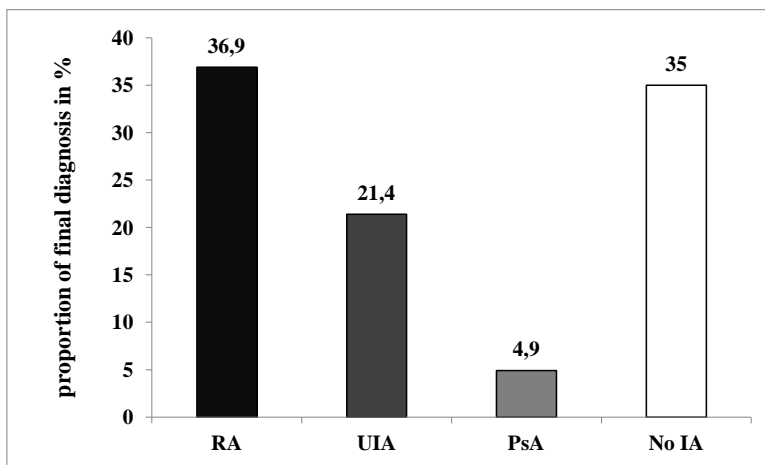


FIGURE 24: At the end of the follow up time, 65% (67/103) of patients were diagnosed as having any inflammatory arthritis

4.4.2 The impact of MSUS in early assessment of patients with suspected inflammatory arthritis

In this study 63.1% of patients had MSUS finding in B-mode and/or color Doppler ultrasound that indicated inflammatory arthritis. The diagnostic certainty for inflammatory arthritis and RA increased after performing MSUS, as shown in figure 25. McNemar statistical test was used to analyze changes in proportions from pre-test to post-test likelihood. After presentation of MSUS information to our four rheumatologists, the number of patients with highest and lowest diagnostic probability was increased. Parallel reduction was observed in proportion of patients with greatest diagnostic uncertainty.

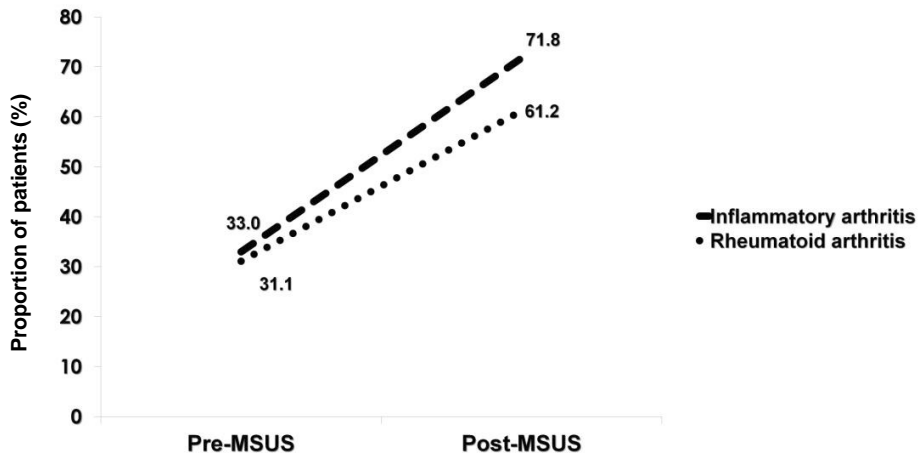


FIGURE 25: The proportion of patients with maximal diagnostic certainty for inflammatory arthritis and RA before and after performing MSUS ($p < 0.001$ for both IA and RA).

4.4.3: The relation between MSUS findings at the first evaluation and final diagnosis/ongoing anti-rheumatic treatment at the end of follow-up time

In more than 95% of patients it was agreement between MSUS positive/negative findings and the final diagnosis. Similar results were obtained when accuracy of MSUS was investigated by the number of patients with anti-rheumatic treatment (ART) at the end of the follow up time. The patients were very unlikely to be prescribed ART when the pre-test and post-test likelihood was less than 40% (pre-test: 2/28; post-test: 0/34). However, a significant increase was observed in proportion of patients for whom diagnostic likelihood was more than 80% and treated with ART before and after MSUS (pre-test: 23/103; post-test: 48/103, $p < 0.001$).

5 DISCUSSION

This thesis is based on the clinical use and role of X-ray imaging and musculoskeletal ultrasound of the joints in diagnosis and management of inflammatory arthritis in general and rheumatoid arthritis specifically.

5.1 Paper I

Paper I provided new information about the clinical and structural outcomes of RA during the first two years of the disease course in patients who responded well to the first treatment already after 3-4 months. The core of this paper is that early RA patients with initial good response to MTX monotherapy continue to do well clinically during the first two years but radiographic damage is surprisingly high in certain number of these patients. One reflection here is whether MTX monotherapy is enough and acceptable therapy for all patients with early RA and one plausible explanations regarding radiographic progression in the certain number of these RA patients is maybe subclinical synovitis in a group of RA patients that can be identified by the modern imaging modalities including MRI and MSUS [147]. Based on the results from paper I, some clinical points can be discussed.

- MTX has been shown to have a protective effect in terms of radiographic destruction [27]. Additionally the practical ease of use of MTX and lack of frequently serious adverse event have contributed that MTX has been dominant DMARD during the last 20 years. Some previous studies including paper I in this thesis have demonstrated that MTX does not have a protective radiographic effect in all patients with good initial clinical response and a proportion of patients treated with MTX as a monotherapy have radiographic progression despite no or low disease activity [84, 98, 148, 149].
- MTX is still the most common used anti rheumatic drug for treatment of RA. Although other DMARDs and biologic agents in combination with MTX have been shown to be superior to MTX as a monotherapy regarding both clinical and radiographic outcomes, the cost and risk for adverse events of combination therapy should be considered. O'Dell et al showed that combination therapy with MXT, SSZ and HCQ was superior to MTX monotherapy in RA patients who did not responded to at least one DMARD [35]. It is actually reasonable to treat this group of patients more intensified even with combination biologics and MTX. The RA population in

paper I and study by O'Dell et al. are different since in the SWEFOT trial, all patients were treated by MTX initially and as explained in the results 147 of 487 patients responded well to MTX monotherapy. In COBRA trial, the patients treated with combination SSZ, MTX and high-dose rapidly tapered steroids had better radiographic outcomes than those treated with a single DMARD which was SSZ and not MTX [150]. MTX in combination with biologics has also been shown to be superior to MTX alone in early RA patients regarding radiographic progression [98, 99]. Considering all above, the important question is whether it is necessary to treat all early RA patients more intensified initially or not and the answer is still "No". The explanation is the cost of treatment with biologics and more importantly the side effect of these drugs and also the combination of DMARDs that leads to more often monitoring. Radiographic progression has been observed in a group of early RA patients with good initial clinical response. Importantly, identifying this group of RA patients at the time of diagnosis and/or during the first year should be considered more.

- Most early RA patients who achieved low disease activity after 3-4 months of MTX monotherapy continued to have low disease activity during 2 years follow-up, and additional treatment was needed infrequently but some radiological progression occurred in a proportion of the patients, and may be marked or severe in some, even despite sustained DAS28 remission. One important reflection here is whether DAS28 remission criteria is enough for assessment of disease activity since it does not include evaluation of the feet and also allows for a few swollen joint which means patients in DAS28 remission may actually be in minimal disease activity state and not true remission [151]. In study I, When SDAI and CDAI criteria were used for definition of remission, no significant difference was observed neither for radiographic progression since both these index are simplifications of DAS28. Accordingly, two main points should already be considered at the diagnose time and during the first year of the disease course: 1- selecting the patients with the risk factor for poor prognosis and worse outcome from the beginning as will be discussed later in paper III. 2- Taking advantage of modern imaging modalities including DXR, MSUS or MRI more frequently specially during the first year of RA. Based on our experience from early RA screening at the Karolinska University Hospital, at the disease onset and also at the early stage of the disease course in a group of early RA patients, affected joint areas are the feet and also tendons. So the careful evaluation of RA patients with modern imaging modalities like MSUS should be considered more frequently since

the method has been shown to be superior to clinical examination to identify synovitis and other inflammatory conditions [92, 126].

- Despite a subset of patients had severe radiographic progression after 2 years there was no significant difference in the decrease of functional status measured by HAQ disability index in this group compared to non-progressors. Part of explanation here is that the HAQ mainly evaluates reversible disability in the short terms and irreversible disability in the long terms. Another explanation may be that HAQ values in our patient cohort were generally low and HAQ has a floor effect. Radiographic progression did not have significant influence on functional status. Accordingly, the question is whether it could be necessary to consider more intensified therapy for patient with radiographic progression? To be able to answer this important question, clinical and radiographic data from 5 and 10 years follow-up of the SWEFOT population are needed.

Taken together, identifying the patients who need more intensified treatment in the beginning of the disease is certainly important. Monitoring of the disease activity during the first years of RA with more sensitive methods in clinical rheumatologic practice and using of potential clinical predictors for radiographic progression at the time of diagnosis should be considered more in the future.

5.2 Paper II

The main finding of study II was that HBL (DXR-BMD ≥ 2.5 mg/cm² per month) after one year predicted radiographic progression after 2 years in patients with early RA. The finding is consistent with previous studies [119-121, 152]. Since the SWEFOT trial was not designed for this study from the beginning, only in 159 patients the DXR analysis was performed on the radiographs of the hands that were correctly timed and taken with the same modality at the baseline and after one year. As a consequence, for some patients, the baseline and 12-month radiographs were not taken using the same type of instrument and these images could not be analyzed. Based on the results from paper II, some observations could be discussed:

- There is no consensus for definition of hand bone loss, measured by DXR technique. In two previous studies, the smallest detectable change in DXR-BMD was used for definition of HBL [119, 120] while in the study by Kaptanovic et al, the definition of HBL was BMD reduction more than median for the whole group of patients and

those with HBL at one year had elevated Larsen score at 1 year and up to 20 years [121]. In the study by Hoff et al. HBL at one year predicted radiographic progression after 5 and 10 years. In paper II and also the study by Forslind et al. HBL at one year was predictor for radiographic progression after 2 years. However the cut-off for definition of HBL was different in these two studies. In our study, the fixed threshold levels, recommended by the device manufacturer (Sectra, Sweden), were used for analysis and HBL was defined as DXR-BMD change rate ≥ 2.5 mg/cm²/month (0.03 g/cm² per 12 months) . This value is higher than the thresholds used in the previous studies. One explanation is that using the fixed threshold levels makes the findings as usable as possible for clinical interpretations but to be able to conclude this, it is necessary to use similar threshold levels in other RA populations.

- Less HBL was observed in patients with good clinical response to initial MTX treatment after 3-4 months. One explanation here is the findings from the study by Revu et al. showing that MTX decreases synovial cellularity as well as RANK expression and RANKL/OPG ratio and might have a direct effect on bone metabolism in treatment of RA [34]. Less HBL in MTX monotherapy group in our study is not consistent with BeSt and PREMIER studies [124, 153]. One plausible explanation is that in the SWEFOT trial MTX monotherapy group had good clinical response to the treatment already at the 3-4 months follow-up visit. Despite less HBL in this group, radiographic progression was more pronounced compared to patients who received combination MTX + INF, showing the protective role of TNF inhibition regarding radiographic progression in RA patients.
- Maybe the main important reflection from paper II and similar studies is the practical usefulness of the DXR technique to find the patients who are categorized as having higher risk for radiographic progression. In all studies the assessment of HBL has been done after one year. It means that the rheumatologists in the clinical praxis should have two radiographs of the hands (importantly taken for the aim of DXR analysis) with one year time interval to be able to evaluate BMD change in order to predict radiographic outcomes later in the disease course. This is actually not practical and neither reasonable since treatment of RA should be evaluated earlier as EULAR recommended [89]. Therefore an important question is whether DXR-BMD change after 3 or 6 months can provide useful information.

Taken together, DXR-technique may have a role in predicting radiographic outcome in RA patients if there is a specific definition for HBL and also if future studies indicate that DXR-

BMD change after 3-6 months provides the similar results as in the paper II and other referred studies.

5.3 Paper III

As previously discussed, it is important to find RA patients who are likely to develop significant radiographic progression as early as possible, preferably at the time of diagnosis. In paper I we indicated that a proportion of early RA patients developed significant radiographic progression despite having no or low clinical disease activity, during the follow-up period.

Results from paper III indicated that smoking habits associated significantly with rapid radiographic progression in early RA patients, visualized by a multivariate logistic regression. Several studies indicated that using a risk matrix may be clinically useful to predict rapid radiographic progression (RRP, increase in SHS score ≥ 5 unit after 1 year) [85-88]. Visser et al. showed that seropositivity, baseline CRP level and presence of erosions at the baseline visit were significant independent predictors for RRP in the risk matrix [88]. Risk matrix model, generated from ASPIRE early RA data set demonstrated that radiographic damage at the baseline was not among the main prognostic variable [87]. None of the previous studies has evaluated whether smoking habits associate with RRP. However several earlier studies indicated that RA patients who smoke develop more radiographic damage and also respond worse to ART [85-88]. Some practical conclusions could be made based on the results from paper III:

- Current smoking habits should be considered as a strong independent predictor for radiographic progression in patients with early RA. The finding was perhaps not surprising since several earlier study demonstrated an association between smoking habits and both clinical and radiological outcomes of RA. However, smoking habits have not been included in any of the previously published studies on risk matrices of radiographic progression.
- Based on the previously published studies about pathogenesis of RA, smoking induces citrullination and may be regarded as a mediator of ACPA-positivity. Therefore, patients in this study were stratified into two aetiologically distinct subgroups of ACPA-positive and ACPA-negative disease. However ACPA-positivity can also be an outcome of smoking and thus a potential collider.

- The patients in this study represent an unselected early RA population. Additionally the management of the patients reflects common standard care [49]. The findings for the independent predictors remained even after adjustment for treatment strategy which surprisingly is not consistent with previous studies[87, 88].
- In clinical praxis, it is maybe easier to translate the findings from paper III and prior similar studies into choice of treatment and management for individual patients with recently diagnosed RA.

Taken together, the identified clinical predictors in this study and similar earlier studies are easily accessible and actually include as part of routine rheumatologic care at the time of diagnosis. Thus these objective clinical findings should be considered more in order to manage every individual RA patient.

5.4 Paper IV

Paper IV provided information about the role of diagnostic MSUS in patients with suspected inflammatory arthritis. The core of the paper IV is that MSUS greatly increased the diagnostic certainty for inflammatory arthritis in general and for RA in particular. Since earlier treatment of RA results in better structural and functional outcome [154, 155] there is a need to identify RA-patients at the early stages and with more certainty. Traditional evaluation of patients with suspected inflammatory arthritis used to include medical history, physical examination, complemented by blood test and conventional radiography. Using these tools, a sizeable proportion of patients with suspected inflammatory arthritis are not reliably diagnosed in the early stages of the disease. More recently MSUS has been shown to be superior to traditional methods to identify synovitis and soft tissue inflammation and several studies have confirmed the validity of MSUS for detecting synovitis and soft tissue inflammation [125, 127-130, 156-158].

As EULAR has recommended, when there is diagnostic doubt, MSUS or MRI can be used to improve the diagnostic certainty of RA above clinical criteria alone [144]. This recommendation is based on five observational studies (2 with MSUS and 3 with MRI). One of these [159] showed a significant improvement in diagnostic certainty for seronegative arthritis, primary and inflammatory osteoarthritis but an increase in diagnostic certainty for RA was not statistically significant in that study as shown in table 9.

Overall diagnosis	Patients with certainty pre-US (%)	Patients with certainty post-US (%)	p-value
Rheumatoid arthritis	26 (42.0)	33 (53.2)	0.17
Seronegative arthritis	29 (46.8)	38 (61.3)	0.05
Primary OA	29 (46.8)	45 (73.0)	0.002
Inflammatory OA	29 (46.8)	54 (87.1)	<0.001
Gout	55 (88.7)	62 (100.0)	–
Infectious arthritis	60 (96.8)	62 (100.0)	–
Normal	50 (80.6)	57 (92.0)	0.12
Other*	48 (77.4)	51 (82.3)	0.51

TABLE 9: Diagnostic certainty before and after MSUS in study by Matsos et al.

Similar to this original study we aimed in paper IV to estimate the diagnostic confidence for inflammatory arthritis using a five-point scale before and after performing MSUS in patients with suspected inflammatory arthritis. The McNemar statistical test was used in both paper IV and the study by Matsos et al. to determine the differences in pre-test and post-test diagnostic likelihood. The main difference is that the increase in diagnostic certainty for RA (pooling seropositive and seronegative) was statistically significant in our study maybe due to that in the study by Matsos et al, only joints requested by the rheumatologists were scanned rather than a pre-specified number of joints in the hands and feet as in our study. Based on the results from paper IV, six interesting observations could be made which supported the utility of MSUS in early diagnosis of inflammatory arthritis:

- The increase in diagnostic certainty for inflammatory arthritis in general and for RA in particular was highly significant supporting the first EULAR recommendation for the use of MSUS in management of RA.
- MSUS reduced the number of patients in whom diagnostic uncertainty was maximal. Some patients moved to the higher likelihood and were diagnosed as having inflammatory arthritis and accordingly started treatment with ART earlier increasing the chance of a better outcome. Another group of patients moved to the lesser likelihood and referred back to the general practitioner.
- Theoretically, increase in the diagnostic certainty might have less to do with the patients' final diagnosis and more with the rheumatologists' certainty after performing the test (in this study MSUS). However, the patients with inflammatory

arthritis in general and RA in particular as final diagnosis moved to the higher certainty in post-MSUS evaluation when the classical analysis was performed. For classical analysis, MSUS findings were divided in 4 categories as explained in paper IV. The categorisation was only performed in order to investigate the reliability of MSUS evaluation performed by the ultrasound specialist and also comparison of MSUS finding with the final diagnosis and the number of patients with anti-rheumatic treatment at the end of follow up time. This observation is consistent with the previous study that confirmed validity of MSUS in identification of synovitis and soft tissue inflammation.

- In the vast majority (>95%) of patients, there was agreement between MSUS findings and final diagnosis. Similar results were also obtained when MSUS findings and anti-rheumatic treatment were compared at the end of the follow up time. Cut-off for MSUS positive findings was grade one for definition of positive signs in both B-mode and CDUS according to the scoring system by Ohrnhorf et al [160]. In 5 patients there was disagreement between MSUS findings and final diagnosis. Two patients with sign of synovitis in MSUS achieved no final diagnosis of inflammatory arthritis and 3 patients without any sign of inflammation in MSUS were diagnosed as having UIA. Follow-up of these 5 patients showed that 3 patients without any MSUS sign of inflammation had no obvious clinical arthritis and no anti-rheumatic therapy neither at the last follow up visit. So MSUS findings could be trusted even more in these cases. The main MSUS finding in 2 patients who were referred back was sign of inflammation in one wrist and one of them also had increased acute phase reactant. Our rheumatologist's assessment in these 2 patients disregarded these findings.
- Increase in diagnostic certainty using MSUS was observed in both ACPA/RF positive and negative patients. This is not consistent with a previous study by Pratt et al. In that study seropositivity had an excellent discriminatory ability and addition of MSUS did not improve more predictive accuracy [140]. However there are some main structural differences between our study and that study. One key difference between the two studies is the number of scanned joints which was 16 in that study and at least 26 in our study. We performed MSUS of the wrist in 3 positions as described in paper IV while scanning of the wrist was not performed at all in that study. Another difference here is that we had a prospective design and our focus was on whether MSUS could influence and increase the diagnostic certainty during the rheumatologic investigation.

- MSUS examination of the hands and feet was performed in the whole group irrespective of symptoms reported by the patients. Moreover, any symptomatic joint was also scanned by MSUS. It is one of the main differences between this paper and study by Matsos et al. As previously shown, in RA patients with asymptomatic joints and normal clinical examination, modern imaging technique including MSUS has shown subclinical synovitis in a large proportion of patients [141]. This was also the case in a certain number of our patients in paper IV.

Based on these findings, routine MSUS examination of the hands and feet in patients with suspected inflammatory arthritis has great clinical significance at the time of diagnosis.

6 CONCLUSION

- i. RA patients with an initial good response to MTX monotherapy continue to do well clinically during the first two years, but the findings about structural damages in significant proportion of these patients suggest that MTX monotherapy might not be the perfect initial therapy for all early RA patients.
- ii. Monitoring of radiographic response in early RA patients with good clinical response to the first DMARD therapy seems to be an important complement to the clinical assessment.
- iii. Integrating MSUS into clinical practice and possibly extended use of MRI to detect subclinical synovitis in early RA patients should be considered more often in the future.
- iv. DXR-technique may have a role in predicting radiographic outcome in early RA patients but further studies are needed.
- v. In RA patients, subjective and objective clinical variables (e.g. smoking status, erosions and acute phase reactant) at the time of diagnosis should be considered more in order to predict radiographic outcome and accordingly to decide the type of treatment.
- vi. In patients with suspected inflammatory arthritis, the utility of MSUS is most impressive when diagnostic uncertainty is maximal. Accordingly, by increasing diagnostic certainty patients will be prescribed anti-rheumatic therapy with more certainty.
- vii. Musculoskeletal ultrasound screening of patients with suspected inflammatory arthritis greatly increases the diagnostic certainty when added to routine clinical and laboratory examination.

7 FUTURE PLANS

- To study 5 and 10 years clinical and radiographic outcomes of MTX responders patients in the SWEFOT population. Since this group of patients have been followed based on clinical routine, there is risk for many missing data specially radiographic data. Maybe one of the interesting point to be studied is changes in functional status measured by HAQ disability index in the group of patients with radiographic progression since we did not observed any signifanct difference between progressors and non-progressor regarding decrease in HAQ after 2 years. Another point to be studied may be change of ART during the time in the progressors vs. non-progressor.
- To study the relationship between RA disease activity measured by Doppler quantification technique at the baseline and the subsequent clinical response (EULAR response) to anti-rheumatic treatment during 12 months.
- To compare the RA disease activity measured by Doppler quantification technique with conventional clinical methods and semi- quantitative Doppler assessment. Additionally, to define different grades of semi-quantitative ultrasound Doppler score with doppler quantifiation technique. The interestning question here is that in defferent grades of semi-quantitative ultrasound Doppler score, how many Doppler pixels can be indicated and if Doppler quatification technique verify semi-quantitative ultrasound Doppler score.
- To study the clinical utility of flouresence Optical Imaging (FOI) in patients with early inflammatory arthritis and compare results to musculoskeletal ultrasound findings at the same time.
- Identification of early RA patients with higher risk for radiographic progression according to the risk matrix model and combine the result with musculoskeletal ultrasound finding at the time of diagnosis. The main question here is whether the grade of inflammation measured by Doppler ultrasound, together with other clinical variables can predict radiographic progression in the risk matrix (Ongoing collecting of data in the NORD-STAR trial).

- To determine how different degrees of disease activity, measured by ultrasound semi-quantitative score in B-mode and CDUS, at baseline and at 12 weeks follow-up correlate with clinical response and radiographic progression at 6 or 12 months in patients with early RA who receive 4 different anti rheumatic treatments: MTX in combination with 1- SSZ and GCs with tapering; 2- Certolizumab; 3- Abatacept; 4- Tocilizumab (Ongoing collecting of data in the NORD-STAR trial).

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