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Extra-articular manifestations in rheumatoid arthritis with special focus on osteoporosis

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DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Medicine at Lund University to be publicly defended on 31st of January 2025 at 09.00 in Agardhsalen, Clinical Research Centre, Jan Waldenströms gata 35, Skånes Universitetssjukhus Malmö

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Study II and IV were based on the Malmö early RA register (N=233, symptom duration <12 months, recruited 1995-2005). Patients were examined according to a structured protocol including dual-energy X-ray absorptiometry (DXA) over 10 years. Mean Z-scores over the study period and change in Z-scores were estimated and the impact of baseline characteristics on the mean Z-scores over 10 years was analysed. Fracture data were retrieved as in study III and the fracture incidence compared to that in matched controls.

Results and conclusions: Patients treated with TNF inhibitors were at a slightly increased risk of developing severe ExRA (age- and sex adjusted hazard ratio 1.21 (95% confidence interval 1.02–1.43)). This may partially be explained by residual confounding by indication because of higher disease activity in this group of patients. Rheumatoid factor-positive patients with disabling disease of long duration were more likely to develop severe ExRA.

Men with early RA had reduced femoral neck BMD at diagnosis compared with healthy men of the same age, with a further significant but marginal decline during the first 5 years. Lumbar spine BMD Z-scores were not reduced in men or women with early RA. Both men and women with RA had increased risk of fractures compared with the general population. Men with established disease had particularly high risk of hip fractures. BMD Z-scores in the femoral neck and spine were significantly associated with the risk of fractures in RA patients.

Key words: Rheumatiod Arthritis, Extra-articular manifestation, Osteoporosis, Fractures

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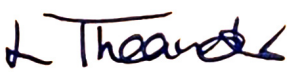
Signature  Date 2025-12-10

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The more you know,
the more you know
you don't know

Derived from Greek philosophical considerations about
the paradox of knowledge

Table of Contents

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Populärvetenskaplig sammanfattning

Reumatoid artrit (som förkortas RA), eller ledgångsreumatism som det också kallas, drabbar inte bara leder utan kan leda till besvär och sjukdom i andra delar av kroppen. Ibland kallar vi det extra-artikulär RA (i texten nedan förkortat som ExRA, extra-artikulär = utanför lederna) men ibland är det besvär som kan drabba alla där RA patienter har högre risk, t.ex. benskörhet och benbrott. I min avhandling har jag undersökt hur stor risken för just ExRA, benskörhet och benbrott är hos patienter med ledgångsreumatism i Malmö. Jag har också försökt identifiera vad som gör att en patient har extra hög risk för detta, och vad vi som doktorer ska vara uppmärksamma på när vi träffar en patient för att, om möjligt, förebygga dessa tillstånd.

Mitt första arbete handlar om det som vi kallar för ExRA manifestationer. ExRA kan vara inflammation i njurar, nerver, ögon men också i delar av hjärtat eller lungorna. När jag påbörjade min forskning fanns det en farhåga att en relativt ny och mycket välfungerande läkemedelsgrupp mot ledgångsreumatism kallad TNF-hämmare skulle öka risken för ExRA, speciellt risken för en fruktad form som ger tilltagande ärrbildning i lungorna: lungfibros. I mitt arbete försökte jag ta reda på om så var fallet. Mina resultat visade att ExRA och däribland lungfibros var ovanliga både hos patienter som behandlades och patienter som inte behandlades med TNF-hämmare. De som stod på TNF-hämmare hade något ökad risk för ExRA, men eftersom man endast behöver TNF-hämmare vid svår ledgångsreumatism och svår ledgångsreumatism i sig ökar risken för ExRA, var vår teori att det var den svårare ledgångsreumatismen som låg bakom den högre risken snarare än läkemedlet. Vår slutsats var att det är låg risk för ExRA under behandling med TNF-hämmare.

I kommande arbeten undersökte jag risken för benskörhet och frakturer hos RA-patienter. Jag fann att risken för benskörhet är hög hos patienter med RA redan vid insjuknandet. I förhållande till friska individer var risken för benskörhet speciellt hög hos män, medan bentätheten hos kvinnor med RA var någorlunda jämförbar med den hos friska kvinnor (där den generella risken för benskörhet dock är högre än hos friska män). Resultaten visade också att kvinnorna fick mer frakturförebyggande behandling än män. Jämfört med jämnåriga kontrollpersoner var risken för att drabbas av benbrott tydligt högre både hos män och kvinnor med RA. Benskörhet brukar ses som en av de främsta riskfaktorerna för benbrott. Att kvinnor med RA, som enligt mina resultat hade jämförbar benmassa med friska kvinnor, ändå hade högre risk för frakturer fick mig att fundera på vilka faktorer utöver låg benmassa som gör att kvinnor med RA bryter sina ben lättare än friska kvinnor. Finns det faktorer som behöver uppmärksammas mer av oss läkare? Precis som hos friska individer ökade risken för benbrott med åldern. Utöver det ökade risken för benbrott med tiden en patient hade haft sin sjukdom och ju mer sjukdomen hade påverkat patientens funktion i dennes dagliga aktiviteter. Hög bentäthet vid undersökning av benmassan minskade som väntat risken för benbrott. Detta är sedan tidigare kända riskfaktorer och mina studier har därmed inte riktigt besvarat frågan om vad vi inom vården kan göra mer. Det finns dock gott om teorier kring detta och jag har sammanfattat en del av dessa i avhandlingens bakgrundskapitel för att kunna ställa dem i relation till mina resultat.

List of Papers

Paper I

Theander L, Nyhäll-Wåhlin BM, Nilsson JÅ, Willim M, Jacobsson LTH, Petersson IF and Turesson C. Severe extraarticular manifestations in a community-based cohort of patients with rheumatoid arthritis: risk factors and incidence in relation to treatment with tumor necrosis factor inhibitors. *J Rheumatol* 2017;44:981-987. doi: 10.3899/jrheum.161103.

Paper II

Theander L, Willim M, Nilsson JÅ, Karlsson M, Åkesson KE, Jacobsson LTH and Turesson C. Changes in bone mineral density over 10 years in patients with early rheumatoid arthritis. *RMD Open* 2020;6:e001142. doi: 10.1136/rmdopen-2019-001142.

Paper III

Theander L, Jacobsson LTH and Turesson C. Osteoporosis-related fractures in men and women with established and early rheumatoid arthritis: predictors and risk compared with the general population. *BMC Rheumatol* 2023Sep8;7(1):28. doi: 10.1186/s41927-023-00354-7.

Paper IV

Theander L, Sharma A, Karlsson MK, Åkesson KE, Jacobsson LTH and Turesson C. Risk and predictors of fractures in early rheumatoid arthritis - A long term follow up study of an inception cohort. *Semin Arthritis Rheum.* 2024 Oct;68:152497. doi: 10.1016/j.semarthrit.2024.152497.

Author's contribution to the papers

Paper I

I performed a major part of the data collection, performed the statistical analyses with help from our statistician and wrote the first draft of the manuscript.

Paper II

The study was designed in collaboration with all coauthors. I participated in the data collection, performed the statistical analyses and wrote the first draft of the manuscript.

Paper III

The study was designed in collaboration with all coauthors. I was involved in the retrievement of data, performed the major part of the organization of data for statistical analysis, performed the statistical analyses and wrote the first draft of the manuscript.

Paper IV

Together with my supervisor I designed the study and I participated in the data collection. I performed a major part of the organization of data for statistical analysis and performed the statistical analyses. I wrote the first draft of the manuscript.

Abbreviations

ACPA	Anti-Citrullinated Protein Antibody
ACR	American College of Rheumatology
Anti-CCP	Anti-Cyclic Citrullinated Protein
bDMARDs	Biologic DMARDs
BMC	Bone Mineral Content
BMD	Bone Mineral Density
BMI	Body Mass Index
CCI	Charlston Comorbidity Index
CDAI	Clinical Disease Activity Index
CI	Confidence Interval
CRP	C-reactive Protein
csDMARDs	Conventional synthetic DMARDs
DAS28	Disease Activity Score 28
DKK1	Dickkopf-1
DMARD	Disease-modifying Antirheumatic Drug
DXA	Dual-energy X-ray Absorptiometry
ESR	Erythrocyte Sedimentation Rate
EULAR	European League Against Rheumatism
ExRA	Extra-articular RA
FRAX	Fracture Risk Assessment Tool
HAQ	Health Assessment Questionnaire Disability Index
HLA	Human Leukocyte Antigen
HR	Hazard Ratio
HRpQCT	High Resolution peripheral Quantitative Computed Tomography
HRT	Hormone Replacement Therapy
ICD	International Classification of Disease
IL	Interleukin
ILD	Interstitial Lung Disease

IMF	Index of Muscle Function
IQR	Interquartile Range
LSC	Least Significant Change
MHC	Major Histocompatibility Complex
MTX	Methotrexate
PE	Precision Error
PYR	Person Years at Risk
QUS	Quantitative Ultrasound
RA	Rheumatoid Arthritis
RANK	Receptor Activator for Nuclear factor Kappa b
RANKL	Receptor Activator for Nuclear factor Kappa b Ligand
SD	Standard Deviation
SDAI	Simplified Disease Activity Index
SHS	Sharp/van der Heijde Score
SRQ	Swedish Rheumatology Quality Register
SSATG	South Sweden Arthritis Treatment Group
TBS	Trabecular Bone Score
TNF-α	Tumour Necrosis Factor α
VAS	Visual Analogue Scale
VFA	Vertebral Fracture Assessment
WHO	World Health Organization

Introduction

Rheumatoid Arthritis

Epidemiology and predictors

Rheumatoid arthritis (RA) is a chronic autoimmune disease with symmetrical synovitis and systemic inflammation, leading not only to joint pain and deformation, but also to many extra-articular comorbidities including specific extra-articular organ manifestations, osteoporosis and fragility fractures, as well as cardiovascular disease and preterm mortality (1-3). The prevalence of RA is estimated to about 0.5-1% in western populations, with a peak incidence around the 5th decade of life and with incidences about 2-3 times higher in women than men (2). RA is a heterogenic disease with apparent differences in disease course. It is typically divided into seropositive and seronegative disease, based on the presence of autoantibodies (to date, rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA)) or not, and patients with autoantibodies are at higher risk of a worse disease outcome (1). The cause of RA has been and is profoundly studied and although a great deal of knowledge has come out of this research, the puzzle of the pathogenesis of RA is not yet completed. More is known about seropositive disease where associations between both genetic and environmental risk factors are stronger. First-degree relatives of RA patients are at increased risk of developing RA but, although the human leukocyte antigen (HLA)-DRB1 shared epitope (a key-sequence of amino acids on the β-chain of the major histocompatibility complex (MHC) class II molecule) is recognized as a strong genetic factor (especially in ACPA-positive disease), many other genetic mechanisms have been proposed to influence the risk of developing RA (4). The strongest environmental risk factor for RA is smoking, which affects the risk of development of disease but also increases the risk of severe disease outcome, systemic comorbidities and impaired treatment response (2, 5). Other factors include low socioeconomic status, hormonal influence, obesity, and changes in the lung, gut, and oral microbiome (1, 2).

Pathogenesis

For many years scientists have been searching for the pathogenic mechanisms leading to development of RA. The results of this research indicate that changes in the immune system occur several to many years before clinical signs of RA are

apparent. This hypothesis is mainly based on the detection of circulating antibodies to post-translationally modified self-proteins, especially ACPAs, in the pre-symptomatic phase of RA. Due to early findings of such autoantibodies and associated immunological changes in mucosal sites (oral, intestinal and lung tissue), it is further hypothesized that the very first changes of the immune system leading to development of RA might begin at these sites. Such changes could hypothetically be induced by for instance smoking, periodontitis or altered mucosal microbiome in the intestine (6-8). In some, but not all individuals with ACPAs, eventually ACPAs increase in concentration and epitope diversity. This seems to happen predominantly in genetically susceptible individuals. Alterations in T-cell composition and function has been demonstrated in ACPA-positive patients before symptom start. This has raised the theory of CD4+ T cells recognising the citrullinated and other post-translationally modified proteins presented by MHC class II molecules and through interaction with B-cells help stimulating antibody maturation, activation of macrophages and production of proinflammatory cytokines (6-12). It is still unclear what triggers the shift from the early systemic autoimmune process to the manifest inflammatory processes in joints featuring rheumatoid arthritis (6-8).

For still unknown reasons, cells of the innate and adaptive immune system infiltrate the synovial membrane, and signs of inflammation become visible. Early changes in the synovium include proliferation and activation of the fibroblast like synoviocytes, deposition of extracellular matrix, and a thickened synovial membrane with increased vascularization and formation of lymphoid structures. Although the distribution of the various inflammatory cells has been shown to be heterogeneous (possibly explaining different clinical phenotypes and treatment response), the inflamed synovia is further characterized by high numbers of activated macrophages and T-cells, but also B-cells, dendritic cells, neutrophils and mast cells. Immune complexes (antibodies bound to antigens) are found at high concentration in the synovial fluid. At the junction of the synovium, cartilage and periarticular bone, the pannus formation results in invasion of activated synovial fibroblasts and macrophages into cartilage, with release of cartilage degrading matrix metalloproteinases, and accumulation of osteoclast precursor cells (12-14). Osteoclasts are responsible for degradation of bone matrix and the subsequent emergence of bone erosions in RA. Osteoclasts not only generate erosions at contact areas between bone and the synovium but are also involved in the periarticular bone loss seen in subchondral bone. Although studies have demonstrated ACPA to be involved in the induction of osteoclast activation (either through binding to citrullinated proteins expressed on the surface of osteoclast precursor cells or through effects derived by ACPA-containing immune complexes directly binding to Fc-receptors of osteoclasts), the cascade of inflammatory cytokines induced by synovitis triggers osteoclast differentiation and activation as well (14, 15). Even though many cytokines are involved in the pathogenesis of RA, the discovery that the blocking of the Tumour Necrosis Factor α (TNF-α) down-regulates many other cytokines, suggested that TNF-α may be somewhat of a key regulator of the inflammatory responses in RA (13). Cytokines are highly abundant in inflamed

joints, but are also elevated in peripheral blood. Such cytokines and other changes in the repertoire of immune cells, but also the circulating antibodies and their tendency to build immune complexes may be part of the explanations of extra-articular symptoms and comorbidities in RA (14, 16).

Diagnosis, assessment of disease activity and other scoring systems used in this thesis

Classification criteria of RA. The diagnosis of RA is based on clinical judgement, but for consistent definitions in clinical research studies, classification criteria are useful. Since 1956, when the American Rheumatism Association first proposed their classification criteria for RA, the criteria have been revised repeatedly. At the time of establishment of the two cohorts of RA patients used in this thesis, the 1987 American College of Rheumatology criteria for RA (17) were the most recent. These criteria included clinical features, laboratory and radiographic results (table 1) and were demonstrated to have 91-94% sensitivity and 89% specificity for RA in analyses of patients with established RA and control subjects with other rheumatic diseases (17). In response to the recognition of the importance of early diagnosis and treatment of RA, updated criteria were published in 2010 (18). These new 2010 ACR/EULAR classification criteria were shown to be more sensitive in recognizing RA soon after the first symptoms, but with, at least in some studies, somewhat lower specificity and with, in some cases, milder disease being classified as RA (19).

Table 1.
The 1987 American College of Rheumatology criteria for RA (17)

Criterion	Definition
1. Morning stiffnes	Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement
2. Arthritis of 3 or more joint areas	At least 3 joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible joint areas are right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints
3. Arthritis of hand joints	Soft tissue swelling or fluid (not bony overgrowth alone) of the specified area observed by a physician. Where 2 areas are specified, involvement must have been simultaneous
4. Symmetric swelling (arthritis)	Simultaneous involvement of the same joint areas (as defined in I) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry)
5. Rheumatoid nodules	Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxtaarticular regions, observed by a physician
6. Serum rheumatoid factor	Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in 4% of normal control subjects
7. Radiographic changes of rheumatoid arthritis	Radiographic changes typical of rheumatoid arthritis on posteroanterior hand and wrist radiographs which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify)

Requirements for RA diagnosis: ≥ 4 of the above 7 criteria. Criteria 1-4 must have been present for at least 6 weeks.
PIPs: proximal interphalangeal joints; MCPs: metacarpophalangeal joints; MTPs: metatarsophalangeal joints.

The disease activity score 28 (DAS28). To evaluate disease outcome, response to treatment and prognosis and because symptoms and signs of RA may include not just joint pain, joint stiffness, joint swelling or functional impairment related to arthritis, but also systemic symptoms and inflammation, in the 1980's efforts were made to find a simple but multivariable scoring system for disease activity in RA. Eventually several scoring systems were developed, with some similarities but also differences. The disease activity score 28 (DAS28), which is used in two of the studies included in this thesis evaluates tenderness and swelling of 28 joints (shoulders, elbows, wrists, metacarpophalangeal joints, proximal interphalangeal joints, and knees), level of erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) and patients' assessment of general health with a visual analogue scale (VAS). A formula is used to calculate the score (0-9.4) and there are established cutoffs for remission and low-high disease activity (table 2). DAS28 has been shown to correlate with functional capacity and progression of disease, and is thoroughly validated, but also criticized for being unprecise in patients with low disease activity, with allowance for swollen joints in remission, and for putting too much weight on the laboratory tests in the formula deciding the score (20, 21). In order to facilitate use in clinical practice, avoiding the somewhat complicated formula and the weighting of the included parameters, the Simplified Disease Activity Index (SDAI) was developed. SDAI is simply the numerical sum of values for tender and swollen joint counts (using the same 28 joint assessment), patients' and evaluators' global assessments (scored 0-10 cm by VAS) and CRP. Because of discussions of the value of CRP in disease activity assessment, a further simplified Clinical Disease Activity Index (CDAI) was created excluding CRP from the calculation. Although ESR and CRP may measure processes unrelated to RA, they may also reflect extra-articular inflammation which may then be missed by CDAI (21, 22).

Table 2.
DAS-28 cutoffs

Cutoff	Definition
< 2.6	RA in remission
≤ 3.2	Low disease activity
> 3.2 to 5.1	Moderate disease activity
> 5.1	High disease activity

The Health Assessment Questionnaire Disability Index (HAQ) was developed in 1978 by James F. Fries and colleagues at the Stanford University. It was constructed to measure disability over the last week through a total of 20 questions divided into eight categories of function in daily life: dressing, arising, eating, walking, hygiene, reach, grip and activities. Every question was scored from 0-3 (0 = no difficulty, 1 = with some difficulty, 2 = with much difficulty or with the help of equipment/assistance, 3 = unable to do) and the highest score of the questions included in every category determined the score for the category. The score of each

category were summarized and the average score of the 8 categories gave the final score. HAQ has been validated in numerous studies and is widely used in rheumatoid arthritis (23). In the studies included in this thesis the Swedish version of HAQ was used (figure 1) (24). In early disease, impaired function is often related to current inflammation and disease activity, whereas in established disease, the level of disability is influenced by irreversible joint damage to a greater extent (25). However, there is some association between erosive joint damage and higher HAQ-scores already in early RA (26). A high HAQ has been shown to predict a range of comorbidities in RA such as cardiovascular disease (27), fractures (28), other extra-articular manifestations (29) and mortality (30), although when assessing very early in disease it might be less accurate as a predictor (31).

Funktionsfrågeformulär (HAQ) Pers nr:

Svensk Reumatologis Kvalitetsregister, SRQ

Namn:

090224

Sätt ett kryss i den ruta som bäst beskriver Din situation under den senaste veckan	Utan svårig-het	Med viss svårig-het	Mycket svårt	Använder hjälpmedel	Hjälp av annan person	Kan inte alls	
Kan du tvätta håret?	☐	☐	☐	☐	☐	☐	
Kan du klä på dig, inklusive knyta skoband och knäppa knappar?	☐	☐	☐	☐	☐	☐	
Kan du resa dig från en stol som saknar armstöd?	☐	☐	☐	☐	☐	☐	
Kan du komma i och ur sängen?	☐	☐	☐	☐	☐	☐	
Kan du skära kött?	☐	☐	☐	☐	☐	☐	
Kan du laga din egen mat?	☐	☐	☐	☐	☐	☐	
Kan du lyfta ett fullt glas till munnen?	☐	☐	☐	☐	☐	☐	
Kan du gå ned för fem trappsteg?	☐	☐	☐	☐	☐	☐	
Kan du gå utomhus på plan mark?	☐	☐	☐	☐	☐	☐	
Kan du bada i badkar?	☐	☐	☐	☐	☐	☐	
Kan du sätta dig på och resa dig från en toalettstol?	☐	☐	☐	☐	☐	☐	
Kan du tvätta och torka dig överallt?	☐	☐	☐	☐	☐	☐	
Kan du ta ned ett 2kg paket med t.ex. socker från en hylla i huvudhöjd?	☐	☐	☐	☐	☐	☐	
Kan du böja dig ned och ta upp kläder från golvet?	☐	☐	☐	☐	☐	☐	
Kan du öppna bildörrar?	☐	☐	☐	☐	☐	☐	
Kan du öppna burkar med skruvlock, som varit öppnade förut?	☐	☐	☐	☐	☐	☐	
Kan du vrida på en vanlig vattenkran?	☐	☐	☐	☐	☐	☐	
Kan du dammsuga?	☐	☐	☐	☐	☐	☐	
Kan du klara dina inköp till hushållet?	☐	☐	☐	☐	☐	☐	
Kan du komma i och ur en bil?	☐	☐	☐	☐	☐	☐	

/ / /

Läkaren summerar och ringar in i följande tabell:

Summa:	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
HAQ-värde:	0,0	0,13	0,25	0,38	0,5	0,63	0,75	0,88	1,0	1,13	1,25	1,38	1,5

13	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**
1,63	1,75	1,88	2,0	2,13	2,25	2,38	2,5	2,63	2,75	2,88	3,0

Figure 1.
The Swedish version of the Health Assessment Questionnaire. The exact form used in the studies included in this thesis, based on (24).

Visual Analogue Scales (VAS) are often used to evaluate pain or general health. Patients are asked to mark their experience of pain or general health on a 100-mm horizontal line with the best and worst outcome in each end of the line, and the score is determined by the amount of mm from the left end. In the current studies the patients have been asked to evaluate their symptoms of the last week.

The Index of muscle function (IMF) is an array of functional performance tests, consisting of 13 tests evaluating 1. general functional ability (working as a pretest deciding if the patient is suitable for the rest of the test), 2. muscle strength, 3. endurance and 4. balance/coordination, aiming to measure muscle function in the lower extremities. The IMF was originally designed for patients with RA with low to moderate disease activity. Its' applicability is limited if a patient has an insufficient range of motion or extreme joint pain (32). It was validated in various methodological studies and, later, also in the patients included in the early RA cohort investigated in this thesis, where it was shown to correlate with results of HAQ and associated with synovitis in the lower extremities (33).

The Charlson Comorbidity Index (CCI) was developed in 1987 to assess prognosis and long-term mortality in different patient populations and has been used widely to assess comorbidity in clinical research. The CCI consists of 19 medical conditions which have been given different weights on the basis of the adjusted risk of 1-year mortality in the patients in the original cohort on which the index was based. The score of the CCI is the sum of the weights and a higher score predicts a greater mortality risk (34, 35).

Treatment – and change of management of RA over time

During the last decades, treatment of RA has changed dramatically with the introduction of a range of new pharmacological alternatives and with the acknowledgement of the importance of treatment to remission at early stages of disease. During the first half of the 20th century the treatment of RA was limited to the mere symptom relieving non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin and later to glucocorticosteroids. The patients with the most severe disease may have been treated with gold salts which were invented already in the 1920's. From the 1950's and onwards, slowly new antirheumatic drugs emerged (figure 2). Antimalarials came into widespread use during the 1950-1960's and Sulfasalazine, Azathioprine and Cyclophosphamide in the 1970's (36). Still the treatment had a pyramid approach meaning most patients were settled on analgesics, NSAIDs, rest or physiotherapy and decisions on addition of more potent therapy taken gradually. The approval of Methotrexate for treatment of RA in 1988 and the parallel idea of a treat-to-target approach early in disease were milestones in the history of RA treatment. The treatment target advanced from symptom release to reduction in disease activity and arrest of the progression of structural joint damage (37). Despite rising numbers of patients receiving early Disease-modifying Antirheumatic Drug (DMARD) treatment and obvious improvements in the RA therapy, many patients did and still do not reach RA remission with Methotrexate, not even with co-

treatment with glucocorticoids. Combinations of different so called conventional synthetic DMARDs (csDMARDs) remains a second line alternative. However, in 1998, the first biologic DMARDs, the TNF-inhibitors, were approved, further improving the outcomes of RA treatment (38). As seen in the timeline below many more biologics (B-cell, T-cell, Il-1 and IL-6 receptor inhibitors) and targeted synthetic therapies have been developed since then, enriching the therapeutic palette of RA (36, 37). The new therapeutic opportunities have had a steroid sparing effect in RA patients. Nonetheless glucocorticosteroids are still widely used (38) for a rapid reduction of inflammation and symptoms in the early phases and for treating flares and insufficient treatment response in established RA. Despite improved treatment opportunities there is a group of patients with unsatisfactory treatment outcomes and persistent high disease activity (39).

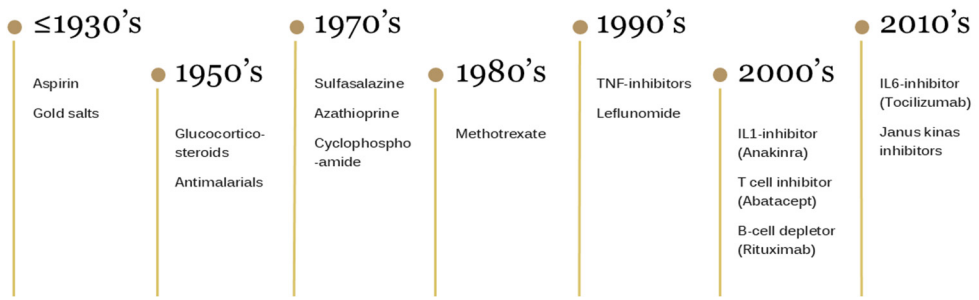

Figure 2.
Timeline of the approval of the antirheumatic drugs.

Extra-articular Manifestations

Epidemiology, risk factors and mortality

There is no fully acknowledged definition of extra-articular RA (ExRA). Some definitions widely include comorbidities associated with RA, such as cardiovascular disease, osteoporosis and fractures, and some (as done in the first study of this thesis) use a more distinct definition of manifestations more closely related to autoimmunity and RA. ExRA defined this way can be divided into severe and less severe manifestations, where the ExRA manifestations presented in table 3 (40) represent severe manifestations while rheumatoid nodules and the keratoconjunctivitis sicca syndrome are typical examples of less severe ExRA. Due to the lack of consensus on how to classify ExRA, due to the differences in populations studied (where some studies include patients treated at university clinics whereas other studies are based on broad population-based cohorts) and perhaps also due to the substantial subclinical proportion of tissue abnormalities (41-44)

making screening and detection methods influence incidence rates, there is a wide variation in the reported incidence of ExRA. In previous studies on severe ExRA, using criteria similar to those in table 3, incidence rates of 0.8-2.92/100 person years at risk have been reported, where the higher numbers were reported in a cohort of patients explicitly referred to the hospital due to special needs related to the severeness of their RA (45-47). Although the clinical impression is that ExRA manifestations have been seen less frequently over time (40, 43), epidemiological studies have presented conflicting results. Some studies have indicated a decline in ExRA overall, with a shift in the early 2000's (48-51), whereas some have not (52, 53). However, most report decline in certain (subcutaneous rheumatoid nodules (49), vasculitis (50-52), Felty syndrome and pericarditis (48)) but not in other (e.g. rheumatic lung disease (48)) ExRA manifestations. Declining rates of ExRA could be a result of better treatment of RA, but possibly also of lower smoking rates in many countries and decreasing proportions of antibody-positive RA patients (52).

Table 3.
Criteria for severe extra-articular manifestations in RA (40) used in study I

Manifestation	Definition
Pericarditis	Clinical judgement and exudation verified by echocardiography. Other causes improbable, such as tuberculosis or other infection, metastases, primary tumour, postoperative status or other trauma.
Pleuritis	Clinical suspicion and exudation verified by X-ray. Other causes improbable, such as tuberculosis or other infection, metastases, primary tumour, postoperative status or other trauma.
Interstitial lung disease	Clinical symptoms and either vital capacity or carbon monoxide diffusion capacity reduced by 15 % from normal. In addition, either HRCT or a lung biopsy compatible with interstitial lung disease.
Felty's syndrome	Splenomegaly (clinically evident or measured by ultrasound) and neutropenia (<1.8|10^9/L) on two occasions. Other causes improbable, such as drug side effect or infection.
Neuropathy	Clinical judgement and signs of mononeuropathy/polyneuropathy at EMG/ENeG.
Scleritis, episcleritis or retinal vasculitis	Clinical judgement by ophthalmologist.
Glomerulonephritis	Clinical judgement by nephrologist and positive biopsy.
Major cutaneous vasculitis	Diagnostic biopsy or clinical judgement by dermatologist
Vasculitis involving other organs	Clinical judgement by organ specialist and biopsy compatible with vasculitis

HRCT: High resolution computerized tomography; EMG: Electromyography; ENeG: Electroneurography
Adapted from Turesson et al. (40)

Traditionally the risk of severe ExRA has been related to high titres of RF, smoking, carriage of the HLA-DRB1 shared epitope, and longstanding RA with high disease activity (16, 29, 40). Other risk factors such as male sex and the presence of rheumatoid nodules are inconsequently reported and may vary between different ExRA and populations (16, 52). Interstitial lung disease (ILD) might have a different genetic background (16) and is more often associated with the presence of ACPAs (44). Eventually it has been recognised that ExRA can also occur early after diagnosis or even before first symptoms of RA.

Patients with ExRA are at an increased risk of premature mortality compared to RA patients without ExRA (16, 45, 47, 52). This is partly due to a higher risk of cardiovascular disease (45) and infections (16, 40), but also due to the high mortality in patients with ILD (44).

Classification and current understanding of pathogenesis

The severe ExRA manifestations studied in this thesis were chosen in accordance with the criteria proposed by Carl Turesson and Lennart Jacobsson, in 2004, to enable comparison between different studies of severe ExRA. The rational for choosing the specific ExRA included in the criteria was to ensure "the capturing of clinically important extra-articular manifestations in retrospective structured chart reviews" and with a design to 1. "identify manifestations that virtually always come to clinical attention" and 2. "include events for which data for evaluation are likely to be available". The authors emphasize the importance of clinical signs and symptoms to support the diagnosis (40).

These manifestations are heterogeneous at a first glance, and although for the most part, the pathogenesis is not fully understood, there are similarities in the findings of pathogenic patterns in the various ExRA and in the joints. The role of autoantibodies and their associated immune complexes are believed to be important in the pathogenesis of severe ExRA, since many ExRA mainly occur in seropositive patients, where high levels of circulating immune complexes have been found (16). These immune complexes could potentially activate the complement cascade and trigger inflammation outside the joints, for instance in the vessels of various organs (54). Indeed, Happonen et al. found that patients with ExRA had higher plasma levels of soluble terminal complement complexes (the end-product of local or systemic complement activation) than RA controls without ExRA, indicating a higher degree of complement activation in ExRA (55). Rheumatoid vasculitis is considered an immune complex driven inflammation (56), even if the actual immune complex deposits have not yet been demonstrated (but deposits of both immunoglobulins and complement components in both dermal vessels and the vasa nervorum of peripheral nerves have been described (57)). Immune complexes have also been found in pericardial effusion in RA associated pericarditis (42) and in bronchoalveolar lavage fluid of RA patients with ILD but not in RA patients without signs of ILD (58). Immune deposits and fibrinoid necrosis with surrounding

granulomatous inflammation has been found in scleritis (59), and RF-antibodies combined with high levels of pleural SC5b-9 (a late product of activation of the complement system) and low complement C3 and C4 have been demonstrated in pleural effusions, presumably reflecting complement activation in patients with pleuritis (41). In some pleural biopsies, structures resembling pulmonary and subcutaneous rheumatoid nodules have been seen (41), suggesting similar immunological processes.

The presence of ACPA in bronchoalveolar lavage fluid has been demonstrated both in early untreated ACPA-positive RA patients (without ILD) (60) and in patients with established RA-associated ILD (61). In addition, enzymes involved in the citrullination of proteins (peptidylarginine deiminase type 2) were shown to be highly expressed in ILD-lungs, and associated with formations of ectopic germinal centres, consisting of dendritic cells, T cells and B cells, called "inducible bronchus associated lymphoid tissue" (iBALT) (61). Other studies found peribronchiolar lymphoid aggregates with increased presence of CD20+ B cells in RA associated ILD tissue (62), as well as high numbers of CD4+ cells (63). Similar structures were also seen in bronchial biopsies of early RA patients without ILD, as well as signs of increased protein citrullination (60, 64). Thus, ACPAs and local activation of the adaptive immune system in lung tissue of RA patients could have a role in the pathogenesis of ILD. The link between RA-related pulmonary inflammation and the proliferation of fibroblasts/myofibroblasts with accumulation of extracellular matrix resulting in interstitial fibrosis in some but not all RA patients is still not known.

A special subset of CD4+ T-cells lacking the major costimulatory receptor CD28, so called CD4+ CD28 null cells, have been found in higher rates of RA patients with extra-articular involvement (65, 66). These cells are thought to be chronically activated and clonally expanded, and to participate in a maladaptive immune response. Furthermore, some of these cells express CD56 and produce increased levels of cytokines, amongst others IL-2 and TNF-α. Such CD56 expressing cells were shown to be present in lung biopsies of patients with RA-related ILD (67). In concordance with a possible role of altered T-cells, a double gene dose of the DRB1*04 SE is associated with vasculitis and other severe ExRA, which might be an explanation for the decreased T-cell diversity and the clonal expansion of some T-cell lines seen in RA and ExRA (68, 69).

The role of TNF-α in ExRA and relation to TNF-inhibitors

Already in the 1980's studies of various animals proposed a role of TNF-α in the pathogenesis of alveolitis and acute lung injury. Together with IL-1, TNF-α was suggested to trigger vasodilation and expression of adhesion molecules, resulting in accumulation of immune cells in the extracellular matrix (70, 71). It was shown that macrophage secretion of TNF-α could be induced by IgG immune complexes. Later studies on pulmonary fibrosis in animal models have demonstrated both pro- and antifibrotic properties of TNF-α, where overexpression or adding of TNF-α either

has been shown to stimulate inflammation and development of fibrosis or to protect from fibrosis (72). Conversely, $TNF^{-/-}$ knock-out mice suffering from Bleomycin-induced pneumonitis were found to have persistent infiltration of lymphocytes and honeycomb structures in lung tissue with a failure to eliminate inflammatory cells from the bronchoalveolar space compared to $TNF^{+/+}$ mice. Airway treatment with a murine TNF solution promoted clearance of inflammation and restoration of tissue structure in $TNF^{-/-}$ mice, suggesting TNF-α to have a regulatory role in inflammation in murine lungs, although treatment with extra TNF in $TNF^{+/+}$ mice did not accelerate the spontaneous recovery seen in these mice (73). In human RA patients (both with and without subclinical signs of ILD) alveolar macrophages were shown to release significantly higher levels of TNF-α than a control group without RA, indicating overexpression of TNF-α in the lungs of RA patients (58). *In vitro* studies (generally on dermal fibroblasts) have shown mostly anti-fibrotic effects of TNF- α through suppression of the production of collagen and by upregulation of the expression of metalloproteinases which degrade extracellular matrix/fibrotic tissue (72). Finally, a recent study of TNF-α overexpressing mice found that early treatment with TNF-inhibitors reduced interstitial inflammatory infiltrates, alveolar macrophages and perivascular inflammation, preventing progression of lung disease which is normally seen in these mice (74).

After the introduction of TNF-inhibitors case reports of patients suffering from new-onset or worsening of ExRA started to appear (75-80). Especially reports on progression of ILD raised concerns about the safety of TNF-inhibitors in patients with known lung disease. Since patients with severe ExRA were excluded from the controlled trials for evaluation of the efficacy of TNF-inhibitors, there are no randomized studies for the analysis of their effects on ExRA. However, a few cohort studies have been published, where four (one study following RA patients with and without ILD after initiation of TNF-inhibitors, two studies following patients without known ILD comparing anti-TNF treated patients to patients with intensified Methotrexate therapy, and other bDMARDs respectively, and one study comparing rates of new-onset ILD and hospitalisation due to ILD-related complications in patients with different bDMARDs in health insurance databases where all patients had had at least one previous bDMARD) did not find any association between new onset or progression of ILD and treatment with TNF-inhibitors (81-84). In all these studies treatment was based on clinical decision and no randomization was performed. Dixon et al. reported that RA patients with ILD receiving TNF-inhibitors (based on clinical decision) had a comparable mortality rate with patients instead receiving csDMARDs. The cause of death was more often related to ILD in anti-TNF treated patients than in the csDMARDs group, although the authors state several limitations of the study design, such as a selection of certain ILD patients receiving TNF-inhibitors due to the already raised safety concerns about TNF-inhibitors in RA related ILD, unavailability of baseline ILD-severity data and the small number of ILD patients leading to even smaller numbers of deaths (85). There are also case reports of patients stabilizing or improving after initiation of TNF-inhibitors, both for ILD and for other ExRA (86-90). The explanation for this

apparent paradox has not been elucidated, but the conflicting findings of the role of TNF-α in *in vivo* animal studies and *in vitro* studies have given rise to speculations that TNF-α might have different effects in the fibrotic process depending on the setting, where the function of TNF-α could be different in an inflammatory milieu compared to that in tissues in balance or in late stages of fibrosis (72).

Osteoporosis and fractures

Epidemiology

Osteoporosis is characterized by low bone mass and altered bone microarchitecture leading to increased risk of fractures. Although the prevalence in the general population varies widely between study populations, likely related to methodological issues, a metaanalysis based on 343,704 participants from 37 countries around the world estimated the total prevalence of osteoporosis to 19,7% (91). The prevalence in the Swedish population has been estimated to be lower (5,6%) (92), although it increases with age and about 50% of all women and 25% of men will suffer from an osteoporosis related fracture during their lifetime (93). Women and especially postmenopausal women have more osteoporosis and fragility fractures than men, which is a result of the sudden loss of estrogen after menopaus, causing a sudden loss of bone mass. Other risk factors for osteoporosis are high age, family history of osteoporosis or fragility fractures, low body mass index (BMI), smoking, immobility and malnutrition/low calcium intake (94, 95). Conditions like vitamin D deficiency, alcoholism and many chronic diseases and their treatment are associated with osteoporosis (91, 93, 95, 96).

RA is one of the most recognized diseases with high risk of osteoporosis. The prevalence of osteoporosis in RA patients varies greatly in different studies. A recent metaanalysis with a sample size of 227,812 RA patients from 57 studies estimated the prevalence to 27,6%, although numbers varied as much as from 3.7 to 62.2% (97). In previous studies comparing the prevalence of osteoporosis in RA patients and controls, the estimate was almost doubled in patients with RA (98, 99). Erosive disease and worse disability has been associated with higher risk of general osteoporosis in RA (100-104), probably due to longstanding inflammation, leading to molecular changes in bone tissue and, in many patients, to behavioural changes like avoidance of physical activity, but also prolonged treatment with glucocorticosteroids (105). Frequent occurrence of vitamin D deficiency (106-108) and smoking could contribute to the high prevalence of osteoporosis in RA (109-112). On the other hand, loss of bone mass has been apparent in many patients already early in disease (112-115), especially in autoantibody-positive patients (116-118). During later years, studies have found that patients treated to remission or low disease activity, combined with anti-osteoporotic treatment, can preserve their bone mineral density better than those with higher disease activity (104, 116,

119-121). So far, the improved treatment opportunities have not been shown to normalize fracture rates in RA (28).

Typical fragility fractures, associated with osteoporosis, are vertebral fractures, hip fractures and distal forearm fractures. Proximal humeral fractures and pelvic fractures are often included in the definition. Fractures, especially hip fractures, bring about substantial loss of quality of life, with pain, walking difficulties, loss of independence and even premature mortality (93, 122). Apart from the far-reaching consequences for the patients, fractures also entail high costs for the society (93, 122). Except osteoporosis, the tendency of falling is a major risk factor for fractures (122, 123). Impaired eyesight, postural hypotension, dizziness, poor balance and sarcopenia are in turn risk factors for falls, as well as treatment with many medicines with such side effects (123-126). RA patients are at a high risk of falling (127) and stiffness, pain and swollen joints in the lower extremities add up to the general risk factors for falls (124, 128). Not surprisingly with increased risk of both osteoporosis and falling, meta-analyses of patients with RA have found an about 1.5-2 fold higher risk of experiencing a fracture compared to the general population (28, 129, 130). The incidence of fractures in RA populations was estimated to 3.3 per 100 person-years of risk, although numbers varied from 0.7 to 8.6 per 100 person-years of risk (28).

Bone physiology – a background for understanding mechanisms of osteoporosis

The skeleton consists of trabecular and cortical bone, where the cortical bone is dense and compact, constituting about 80% of skeletal mass. Trabecular bone is encapsulated in cortical bone, filled with bone marrow and fat and found dominantly in weight-bearing parts of the skeleton such as the vertebrae but also in end parts of long bones, where it helps transfer mechanical load from the articular surfaces to the cortical bone. In general, bone turnover is described to be higher in trabecular bone, which thanks to its' large surface area is more metabolically active than cortical bone. This is seen as an explanation for the higher susceptibility to processes leading to osteoporosis (although this is a simplified view since bone loss is not isolated in either trabecular or cortical bone, and fracture risk depends on the quality of both).

Bone is a dynamic tissue with continuously ongoing degradation and reformation. This is called the bone remodelling cycle and is a complex process, which is not yet fully understood. Bone consists mainly of mineralized extracellular matrix (collagen and minerals) and cells derived from two different cell lines: mesenchymal stem cells (fibroblast like cells), which differentiate into osteoblasts, osteocytes and bone lining cells, and osteoclasts, which are derived from hemopoietic progenitor cells and belong to the same lineage as macrophages. Osteoblasts are responsible for bone formation and osteoclasts for bone resorption. Together they maintain the bone remodelling cycle, where bone is constantly renewed and adapted to strain (local microdamage) and regulated by systemic processes, such as ageing, hormonal

influence, and inflammation. Osteocytes, which account for >90% of bone cells, have an important role in this maintenance of balance, reacting to environmental changes and communicating with and regulating osteoblasts and osteoclasts. The two major and best-known signalling pathways for remaining balance between bone resorption and formation are called the Wnt/β-catenin pathway for osteoblast activation and Receptor Activator for Nuclear factor Kappa b (RANK)/RANK-Ligand pathway for osteoclast function. β-catenin is an intracellular glycoprotein that, if Wnts (secreted growth factor proteins with many functions in our bodies) are present and bind to receptors of bone forming cell surfaces, activates gene transcription necessary for osteoblast proliferation and differentiation. Wnts and other components of this pathway are further regulated in complex ways, where the two Wnt-inhibitors Sclerostin and Dickkopf-1 (DKK-1), secreted for instance by osteocytes in response to mechanical load, are of special interest since they are both potential therapeutic targets for anti-resorptive treatments. RANK is a receptor at the surface of bone degrading cells that needs to be activated by the RANK-Ligand (RANKL) for osteoclast differentiation, activation and survival. RANKL is expressed in both soluble and membrane-bound forms by osteocytes and osteoblasts in response to change in load, microdamage in bone tissue, cytokines (for instance IL1, IL6 and TNF-α), and hormones. RANKL is also expressed by various immune cells and fibroblasts (131-133).

Factors driving osteoporosis - overall and in RA

Osteoporosis is, as mentioned, characterized by low bone mass and altered bone microarchitecture leading to increased risk of fractures. Aging and estrogen deficiency are causes of primary osteoporosis, whereas inflammation and side effects of pharmaceutical treatment, e.g. high doses of glucocorticoids can result in secondary osteoporosis, as seen in RA. The pathogenesis of osteoporosis seems to differ somewhat with the cause of bone loss, but has in common the imbalance between bone formation and bone resorption (131). Although low bone mineral density (BMD), measured by dual-energy X-ray absorptiometry (DXA), is a common way of defining osteoporosis and is a well-known risk factor for fractures, a discrepancy between BMD levels and fracture risk is often described (95, 134-136). This is sometimes attributed to low bone quality, i.e. effects on microscopic or even sub-microscopic architecture of bone (bone structure, composition of minerals and collagen, and accumulation of microdamage amongst others), not reflected by changes in BMD (132). Covarying risk factors for osteoporosis and fractures, such as loss of muscle mass, disability and other comorbidities in relation to aging, probably contribute to this discrepancy since fracture risk assessment is complex and dependent on many factors (135) which can probably increase fracture risk also in individuals with normal BMD.

Osteoporosis in RA has many possible explanations, such as high abundance of known risk factors in patients with RA, but also circumstances related to autoantibodies and increased levels of many cytokines. ACPA, and perhaps other

posttranslationally modified protein-antibodies, are thought to have an impact on bone tissue early in disease or even before signs of arthritis are apparent. The underlying mechanism seems to be partly a direct effect on bone degrading cells, where the differentiation and activation of osteoclasts is stimulated, but also an indirect effect via the formation of immune complexes which then activate immune cells (like macrophages) and the production of proinflammatory cytokines. High levels of cytokines like TNF-α, IL1, IL6 and IL17 induce upregulation of the RANK-RANKL system since a range of cells including osteoblasts, fibroblasts, Th17-lymphocytes and B-lymphocytes express high levels of RANKL in response to inflammation. In addition, osteoclasts upregulate their expression of RANK – thereby promoting bone resorption. The Wnt/β-catenin pathway is also thought to be affected in RA since the inhibitory factors Sclerostin and DKK-1 are increased, leading to reduced bone formation (3, 137). Yet, this is a simplified description of the mechanisms of bone loss in RA, which are complex, incompletely clarified and with some cytokines found to have dual roles, leading to difficulties in evaluating their full effects on bone health (138). Lately a range of studies have examined the effects of anti-rheumatic treatment on general osteoporosis in RA, with some studies indicating benefits, but also conflicting results (139-141). According to the mechanisms described above and the prevention of articular bone erosions which is achieved with many modern DMARDs, positive effects on systemic bone loss could be expected, but so far it has been difficult to separate the effects of reduced inflammation from actual bone strengthening effects of DMARDs, and systematic reviews/meta-analyses have not been able to conclude significant positive effects on general osteoporosis or fracture risk (142-144).

Patients with RA are frequently prescribed glucocorticoids, a known risk factor for osteoporosis and fractures. Although bone loss (and increased fracture risk) due to corticosteroids seem to vary with individual susceptibility, there seems to be an early phase within months after treatment start, with a high degree of bone loss due to a combination of an increase in bone resorption and a decrease in bone formation. This is followed by a later phase with a slower rate of bone loss, and with a predominance of reduced bone formation. This pattern is probably influenced by tapered doses of corticosteroids over time, but also by the reduced inflammation resulting from treatment and changed interactions between osteocytes, osteoblasts and osteoclasts over time. Although the effects on bone health are dose dependent, low doses seem to be enough to increase fracture risk (134, 145, 146). On the other hand, in RA the positive effects with reduced inflammation may outweigh the harm of glucocorticosteroids, at least in low doses and in combination with anti-osteoporotic treatment (104, 119, 147).

Diagnosis of osteoporosis and assessment of fracture risk

Until today, the most frequently used method for diagnosing osteoporosis is the measuring of the bone mineral density by DXA, where the World Health Organisation (WHO) back in 1994 defined osteoporosis as a T-score < -2.5 at the

femoral neck or spine, which means that the BMD value is 2.5 standard deviations (SD) below the average BMD value of a healthy young adult Caucasian woman. A T-score between -2.5 and -1.0 defines osteopenia, e.g. low bone mass but not yet osteoporosis. WHO also included a clinical definition of osteoporosis, where the diagnosis is based on the presence of a fragility fracture. DXA is based on the fact that variable body components absorb X-ray to a variable degree. It uses high energy and low energy X-ray photons and measures the amount of energy that is absorbed in every specific area. To calculate the BMD, the bone mineral content (BMC), i.e. the quantity of calcium estimated to absorb energy in every specific region, is measured, and BMD is then estimated by dividing the BMC by the surface of the body; g/cm^2 (95). Thanks to validated reference materials, an individual's BMD can also be compared to the reference value for the given age and sex, giving the Z-score (number of SD above or below the mean BMD for the given age and sex). For every 1 SD reduction in BMD, a twofold increase in the likelihood of a fracture can be expected. Fracture risk estimation by DXA is most accurate at the specific site measured, i.e. hip fractures are best predicted by DXA of the hip (135). There are several limitations of DXA measurement, such as difficulties in assessing regions with surgical materials, calcifications, fractures or other skeletal pathologies such as spondyloarthritis or lytic or sclerotic lesions. In addition, it is important to have an accurate examination programme, including calibration of machines and ensuring precise patient positioning and selection of region of interest for the analysis. Although the reproducibility of repeated DXA measurements is generally claimed to be good compared to many other tests, there is a variability which is important to have in mind when comparing DXA results from time to time. This variability is assessed by performing repeated DXA scans on representative individuals during a short time where no change in BMD is expected. The outcome is called the precision error (PE) and can be used for calculating the "least significant change" (LSC=PE*2.77) with 95% confidence, which constitutes the smallest change in percent that is considered statistically significant (136). DXA does not give much information on bone structure or structure-related quality (95). Therefore, other methods for diagnosis of osteoporosis and prediction of fractures have been proposed: *Trabecular Bone Score (TBS)* measures gray-level variations in DXA images of the lumbar spine and gives a complementary index for estimation of the 3D bone structure, giving a better idea of the quality of the microarchitecture of the vertebral bone. Since TBS has been shown to provide complementary information about fracture risk, and may be less affected by other lumbar bone varieties, it has recently been proposed as an addition to BMD and FRAX-score assessment (see below for definition of FRAX) to enhance fracture risk prediction (148, 149). *Vertebral fracture assessment (VFA)* is another way of enhancing fracture prediction, since vertebral fractures are strong predictors of future fragility fractures, and many vertebral fractures stay clinically undetected. VFA can be done either by using lateral lumbar and thoracic spine radiographs or by lateral spine DXA imaging (150). *High Resolution peripheral Quantitative Computed Tomography (HRpQCT)* uses CT systems for volumetric measurements of BMD

(g/cm^3) and assessments of bone microarchitecture at the distal radius and tibia. It allows differentiation between cortical and trabecular bone and provides densitometric and structural parameters which gives a more precise estimation of BMD and bone quality. HRpQCT systems still lack standardisation, are in need of improved reproducibility, and have limited availability of reference normative data sets. So far, it is mostly used in research settings (151). *Quantitative ultrasound (QUS)* utilizes sound waves at approximately 20 kHz to measure physical and mechanical properties of bone, including elasticity, microarchitecture and strength. QUS of the heel has been shown to predict fracture risk in elderly women and is a cheap, handy and radiation free method for diagnosing osteoporosis. Unfortunately until today there is a major heterogeneity in measurement techniques, making it difficult to interpret results and set diagnostic cut offs (152). *Bone turnover markers* are products released from osteoblasts, osteoclasts or bone matrix in response to bone remodelling. So far, such markers have not been shown to contribute independently to fracture risk evaluation but may help in assessment of the effectiveness of pharmacological treatment of osteoporosis (95, 153). *The fracture risk assessment tool FRAX®* is a computer based algorithm that integrates the influence of several well validated risk factors for fractures and permits the calculation of the 10-year probability of a major osteoporotic fracture. It is thoroughly validated and incorporated in many guidelines for management of osteoporosis, and although it has sometimes been criticised for being unprecise for example in some groups of RA patients, a recent study validating the tool in a North American RA population, concluded that FRAX is an acceptable method for estimation of major osteoporotic fractures in RA (96, 154).

Treatment of osteoporosis and prevention of fragility fractures

Pharmacologic treatment

There are many different guidelines for the treatment of osteoporosis, which might reflect uncertainties regarding assessment of fracture risk and insufficient high quality data regarding treatment of secondary osteoporosis. In summary first-line treatment for most Swedish patients with osteoporosis and high risk of fractures includes bisphosphonates such as Alendronate, Risendronate or Zolendronic acids (150). The main function of bisphosphonates is inhibition of osteoclast activity by binding with high affinity to the mineralized matrix of the bone, and thereby reducing bone resorption. Reduced bone resorption can be achieved as soon as 3 months after start of treatment and eventually, also bone formation is slowed down leading to a low rate of bone turnover in patients treated with bisphosphonates (155). Improvements in BMD are seen, but since fracture risk (especially vertebral fractures) is reduced more than expected from these BMD improvements (134, 136, 156), and often before changes in bone mass are measurable, it has been proposed that other aspects of bone quality are improved as well (156, 157). The reduced fracture risk is well documented in postmenopausal women, but has also been

shown in men and in patients with glucocorticoid induced osteoporosis (145, 155, 158). Although RCTs in pure RA groups with fractures as main outcome are lacking, many studies on BMD in RA find better results for patients treated with bisphosphonates (104, 116, 120, 159-161). Bisphosphonates are usually administered together with substitution of calcium and vitamin D. Frequently reported side effects of bisphosphonates include upper gastrointestinal symptoms and flu-like symptoms after infusion of Zolendronic acids. More concerning but rare adverse effects are osteonecrosis of the jaw and atypical femoral fractures (145). Studies have revealed a relatively low compliance with bisphosphonates, and side effects might be one reason for this (145, 155, 157, 162).

Second line treatment include *Denosumab*, a human monoclonal antibody against RANKL, which blocks osteoclast maturation, function and survival and thereby reduces resorption of both cortical and trabecular bone and reduces both vertebral and non-vertebral fractures, but with a rapid loss of effect after cessation, *Teriparatide*, a recombinant human parathyroid hormone analogue and *Romosozumab*, a monoclonal antibody inhibiting sclerostin, which both stimulate new bone formation and reduce fractures more than bisphosphonates. In Sweden, the last two alternatives are recommended primarily for patients with very high fracture risk (150).

Non-pharmacologic treatment

In concordance with the knowledge about modifiable risk factors for osteoporosis and fragility fractures, most guidelines give advice on lifestyle changes, such as smoking cessation, limitation of alcohol intake, adequate intake of calcium, vitamin D and proteins, and physical activity (multiple types of exercise such as balance and functional exercises plus resistance exercises). In frail individuals, environment modifications, and footwear- and eye vision evaluation, are recommended. If possible, polypharmacy should be avoided and the need of fall risk-inducing drugs such as opioids, antihypertensives and sedatives reevaluated. Not the least, education on bone health enable patients to accomplish the recommended lifestyle changes (93, 123, 150, 163).

External registers used in this thesis

The Swedish National Patient register was established in 1964 and provides information (diseases and symptoms, surgery and treatments and injuries via external codes amongst others) on all completed inpatient stays, with all regions in Sweden included since 1987 (Skåne since 1970). In 2001 also information on patients treated in specialized outpatient care was included, but until today no data from primary care or from patients treated solely by other health professionals than doctors are included. The purpose of the register is to 1. monitor long-term health trends in the population 2. improve the prevention and treatment of disease 3.

contribute to the development of health care and 4. monitor the quality of health care services (164). Since 1998 it is mandatory for healthcare providers to continuously deliver data on personal identity number, admission and discharge dates and diagnostic codes according to the Swedish version of the international classification of disease (ICD) (165). The National Patient register has been validated several times, both through reviews of patient records and by comparison with the Swedish Hip Fracture Register. In 2011 it was reported that the coverage of the inpatient part of the register was almost 100%, whilst the coverage of the outpatient specialized care was about 80% because private caregivers were missing (data from public caregivers again, almost 100%). Back in 1983, about 85% of inpatient care were reported to the register. The validation of ICD codes from the inpatient register has continuously shown good results for most diagnoses, although mild diseases have had lower specificity (165). There was a high agreement between the Swedish Hip Fracture register and the National Patient register regarding hip fractures, although the latter was believed to overestimate the number of recurrent fractures (166). This was also seen in humeral fractures when comparing the National Patient register to the Swedish Fracture register (167).

The Cause of Death register is based on the mandatory cause-of-death certificates written by a doctor for every person who dies in Sweden. It contains the main underlying cause of death (disease or injury) and multiple contributing causes if relevant from the year of 1952. The register is updated annually and considered highly complete since < 1% of all deaths since 2013 in Sweden have a missing cause-of-death certificate. About 3% have what is considered insufficiently specified causes of deaths, and in such cases follow-up questions are sent for clarification if the person was <65 years old at the time of death. The cause of death register has not been validated in scientific reports to a high degree (168).

South Sweden Arthritis Treatment Group (SSATG) was a treatment register officially established in March 1999 with the purpose to monitor and evaluate tolerability and efficacy to the new antirheumatic drugs approved at the time of establishment (169). Seven rheumatology units, and eventually all together ten units in southern Sweden continuously reported dates of starting and stopping biologic agents and concomitant antirheumatic treatment, as well as disease severity measurements at start of treatment and during follow-up. In 2005 SSATG was estimated to include >90% of patients with arthritis treated with biologic agents, when compared with year-specific pharmacy unit drug costs (170).

The Swedish Rheumatology Quality Register (SRQ) was started in 1995 with the ambition to improve treatment and healthcare outcomes of patients with RA. Initially antirheumatic treatment was mainly registered in other regional registers (such as SSATG) but over time as SRQ developed into a national register, antirheumatic treatment was included in addition to other clinically useful information collected for evaluation of RA care. In 2011 SRQ was estimated to cover 87-95% of all patients with RA in Sweden (171).

A brief overview of the main statistical methods used in this thesis

The Poisson distribution can be used to calculate the 95% confidence intervals around an incidence rate if events occur randomly over time and randomly in relation to each other. This can be done either by using standard tables giving lower and upper 95% limits which are used to calculate the intervals or by calculating the intervals by using a formula for the purpose.

The Cox regression analysis is a survival analysis where the influence of one or more variables on the time it takes for an event to happen (time-to-event / survival time) is investigated. The hazard rate (the risk of suffering from the event for one individual at one specific time unit) in those with the investigated exposure is compared to the hazard rates of those lacking this exposure, giving the hazard ratio (HR). The hazard rate can also be thought to represent the observed number of events per time unit and the HR the ratio of the number of observed events in independent observation groups. For a categorical variable the HR represents the difference in hazard rate between the groups studied (with one group representing the reference group) and for continuous variables the HR represents the difference in hazard rate per unit up or down of the variable. If the HR is less than 1 the risk related to a covariate is reduced and if HR is more than 1 the risk is increased. Thus, a HR of 1.25 is sometimes expressed as a 25% higher risk of an event between those exposed or not, or per unit increase of the given covariate. A variable can be fixed over the study period or change over time. In the latter case the analysis is considered time-dependent. Cox regression models may also assess matched sets of cases and controls. The matched sets are then investigated as separate strata, and the estimates are based on pooled analyses of all strata.

There are some assumptions that must be fulfilled for a Cox regression analysis to work out. First, the model assumes that the effect of the predictor is constant over time, i.e the influence of the variable is the same at the beginning, in the middle and in the end of the study period. This is called the proportional hazards assumption. The proportional hazards assumption can be tested through visual assessment of log-minus-log plots for dichotomous variables, which should be fairly parallel to each other (figure 3), or through testing if the Schoenfeldt residuals (the difference between an individual's covariate value at a given event time and the value that would have been expected based on the average values of all those at risk at the given time) correlate with the time to event/survival time, which they should not in the case of proportional hazards over time.

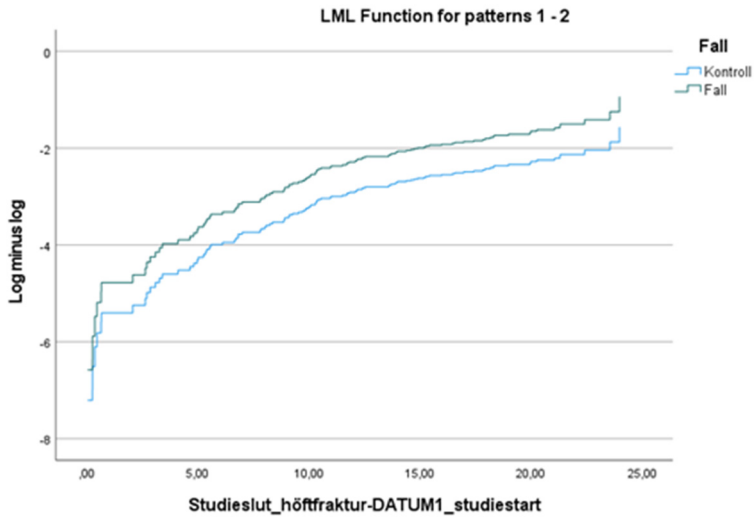

Figure 3.
Log-minus-log plots for testing proportional hazards assumption (in this case for the association between RA and the risk of hip fractures).

Second, the time to event in different individuals is assumed to be independent of each other and the reason for censoring (individuals dropping out due to other reasons than having an event) should be unrelated to the risk of having an event and to the covariates tested. Third, the covariates tested should not correlate to a high degree.

Censoring is sometimes divided into left and right censorship, where left censoring means that the event studied has occurred before study start or start of data sampling, whereas right censorship includes both those who leave a study before the end due to reasons like death, migration, or unwillingness to participate any more, and those who have not yet had an event at study end, but potentially could have had one if the observation time had been longer. If there could be individuals at risk prior to baseline who did not remain observable until the start of follow-up of the study, this is called left truncation and could induce sample bias into the study.

The propensity score is used to measure the probability of an individual to be allocated to one or another group of exposure examined in observational studies where there is a risk of systematic differences in baseline characteristics between the groups. In this thesis the propensity score was based on a logistic regression analysis (model for estimating the association between categorical or continuous independent variables with a dichotomous dependent variable) including baseline characteristics which were associated with initiation of anti-TNF-agents. The resulting "predicted probability" of an individual starting TNF-inhibitors made out the propensity score ranging from 0-1. Using a propensity score can be an alternative

to adjusting for confounders in multivariable models when events are few in relation to the number of potential confounders. For a propensity score to work reasonably well, relevant confounders need to be included in the model and there should be a spread of baseline characteristics between study groups.

Matching is another method of limiting confounding. When matching a control population, the included individuals are selected based on their similarities regarding specific characteristics of the study population that are thought to be associated with both the exposure and influence the risk of the outcome. Matching can of course only be done for characteristics known in both populations – typically age and sex. To consider is also not to match for differences that are relevant for the outcome examined and not to overmatch the populations so that the groups are so alike that also their exposure frequency is very similar. When cases are rare the power (explained below) of the study can be increased by increasing the number of controls per case with up to approximately four controls per case. More controls do not increase the power substantially, which is why the ratio 1:4 is commonly seen.

Spearman's correlation is used for examination of the relationship between two variables that are either continuous or ordinal (values following a scale or specific intervals). The test tells us the strength and direction of the correlation and gives a value between -1 and 1, where 0 means no correlation and -1 or 1 means perfect correlation. The spearman's test does not require data to be normally distributed (as in the Pearson correlation) since the values of the variables are ranked before being analysed. However, the data must be monotonic meaning the relationship must be somewhat although not perfectly linear and cannot change direction.

Mixed linear effect models are useful if data are not independent from each other, as in study II in this thesis, where patients are followed longitudinally with repeated measurements. Mixed models allow for both fixed and random effects on the outcome, where a fixed effect corresponds to an independent variable or an exposure that is assumed to have some sort of effect on the dependent outcome variable, whereas the random effect comes from the sampling procedure where a covariance/ a dependence of data could be introduced, and is adjusted for in the model. Mixed models also allow for a varying number of data in each category (in this case measurements per patient), so called imbalanced data, and missing values. It assumes that there is a linear relationship between explanatory (fixed) variables and the dependent outcome variables, that multicollinearity and obvious interactions between covariates is avoided, and that there is a constant variance of the residuals, giving no specific pattern when plotting the residuals, with an average equal to around zero. In addition, residuals should be normally distributed (more about normal distribution below).

The paired T-test is used to determine the mean difference between two measurements from a set of pairs (for instance two measures from the same

individual in a group) and whether it is significantly different from zero. The outcomes must be continuous variables, independent between sets of pairs and the measured differences must be fairly normally distributed.

Piecewise linear regression is used when the relationship between the independent and the dependent variable change at specific sections of the independent variable values, making the direction of the line and the coefficient change, and a simple linear regression inappropriate. This is the case when plotting the relationship between age and bone mineral density in study II of this thesis, since loss of bone mass accelerates approximately at midlife (figure 4). The regression function is modelled in pieces and the coefficient of the simple regression equation complemented with another coefficient more appropriate after the breakpoint of the line.

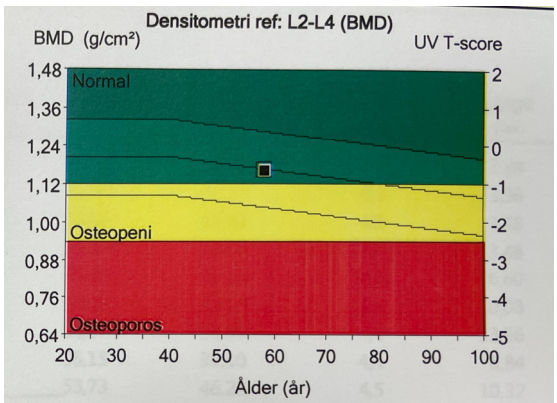

Figure 4.
Linear relationship between age and BMD in the lumbar spine of men, with a breakpoint where the direction of the line describing the relationship changes.

Normal distribution is mentioned a couple of times above and means that the distribution of data points is symmetric around the mean value, with data points near the mean being more frequent than observations far from the mean. When plotting data they will have an appearance similar to a bell-shaped curve, and the area under the curve gives information about the probability of values falling within a specific range. Observations are assumed to be independent and random. Other ways of testing if data are normally distributed is to use a quantile-quantile (Q-Q) plot where the residuals should follow a 45-degree angle line, or by formal statistic test (several different). In normally distributed data the mean and the median will be closely related. The standard deviation (SD) determines the spread of the data (in relation to the mean) and in normally distributed data about 68% of all observations will appear within +/- 1 SD and 95% within +/- 2 (1.96) SD. This is related to the standard error, which is used in the function for the 95% confidence intervals: *mean of data +/- 1.96 x standard error*. The standard error is an estimation of the

variability across multiple samples of a population and helps estimating how well one specific sample represents the whole population. Generally, a larger sample size gives a lower standard error and a sample mean that is closer to the true population mean.

Statistical power describes the probability of a test to find a significant effect when there is indeed a true effect and to reject the null hypothesis of no effect in such cases. The power depends 1. on sample size, where a larger sample increases the probability of finding a true effect and decreases the risk of collecting an unrepresentative sample from the population, 2. on the desired significance level (the risk of incorrectly rejecting the null hypothesis), usually set to 5%, and 3. on the expected effect size (the magnitude of an effect to detect), where large effects increase the probability of rejecting the null hypothesis. The desired power is usually set to around 80% or higher. Once you have decided on significant level, assumed the relevant effect size (based on previous studies) and set the power, it is possible to determine how large of a sample size is needed to avoid type I and II errors (either concluding on an effect when in reality there is none, or concluding on no significant effect when in the whole population one would find it). Except for these factors included in the equation of power calculations, the probability of finding true associations depends on study design, how large the variance of the studied variable is in the population tested, how accurate the measurement techniques are, and how well confounding factors are managed. Problems in these areas can induce bias, i.e. false results based on systematic flaws in the methodology of the study.

Aims

Study I: To evaluate whether treatment with TNF inhibitors has any effect on the risk of developing severe ExRA and to investigate potential predictors of ExRA using questionnaire data obtained at the beginning of and during the study period.

Study II: To examine BMD by sex over the 10 first years of RA and to investigate whether patients with RA have lower BMD than expected already at diagnosis, whether BMD changes during the course of disease and which baseline factors predict changes in bone mass.

Study III: To examine the incidence of osteoporosis-related fractures (hip, proximal upper arm, distal forearm and vertebral fractures) in men and women with RA and compare it to that of the general population, with subanalyses of patients with a short disease duration, and to investigate potential baseline predictors of such fractures in patients with RA. In addition, since hip fractures lead to a greater morbidity burden and are probably more reliably captured in the National Inpatient register than other osteoporosis-related fractures, another aim was to analyse the incidence of hip fractures compared with the general population and predictors of hip fractures specifically.

Study IV: To compare the incidence of fractures in the RA patients studied in study II to that in the general population, to investigate the relation between BMD at diagnosis and over the first 10 years with fractures in RA, and to examine other potential predictors of future fractures in early RA through baseline- and time dependent analyses of clinical parameters and upper and lower extremity functional tests.

Methods

Study cohorts and controls

This thesis was based on two different cohorts of patients with RA described below. A summary of the aims and methods of every study is given at the end of this chapter in figure 6.

Study I and III were based on the Malmö RA register (N=1977), a register established in 1997 including all known RA patients in Malmö and extended with newly diagnosed patients until the year of 2006. The patients were recruited from the rheumatology outpatient clinic of Malmö University Hospital and from the four rheumatologists in private practice in Malmö at the time. All patients were diagnosed with RA regarding to the 1987 American College of Rheumatology criteria for RA (17). Furthermore, it was verified that the diagnoses had not been changed at a later time point through review of medical records at the beginning of the first study. At the time of establishment, the register covered about 95% of the patients with RA in Malmö (172, 173).

In 1997, 2002, 2005, and 2009, all patients received questionnaires including the Swedish validated version of the Health Assessment Questionnaire (HAQ), visual analogue scales (VAS) for the patients' assessment of current pain and global health, and questions on previous and current antirheumatic treatment. After one reminder, at least one completed questionnaire was obtained from 1551 (78%) of the included patients during the study period.

Study II and IV were based on the Malmö early RA register (N=233), an inception cohort of consecutive patients with newly diagnosed RA (symptom duration <12 months), recruited between 1995 and 2005 from the rheumatology outpatient clinic of Malmö University Hospital and from the rheumatologists in private practice in Malmö at the time.

The patients were examined at inclusion and after 0.5, 1, 2, 5 and 10 years by the same rheumatologist according to a structured protocol. The Swedish validated version of HAQ was used to assess disability (24), visual analogue scales were used to evaluate the patients' assessment of current pain and global assessment of disease activity, and information on height, weight, smoking history and menopausal status was collected at inclusion through self-administered questionnaires. Information on current use of conventional synthetic disease modifying antirheumatic drugs (csDMARDs), glucocorticosteroids, anti-osteoporotic agents and hormone

replacement therapy (HRT) was obtained through a structured interview at each visit.

Grip force (Newton) was measured using the electronic instrument Grippit (AB Detektor, Gothenburg, Sweden) at inclusion and after 1, 2, 5 and 10 years. The average grip force during 10 seconds uninterrupted grip in the dominant hand was compared to the expected grip force, based on age- and sex-specific reference values (174, 175). A subset of patients (n=105) was also assessed according to the Index of Muscle Function (IMF) (32, 176) by a physiotherapist at inclusion and after 1, 2 and 5 years.

At inclusion and after 2, 5 and 10 years of follow-up, radiographs of hands and feet were obtained, and scored according to the Sharp-van der Heijde score (SHS) (177) on every occasion (except at the 10 year follow up), by the same trained evaluator, who was unaware of the clinical status of the patient.

Finally, the patients were examined with DXA at the femoral neck and second to fourth lumbar spine vertebrae (L2-L4) at inclusion and after 2, 5 and 10 years of follow-up. Most patients had all their measurements done by the Lunar DPX-L equipment (1.3z Lunar, Madison, Wisconsin, USA) but 67 patients were examined by either the Lunar DPX-NT or Lunar Prodigy equipment (seven patients with one measurement on the Lunar Prodigy and the others on DPX-NT). The precision of the Lunar DPX-L was previously reported to be 0.5% for the lumbar spine and 1.6% for the femoral neck (178) and of the Lunar Prodigy 0.65% for the lumbar spine and 0.90% for the femoral neck (179). Unpublished data from our DXA centre indicate that the differences between the machines was marginal. Quality control was performed daily using a manufacturer-supplied phantom. From the BMD values (g/cm^2), Z-scores (number of SD above or below the mean BMD for the given age and sex) were calculated using a cohort of healthy individuals (146 men and 178 women, age 20–87) from the same area as a reference population (178). Gender-specific reference values were estimated using piecewise linear regression separately for patients aged 20–44 and ≥45 in the femoral neck in men and women and in the lumbar spine in men, but for patients aged 20–44, 45–64 and ≥65 in the lumbar spine in women (figure 5) (178). BMD values exceeding ±3 SD from the mean for the given age and sex were considered outliers and excluded from the analyses.

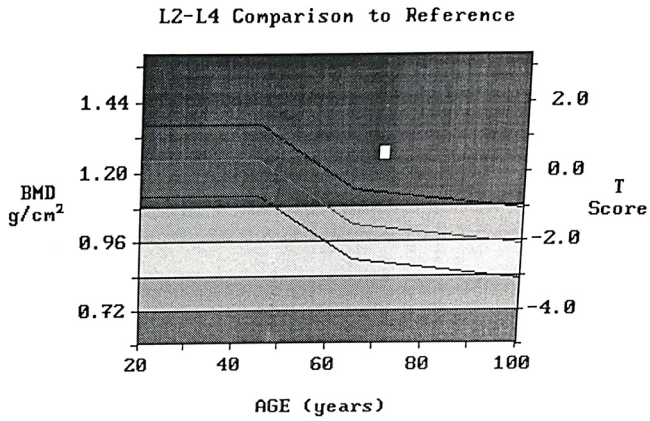

Figure 5.
Reference graph for BMD in the lumbar spine of women.

In all studies, information on biologic DMARDs (bDMARDs) was retrieved from the South Swedish Arthritis Treatment Group (SSATG) register (169, 170) and/or the Swedish Rheumatology Quality register (SRQ) (171). In study I, patients with bDMARDs were classified as exposed until 30 days after registered cessation of the drug according to the SSATG register.

In study I and III only data on Rheumatoid Factor (RF) tests were retrieved from the databases of the two clinical immunology laboratories in the area. In study II and IV also antibodies to cyclic citrullinated peptides (anti-CCP) were analysed at inclusion using standard ELISA methods at the immunology laboratories at the University Hospitals in Malmö and Lund. ESR and CRP for study II and IV were assessed according to standard methods at the Department of Clinical Chemistry, Malmö University Hospital.

In study III and IV, four controls per patient in the respective cohort were identified using the national census register from the general population. The controls did not have diagnosed RA and were individually matched for age at inclusion of the case in the register (+/- 1 year), sex and residential area at the time of inclusion. Retrieval of matched controls was performed by Statistics Sweden. In the fourth study information on country of birth and formal education was obtained for patients and controls from Statistics Sweden.

Study I

Aims: To evaluate whether treatment with TNF inhibitors has any effect on the risk of developing severe ExRA and to investigate potential predictors of ExRA.

Patient cohort: Malmö RA register (n 1977)

Key points of methods:
- Questionnaires in 1997, 2002, 2005 and 2009
- Information on bDMARDs from SSATG
- Laboratory tests: RF
- Severe ExRA identified through review of medical records

Main statistical methods: Cox regression analysis

Study II

Aims: To examine bone mineral density by sex over the 10 first years of RA and which baseline factors predict changes in bone mass.

Patient cohort: Malmö early RA register (n 233)

Key points of methods:
- Clinical assessment at inclusion and after 0.5, 1, 2, 5 and 10 years according to a structured protocol
- Questionnaires, structured interview and blood samples at each visit
- Radiographs of hands and feet at inclusion and after 2, 5 and 10 years
- DXA at inclusion and after 2, 5 and 10 years

Main statistical methods: Mixed linear effect models and paired T-tests

Study III

Aims: To examine the incidence of fractures in men and women with RA and compare it to that of the general population, with subanalyses of patients with a short disease duration, and to investigate baseline predictors of fractures in patients with RA.

Patient cohort: Malmö RA register (n 1928)

Key points of methods:
- Questionnaires in 1997, 2002, 2005 and 2009
- Fractures identified by ICD codes and linkage to the Swedish national inpatient register and the cause of death register
- Four controls per patient from the general population

Major statistical methods: Cox regression analysis

Study IV

Aims: To compare the incidence of fractures in early RA to that in the general population, to investigate the relation between BMD and fractures in early RA patients, and to examine potential predictors of future fractures.

Patient cohort: Malmö early RA register (n 233)

Key points of methods:
- Clinical assessment at inclusion and after 0.5, 1, 2, 5 and 10 years
- Questionnaires, structured interview and blood samples at each visit
- Measurement of grip force at inclusion and after 2, 5 and 10 years
- IMF in a subset of patients at inclusion and after 2 and 5 years
- DXA at inclusion and after 2, 5 and 10 years
- Fractures identified by ICD codes and linkage to the Swedish national in- and outpatient register and the cause of death register
- Four controls per patient from the general population

Main statistical methods: Cox regression analysis

Figure 6.
Summary of aims and methods of the four studies of this thesis

Identification of patients with severe ExRA

The first study of this thesis was an extension of a previous study by Nyhäll-Wåhlin, et al (180), which covered the period from July 1, 1997, to December 31, 2004. To identify further cases of severe ExRA, an extended retrospective review of medical records from the hospital and rheumatologists in private practice from January 1, 2005, to December 31, 2011, was performed, as well as a complete review of the entire medical records for newly diagnosed patients. Identified cases were added to the cases previously reported by Nyhäll-Wåhlin et al (180). Predefined criteria (table 3) (40) were used for classification of severe ExRA. Patients with a history of ExRA before January 1, 1998 (start date of the study) were excluded from the study.

Table 3. (same as in introduction)
Criteria for severe extra-articular manifestations in RA (40) used in study I

Manifestation	Definition
Pericarditis	Clinical judgement and exudation verified by echocardiography. Other causes improbable, such as tuberculosis or other infection, metastases, primary tumour, postoperative status or other trauma.
Pleuritis	Clinical suspicion and exudation verified by X-ray. Other causes improbable, such as tuberculosis or other infection, metastases, primary tumour, postoperative status or other trauma
Interstitial lung disease	Clinical symptoms and either vital capacity or carbon monoxide diffusion capacity reduced by 15 % from normal. In addition, either HRCT or a lung biopsy compatible with interstitial lung disease.
Felty's syndrome	Splenomegaly (clinically evident or measured by ultrasound) and neutropenia (<1.8|10^9/L) on two occasions. Other causes improbable, such as drug side effect or infection.
Neuropathy	Clinical judgement and signs of mononeuropathy/polyneuropathy at EMG/ENeG.
Scleritis, episcleritis or retinal vasculitis	Clinical judgement by ophthalmologist.
Glomerulonephritis	Clinical judgement by nephrologist and positive biopsy.
Major cutaneous vasculitis	Diagnostic biopsy or clinical judgement by dermatologist
Vasculitis involving other organs	Clinical judgement by organ specialist and biopsy compatible with vasculitis

HRCT: High resolution computerized tomography; EMG: Electromyography; ENeG: Electroneurography
Adapted from Turesson et al. (40)

Identification of fractures and comorbidities

In study III information on fractures in patients and controls during the period January 1, 1987 to December 31, 2017, was obtained by linkage to the Swedish National Inpatient register (which contains mandatory reports on diagnoses in inpatient care) and the Cause of Death register. In study IV this was done in a similar way from January 1, 1987 to December 31, 2019, but including also diagnoses from specialized outpatient care from 2001 (start of this register), and including, in addition predefined comorbidities for baseline comparison between patients and controls. Fractures of the hip, proximal upper arm, distal forearm, vertebra, and pelvis (table 4), as well as predefined comorbidities were identified based on ICD-9 and ICD-10 diagnostic codes. A somewhat different set of codes were used in the two studies. Patients and controls with identified fractures before the start of the studies were excluded from the main analyses but included in sensitivity analyses. High-energy traumatic fractures during the study period were identified using ICD-10 external cause codes (181).

Table 4.
ICD diagnostic codes for fractures in study III and IV

	Study III		**Study IV**	
	ICD 10	**ICD 9**	**ICD 10**	**ICD 9**
Hip fractures	S720-722	820	S720-S722	820
Vertebral fractures	S220, S221, S320, S327	805C, 805D, 805E, 805F		
Vertebral and pelvic fractures			S22, S32, M485	805, 808
Forearm fractures	S525, S526, S528	813E, 813F	S52	813
Upper arm fractures	S422	812A, 812B	S42	812

Statistics

For ExRA manifestations (study I) and for fractures in patients and controls (study III and IV) incidence rates and incidence rate ratios were calculated and the Poisson distribution ratio was used to estimate the 95% confidence intervals (CI). Cox regression analyses were used in the first study to compare the risk of ExRA in patients treated with, to patients not treated with TNF-inhibitors, and to assess the association between baseline- and time-dependent variables and future ExRA. The models were also adjusted 1. for a propensity score for anti-TNF-treatment, based on logistic regression analysis including demographic data and baseline clinical characteristics associated with initiation of treatment with TNF-inhibitors and 2. for

HAQ in a time dependent way since HAQ was assessed repeatedly during the study period.

Cox regression models were also used to compare the risk of fractures in RA patients and controls in study III and IV, as well as for analysis of baseline and time-dependent variables associated with future fractures in RA patients. For adjustment for comorbidities in study IV, a modified Charlson Comorbidity Index (CCI), based on the already predefined comorbidities, was created and patients and controls categorized into three groups depending on the comorbidity weight (0, 1 or ≥2). In the third study patients were divided into early (<1 year of disease duration at study start) and established (≥5 years since RA diagnosis at study start) RA. To analyse the risk of fractures early in RA, separate analyses were done for the first 10 years of disease in the group of newly diagnosed patients. If the numbers of fractures were <10, no Cox regression models were performed.

In Study II, mean BMD Z-scores over the study period were estimated by mixed linear effect models. The regression line intercept corresponded to the estimated mean Z-score at baseline. The association between baseline characteristics and the mean Z-scores over the 10 years studied was assessed in univariate models, and the variables with significant associations were further analysed in multivariate models. Collinearity between included variables were controlled for in Spearman's test.

Changes in BMD Z-scores between follow-up visits were analysed in paired T-tests for those patients with data at the two corresponding time points.

Ethics

All studies have been approved by the Regional Ethical Review Board for southern Sweden (LU336-96, LU-607-02, LU410-94, LU311-02, LU336-01, LU2016/923, LU410-94, LU311-02, 2021-01878). The first and third study (based on the Malmö RA register) were included in long term projects of disease severity and adverse outcomes in the Malmö RA register. For those studies, informed consent for the specific study was waived by the Ethic Review Board and was not obtained. All patients in the Malmö early RA register (which was used in the second and fourth project) gave their written informed consent to participate at inclusion in the cohort.

Results

Study I

Severe extraarticular manifestations in a community-based cohort of patients with RA: risk factors and incidence in relation to treatment with TNF inhibitors

Patient characteristics and distribution of identified severe ExRA. Baseline characteristics of the total cohort as well as patients treated vs not treated with TNF inhibitors during follow-up are shown in table 5. Of the 1977 patients included in the study, 539 (27.3%) were treated with TNF-inhibitors as their first biologic DMARD. Patients with anti-TNF treatment were younger, RF-positive to a higher degree, had somewhat higher HAQ scores and were more often treated with Methotrexate (MTX) and glucocorticosteroids.

Table 5.
Baseline characteristics overall and by anti-TNF exposure

	Total cohort	Anti-TNF during follow-up	No Anti-TNF during follow-up
Number of patients (%)	1977	539 (27.3)	1418 (71.7)
Age (years) mean (median)	59.9 (61.3)	50.4 (51.7)	63.6 (66.0)
RA duration (years) mean (median)	9.6 (4.0)	7.2 (3.0)	10.5 (5.0)
Women n (%)	1435 (72.6)	420 (77.9)	999 (70.5)
Previous ExRA n (%)	72 (3.6)	20 (3.7)	52 (3.7)
HAQ score* mean (SD)	1.02 (0.76)	1.12 (0.69)	0.97 (0.79)
VAS pain* mm mean (SD)	42.9 (26.9)	44.6 (25.6)	42.0 (27.5)
VAS global health* mm mean (SD)	41.7 (26.5)	42.9 (24.9)	40.9 (27.2)
RF-positive n (%)	1209 (73.6)	387 (83.9)	806 (69.2)
Methotrexate* n (%)	679 (45.3)	291 (58.7)	380 (38.6)
csDMARDs except Methotrexate* n (%)	760 (50.7)	196 (39.5)	554 (56.3)
Glucocorticoids* n (%)	422 (28.2)	202 (40.7)	213 (21.6)

* Based on first available questionnaire. Twenty patients had a first biologic agent other than a TNF inhibitor, and were excluded from the analyses of anti-TNF treatment during followup. Data on HAQ were available from 1623 patients (538 anti-TNF treated, 1065 not anti-TNF treated), on VAS pain from 1501 patients (458 anti-TNF treated, 1023 not anti-TNF treated), on VAS global health from 1498 patients (458 anti-TNF treated, 1020 not anti-TNF treated), and on pharmacological treatment from 1498 patients (496 anti-TNF treated, 984 not anti-TNF treated). csDMARD: conventional synthetic disease-modifying antirheumatic drug; ExRA: extraarticular rheumatoid arthritis; HAQ: Health Assessment Questionnaire; RF: rheumatoid factor; TNF: tumor necrosis factor; VAS: visual analog scale.

A total of 135 (6.8%) patients developed severe ExRA during the study period (median follow-up time 10 years), and after exclusion of 8 patients who had been diagnosed with ExRA before study start and 3 patients with ExRA before the date of RA diagnosis, the incidence of new-onset ExRA was 0.67/100 person years at risk (pyr), 95% CI 0.56; 0.80. The distribution of the different extra-articular manifestations during the study period is shown in table 6.

Table 6.
Distribution of new-onset ExRA manifestations during the follow-up period. Values are n

	All	During Anti-TNF treatment	Not during Anti-TNF treatment
Any severe ExRA manifestation during follow-up*	124	17	104
Pericarditis	21	0	21
Pleuritis	41	7	34
Felty's syndrome	11	1	10
Interstitial lung disease	19	3	16
Glomerulonephritis	1	0	1
Neuropathy	13	1	12
Scleritis, episcleritis or retinal vasculitis	21	6	14
Major cutaneous vasculitis	31	3	27
Vasculitis involving other organs	4	0	4

* Some patients had more than 1 severe ExRA during followup. Three patients had ExRA during or after treatment with biologic DMARDs other than TNF inhibitors. There were no cases of retinal vasculitis.
DMARD: disease-modifying antirheumatic drugs; ExRA: extraarticular rheumatoid arthritis; TNF: tumor necrosis factor.

Predictors of severe ExRA. Higher age and male sex were predictive of severe ExRA. Furthermore, longer duration of RA and positive RF at baseline were significantly associated with occurrence of ExRA during the study period, after adjustment for sex and age. There was a trend towards an association with HAQ at baseline (sex- and age-adjusted HR 1.23, 95% CI 1.00; 1.54) and in time-dependent analyses of HAQ measured repeatedly during follow-up (age- and sex-adjusted HR 1.45, 95% CI 0.94; 2.24). In RF-negative patients, repeatedly measured HAQ during follow-up was strongly associated with ExRA (HR 4.68, 95% CI 1.84; 11.86).

Associations between anti-TNF treatment and severe ExRA. Seventeen patients developed new-onset severe ExRA during treatment with TNF-inhibitors. With 2400 person years of anti-TNF exposure during the studied period, the incidence of severe ExRA during treatment with anti-TNF-agents was 0.71/100 pyr (95% CI 0.41-1.13). There were 104 cases of ExRA in patients not treated with TNF-inhibitors in 15,599 unexposed person years, giving an incidence rate of 0.67/100 pyr (95% CI 0.54; 0.81). The incidence rate ratio comparing the groups of treated and not treated patients was 1.06 (95% CI 0.60; 1.78), illustrated in figure 7. Pericarditis and vasculitis were less often seen in patients with TNF-inhibitors, whereas there was no difference in the proportion of interstitial lung disease (ILD)

between the groups (18% vs 15% of all manifestations with or without exposure of TNF inhibitors). The incidence of ILD/100 pyr during anti-TNF exposure was 0.13, 95% CI 0.03; 0.37 and without anti-TNF exposure 0.10, 95% CI 0.06; 0.17, and the incidence rate ratio 1.22, 95% CI 0.23; 4.43.

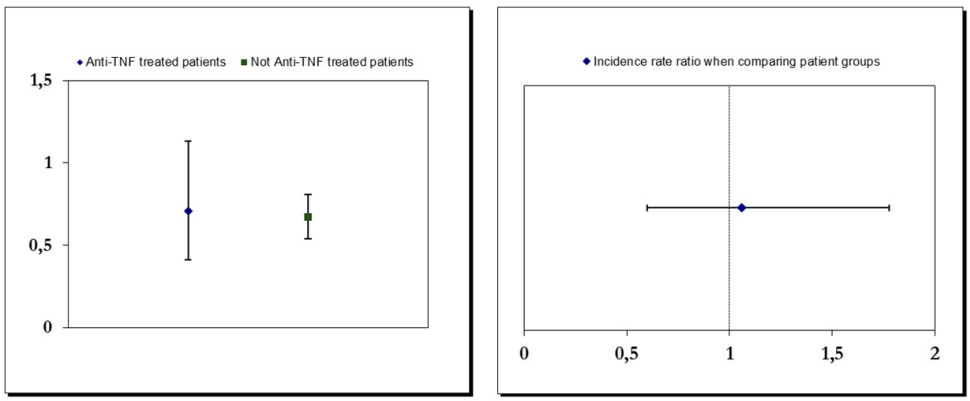

Figure 7.
Incidence/100 person years at risk and incidence rate ratio of severe ExRA in anti-TNF treated and not anti-TNF treated patients (bars representing 95% CI).

In the time-dependent cox regression analysis there was a significant association between anti-TNF-treatment and the risk of severe ExRA after adjustment for age and sex (HR 1.21, 95% CI 1.02; 1.43). The results were similar after further adjustments for HAQ as a time-dependent covariate and a propensity score for treatment with TNF-inhibitors (based on age, sex, RA duration, RF-status, first available HAQ score and treatment with MTX and glucocorticoids), illustrated in figure 8.

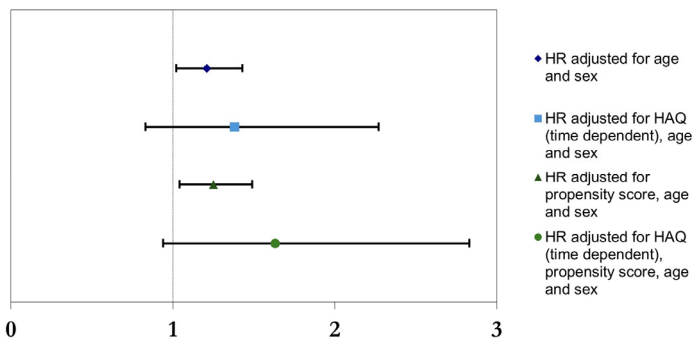

Figure 8.
Time-dependent associations between treatment with TNF-inhibitors and severe ExRA. Figure showing adjusted hazard ratios (HR) and 95% confidence intervals for multivariable time-dependent cox regression analyses.
HAQ: health assessment questionnaire. HR: Hazard Ratio

Study II

Changes in bone mineral density over 10 years in patients with early RA

Patient characteristics and treatment. Of the 233 included patients, 220 patients were examined with DXA at inclusion. Ten more patients had their first DXA scan later during the study period. Clinical characteristics at baseline and at every point of follow-up for patients with DXA data are shown in table 7. Mean age was 58.5 years in women and 63.2 years in men. The duration of RA symptoms at study start was on average just over 7 months. Over 80% of the patients were treated with csDMARDs and 36.3% of the women and 49.2% of the men had treatment with glucocorticosteroids at inclusion. Both the proportion of patients treated and the doses of corticosteroids decreased during the study period. Proportions of patients with anti-osteoporotic treatment increased during the study period and at the 5-year follow-up visit 35.5% of the women and 16.7% of the men had treatment with bisphosphonates.

Table 7.
Clinical characteristics, treatment and BMD at inclusion and follow-up visits for patients with available DXA data

	Women				Men			
Clinical characteristics	**Inclusion**	**2 years**	**5 years**	**10 years**	**Inclusion**	**2 years**	**5 years**	**10 years**
Number	157	138	122	89	63	58	51	33
Age (years) mean (SD)	58.5 (15.6)	60.8 (15.7)	64.1 (15.2)	66.9 (14.4)	63.2 (11.1)	64.9 (11.3)	66.5 (11.2)	69.3 (11.5)
BMI (kg/m^2) mean (SD)	24.9 (3.9)	25.6 (4.3)	NA	NA	25.3 (3.6)	25.8 (4.1)	NA	NA
CRP (mg/l) median (IQR)	<9.0 (<9.0; 22.0)	<9.0 (<9.0; 10.0)	<9.0 (<9.0; 9.0)	<9.0 (<9.0; 9.0)	13.0 (<9.0; 33.0)	<9.0 (<9.0; 15.0)	<9.0 (<9.0; 12.0)	<9.0 (<9.0; 23.0)
ESR (mm) median (IQR)	21.0 (10.0; 43.0)	15.0 (8.0; 24.0)	15.0 (9.0; 24.0)	15.5 (11.0; 26.0)	22.0 (10.0; 46.0)	15.5 (9.0; 30.5)	16.0 (9.0; 25.3)	18.5 (10.3; 31.8)
Erosions n (%)	21 (13.4)	37 (28.5)	41 (35.7)	25 (37.3)	11 (17.5)	28 (49.1)	27 (57.4)	16 (69.6)
HAQ median (IQR)	0.75 (0.38; 1.25)	0.63 (0.13; 1.06)	0.75 (0.38; 1.25)	0.75 (0.38; 1.19)	0.63 (0.13; 1.13)	0.32 (0.00; 0.91)	0.25 (0.00; 0.88)	0.57 (0.13; 1.00)
DAS28 mean (SD)	4.63 (1.37)	3.75 (1.39)	3.69 (1.41)	3.24 (0.96)	4.57 (1.48)	3.39 (1.40)	3.25 (1.31)	3.01 (1.09)
VAS global (mm) mean (SD)	43.3 (27.1)	36.6 (27.3)	36.2 (25.2)	31.6 (23.4)	43.3 (26.1)	26.6 (21.9)	29.9 (23.7)	28.9 (25.7)
VAS pain (mm) mean (SD)	40.3 (25.6)	35.2 (28.3)	32.4 (24.5)	29.9 (23.3)	42.9 (28.7)	24.8 (20.3)	25.1 (21.8)	26.4 (21.6)
csDMARDs n (%)	128 (81.5)	110 (82.7)	93 (76.9)	57 (70.4)	54 (85.7)	48 (82.8)	41 (80.4)	26 (81.3)
bDMARDs n (%)	0 (0)	9 (6.5)	21 (17.2)	21 (23.6)	0 (0)	4 (6.9)	8 (15.7)	7 (21.2)
Corticosteroids n (%)	57 (36.3)	44 (33.1)	38 (31.4)	20 (22.5)	31 (49.2)	15 (25.9)	12 (23.5)	8 (25.0)
Corticosteroids dose (mg/d) mean (SD)	8.0 (4.3)	5.2 (2.2)	5.0 (2.7)	6.4 (8.1)	11.1 (6.3)	5.3 (3.3)	5.8 (5.0)	6.6 (3.0)
Calcium & D-vitamin n (%)	50 (33.1)	87 (66.9)	74 (69.2)	34 (51.5)	16 (26.7)	29 (55.8)	21 (58.3)	14 (66.7)
Bisphosphonates n (%)	5 (3.3)	33 (25.4)	38 (35.5)	17 (25.8)	0 (0)	9 (17.3)	6 (16.7)	7 (33.3)
HRT n (%)	24 (15.8)	20 (15.4)	15 (14.1)	0 (0)	NA	NA	NA	NA
BMD femoral neck (g/cm^2) mean (SD)	0.85 (0.17)	0.83 (0.17)	0.82 (0.18)	0.82 (0.15)	0.88 (0.16)	0.87 (0.14)	0.86 (0.15)	0.86 (0.13)
BMD lumbar spine (g/cm^2) mean (SD)	1.07 (0.20)	1.08 (0.19)	1.10 (0.20)	1.14 (0.18)	1.16 (0.20)	1.16 (0.20)	1.15 (0.20)	1.18 (0.22)
Z-score femoral neck mean (SD)	-0.04 (1.03)	-0.09 (0.98)	-0.07 (1.11)	0.11 (0.92)	-0.27 (1.10)	-0.37 (0.99)	-0.38 (1.09)	-0.30 (0.91)
Z-score lumbar spine mean (SD)	-0.02 (1.04)	0.06 (0.99)	0.26 (1.05)	0.58 (0.99)	-0.12 (1.06)	-0.07 (1.07)	-0.15 (1.02)	-0.01 (1.13)

bDMARDs: biological disease-modifying antirheumatic drugs; BMD: bone mineral density (g/cm^2); BMI: body mass index; CRP: C reactive protein; csDMARDs: conventional synthetic disease-modifying antirheumatic drugs; DAS28: Disease Activity Score-28 Joints; ESR: erythrocyte sedimentation rate; HAQ: Health Assessment Questionnaire; HRT: hormone replacement therapy; IQR: interquartile range; NA: not available/not applicable; SD: standard deviation; VAS: Visual Analogue Scale.

BMD Z-scores over the study period. In men, the mean Z-score in the femoral neck over the 10 years studied was significantly reduced to -0.33 (95% CI -0.57; -0.08) and the intercept Z-score value, estimating the average Z-score at inclusion, to -0.35 (95% CI -0.61; -0.09). In women, the mean Z-scores were not significantly reduced at inclusion or over the study period in the femoral neck. Similarly, Z-scores were not reduced in the lumbar spine, neither in men nor women (table 8).

Table 8.
Z-scores in the lumbar spine and the femoral neck over 10 years of follow-up, mixed linear effect models

	Mean Z-score		Intercept		Change/year	
	Estimate	**95% CI**	**Estimate**	**95% CI**	**Estimate**	**95% CI**
Lumbar spine women	0.057	-0.100; 0.213	-0.043	-0.205; 0.119	**0.039**	**0.025; 0.053**
Lumbar spine men	-0.053	-0.294; 0.187	-0.094	-0.365; 0.176	**0.023**	**0; 0.045**
Femoral neck women	-0.073	-0.222; 0.076	-0.082	-0.593; 0.429	0.003	-0.012; 0.017
Femoral neck men	**-0.327**	**-0.570; -0.085**	**-0.352**	**-0.614; -0.090**	0.004	-0.014; 0.023

Bold text indicates significant associations.
CI: Confidence Interval

In paired T-tests, the femoral neck Z-scores in men decreased significantly from inclusion to the 5-year follow-up visit (mean change in Z-score -0.23, 95% CI -0.43; -0.03, corresponding to a change in mean BMD of -6.9%, 95% CI -4.3; -9.3), but after 5 years no further reduction was seen (figure 9, A). Lumbar spine Z-scores increased significantly in both men and women over the study period (figure 9, C and D).

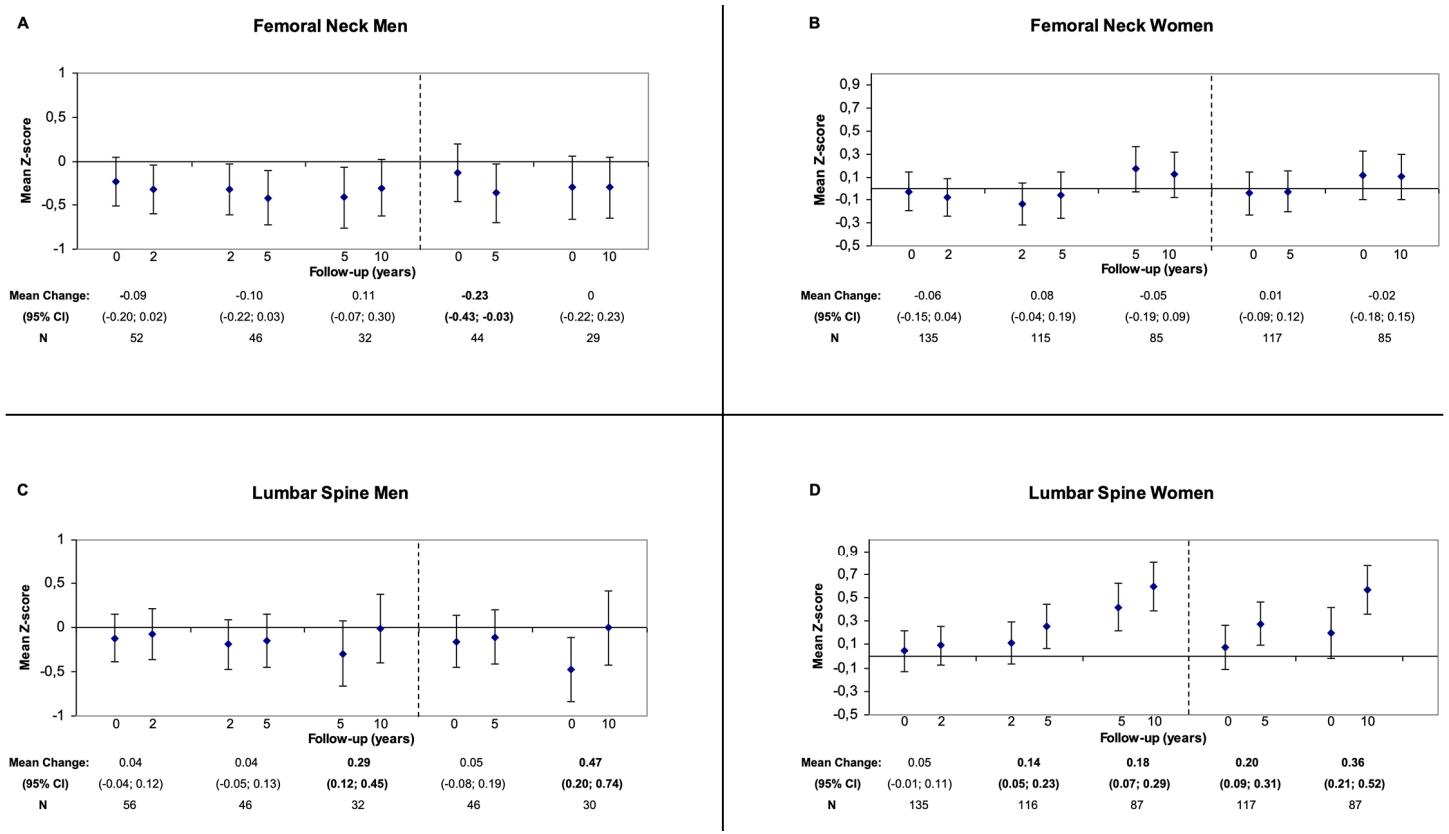

Figure 9.
Pairwise comparisions of mean Z-scores between different follow-up visits, with mean changes of Z-scores.

Predictors of BMD Z-scores over time. High BMI at baseline was associated with high BMD Z-scores over time in both femoral neck and lumbar spine in both men and women, in univariate and multivariate models. In women, high age and postmenopausal status were associated with lower Z-scores in the femoral neck, whereas positive anti-CCP and a history of smoking was associated with lower Z-scores in the lumbar spine. None of the disease related factors were associated with BMD in men. In multivariate models (in which age was not included due to high correlation to postmenopausal status), smoking lost its' significant association with low Z-scores in the lumbar spine in women, but the remaining results were similar to those in the univariate analyses. In women, treatment with hormone replacement therapy (HRT) at baseline predicted higher Z-scores in the lumbar spine, but neither treatment with calcium and D-vitamin, bisphosphonates nor glucocorticosteroids at baseline, had any impact on average Z-scores over the following 10 years in men or women.

Study III

Osteoporosis-related fractures in men and women with established and early RA: predictors and risk compared with the general population

Study population and baseline characteristics. This study included 1928 patients and 7712 sex- and age-matched controls (49 patients in the original Malmö RA register were not registered in Sweden at the time of diagnosis according to Statistics Sweden and were hence excluded from the study). Mean age of patients and controls was 60 years (SD 15.6) and median duration of disease in RA patients was 3 years, with an interquartile range of 0 to 14 years. A total of 13 (2.5%) men and 81 (5.8%) women with RA had had at least one of the studied fractures before the start of the study (and were excluded from further analyses of the corresponding fractures). In the control group the corresponding numbers were 33 (1.6%) men and 186 (3.3%) women. Baseline characteristics for patients in total, for a subset of patients with early (<1 year of disease duration at study start) and established (patients with RA diagnosis for ≥5 years at study start) RA are shown in table 9. The 738 patients with newly diagnosed RA were on average younger, less frequently RF-positive and had more often been treated with Methotrexate and bDMARDs at the time of their first answered questionnaire. Patients with established RA had a mean age of 64 years, a mean duration of RA of 15 years, had somewhat higher RF-positivity and HAQ scores and less treatment with Methotrexate than the average in the full patient group.

Table 9
Baseline characteristics in RA patients

Malmö RA register, total cohort (n)	Men (527)	Women (1401)	All (1928)
Age (years) mean (SD)	60.5 (14.7)	59.5 (15.9)	59.8 (15.6)
Duration at inclusion (years), median (IQR)	3 (0-14)	3 (0-14)	3 (0-14)
Duration at first questionnaire (years), median (IQR)	7 (4-17)	7 (4-17)	7 (4-17)
RF-positive n (%)	322 (73.5)	855 (73.3)	1177 (73.3)
HAQ mean (SD)*	0.75 (0.68)	1.1 (0.76)	0.97 (0.75)
VAS pain (mm) mean (SD)*	37.9 (27.4)	44.5 (26.5)	42.7 (26.9)
VAS global health (mm) mean (SD)*	38.2 (26.4)	42.7 (26.2)	41.5 (26.3)
Methotrexate n (%)*	189 (46.1)	479 (43.0)	668 (43.9)
csDMARDs other than Methotrexate n (%)*	114 (27.8)	321 (28.8)	435 (28.6)
bDMARDs n (%)*	42 (10.2)	121 (10.9)	163 (10.7)
Prednisolone n (%)*	105 (25.6)	273 (24.5)	378 (24.8)
Previous fracture n (%)	13 (2.5)	81 (5.8)	94 (4.9)
Early RA[1] (n)	**Men (211)**	**Women (527)**	**All (738)**
Age (years) mean (SD)	57.9 (14.7)	55.4 (16.8)	56.1 (16.3)
Duration at inclusion (years), median (IQR)	<1 (<1-<1)	<1 (<1-<1)	<1 (<1-<1)
Duration at first questionnaire (years), median (IQR)	4 (2-5)	4 (2-5)	4 (2-5)
RF-positive n (%)	127 (67.7)	303 (66.3)	430 (66.7)
HAQ mean (SD)*	0.63 (0.59)	0.77 (0.57)	0.73 (0.58)
VAS pain (mm) mean (SD)*	37.3 (27.1)	40.1 (24.9)	39.4 (25.5)
VAS global health (mm) mean (SD)*	38.1 (26.6)	39.1 (24.4)	38.9 (25.0)
Methotrexate n (%)*	101 (67.3)	256 (62.6)	357 (63.9)
csDMARDs other than Methotrexate n (%)*	41 (27.3)	105 (25.7)	146 (26.1)
bDMARDs n (%)*	26 (17.3)	72 (17.6)	98 (17.5)
Prednisolone n (%)*	37 (24.7)	94 (23.0)	131 (23.4)
Previous fracture n (%)	1 (0.5)	12 (2.3)	13 (1.8)
Established RA[2] (n)	**Men (237)**	**Women (638)**	**All (875)**
Age (years) mean (SD)	64.1 (13.3)	63.4 (13.9)	63.6 (13.7)
Duration at inclusion (years), median (IQR)	14 (9-22)	15 (9-26)	15 (9-25)
Duration at first questionnaire (years), median (IQR)	18 (11-25)	18 (11-27)	18 (11-27)
RF-positive n (%)	141 (79.2)	402 (80.9)	543 (80.4)
HAQ mean (SD)*	0.96 (0.74)	1.35 (0.80)	1.24 (0.80)
VAS pain (mm) mean (SD)*	41.1 (27.7)	48.7 (27.2)	46.6 (27.6)
VAS global health (mm) mean (SD)*	41.3 (27.0)	46.5 (27.2)	45.0 (27.2)
Methotrexate n (%)*	62 (32.3)	157 (30.8)	219 (31.2)
csDMARDs other than Methotrexate n (%)*	52 (27.1)	149 (29.3)	201 (28.7)
bDMARDs n (%)*	13 (6.8)	38 (7.5)	51 (7.3)
Prednisolone n (%)*	56 (29.2)	130 (25.5)	186 (26.5)
Previous fracture n (%)	10 (4.2)	61 (9.6)	71 (8.1)

* At the date of the first available questionnaire. [1]Early RA: patients diagnosed in 1997 or later, within 1 year before inclusion with follow-up time maximal 10 years. [2]Established RA: patients with RA diagnosis for ≥5 years at study start (1997).
bDMARDs: biologic disease-modifying antirheumatic drugs; csDMARDs: conventional synthetic disease-modifying antirheumatic drugs; HAQ: Health Assessment Questionnaire; IQR: interquartile range; RA: rheumatoid arthritis; RF: rheumatoid factor; SD: standard deviation; VAS: Visual Analogue Scale.

Incidence and risk of fractures in RA patients compared to controls. A total of 51 (10.2%) men and 202 (15.8%) women with RA suffered from their first registered fracture during the study period. Among controls, the numbers were 118 (6.6%) for men and 602 (12.3%) for women. The incidence of fractures in total per 1000 person

years at risk was 7.86 (95% CI 5.85; 10.33) in men with RA compared to 4.70 (95% CI 3.89; 5.62) in male controls, and 11.6 (95% CI 10.0; 13.3) in women with RA compared to 8.27 (95% CI 7.62; 8.95) in female controls. The incidence in total for the RA cohort was 10.6/1000 pyr (95% CI 9.31; 12.0).

As shown in table 10, both men and women with RA had increased risk of fractures in total and in the hip compared with the matched controls. In analyses of the first 10 years of disease in the group of newly diagnosed patients, no increased risk of fractures overall or hip fractures was seen. Since there were only 7 fractures in total in men with early RA, no Cox regression analyses were done for this patient group. The risk of fractures in established RA (duration ≥5 years at study start) was slightly higher, especially the risk of hip fractures in men (HR 3.77, 95% CI 1.79; 7.96).

Table 10.
Incidence rate ratios and hazard ratios for fractures in RA patients compared with matched controls

	Incidence rate ratio (95% CI)			Hazard ratio (95% CI)		
Total cohort	**Men**	**Women**	**All**	**Men**	**Women**	**All**
Hip fracture	**1.81 (1.23; 2.61)**	**1.31 (1.08; 1.58)**	**1.39 (1.17; 1.64)**	**1.68 (1.05; 2.68)**	**1.41 (1.14; 1.75)**	**1.46 (1.20; 1.77)**
Fractures in total	**1.67 (1.18; 2.33)**	**1.40 (1.19; 1.64)**	**1.44 (1.24; 1.66)**	**1.55 (1.03; 2.34)**	**1.52 (1.27; 1.83)**	**1.53 (1.29; 1.81)**
Early RA[1]						
Hip fracture	0.97 (0.33; 2.46)	0.93 (0.50; 1.61)	0.94 (0.56; 1.50)	NA	0.85 (0.49; 1.49)	0.81 (0.50; 1.33)
Fractures in total	0.82 (0.31; 1.88)	1.13 (0.72; 1.72)	1.05 (0.71; 1.53)	NA	1.14 (0.74; 1.75)	1.01 (0.69; 1.49)
Established RA[2]						
Hip fracture	**3.11 (1.88; 5.06)**	**1.38 (1.06; 1.77)**	**1.61 (1.28; 2.00)**	**3.77 (1.79; 7.96)**	**1.76 (1.31; 2.38)**	**1.97 (1.50; 2.59)**
Fractures in total	**2.90 (1.81; 4.58)**	**1.44 (1.15; 1.80)**	**1.62 (1.32; 1.97)**	**2.99 (1.57; 5.70)**	**1.77 (1.36; 2.30)**	**1.91 (1.50; 2.43)**

Bold text indicates statistically significant results. [1]Early RA: patients diagnosed in 1997 or later, within 1 year before inclusion with follow-up time maximal 10 years. [2]Established RA: patients with RA diagnosis for ≥5 years at study start (1997).
CI: confidence interval; NA: not applicable due to <10 events in patients with RA; RA: rheumatoid arthritis.

Predictors of fractures in RA patients. Higher age, longer duration of RA, higher HAQ scores and higher scores in the VAS for global health at baseline were significantly associated with higher risk of fractures overall in unadjusted analyses, with similar results in stratified analyses of men and women (table 11). After adjustment for age, associations with HAQ scores and VAS for global health remained in the full group but were no longer significant in sex-stratified analyses. The associations seen between treatment with corticosteroids and fracture risk in unadjusted analyses were not statistically significant after adjustment for age. The results were similar in analyses of hip fractures only, and in patients with RA diagnosis for 5 years or more at study start. No predictor analyses were performed for the patients with early RA since no increased risk of fractures was found compared to the control group in these patients.

Table 11.
Baseline parameters and the risk of fractures overall in the full RA cohort, unadjusted and age-adjusted cox regression analyses

	Men (n 391)		Women (n 1008)		All (n 1399)	
	HR (95% CI)	Age-adjusted HR (95% CI)	HR (95% CI)	Age-adjusted HR (95% CI)	HR (95% CI)	Age-adjusted HR (95% CI)
Age, per 10 years	**3.59 (2.52; 5.12)**	NA	**2.32 (1.99; 2.71)**	NA	**2.51 (2.18; 2.90)**	NA
RA duration, per 10 years	**1.49 (1.19; 1.87)**	1.23 (0.99; 1.51)	**1.23 (1.09; 1.39)**	1.08 (0.96; 1.21)	**1.28 (1.15; 1.43)**	1.11 (1.00; 1.22)
RF-positive	1.02 (0.46; 2.23)	1.76 (0.79; 3.90)	NA[1]	NA[1]	1.07 (0.74; 1.53)	1.34 (0.93; 1.93)
HAQ, per SD	**1.68 (1.20; 2.34)**	1.40 (0.99; 1.96)	**1.36 (1.14; 1.63)**	1.11 (0.93; 1.33)	**1.45 (1.24; 1.69)**	**1.20 (1.03; 1.40)**
VAS pain, per SD	1.19 (0.86; 1.65)	1.31 (0.96; 1.80)	1.07 (0.90; 1.27)	1.01 (0.85; 1.20)	1.11 (0.96; 1.29)	1.10 (0.94; 1.28)
VAS global health, per SD	1.36 (0.98; 1.89)	**1.55 (1.11; 2.15)**	**1.20 (1.01; 1.43)**	1.10 (0.93; 1.32)	**1.25 (1.08; 1.46)**	**1.20 (1.03; 1.40)**
Methotrexate	NA[1]	NA[1]	0.84 (0.60; 1.17)	0.93 (0.66; 1.30)	NA[1]	NA[1]
bDMARDs	0.24 (0.03; 1.77)	0.65 (0.09; 4.85)	0.47 (0.22; 1.01)	1.01 (0.46; 2.19)	**0.41 (0.20; 0.85)**	0.90 (0.44; 1.85)
Prednisolone	1.68 (0.84; 3.34)	1.78 (0.88; 3.61)	**1.56 (1.09; 2.23)**	1.24 (0.86; 1.77)	**1.58 (1.16; 2.17)**	1.31 (0.95; 1.80)

At the date of the first available questionnaire. Bold text indicates statistically significant results.
bDMARDs: biologic disease-modifying antirheumatic drugs; CI: confidence interval; HAQ: Health Assessment Questionnaire; HR: hazard ratio; n: number of patients with at least one answered questionnaire after exclusion of patients with fractures before baseline; NA: not applicable; NA[1]: not applicable since proportional hazards assumptions were not fulfilled; RA: rheumatoid arthritis; RF: rheumatoid factor; SD: standard deviation; VAS: visual analogue scale.

Study IV

Risk and predictors of fractures in early RA - A long term follow-up study of an inception cohort

Study population, baseline characteristics and follow-up. Of the 233 patients (164 (70.4%) women and 69 (29.6%) men) and 932 matched controls (656 (70.4%) women and 276 (29.6%) men) selected for this study, one patient and one control were excluded because they were not registered in Sweden at the time of study start according to Statistics Sweden. Looking into the baseline characteristics of patients and controls, the proportions with upper-secondary education or higher, as well as individuals born in Sweden, were slightly higher in the patient group than in the controls, whereas there were similar rates (>80%) of individuals with 0 weights in the modified Charlson Comorbidity Index (CCI) (meaning none of the comorbidities included in the index were registered in the national patient register at baseline). Mean age of patients (and controls) was 60.5 years and as in study II mean duration of RA symptoms in patients was just over 7 months at inclusion. Baseline characteristics of patients with RA are shown in table 12. Of the women, 74% were postmenopausal. About 31% of women and 46% of men with RA were currently smoking, and 36% of the female and 46% of the male patients were treated with corticosteroids, with a mean dose of 8 and 11 mg/day respectively, at inclusion. Results of DXA measurements showed that 42 (27%) of the women with RA and 22 (35%) of the men had osteoporosis (T-score <-2.5) at baseline, and that 58 (36 %) of the women and 27 (40%) of the men had osteoporosis at at least one DXA examination during the 10 first years of follow-up. Six women but no men were treated with bisphosphonates at baseline. At the 10-year follow-up 53 (34%) women and 13 (20%) men had been treated with bisphosphonates at any point of follow-up.

Table 12.
Baseline characteristics in patients with early RA

Malmö early RA cohort (n)	Men (69)	Women (163)	All (232)
Age (years) mean (SD)	63.4 (11.1)	59.3 (15.7)	60.5 (14.6)
BMI (kg/m^2) mean (SD)	25.8 (3.9)	25.1 (4.2)	25.3 (4.1)
Smoking ever n (%)	57 (85.1)	97 (62.2)	154 (69.1)
Current smoking n (%)	31 (46.3)	48 (30.8)	79 (35.4)
Postmenopausal n (%)	NA	118 (73.8)	NA
Duration of symptoms (months) mean (SD)	7.0 (2.9)	7.6 (2.9)	7.4 (2.9)
RF-positive n (%)	47 (68.1)	97 (59.5)	144 (62.1)
Anti-CCP-positive n (%)	34 (59.6)	82 (56.6)	116 (57.4)
CRP (mg/l) median (IQR)	10.0 (<9.0; 33.5)	<9.0 (<9.0; 22.0)	9.0 (<9.0; 26.8)
ESR (mm) median (IQR)	22.0 (10.5; 44.5)	21 (10.0; 43.0)	21.0 (10.0; 43.0)
HAQ median (IQR)	0.75 (0.19; 1.13)	0.88 (0.47; 1.25)	0.75 (0.38; 1.25)
DAS28 mean (SD)	4.58 (1.49)	4.66 (1.36)	4.64 (1.40)
VAS global health (mm) mean (SD)	42.4 (26.2)	43.7 (27.1)	43.3 (26.8)
VAS pain (mm) mean (SD)	42.7 (29.0)	40.4 (25.8)	41.2 (26.7)
csDMARDs n (%)	57 (82.6)	134 (82.2)	191 (82.3)
bDMARDs n (%)	0 (0)	0 (0)	0 (0)
Corticosteroids n (%)	32 (46.4)	58 (35.6)	90 (38.8)
Corticosteroids dose (mg/day) mean (SD)	11.1 (6.2)	8.0 (4.3)	9.1 (5.2)
Calcium and vitamin D n (%)	16 (25.0)	52 (33.8)	68 (31.2)
Bisphosphonates n (%)	0 (0)	6 (3.9)	6 (2.6)
HRT n (%)	NA	24 (15.5)	NA
Index of muscle function median (IQR)	11.5 (6.0; 14.0)	10.0 (4.3; 18.8)	11.0 (5.0; 17.0)
Grip force in dominant hand (% of expected value) mean (SD)	41 (24)	39 (27)	40 (26)
Osteoporosis (T-score <-2.5)* n (%)	22 (34.9)	42 (27.1)	64 (29.4)
Osteopenia (T-score -1 to -2.5)* n (%)	16 (25.4)	49 (31.6)	65 (29.8)
Previous fracture n (%)	1 (1.4)	3 (1.8)	4 (1.7)

*in the femoral neck or in the lumbar spine (L2L4)
Data at inclusion were complete for age, symptom duration, RF status, CRP, ESR and treatment with csDMARDs, bDMARDs and corticosteroids. Ten patients had missing data on BMI, 9 patients on smoking history and 30 patients on anti-CCP. One patient had missing values on HAQ, DAS28 and VAS global and pain. Fourteen patients had missing data on treatment with calcium, vitamin D and bisphosphonates and on T-scores at baseline. Of the women, 3 had missing data on menopausal status and 8 on treatment with HRT. 126 patients had missing data on index of muscle function and 32 on grip force in dominant hand.
Anti-CCP: anti-cyclic citrullinated protein; bDMARDs: biologic disease-modifying antirheumatic drugs; BMI: body mass index; CRP: C-reactive protein; csDMARDs: conventional synthetic disease-modifying antirheumatic drugs; DAS28: Disease Activity Score-28; ESR: erythrocyte sedimentation rate; HAQ: Health Assessment Questionnaire; HRT: hormone replacement therapy; IQR: interquartile range; RA: rheumatoid arthritis; RF: rheumatoid factor; SD: standard deviation; VAS: visual analogue scale.

Incidence and risk of fractures in patients compared to controls. Four (1.7%) of the patients with RA and 31 (3.3%) of the controls had been diagnosed with at least one of the studied fractures before study start and were excluded from further analyses of the corresponding fractures. During the study period 78 (34%) patients and 218 (23%) controls suffered from their first incident fracture. The incidence ratio per 1000 person years of risk was 26.5 (95% CI 20.9; 33.1) in patients and 17.4 (95% CI 15.1; 19.8) in controls, giving an incidence rate ratio of 1.53 (95% CI 1.16; 1.98).

Details on the distribution of fractures and their incidence ratios are found in table 13.

In Cox regression models the risk of fractures was likewise significantly higher in patients with RA than in controls (HR 1.51, 95% CI 1.13; 2.02), with similar results for fractures in the lumbar spine and pelvis, and in the hip, although the difference did not reach statistical significance for hip fractures (table 13). Adjustments for level of education, country of birth and the modified CCI did not change the results.

Predictors of fractures in RA patients. At baseline, high age, low BMI and an index of muscle function (IMF) score over median were associated with higher risk of fractures (IMF only in unadjusted analyses). None of the RA severity measures or treatment were significantly associated with fracture risk after adjustment for age and sex at baseline. High Z-scores in the femoral neck and in the lumbar spine at baseline predicted lower risk of fractures overall, and in the respective location (hip/vertebra) during the study period. In time-dependent analyses higher HAQ-scores over the study period were associated with higher risk of fractures, and again high Z-scores in the femoral neck and lumbar spine predicted lower risk of fractures. These results remained statistically significant in multivariate models including age, time-dependent HAQ and Z-scores in the femoral neck or lumbar spine.

Table 13.
Number of individuals with fractures, incidence per 1000 person years at risk (pyr) and incidence ratios in patients with RA and controls, and risk of fractures in patients with RA vs controls: crude and adjusted cox regression models.

		Men		Women		All	
Fracture site		Patients	Controls	Patients	Controls	Patients	Controls
Any	n (%)	18 (26.1)	48 (17.5)	60 (36.8)	170 (25.9)	78 (33.6)	218 (23.4)
	Incidence per 1000 pyr (95% CI)	22.6 (13.4; 35.8)	13.8 (10.2; 18.3)	27.9 (21.3; 35.9)	18.7 (16.0; 21.8)	26.5 (20.9; 33.1)	17.4 (15.1; 19.8)
	Incidence ratio (95% CI)	1.64 (0.90; 2.85)		**1.49 (1.09; 2.00)**		**1.53 (1.16; 1.98)**	
	Hazard ratio, crude (95% CI)	1.55 (0.84; 2.84)		**1.50 (1.07; 2.09)**		**1.51 (1.13; 2.02)**	
	Hazard ratio adjusted for education, country of birth, modified CCI (95% CI)	ND		**1.53 (1.09; 2.15)**		**1.52 (1.13; 2.06)**	
Hip	n (%)	7 (10.1)	18 (6.5)	23 (14.1)	51 (7.8)	30 (12.9)	69 (7.4)
	Incidence per 1000 pyr (95% CI)	8.08 (3.25; 16.7)	4.81 (2.85; 7.60)	9.63 (6.10; 14.5)	5.09 (3.79; 6.69)	9.22 (6.22; 13.2)	5.01 (3.90; 6.34)
	Incidence ratio (95% CI)	1.68 (0.59; 4.26)		**1.89 (1.10; 3.13)**		**1.84 (1.16; 2.84)**	
	Hazard ratio, crude (95% CI)	NA		1.76 (1.00; 3.11)		1.59 (0.97; 2.59)	
	Hazard ratio adjusted for education, country of birth, modified CCI (95% CI)	NA		ND		ND	
Vertebral/pelvic	n (%)	6 (8.7)	19 (6.9)	25 (15.3)	60 (9.1)	31 (13.4)	79 (8.5)
	Incidence per 1000 pyr (95% CI)	6.75 (2.48; 14.7)	5.13 (3.09; 8.01)	10.5 (6.78; 15.5)	5.96 (4.55; 7.67)	9.46 (6.42; 13.4)	5.74 (4.54; 7.15)
	Incidence ratio (95% CI)	1.32 (0.43; 3.47)		**1.76 (1.06; 2.82)**		**1.65 (1.05; 2.51)**	
	Hazard ratio, crude (95% CI)	NA		**2.01 (1.18; 3.44)**		**1.71 (1.07; 2.76)**	
	Hazard ratio adjusted for education, country of birth, modified CCI (95% CI)	NA		**2.14 (1.22; 3.73)**		**1.78 (1.09; 2.90)**	
Upper arm	n (%)	6 (8.7)	13 (4.7)	17 (10.4)	57 (8.7)	23 (9.9)	70 (7.5)
	Incidence per 1000 pyr (95% CI)	6.98 (2.56; 15.2)	3.48 (1.85; 5.94)	7.05 (4.11; 11.3)	5.71 (4.32; 7.40)	7.03 (4.46; 10.6)	5.10 (3.98; 6.44)
	Incidence ratio (95% CI)	2.01 (0.63; 5.85)		1.23 (0.67; 2.14)		1.38 (0.82; 2.22)	
	Hazard ratio, crude (95% CI)	NA		1.31 (0.74; 2.33)		1.44 (0.87; 2.38)	
	Hazard ratio adjusted for education, country of birth, modified CCI (95% CI)	NA		ND		ND	

Forearm	n (%)	4 (5.8)	8 (2.9)	21 (12.9)	70 (10.7)	25 (10.8)	78 (8.4)
	Incidence per 1000 pyr (95% CI)	4.64 (1.26; 11.9)	2.13 (0.92; 4.19)	8.81 (5.45; 13.5)	7.17 (5.59; 9.06)	7.70 (4.98; 11.4)	5.76 (4.56; 7.20)
	Incidence ratio (95% CI)	2.18 (0.48; 9.29)		1.23 (0.72; 2.01)		1.34 (0.82; 2.11)	
	Hazard ratio, crude (95% CI)	NA		1.13 (0.68; 1.88)		1.30 (0.81; 2.09)	
	Hazard ratio adjusted for education, country of birth, modified CCI (95% CI)	NA		ND		ND	

Bold text indicates statistically significant results.
CCI: Charlson Comorbidity Index; CI: confidence interval; NA: not applicable due to less than 10 fractures in male RA patients; ND: not done due to lack of association in crude analysis or too few fractures for multi-adjusted analysis; Pyr: person years at risk.

Discussion

Severe ExRA and the relation to TNF-inhibitors

The overall incidence of new-onset ExRA was 0.67/100 person years at risk. Patients with higher age, male sex, longer duration of RA and positive RF had the highest risk of later onset of ExRA in this cohort of patients. These findings were in line with the findings of many other studies (16, 40). The reason for men having higher risk of ExRA is not extensively discussed in previous literature, although higher smoking rates are often suggested to contribute and one could speculate in hormonal differences affecting the risk, although neither smoking rates nor data on hormonal status were included in this study. There was a trend towards an association also with high HAQ at baseline, and there was a strong association with repeatedly high HAQ scores in time-dependent analyses of RF-negative patients. The association between higher HAQ and future ExRA has been shown before (29), and suggests a higher risk of severe ExRA in patients with a greater impact of RA on their functional ability.

The rationale for study I was the uncertainty about the risk of new-incidence or worsening of different ExRA manifestations after initiation of TNF-inhibitors. Especially the risk of RA-related ILD is still a question that seems to worry colleagues around the world (182). Most information on this topic comes from case reports (75-80), where there are also reports on patients improving in their ILD (and other ExRA manifestations) after initiation of TNF-inhibitors (86-90). Most cohort studies have not found anti-TNF agents to induce ILD to a higher extent than other DMARDs (81, 83, 84). In study I in this thesis, the incidences of new-onset severe ExRA, especially clinically relevant ILD, were relatively low in both anti-TNF treated and not anti-TNF treated groups of RA patients. Yet, although relatively uncommon, and although the incidence of severe ExRA over the study period was not substantially different in patients treated with TNF-inhibitors compared to those not receiving such treatment, there was a small but significant risk increase in age- and sex-adjusted time-dependent analyses. The patients with anti-TNF agents had a shorter history of disease and had more often been treated with Methotrexate and corticosteroids indicating higher disease activity earlier in the disease course. Methotrexate itself has also been associated with pneumonitis. Indeed, when the first case reports on anti-TNF-related ILD were published, one theory was that Metotrexate-related pneumonitis was induced by a synergistic effect of TNF-inhibitors (75, 77). The clinical records were notoriously examined in this study to eliminate this type of misclassification. Previous studies have reported higher risk

of ExRA in patients with high burden of disease activity and disability over time (29), which is also what indicates need of more potent treatment like TNF-inhibitors. Accordingly, there is risk of confounding by indication in this study. To control for differences in disease severity between patients treated and not treated with TNF-inhibitors, the analysis was adjusted for HAQ as a time-dependent covariate, and for a propensity score for anti-TNF treatment, but with similar results. Still, it cannot be ruled out that there is residual confounding that affects the results. Unfortunately, no other disease activity score was recorded in this cohort of patients, which limited further adjustments for disease activity. Looking into ILD specifically, there were only three cases diagnosed during treatment with TNF-inhibitors. All three patients continued with the anti-TNF agent after their ILD was confirmed.

In the light of the reports of high rates of patients with signs of ExRA when screening asymptomatic or post-mortem RA patients (41-44), the incidence of severe ExRA reported in this study is low, although not far from the incidences reported in previous studies using similar criteria for ExRA (45-47) or health insurance based data cohorts (83, 84). The low number of cases with vasculitis is in line with the impression of vasculitis being a diminishing clinical problem (50-52). Regarding ILD however, some authors argue that the awareness of ILD in RA has been relatively low, perhaps partly because symptoms can be diffuse or come gradually (44), maybe being drowned by articular symptoms, and therefore being missed, and it cannot be ruled out that this could have been the case also in our cohort. Yet, case series on anti-TNF-induced ILD report patients with clear symptoms and a relatively high death rate (75, 77). Therefore, it seems unlikely that this type of reaction should have been missed. More likely, the fact that the cohort included almost all patients with RA in the area, thus including both patients with severe and mild RA, could result in a lower incidence as in the other cohort studies mentioned above. The retrospective detection of ExRA in medical records, meaning that no further investigations were possible if not all criteria had been objectively verified or documented, could have led to a few cases not being captured in our study. However, our impression was that this was probably an unusual situation. The patients were treated according to the need of their disease which means that the results could be applicable to other RA patients living with similar health care opportunities. To note, this was a study of new-onset of ExRA, meaning patients with already known ExRA before study start were excluded. Accordingly, this study does not give any information about the risk of worsening of prevalent ExRA, and its' relation to drug treatment.

Bone mineral density in early RA

Women with RA had relatively well-preserved bone mass compared to healthy women of the same age during the first 10 years of disease, whereas men with RA had significantly lower bone mass than healthy men, although the difference was

modest. The first question is if the decline in bone mass, seen already at disease onset in men and further after 5 years, is clinically relevant, and if this decline influences the risk of future fractures. The least significant change (precision error*2.77: 1.6*2,77 or 0.9*2,77) (136) in BMD between the two measurements was around 4% so the decline seen in men (6.9%) was more than that. The rates of low T-scores and osteoporosis (presented in study IV) were higher than in the general population, especially in men, indicating that men in this cohort indeed had a clinically relevant loss of bone mass early in disease. Although not statistically significant, there was also a clear trend towards higher fracture risk in men, with incidence ratios >1.6 for all fracture types, indicating the results on BMD in men could indeed be of clinical importance. The second question is to what extent treatment of osteoporosis affected the results during follow-up in these patients. Since previous studies have indicated decreasing bone mass during the first years of disease (103, 113, 114), the fact that women in this cohort kept their Z-scores up could mean that women in this cohort were treated relatively well for their osteoporosis. At the end of the study about 35% had been treated with bisphosphonates at any point, which in relation to the osteoporosis rate of 36% is fairly good, although it is known that compliance with oral bisphosphonates is low (145, 155, 162). Men on the other hand were treated to a lesser extent, despite having higher rates of osteoporosis, which could be an explanation to the continuing loss of bone mass over the first 5 years. Looking at the descriptive characteristics at baseline and follow-up, men were a couple of years older on average, were more likely to be smokers at study start (shown in study IV) and had a slightly different course of disease with a higher proportion with erosive disease, somewhat more autoantibody-positivity, and more corticosteroids at study start which then was tapered in accordance with the reduction in disease activity which was more pronounced than in women. These factors are, according to other studies (94, 95, 100-104), all predictors of osteoporosis and fractures and might be complementary explanations for the differences between women and men, even if the predictor analyses in our studies did not support a clear association between disease severity measures and bone mass. Only positive anti-CCP had a significant association with lower Z-scores in the lumbar spine in women, which is indeed in line with the theory of osteoclast activation by ACPA (3, 137). DXA results in the lumbar spine is often affected by age-related degenerations and calcifications in the region (136) and the interpretation of results of increasing values in the lumbar spine of both men and women are somewhat difficult. The absence of spinal radiographs and evaluation of vertebral fractures, hence, is a limitation of the second study (and the following). The loss of patients to follow-up is another limitation since, although there were no obvious differences in baseline characteristics except for higher age in patients measured at inclusion compared to those with DXA results after 10 years, it cannot be ruled out that the patients lost to follow-up would have had different Z-scores than those who remained in the study. Finally, predictor analyses were also limited by the continuously ongoing treatment with anti-rheumatic and anti-osteoporotic agents, blurring the results for such analyses.

Risk of fractures compared with general population controls

According to the results of our two studies, patients with RA had a higher risk of fractures than the background population controls. High fracture rates in RA have been seen in many previous studies (28, 127, 129, 130, 183, 184), but fewer have investigated fracture rates during the early years after disease onset. Unfortunately, the results of study III and IV are conflicting regarding fracture risk in early RA. There are differences between the studies and the patient cohorts. First, we used a somewhat different set of ICD-codes in the two studies (with experience from the third study we adjusted the codes to better include pelvic fractures in the fourth study, but unfortunately the level of precision of the codes was restricted by The National Board of Health and Welfare in this study, resulting in a less detailed fracture capturing). We also asked for addition of codes from the specialized outpatient care in the last study in order to find more of the fractures not treated in inpatient care, which affected the distribution of fractures captured. Nevertheless, the ICD-codes for hip fractures were the same, and since most hip fractures are managed in hospitals the identification rates of hip fractures should be fairly comparable. The hip fracture incidence rates/1000 pyr of the controls in both studies are within the range to incidences reported in other studies of the Swedish general population (3.67, 95% CI 2.96; 4.50 in study III and 5.01 95% CI 3.90; 6.34 in study IV compared to population estimates among those >50 years old, annual age-standardised incidence/1000: 5.39 according to Kanis et al in 1991 (185), 8.5 in women and 3.6 in men according to Rogmark et al in 1992-95 (186), and a decrease from 7.92 to 4.67 and 3.57 to 2.65 in women and men between 1998 and 2017 according to Nordström et al (187)). The two patient cohorts are different in size but did not have different inclusion criteria (other than the early RA cohort exclusively included newly diagnosed patients with symptom duration <12 months). The recruitment of early RA patients in study III could to some extent be more prone to problems with left truncation in that patients were not followed according to a structured protocol from disease onset in contrast to those of the inception cohort used in study IV. Lack of reporting (in particular mild) cases and early mortality before start of follow-up could therefor influence recruitment of patients with early RA, and the assessment of fracture risk in this subset, to a greater extent in study III. Since symptom duration before diagnosis was not restricted and was unknown in the patients of study III this could differ between the patients with early RA in the two studies. On the other hand, the structured study program of the early RA cohort demanded a more active participation from the patients, which could induce some sort of selection of patients (maybe reflected by the slightly higher education and proportions of individuals born in Sweden in the patient group than in the general population controls).

Sweden has one of the highest hip fracture rates in the world (185), but country of birth did not influence fracture risk in study IV. In baseline characteristics there

are no obvious differences in disease severity measures between the patient groups, although the set of patients with early RA in the Malmö RA register answered their first questionnaire on average 4 years after diagnosis. For this reason, it is difficult to compare their treatment which tends to change during follow-up. The patients with early RA in the Malmö RA register were on average four to five years younger which surely affects fracture rates, but probably is not the only reason for the conflicting results. Still, age is relevant in this context since fracture rates generally increase vastly with age (186). Authors of a Spanish study observed that men with RA suffered from hip fractures on average 5-10 years earlier than healthy men, but at a mean age of 76.4 years (188). Perhaps the differences in fracture rates become more marked in older patient groups? The mean followed-up time at risk for fractures in the early RA cohort (study IV) was 14.7 years, whereas the follow-up time for early RA patients was restricted to 10 years (mean 8.1 years in cases, 7.9 in controls) in study III. However, even when restricting the follow-up time in study IV to a maximum of 10 years (mean 8.9 years in patients and controls) as in study III, the fracture risk was higher in the early RA cohort than in the controls (unpublished data: HR 1.62, 95% CI 1.12; 2.34).

The risk of hip fractures turned out to be especially high in men with established RA (disease duration ≥5 years at study start). This might reflect the above-mentioned observations that men with RA have fractures about 5-10 years earlier than other men, and with a mean age at 76 years (188). Men with established RA had a mean age of 64 years at study start and many of those could have reached the age of 76, whereas less men in the control group may have reached the age of 81-86 years during the study period. Men with established RA had a very similar incidence of hip fractures as women with established RA. The difference in risk ratios between men and women in this group might thus be explained by the higher background risk of fractures in women. Nevertheless, this finding highlights the importance of evaluating fracture risk in men with longstanding RA. It is of course worth noting that patients with established RA already in 1997 did not have the same opportunities in terms of treatment as RA patients diagnosed nowadays have.

Predictors of low bone mass and fractures in RA

Age and BMI were the most robust predictors of bone loss and fractures in all three studies, and they are well known risk factors for both osteoporosis and fractures (94-96), but relatively blunt tools for assessment of fracture risk. Further, the results in study IV show that levels of Z-scores had a clear effect on the risk of fractures in the RA patients, confirming the well-known association of low bone mass and fractures also in early RA. Autoantibodies and other signs of low grade inflammation have been demonstrated in many patients years before joint symptoms occur (6-11, 189), and may explain a part of the increased risk of osteoporosis seen already in the early stages of RA (3, 137). As mentioned, and as has been seen in

other studies of early RA (116, 117), positive anti-CCP was associated with lower Z-scores in the lumbar spine in women. Hormone related factors may also play a role. Previous work by for instance Pikwer et al, has revealed hormonal changes in both women and men before onset of RA (190, 191). Lower levels of testosterone compared to controls not developing RA were seen, especially in seronegative men (191), and early menopause was associated with increased risk of later RA diagnosis, with the strongest associations in seronegative women (190). Such hormonal differences could contribute to low bone mass in seronegative patients. However, the fact that women with RA had comparable bone mass with their healthy controls, were relatively well treated in relation to their rate of osteoporosis, and still had a clearly higher fracture risk than the general population controls, supports the concept that there are factors beyond BMD contributing to the difference in fracture rates between RA patients and others. The Z-score gives information on BMD compared with values considered normal for the given age and sex, but does not give information on the structure or quality of bone which is also relevant for evaluation of fracture risk. Until today, there are few studies on bone quality in early RA, but at later stages HRpQCT has indicated lower bone quality and strength in the distal radius and tibia (192), at least in ACPA-positive patients (193). Trabecular bone score has also been demonstrated to be lower in RA patients, and lower in those patients with prevalent fractures, but so far no prospective studies have been made to examine the predictive value of TBS on future fracture risk in RA (149).

Treatment with corticosteroids at baseline of the studies in this thesis did not significantly affect the results of BMD measurements or risk of fractures after adjustment for age, although one could argue that a trend for a higher risk of fractures in patients treated with corticosteroids can be seen, especially in the time dependent analyses in study IV. Treatment with corticosteroids is a well-known risk factor for fractures, but might in low doses early in disease, at least if combined with osteoporosis prophylaxis, have neutral effects in RA since reduced inflammation is thought to be beneficial in relation to osteoporosis development (104, 119, 147). In addition to the relatively low average doses used in the patients included, varying doses in between follow-up visits could be a reason for the statistically non-significant results. Worth mentioning, though, is that there was a strong trend towards elevated fracture risk also in patients not reporting treatment with corticosteroids, according to the exploratory analyses performed in study IV.

Inflammation can trigger loss of muscle mass (194, 195). In meta-analyses, sarcopenia (i.e. low muscle strength and low muscle quantity or quality) has been found in around 25-30% of RA patients (194, 195) and has been demonstrated to some extent already at early stages of disease (196). This has also been examined in a subset of the patients in our early RA cohort, revealing a significant lower lean mass of arms and legs in both women and men compared to healthy controls (197). After 2 years of antirheumatic treatment and, importantly also rehabilitation by occupational and physiotherapists, no further loss of lean body mass was seen compared with controls, but also no significant regain of the lost muscle mass (198).

Sarcopenia is associated with fractures, not only through associations with BMD (because less muscles means less strain and stress to stimulate bone remodelling) but also with falls (194, 195). Patients with RA have an increased risk of falling (127), with around 30% of patients reporting falls in studies (124), and falls are one of the most important risk factors for fractures. The American and British geriatric societies, the World Falls Guidelines and many other guidelines outline important risk factors and interventions to reduce falls in the general population (125, 126). Except for such general risk factors, RA patients have further increased risk related to impaired function in lower extremities due to stiff, swollen or tender joints (128). The risk of falls was not evaluated in the studies of this thesis, although we did look for surrogate markers such as lower extremity muscle function measured by the index of muscle function (IMF), and self-reported disability, measured by HAQ. Higher HAQ scores at baseline in study III (where patients had an average disease duration of 7 years at the time of their first answered questionnaire) and repeatedly higher HAQ scores in the time dependent analyses of study IV predicted higher fracture risk (but not HAQ results at time of diagnosis). In early RA, HAQ might to a greater part reflect physical impairment due to high disease activity, which is highly responsive to antirheumatic treatment, while in later disease stages, HAQ is seen as a relatively robust marker of disability and a more severe disease outcome (25). It is also associated with sarcopenia (194, 195) and, regarding to some but not all studies, with falls (124, 199). Consequently, it is not surprising that a high HAQ score predicted fractures. In study IV we also made an effort to evaluate lower extremity function through IMF, but unfortunately only a subset of the patients had been assessed, leading to limited statistical power for adjusted analyses and time dependent analyses of repeated measures. Grip force did not predict fractures in early RA in this study, in contrast with studies of non-RA individuals (200, 201), and one study of RA patients during the 70's and 80's (202). In early RA grip force is probably highly associated with joint inflammation, and therefore responsive to antirheumatic treatment, which is not the case in the general population where low grip force is linked to sarcopenia and potentially frailty explaining associations with fracture risk (200, 201). It has been difficult to define any specific RA severity measures that robustly identify patients with the highest risk of fractures already at diagnosis. This could have several explanations – high disease activity at diagnosis has the potential to be rapidly reduced by antirheumatic treatment and it has been proposed that where early treat-to-target is successful the risk of osteoporosis decreases, at least when combined with anti-osteoporotic treatment (116, 119). Also, the complexity of fracture prediction where many factors beyond RA severity have an influence might be a reason for the difficulties in selecting specific severity measures already at diagnosis.

Limitations and strengths

The main limitation of the first study is, as mentioned, the risk of confounding by indication – meaning the reason for the association found between treatment with TNF-inhibitors and severe ExRA could be due to the association between a more severe RA, which is a risk factor for severe ExRA, and the probability of being treated with TNF-inhibitors. In the light of the good effects on disease activity and progression of joint damage it would not be ethically correct to randomize patients to active or placebo treatment to clear this question completely and so we are left to try to compensate for this problem by adjusting for disease severity. Unfortunately baseline characteristics in the cohort were somewhat scarce, missing for instance disease activity measures, anti-CCP and smoking habits, and due to the low numbers of severe ExRA the number of patients presenting with new-onset ExRA during anti-TNF-treatment was low, leading to low precision in such adjusted analyses. This study was also limited to examining new-onset of ExRA and was not designed to study the risk of worsening of already present ExRA. Further limitations are the already mentioned retrospective detection of ExRA and the detailed classification criteria for ExRA (although this is also a strength) which could have resulted in some ExRA not being documented well enough or the date of onset being postponed until the diagnosis was assured by proper examination methods. The window of 30 days after discontinuation of TNF-inhibitors classified as anti-TNF-exposed time might have helped in attributing cases where TNF-inhibitors were stopped due to suspicion of ExRA manifestations, but these were fully diagnosed only after complementary examination, to anti-TNF treatment.

A limitation of the studies on fractures in this thesis is the fact that the cohorts used were established in about 1995-2005, which means that many patients were included just before standard use of biologic DMARDs in patients with high disease activity and during a time when treat-to-target was starting to get implemented in clinical practice. This raises the question of whether the results are transferable to patients diagnosed with RA today. Meta-analyses of fracture risk in RA have not shown lower incidences of fractures over time (28, 129) and although treatment to remission seems to mitigate the loss of bone mass otherwise seen in many patients (116, 119-121), so far no studies have demonstrated a clear protective effect against fractures. Nevertheless, it seems likely that the better patients are treated for their RA, the better they can avoid also other risk factors for fractures such as sarcopenia, falls and various side effects of high doses of corticosteroids.

As mentioned above, there was a lack of baseline characteristics in both cohorts (and controls), and more factors than those available would have been interesting to analyse. However, the main limitation of the Malmö early RA cohort is the small sample size making stratified analyses for instance in men difficult. There was a substantial loss to follow-up at least for the DXA measurements at the 10-year visit, and this might have affected the results of the last DXA evaluation (possibly giving somewhat higher values since baseline characteristic show that the group missing were older and thereby potentially frailer). Further, the loss to follow-up probably

affected the power of predictor analyses both of baseline and repeatedly measured factors. Baseline characteristics are valuable to predict the risk of future events but may give insufficient information because the disease phenotype, antirheumatic treatment and other factors generally change over time, and are thus not captured in baseline data. The repeated evaluation of the patients in both cohorts therefore is a strength, but still limited to the fairly long intervals at least after the first years of follow-up in the studies, allowing for fluctuations not captured in our data. RA treatment, and not to forget also treatment of osteoporosis, was continuously monitored according to the decisions of the patients' rheumatologists and in accordance with the (in the patients in the early RA register highly available) DXA scans. Consequently, the results of these studies reflect the treatment outcomes of the best practice at the time period of the studies. Again, this might have affected the chances of sharp predictor analyses in these studies.

The method of detection of fractures from registry databases without verification with radiographic documentation constitutes a limitation, especially for the detection of vertebral fractures. In comparisons between the Swedish Hip Fracture register and the National Patient register, there was a high agreement regarding hip fractures, although the National Patient register was believed to overestimate the number of recurrent fractures (166). This was also seen in humeral fractures when comparing the National Patient register to the Swedish Fracture register (167). Overestimation of recurrent fractures should not have affected the results of the studies in this thesis, since only the first upcoming fracture was analyzed.

Strengths in the studies of this thesis are the community-based cohorts which should make the results relatively applicable to the real-world patients being seen by rheumatologists in Sweden and in places with similar health care opportunities. The detailed criteria for severe ExRA which were developed to capture clinically relevant cases are helpful for the understanding of the scope of the problem of ExRA in relation to TNF-inhibitors. Also, the longitudinal design with a structured programme of follow-up in the early RA cohort gives a thorough description of the cohort for correlation to the results of bone mineral density and fracture risk over time in early RA. Finally, the possibility of relating DXA results in early RA to future fracture risk made it possible to highlight the importance of complementary risk factors for fractures after treating RA and osteoporosis.

Conclusions and future perspectives

In the Malmö RA cohort, ExRA and especially ILD was unusual both in RA patients treated with and not treated with TNF-inhibitors. However, the many case reports around the world on patients developing ILD and other ExRA after initiation of anti-TNF agents indicate that there might be rare circumstances in which inhibition of TNF-α is not optimal, although causality is not always easy to confirm due to the built-in confounding by indication. The mechanisms by which TNF-α affect the development of fibrosis in RA are not well understood, and more knowledge on its' effects in different disease settings, grades of inflammation and fibrosis would perhaps help in solving this question. Also, a deeper knowledge about the mechanisms of RA-related ILD itself is essential for further studies on timing of treatment. Such information could help clinicians make better treatment decision in relation to disease stage and underlying risk factors for ILD.

By contrast, other severe ExRA manifestations, such as vasculitis and pericarditis, were seen less frequently during treatment with TNF-inhibitors. This is compatible with a reduced incidence of these manifestations in recent years due to improved management of RA, and suggests that collaborative efforts are necessary for future studies of this aspect of severe RA.

RA patients are at high risk of osteoporosis and fractures. Antirheumatic treatment and osteoporosis prophylaxis helps reserving bone mineral density, but DXA results do not fully assess fracture risk, and the risk of fractures is still high in RA patients. Further improvements of fracture risk assessment, more information on the benefits of exercise (individual or by rehabilitation lead by physiotherapists and/or occupational therapists) in RA, and a more holistic approach on fracture prevention is needed to improve fracture rates in RA populations. Guidelines give valuable advice on fracture prevention, but further efforts are needed to bring them into clinical practice.

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Paper I

Severe Extraarticular Manifestations in a Community-based Cohort of Patients with Rheumatoid Arthritis: Risk Factors and Incidence in Relation to Treatment with Tumor Necrosis Factor Inhibitors

Lisa Theander, Britt-Marie Nyhäll-Wåhlin, Jan-Åke Nilsson, Minna Willim, Lennart T.H. Jacobsson, Ingemar F. Petersson, and Carl Turesson

ABSTRACT. ***Objective.*** The aims of this study were to evaluate whether treatment with tumor necrosis factor (TNF) inhibitors in patients with rheumatoid arthritis (RA) affects the risk of developing severe extraarticular rheumatoid arthritis (ExRA) manifestations and to investigate potential predictors for developing ExRA.

Methods. A dynamic community-based cohort of patients with RA was studied (n = 1977). Clinical records were reviewed and cases of severe ExRA were identified. Information on exposure to TNF inhibitors was obtained from a regional register. Exposure to TNF inhibitors was analyzed in a time-dependent fashion and the incidence of severe ExRA in exposed patients was compared with the incidence in unexposed patients. Cox regression models were used to assess potential predictors of severe ExRA.

Results. During treatment with TNF inhibitors, there were 17 patients with new onset of severe ExRA in 2400 person-years at risk (PY; 0.71/100 PY, 95% CI 0.41–1.13) compared with 104 in 15,599 PY (0.67/100 PY, 95% CI 0.54–0.81) in patients without TNF inhibitors. This corresponded to an incidence rate ratio of 1.06 (95% CI 0.60–1.78). The age- and sex-adjusted HR for ExRA in anti-TNF–treated patients was 1.21 (95% CI 1.02–1.43), with similar findings in models adjusted for time-dependent Health Assessment Questionnaire and propensity for anti-TNF treatment. Male sex, positive rheumatoid factor (RF), long disease duration, and greater disability were predictors for ExRA.

Conclusion. This study suggests that patients treated with TNF inhibitors are at a slightly increased risk of developing severe ExRA. RF-positive patients with disabling disease of long duration were more likely to develop severe ExRA. (First Release May 1 2017; J Rheumatol 2017;44:981–7; doi:10.3899/jrheum.161103)

Key Indexing Terms:
RHEUMATOID ARTHRITIS EXTRAARTICULAR MANIFESTATIONS TNF INHIBITORS
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Rheumatoid arthritis (RA) is a systemic autoimmune disease associated with extraarticular RA (ExRA) manifestations. ExRA affects various tissues and is divided into severe [e.g., vasculitis, interstitial lung disease (ILD), Felty's syndrome, pericarditis, pleuritis, scleritis] and less severe (e.g., rheumatoid nodules and secondary Sjögren syndrome) manifestations. Severe ExRA is associated with increased comorbidity and premature mortality[1,2,3,4,5,6]. Risk factors for ExRA are closely related to risk factors for more severe RA, including positive rheumatoid factor (RF), carriage of the *HLA-DRB1* shared epitope, and smoking[3,7,8]. High disease activity and disability burden over time in early RA have also been shown to be predictors of severe ExRA[9].

There is a wide variation in the reported incidence of

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ExRA. This variation is partly due to methodological issues, including the lack of consensus on how to classify ExRA. For this reason, in 2004 our group proposed a set of criteria for severe ExRA (Table 1)[3]. With these criteria, a 10-year cumulative incidence of 6.7% for severe ExRA was estimated for patients diagnosed with RA between 1995 and 2007[5]. A decrease in the incidence of some ExRA manifestations has been reported[5,10,11]. Indeed, with early and more aggressive treatment of RA, it may be expected that severe ExRA will be less common, but so far there are very limited data on the incidence of ExRA in relation to treatment.

Tumor necrosis factor (TNF) inhibitors efficiently reduce synovitis and progression of joint damage in RA, but their effect on ExRA is uncertain. There are several case reports on patients suffering from new onset or worsening of ExRA during treatment[12,13,14]. On the other hand, there are also reports of patients with ExRA improving after treatment with anti-TNF agents[15,16]. Patients with active ExRA were excluded from the large controlled trials of TNF inhibitors[12]. Further, these trials were not designed to study the occurrence of incident ExRA manifestations, and did not report this as an outcome. We have previously made an effort to investigate the effect of TNF inhibitors on the risk of ExRA in a study of a community-based sample of patients with RA[17]. We reported a lower estimated incidence of severe ExRA among patients treated with TNF inhibitors than patients not treated with such agents. However, the sample size and length of followup was limited, and the difference did not reach statistical significance[17].

The aim of our study was to extend previous studies to further evaluate whether treatment with TNF inhibitors has any effect on the risk of developing severe ExRA. The aim was also to investigate potential predictors of ExRA in questionnaire data obtained at the beginning of and during the study period.

MATERIALS AND METHODS

Patients and clinical characteristics. The study cohort (n = 1977) was based on a register of all known patients with RA in Malmö, Sweden, established in 1997. The patients in this register were recruited from the rheumatology outpatient clinic of Malmö University Hospital and from all rheumatologists in private practice in Malmö[18]. The register has been extended with newly diagnosed patients throughout the study period. All included patients were seen by a rheumatologist and diagnosed after fulfillment of the 1987 American College of Rheumatology criteria for RA[18,19]. At the time of establishment, the register covered about 95% of all patients with RA in the area[18].

Throughout the study period in 1997, 2002, 2005, and 2009, all patients received questionnaires including the Health Assessment Questionnaire (HAQ), visual analog scales (VAS) for current pain and global health, and questions on current and previous pharmacologic treatment. At least 1 completed questionnaire was obtained from 1551 (78%) of the included patients after 1 reminder.

Data on RF tests were retrieved from the databases of the 2 clinical immunology laboratories in the area. Patients with ≥ 1 positive RF test at any time were considered positive.

Identification of patients with ExRA. The previous survey of severe ExRA manifestations covered the period from July 1, 1997, to December 31, 2004. To identify additional cases of severe ExRA, an extended retrospective review of medical records from the hospital and rheumatologists in private practice from January 1, 2005, to December 31, 2011, was performed, as well as a complete review of the entire medical records for newly diagnosed patients. Identified cases were added to the cases previously reported by Nyhäll-Wåhlin, *et al*[17] from the period between January 1, 1998, and December 31, 2004. Severe ExRA was classified according to predefined criteria (Table 1)[3], which were also used in the previous survey[17]. Exclusion criteria were a history of ExRA before January 1, 1998, and first biologic therapy other than TNF inhibitors. In addition, patients whose diagnosis of RA had been reevaluated and questioned over time were excluded, as well as patients who were not residents in the area during any time of the study period.

Table 1. Criteria for severe extraarticular manifestations in rheumatoid arthritis[3] used in our study. Adapted from Turesson, *et al*. Scand J Rheumatol 2004;33:65-72; with permission.

Manifestation	Definition
Pericarditis	Clinical judgment and exudation verified by echocardiography. Other causes improbable, such as tuberculosis or other infection, metastases, primary tumor, postoperative status, or other trauma.
Pleuritis	Clinical suspicion and exudation verified by radiograph. Other causes improbable, such as tuberculosis or other infection, metastases, primary tumor, postoperative status, or other trauma.
Interstitial lung disease	Clinical symptoms and either vital capacity or carbon monoxide diffusion capacity reduced by 15% from normal. In addition, either HRCT or a lung biopsy compatible with interstitial lung disease.
Felty's syndrome	Splenomegaly (clinically evident or measured by ultrasound) and neutropenia (< 1.8 × 10^9/l) on 2 occasions. Other causes improbable, such as drug side effect or infection.
Neuropathy	Clinical judgment and signs of mononeuropathy/polyneuropathy at EMG/ENeG.
Scleritis, episcleritis, or retinal vasculitis	Clinical judgment by ophthalmologist.
Glomerulonephritis	Clinical judgment by nephrologist and positive biopsy.
Major cutaneous vasculitis	Diagnostic biopsy or clinical judgment by dermatologist.
Vasculitis involving other organs	Clinical judgment by organ specialist and biopsy compatible with vasculitis.

HRCT: high-resolution computed tomography; EMG: electromyography; ENeG: electroneurography.

Exposure to TNF inhibitors. Information on treatment with TNF inhibitors was obtained from the South Swedish Arthritis Treatment Group (SSATG) register, which in 2005 was estimated to include > 90% of patients with arthritis treated with biologic agents in the catchment area[20]. Ten rheumatology centers have joined the SSATG and they continuously report dates of starting and stopping biologic agents, as well as concomitant antirheumatic medication and measures of disease activity at the time of treatment start and followup. The use of personal identification numbers enables linkage to other registers and research databases. This regional register was continuously updated throughout the study period.

The incidence rate of ExRA in the group of patients treated with TNF inhibitors was compared with the incidence rate in the group of unexposed patients. Patients were considered to be exposed to TNF inhibitors until 30 days after registered discontinuation of the treatment. The period of risk for patients in the anti-TNF–treated group started the day they were registered in the SSATG register and ended 30 days after registered cessation of treatment, with registration of a biologic disease-modifying antirheumatic drug (bDMARD) other than TNF inhibitors, development of ExRA, death, emigration, or December 31, 2011, whichever occurred first. For the unexposed group, the period of risk instead started on January 1, 1998, or 30 days after a patient stopped treatment with anti-TNF agents. It stopped with the registration of treatment with TNF inhibitors or another bDMARD, development of ExRA, death, emigration, or December 31, 2011, whichever occurred first. Subjects could change groups over time, and the person-years at risk (PY) for every patient were separated and allocated to the appropriate group.

Ethics. This survey is included in longterm projects on followup of disease severity and adverse outcomes in the Malmö RA register and the SSATG register. These have been approved by the regional research ethics committee in south Sweden (LU336-01, LU-607-02). The study was conducted according to the principles of the Helsinki Declaration.

Statistical methods. Using the Poisson distribution ratio, the 95% CI for incidence rates and incidence rate ratios were estimated. The effect of time-dependent exposure to TNF inhibitors on severe ExRA was examined in Cox regression analyses. Start of followup (index date) was defined as January 1, 1998, or the date of diagnosis for patients with RA onset after this date. The analyses were adjusted for age at the index date and sex. Additional models were adjusted for HAQ, modeled as a time-dependent variable, and for a propensity score for anti-TNF treatment. The propensity score was based on logistic regression analysis and included demographics (sex and age at the index date) and baseline clinical characteristics [duration of RA, first available HAQ score, RF status, and treatment with methotrexate (MTX) and glucocorticoids] that were associated with initiation of anti-TNF treatment. For the analyses, adjusted for HAQ as a time-dependent variable, the date of the first available HAQ score was used as the start of the followup. Sensitivity analyses were stratified for RF status, and by duration of RA at the index date (< 4 yrs vs ≥ 4 yrs). Separate propensity scores were used for the stratified analyses. In models restricted by RF status, RF was excluded from the corresponding propensity scores.

Cox regression models were also used to assess the effect of baseline characteristics and baseline disease severity measures on the risk of ExRA, as well as the effect of time-dependent HAQ scores in bivariate and age- and sex-adjusted analyses. The analyses were performed using SPSS version 22.

RESULTS

Patients and ExRA manifestations. Of the 2481 patients in the register, 504 were excluded because of reasons mentioned (death before study start, not residents in the area during study period, reevaluation of diagnosis, or diagnosis never registered). Of the patients in our previous study, 91.4% were included. Demographic and clinical baseline characteristics of the study cohort are shown in Table 2. There were 1435 women (73%) and 542 men (27%) included in our study. A total of 20 patients naive to anti-TNF treatment started receiving another bDMARD other than TNF inhibitors. These were excluded from our analysis. Five hundred thirty-nine patients (27.3%) were treated with anti-TNF agents as their first bDMARD during the study period. Anti-TNF–treated patients were younger and were more often treated with MTX and glucocorticoids than patients not treated with anti-TNF (Table 2). Among women and men, 27.1% and 19.9%, respectively, were treated with TNF inhibitors during the followup.

In the study cohort, a total of 135 patients (6.8%) developed ExRA during the followup period (Table 3). Of these, 8 (5.9%) had had an extraarticular manifestation before January 1, 1998. Three patients had their first ExRA manifestation after this date, but before the date of RA diagnosis. These cases were also excluded. The total incidence of new-onset ExRA was 0.67/100 PY (95% CI 0.56–0.80). Pleuritis and major cutaneous vasculitis were the most frequent ExRA manifestations during the study period (Table 3).

Clinical predictors of ExRA. In bivariate analyses, higher age, male sex, longer duration of RA, and positive RF at baseline predicted the occurrence of ExRA (Table 4). Male sex was a predictor of ExRA, independent of age (age-adjusted HR 2.16, 95% CI 1.51–3.08). In analyses adjusted for age and sex, longer disease duration and positive RF were associated with increased risk of ExRA (Table 4). There was a borderline association with greater disability, measured by HAQ at baseline (Table 5) and in a time-dependent analysis (age- and sex-adjusted HR 1.45, 95% CI 0.94–2.24). Patient assessment of pain and global health did not have any major effect on the risk of ExRA in bivariate or multivariate analyses.

Association between anti-TNF treatment and ExRA. Seventeen patients developed new-onset ExRA during treatment with anti-TNF agents. Four had been treated with infliximab, 6 with etanercept, and 7 with adalimumab. Two of these patients had more than 1 ExRA during the study period. The distribution of different ExRA manifestations during anti-TNF treatment and without such treatment is shown in Table 3. There were no cases of pericarditis during anti-TNF treatment, whereas this occurred in 21 patients without anti-TNF treatment. Vasculitis also occurred less frequently than expected in patients treated with anti-TNF, whereas ophthalmologic manifestations were somewhat more frequent in this group (Table 3). There was no difference in the proportion of ILD among ExRA manifestations (18% vs 15% of all manifestations during exposure vs without exposure to TNF inhibitors).

With 2400 PY of anti-TNF exposure, the incidence of ExRA during anti-TNF treatment was 0.71/100 PY (95% CI 0.41–1.13). In the group not treated with anti-TNF, there were 104 cases of ExRA in 15,599 PY, with an incidence of 0.67/100 PY (95% CI 0.54–0.81). The incidence rate ratio when comparing the group receiving anti-TNF with the

Table 2. Baseline characteristics of patient groups.

Characteristics	Total Cohort	Anti-TNF during Followup	No Anti-TNF during Followup
Patients, n (%)	1977	539 (27.3)	1418 (71.7)
Age, yrs, mean (median)	59.9 (61.3)	50.4 (51.7)	63.6 (66.0)
RA duration, yrs, mean (median)	9.6 (4.0)	7.2 (3.0)	10.5 (5.0)
Women, n (%)	1435 (72.6)	420 (77.9)	999 (70.5)
Previous ExRA, n (%)	72 (3.6)	20 (3.7)	52 (3.7)
HAQ score*, mean (SD)	1.02 (0.76)	1.12 (0.69)	0.97 (0.79)
VAS pain*, mm, mean (SD)	42.9 (26.9)	44.6 (25.6)	42.0 (27.5)
VAS global health*, mm, mean (SD)	41.7 (26.5)	42.9 (24.9)	40.9 (27.2)
RF-positive, n (%)	1209 (73.6)	387 (83.9)	806 (69.2)
MTX*, n (%)	679 (45.3)	291 (58.7)	380 (38.6)
csDMARD except MTX*, n (%)	760 (50.7)	196 (39.5)	554 (56.3)
Glucocorticoids*, n (%)	422 (28.2)	202 (40.7)	213 (21.6)

* Based on first available questionnaire. Twenty patients had a first biologic agent other than a TNF inhibitor, and were excluded from the analyses of anti-TNF treatment during followup. Data on HAQ were available from 1623 patients (538 anti-TNF–treated, 1065 not anti-TNF–treated), on VAS pain from 1501 patients (458 anti-TNF–treated, 1023 not anti-TNF–treated), on VAS global health from 1498 patients (458 anti-TNF–treated, 1020 not anti-TNF–treated), and on pharmacological treatment from 1498 patients (496 anti-TNF–treated, 984 not anti-TNF–treated). HAQ: Health Assessment Questionnaire; VAS: visual analog scale; TNF: tumor necrosis factor; RA: rheumatoid arthritis; ExRA: extraarticular RA; RF: rheumatoid factor; csDMARD: conventional synthetic disease-modifying antirheumatic drug; MTX: methotrexate.

Table 3. Distribution of new-onset ExRA manifestations during the followup period. Values are n.

Variable	All	During Anti-TNF Treatment	Not during Anti-TNF Treatment
Any severe ExRA manifestation during followup*	124	17	104
Pericarditis	21	0	21
Pleuritis	41	7	34
Felty's syndrome	11	1	10
Interstitial lung disease	19	3	16
Glomerulonephritis	1	0	1
Neuropathy	13	1	12
Scleritis, episcleritis, or retinal vasculitis	21	6	14
Major cutaneous vasculitis	31	3	27
Vasculitis involving other organs	4	0	4

* Some patients had more than 1 severe ExRA during followup. Three patients had ExRA during or after treatment with biologic DMARD other than TNF inhibitors. There were no cases of retinal vasculitis. ExRA: extraarticular rheumatoid arthritis; DMARD: disease-modifying antirheumatic drugs; TNF: tumor necrosis factor.

Table 4. Baseline predictors of ExRA. Bivariate and multivariate Cox regression analyses.

Variable	HR (95% CI)	Sex- and Age-adjusted HR (95% CI)
Male	2.16 (1.51–3.08)	NA
Age, per 10 yrs	1.14 (1.01–1.29)	NA
RA duration, per 10 yrs	1.23 (1.09–1.39)	1.22 (1.07–1.39)
HAQ*, per SD	1.16 (0.94–1.43)	1.23 (1.00–1.53)
VAS pain*, per SD	1.02 (0.82–1.26)	1.06 (0.86–1.31)
VAS global health*, per SD	1.06 (0.86–1.32)	1.09 (0.88–1.35)
RF-positive	1.90 (1.15–3.15)	1.98 (1.19–3.28)

* Based on the first available questionnaire. RA: rheumatoid arthritis; ExRA: extraarticular RA; HAQ: Health Assessment Questionnaire; VAS: visual analog scale; RF: rheumatoid factor; NA: not applicable.

group not receiving anti-TNF was 1.06 (95% CI 0.60–1.78).

When examining the effect of time-dependent exposure to TNF inhibitors on severe ExRA, the risk of having severe ExRA was higher in the anti-TNF–treated group after adjustment for age and sex (HR 1.21, 95% CI 1.02–1.43). Results were similar in analyses further adjusted for HAQ as a time-dependent covariate and a propensity score for anti-TNF treatment, based on age, sex, RA duration, first available HAQ, RF status, and treatment with MTX and glucocorticoids at baseline (Table 5). The estimated HR for ExRA in anti-TNF–treated patients were similar in all tertiles of the propensity score (Appendix 1). The number of ExRA cases was balanced across these tertiles (Appendix 1).

Stratified analyses. A sensitivity analysis including only RF-positive patients was done with results following a similar pattern (Table 5). The association between anti-TNF treatment and ExRA did not reach statistical significance in RF-negative patients (Table 5). However, the statistical power was limited for this subanalysis, which included only 18 cases of ExRA (3 with onset during anti-TNF treatment). Time-dependent HAQ was a robust predictor of ExRA in the RF-negative subset, whereas it was not significantly associated with ExRA in patients with RF-positive RA (Table 5).

Table 5. Time-dependent predictors of ExRA. Cox regression analysis. Values are HR (95% CI).

Variable	Bivariate Analysis	Analysis Adjusted for Age and Sex	Multivariate Analysis*	Multivariate Analysis*, Adjusted for Age and Sex	Analysis Adjusted for Age, Sex, and Propensity Score**	Multivariate Analysis*, Adjusted for Age, Sex, and Propensity Score**
All						
Anti-TNF treatment, time dependent	1.10 (0.75–1.61)	1.21 (1.02–1.43)	1.17 (0.75–1.83)	1.38 (0.83–2.27)	1.25 (1.04–1.49)	1.63 (0.94–2.83)
HAQ, time dependent	1.25 (0.81–1.94)	1.45 (0.94–2.24)	1.24 (0.78–1.99)	1.29 (0.81–2.07)	ND	NA
RF-positive						
Anti-TNF treatment, time dependent	1.00 (0.65–1.55)	1.24 (1.03–1.48)	1.01 (0.60–1.70)	1.39 (0.79–2.44)	1.40 (1.19–1.66)	1.63 (0.91–2.91)
HAQ, time dependent	1.10 (0.65–1.86)	1.31 (0.77–2.23)	1.10 (0.62–1.92)	1.18 (0.67–2.07)	ND	NA
RF-negative						
Anti-TNF treatment, time dependent	2.38 (0.89–6.35)	1.10 (0.66–1.82)	1.24 (0.31–4.95)	1.08 (0.25–4.69)	1.18 (0.70–1.98)	1.33 (0.28–6.40)
HAQ, time dependent	4.68 (1.84–11.86)	4.58 (1.80–11.60)	4.17 (1.28–13.60)	4.39 (1.31–14.70)	ND	NA

* Includes both time-dependent predictors. ** Propensity score for anti-TNF treatment based on age, sex, RA duration, first available HAQ, RF status, and treatment with methotrexate and glucocorticoids at baseline (RF status excluded in propensity scores for only RF-positive or -negative patients). RA: rheumatoid arthritis; ExRA: extraarticular RA; TNF: tumor necrosis factor; HAQ: Health Assessment Questionnaire; RF: rheumatoid factor; ND: not done; NA: not applicable.

The association between anti-TNF treatment and ExRA was similar in patients with RA duration < 4 years at the index date (age-sex adjusted HR 1.24; 95% CI 0.96-1.62) and among those with RA duration ≥ 4 years (age-sex adjusted HR 1.17; 95% CI 0.94-1.46), with similar patterns in models adjusted for time-dependent HAQ and propensity score for anti-TNF treatment (data not shown).

DISCUSSION

The estimated incidence of severe ExRA in our study was not substantially different during treatment with TNF inhibitors compared with that observed in patients with RA not treated with TNF inhibitors. In age- and sex-adjusted analyses assessing the effect of time-dependent exposure to TNF inhibitors on severe ExRA, anti-TNF treatment was associated with a significantly increased risk. The magnitude of the estimated risk increase was limited, corresponding to a 21% increase in the risk of ExRA during the study period. Results were similar in models adjusted for HAQ as a time-dependent covariate, which was added to take into account the time-varying effect of disease severity. To control for differences in disease characteristics between those treated versus not treated with TNF inhibitors, analyses were further adjusted for a propensity score for anti-TNF treatment with similar results. Still, we cannot exclude that residual confounding may have an effect on these results.

Confounding by indication, i.e., signs and symptoms of inflammation due to ExRA manifestations that have not yet been diagnosed and contribute to the decision to initiate anti-TNF treatment, could affect these analyses. Further, patients with severe RA who are at increased risk of developing ExRA are more likely to be prescribed TNF inhibitors; drugs are used mainly in patients with RA who have an inadequate response to first-line therapy[21,22,23].

At baseline, anti-TNF–treated patients were younger, had a shorter history of disease, and more often had been treated with MTX and corticosteroids, indicating higher disease activity earlier in the disease course. The propensity score used in our study was based on baseline characteristics that could influence the probability of being treated with TNF inhibitors. However, changing disease activity over time can affect the need for more potent therapy. The addition of HAQ as a time-dependent covariate was an attempt to deal with this problem, although it may not fully account for the confounding effects of disease activity. Further, because of the lack of information regarding HAQ or the fact that some events occurred before our first registration of HAQ in a proportion of the study population, these adjusted analyses had limited statistical power. Disease Activity Score in 28 joints (DAS28) may have been a better measurement of disease activity, but regrettably, complete consecutive measurements of DAS28 were unavailable in this group of patients.

Men had a higher risk of developing ExRA than women, an association that, to various degrees, has been reported before[3,4,24]. In this sample, men were treated with TNF inhibitors to a lesser extent during the followup, but there was no such difference in a cross-sectional study from our catchment area[25]. Except for HAQ and VAS for current pain where men had lower scores, there were no apparent differences in baseline characteristics such as age, disease duration, RF status, or previous therapy between men and women (data not shown). Other factors may contribute to the higher risk of developing ExRA in men in our study, such as hormone-related factors or differences in lifestyle, including smoking habits. Earlier studies have shown that smoking at disease onset increases the risk of ExRA[8,9]; in a population-based survey from our catchment area, smoking was

more frequent among men than women in individuals who subsequently developed RA[26]. Unfortunately, information on smoking habits was not included in our present study.

Positive RF and longer duration of disease were 2 other factors that had a significant association with the development of ExRA when adjusted for sex and age. Extensive disability, measured as high HAQ scores, tended to be associated with ExRA in sex- and age-adjusted analyses. This is in line with results in previous studies indicating that the disability burden over time predicts severe ExRA[3,7,9]. In contrast, the VAS for pain and global health at baseline did not have a significant effect on the risk of ExRA, which may be due to fluctuation in these measures over time. For these measures, patients were asked to assess their symptoms over the last week, and this may not be representative for the patient's total burden of disease over time, in particular since it can be many years until an ExRA manifestation occurs and there may have been major changes in disease activity by then, not reflected by our data. Unfortunately, there was not sufficient information on anticitrullinated protein antibody status in the patients included in our study to investigate the relationship between this marker and severe ExRA.

In several case series, anti-TNF agents have been associated with new onset and exacerbation of ExRA[13,14,27], in particular ILD[14,28]. Based on *in vitro* studies and mouse models, an important role for TNF-α in the pathophysiology of pulmonary fibrosis has been proposed[29]. However, overall the reports on the role of TNF-α in fibrosis are contradictory[14,30]. In case reports, not only worsening of ILD has been reported, but also clinical improvement after anti-TNF therapy[15,31]. One observational study of the effect of TNF inhibitors on hospitalization for RA-associated ILD concluded that there was no clear evidence for a causal association between anti-TNF treatment and RA-associated ILD[32]. Two other studies found no increased occurrence of ILD in anti-TNF–treated patients[33], or in patients receiving biologic agents overall[34]. In our material, of the 17 cases of ExRA during anti-TNF therapy, only 3 were ILD. None of the cases were temporally associated with the initiation of therapy, and all 3 patients continued with the anti-TNF agent after the diagnosis of ILD. Our present results do not support a major role for TNF inhibitors in the induction of ILD in patients with RA.

There are several limitations in our study. First, owing to the observational study design, there may be confounding by indication. Second, the retrospective detection of ExRA restricts the source of information to medical records and no further investigations could be done if not all criteria for ExRA had been objectively verified. However, because the study was restricted to severe ExRA, it is likely that most events were identified by our review of medical records, although we cannot rule out that some events may have been missed or misclassified. Third, despite the prolonged followup period, the number of patients with ExRA during anti-TNF therapy was limited, leading to low precision for some of the statistical estimates, in particular for stratified and multivariate analyses. Finally, although a window of 30 days after discontinuation was classified as anti-TNF exposure time, a carryover effect of TNF inhibition cannot be excluded.

Strengths in our study include the method for detection of ExRA through the structured and thorough review of medical records, which is the preferred method for consistent assessment of clinical outcome in a retrospective study. In addition, the community-based design, the independent information on exposure to biologic agents prior to ExRA, and the completeness of the register used for this are strengths in our study. Finally, we have used the same classification criteria as in earlier studies, facilitating comparison of our results with the literature.

Our study suggests that patients treated with TNF inhibitors are at a slightly increased risk of developing severe ExRA, which could partially be explained by residual confounding because of higher disease activity in this group of patients. Male sex, RF positivity, long duration of disease, and greater disability were predictors of severe ExRA.

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APPENDIX 1. Time-dependent predictors of ExRA. Cox regression analysis in all patients and separate propensity score tertiles. The number of ExRA events was 37, 34, and 27 in the lowest to highest tertiles of propensity score in the crude and age- and sex-adjusted analyses, and 30, 30, and 21 in the time-dependent. Values are HR (95% CI).

Tertile	Crude Analysis	Adjusted for Age and Sex	Adjusted for HAQ, Time-dependent	Adjusted for Age, Sex, and HAQ, Time-dependent
All: anti-TNF treatment, time-dependent	1.10 (0.75–1.61)	1.21 (1.02–1.43)	1.17 (0.75–1.83)	1.38 (0.83–2.27)
Tertile 1: anti-TNF treatment, time-dependent	2.01 (0.88–4.57)	1.36 (0.89–2.08)	1.32 (0.40–4.41)	1.35 (0.39–4.66)
Tertile 2: anti-TNF treatment, time-dependent	1.30 (0.65–2.61)	1.29 (0.97–1.70)	1.26 (0.56–2.84)	1.31 (0.58–2.97)
Tertile 3: anti-TNF treatment, time-dependent	1.21 (0.54–2.70)	1.14 (0.86–1.52)	1.34 (0.54–3.34)	1.45 (0.58–3.64)

ExRA: extraarticular rheumatoid arthritis; HAQ: Health Assessment Questionnaire; TNF: tumor necrosis factor.

Paper II

RMD Open
Rheumatic & Musculoskeletal Diseases

ORIGINAL RESEARCH

Changes in bone mineral density over 10 years in patients with early rheumatoid arthritis

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ABSTRACT

Objectives To investigate changes in bone mineral density (BMD) in patients with early rheumatoid arthritis (RA) over a 10-year period.

Methods Consecutive patients with early RA (symptom duration <12 months) were followed according to a structured programme and examined with dual-energy X-ray absorptiometry (DXA) at inclusion and after 2, 5 and 10 years. Mean Z-scores over the study period were estimated using mixed linear effect models. Changes in Z-scores between follow-up visits were analysed using paired T-tests.

Results At inclusion, 220 patients were examined with DXA. At the femoral neck, the mean Z-score over 10 years was −0.33 (95 % CI −0.57 to −0.08) in men and −0.07 (−0.22 to 0.08) in women. Men had significantly lower BMD at the femoral neck than expected by age at inclusion (intercept Z-score value −0.35; 95 % CI −0.61 to −0.09), whereas there was no such difference in women. At the lumbar spine, the mean Z-score over the study period for men was −0.05 (−0.29 to 0.19) and for women 0.06 (−0.10 to 0.21). In paired comparisons of BMD at different follow-up visits, femoral neck Z-scores for men decreased significantly from inclusion to the 5-year follow-up. After 5 years, no further reduction was seen.

Conclusions In this observational study of a limited sample, men with early RA had reduced femoral neck BMD at diagnosis, with a further significant but marginal decline during the first 5 years. Lumbar spine BMD Z-scores were not reduced in men or women with early RA. Data on 10-year follow-up were limited.

Key messages

What is already known about this subject?

- Patients with rheumatoid arthritis (RA) have been shown to have an increased risk of osteoporosis and fractures.
- Higher loss of bone mass than expected by age has been apparent soon after diagnosis in several cohorts.

What does this study add?

- In this study of patients diagnosed with RA after 1995, bone mineral density in the femoral neck was reduced at diagnosis of RA in men but not in women.

How might this impact on clinical practice?

- In men with RA, potential benefits of early intervention against bone loss should be further studied.

INTRODUCTION

Patients with rheumatoid arthritis (RA) have been shown to have an increased risk of osteoporosis and fractures.[1–4] Although long standing and active, especially erosive, disease seems to be particularly predictive of osteoporosis in patients with RA,[3–6] higher loss of bone mass than expected by age has also been apparent soon after diagnosis in several cohorts.[7 8] In a study of bone mineral density (BMD) over the first 10 years in patients diagnosed with RA in the 1980s and early 1990s, Kroot *et al* found that bone loss was most marked during the first 2 years.[9] A similar pattern was seen in a study conducted 10 years later (inclusion 1999–2001), where the annual rate of bone loss was higher during the first 2 years compared with the following 8 years.[10] More aggressive antirheumatic treatment during the later part of the study period was suggested to contribute to this pattern.[10] With the rapid progress in the management of patients with RA, including more and better options for treatment to remission,[11] there is a persisting need for re-evaluation of the changes in BMD following RA diagnosis.

Osteoporosis affects both men and women, but there are important differences in incidence and in the course of bone loss. Women start losing bone at an earlier age and at a faster rate than men.[12] Among men, factors associated with secondary osteoporosis, such as alcoholism, excessive smoking and various comorbidities, are more common than in women.[13] Accordingly, there is a rational for separate analyses of BMD in men and women.

BMD varies with age and sex. Z-scores (number of SD above or below the mean BMD for the given age and sex) enable comparisons of BMD from time to time and between different individuals, whereas T-scores give information on whether a patient suffers from osteoporosis or not according to the WHO definition.[14] In previous studies, one SD decrease in BMD has been associated with roughly doubled fracture risk.[15 16]

In this study, we have followed patients with recently diagnosed RA, treated according to the general recommendations, for 10 years with repeated BMD measurements (dual-energy X-ray absorptiometry (DXA)). The aim was to examine changes in BMD by sex over the first 10 years and to investigate whether patients with RA have lower BMD than expected already at diagnosis, whether BMD changes during the course of disease and which baseline factors predict changes in bone mass. Insights on these issues are of importance for further improvement of the management of bone health in patients with RA.

MATERIALS AND METHODS

Patients

An inception cohort of consecutive patients with early RA (n=233, symptom duration <12 months), recruited between 1995 and 2005, was investigated. The catchment area was the city of Malmö, Sweden (population 260 000 in the year 2000). Patients were recruited from the rheumatology outpatient clinic of Malmö University Hospital, the only hospital serving the city, or from the four rheumatologists in private practice in the area. All included patients were diagnosed by a rheumatologist and fulfilled the 1987 American College of Rheumatology criteria for RA.[17] All patients were managed according to standard care without any prespecified protocol for antirheumatic treatment. The patients were included before the current practice of treat to target was implemented,[18] and before early treatment with biological disease modifying antirheumatic drugs (bDMARDs) came into widespread use. Results on other outcomes in this cohort have been reported previously.[19 20]

Clinical assessment

The patients were examined at inclusion and after 6, 12, 24, 60 and 120 months by the same rheumatologist according to a structured protocol. Disability was assessed using the Swedish validated version of the Health Assessment Questionnaire.[21] Visual Analogue Scales were used to evaluate the patients' assessment of current pain and the patients' global assessment of disease activity. Information on height, weight, smoking history (ever/never) and menopausal status was collected at inclusion through a self-administered questionnaire. Information on current use of synthetic disease modifying antirheumatic drugs (sDMARDs), glucocorticosteroids, antiosteoporotic agents and hormone replacement therapy (HRT) was obtained through a structured interview at each visit. Information on use of bDMARDs during the study period was obtained from the South Swedish Arthritis Treatment Group register[22] and the Swedish Rheumatology Quality register.[23]

Laboratory investigations

Rheumatoid factor (RF) and antibodies to cyclic citrullinated peptides (anti-CCP) were analysed at inclusion using standard ELISA methods at the Immunology laboratories at the University Hospitals in Malmö and Lund. IgM RF was analysed using ELISA, which was calibrated against the WHO RF reference preparation. Anti-CCP antibodies were analysed using the Quanta Lite CCP IgG ELISA (INOVA Diagnostics, USA). Erythrocyte sedimentation rate and C reactive protein were assessed according to standard methods at the Department of Clinical Chemistry, Malmö University Hospital.

Radiographic assessment

Radiographic evaluation of hands and feet was carried out at inclusion and after 2, 5 and 10 years of follow-up. The presence of erosions (present versus absent) was determined by a radiologist, unaware of the clinical status of the patient, as part of standard clinical practice.

Bone mineral density measurements

At inclusion and after 2, 5 and 10 years, the patients were examined with DXA at the left femoral neck and second to fourth lumbar spine vertebrae (L2-L4). The majority of patients were measured by the same DXA equipment (*Lunar DPX-L* equipment, 1.3z Lunar, Madison, Wisconsin, USA) during the study period. The centre applies quality control by daily checking the stability of the systems using a manufacturer-supplied phantom. In accordance with recommendations, precision is assessed as previously described: CV% 0.50% (total hip) and 0.65% (lumbar spine),[24] while higher in the very elderly.[25] For practical reasons, 67 of the patients had all their measurements done on either the *Lunar DPX-NT* equipment or *Lunar Prodigy* equipment. Seven of these patients had one measurement done on the *Lunar Prodigy* equipment and their other measurements on the *Lunar DPX-NT* equipment. Our analyses indicate that the difference between the machines is marginal (unpublished results). From the BMD values (g/cm^2) Z-scores (number of SD above or below the mean BMD for the given age and sex) were calculated using a cohort of healthy individuals (146 men and 178 women, age 20–87) from the same area as a reference population.[26] Gender-specific reference values were estimated using piecewise linear regression separately for patients aged 20–44 and ≥45 in the femoral neck in men and women and in the lumbar spine in men, but for patients aged 20–44, 45–64 and ≥65 in the lumbar spine in women.[26] Outliers were managed according to standard procedures used in other studies.[27] BMD values exceeding ±3 SD from the mean for the given age and sex were considered outliers and excluded from the analyses. Over the

study period, three measurements in the femoral neck and three measurements in the lumbar spine were excluded for this reason.

Statistics

The mean Z-scores over the study period were estimated using mixed linear effect models, where the intercept corresponded to the estimated mean Z-score at baseline, based on the regression line. The impact of baseline characteristics on the mean Z-score over 10 years was analysed in univariate models. In order to assess potentially independent effects on BMD Z-scores over time, significant predictors in the univariate models were further evaluated in multivariate analyses. In addition, the two established risk factors for osteoporosis, smoking and (in women) postmenopausal status, were included in all multivariate models. To assess collinearity, correlations between parameters were analysed using Spearman's test.

To evaluate changes in BMD during specific phases of early RA (0–2 years, 2–5 years, 5–10 years, 0–5 years and 0–10 years), changes in Z-scores between follow-up visits for patients with data at both time points were analysed using the paired T-test. Analyses were performed for the femoral neck and L2-L4 separately and stratified by sex. Data are presented as mean (95% CI). The analyses were performed using IBM SPSS statistics V.24.

Ethics

All patients gave their written informed consent to participate, and the study was approved by the Regional Ethical Review Board for southern Sweden (Lund, Sweden, LU 410–94, LU 311–02). The study was conducted according to the principles of the Helsinki Declaration.

RESULTS

Patients—baseline characteristics

A total of 233 patients were included in the cohort. Of these, 220 patients were examined with DXA at inclusion. Ten patients underwent the first DXA scan later during the study period, whereas three patients never came for any DXA examination. In three cases, BMD of the hip was not measured at inclusion. For men and women with baseline DXA measurements, the mean age at inclusion was 63.2 (SD 11.1) and 58.5 (SD 15.6) years, respectively, with a mean duration of symptoms of 7.1 (SD 2.8) and 7.5 (SD 2.9) months, respectively. Seventy-one per cent were women, whereof 73% (113/154) were postmenopausal. Baseline characteristics for patients with DXA data at each time point are shown in table 1. Of the included men, 44.9% had been examined with DXA at all occasions whereas the corresponding number was 50.6% for women. A total of 50 patients (19 men and 31 women) died during the 10-year follow-up. Except for a lower age at inclusion, characteristics of those with DXA data at all evaluations were not substantially different from those with DXA data at inclusion (table 1).

Treatment

sDMARDs were used in over 80% of men and women at baseline. Forty-nine per cent of the men and 36% of the women were treated with glucocorticoids at baseline (table 1). The average daily dose Prednisone at baseline among men was 11.1 mg and among women 8.0 mg. Treatment at every point of follow-up is presented in table 2. Throughout the study period, 11 men and 37 women had been treated with biological DMARDs at some point and all of these except for one woman had been treated with at least one TNF-inhibitor. At the 5-year follow-up, 16.7% of the men were treated with bisphosphonates, compared with 35.5% of the women.

BMD over time

Observed BMD Z-scores were numerically lower in men than in women at inclusion and at every point of follow-up (table 2). At the femoral neck, the mean Z-score over 10 years of time was −0.33 (−0.57 to −0.08) in men and −0.07 (−0.22 to 0.08) in women (table 3). Men had significantly lower BMD at the femoral neck than expected based on age at inclusion (estimated by the intercept Z-score value −0.35, 95% CI −0.61 to −0.09), whereas there was no significant overall change in femoral neck Z-scores over time, neither in men nor in women (table 3). At the lumbar spine, the intercept Z-score values were not significantly reduced in men or women. There was a small but significant increase in Z-scores at the lumbar spine over time in both groups (table 3). However, the mean estimated lumbar BMDs over the study period were not significantly different from the expected.

To examine changes in BMD between assessment points, individual patient Z-scores were compared in paired T-tests (figure 1). In the femoral neck, Z-scores for men decreased significantly from inclusion to the 5-year follow-up visit (mean change in Z-score −0.23, 95% CI −0.43 to −0.03), corresponding to a change in mean BMD of −6.9% (95% CI −4.5 to −9.3) during the same period. After 5 years, no further reduction was seen (figure 1A). Lumbar spine Z-scores increased in both men and women over the study period (figure 1C,D), which was consistent with the results from the mixed linear effect models above.

Predictors of BMD over time

In the univariate analyses, higher body mass index (BMI) was the sole baseline factor that was associated with high Z-scores over time in both the femoral neck and lumbar spine in men as well as women (table 4). In men, none of the RA associated factors were significantly associated with the mean Z-scores over time. In women, higher age and postmenopausal status were associated with lower Z-scores in the femoral neck, and positive anti-CCP and a history of smoking predicted lower Z-scores in the lumbar spine (table 4). None of the RA associated factors were associated with consistent differences in change in BMD over time in univariate or multivariate analyses (see online supplementary files 1 and 2).

Table 1 Baseline characteristics for patients with DXA measurements at each time point

	Women					Men				
Baseline characteristics	**Patients with data at inclusion**	**Patients with data at 2 years**	**Patients with data at 5 years**	**Patients with data at 10 years**	**Patients with complete DXA data**	**Patients with data at inclusion**	**Patients with data at 2 years**	**Patients with data at 5 years**	**Patients with data at 10 years**	**Patients with complete DXA data**
Number	157	138	122	89	83	63	58	51	33	31
Age (years) mean (SD)	58.5 (15.6)	58.2 (15.7)	58.5 (15.2)	56.4 (14.3)	56.6 (14.2)	63.2 (11.1)	62.3 (11.4)	61.0 (11.3)	58.6 (11.5)	58.4 (11.8)
Duration of symptoms (months) mean (SD)	7.5 (2.9)	7.5 (2.9)	7.4 (2.8)	7.5 (3.0)	7.6 (2.9)	7.1 (2.8)	7.0 (2.8)	7.0 (2.9)	7.2 (2.7)	7.0 (2.7)
BMI (kg/m^2) mean (SD)	24.9 (3.9)	25.0 (3.9)	25.2 (4.0)	25.7 (4.1)	25.7 (4.0)	25.3 (3.6)	25.9 (3.9)	25.9 (3.8)	25.9 (4.1)	25.5 (3.7)
Smoking ever n (%)	93 (62.4)	80 (60.2)	69 (59.5)	50 (60.2)	47 (59.5)	54 (87.1)	48 (84.2)	41 (83.7)	26 (81.3)	24 (80.0)
Postmenopausal n (%)	113 (73.4)	99 (72.8)	92 (76.7)	64 (73.6)	60 (74.1)	NA	NA	NA	NA	NA
RF positive n (%)	93 (59.2)	79 (57.2)	75 (61.5)	53 (59.6)	49 (59.0)	44 (69.8)	39 (67.2)	38 (74.5)	25 (75.8)	24 (77.4)
Anti-CCP positive n (%)	79 (57.2)	70 (56.5)	61 (55.5)	43 (54.4)	40 (53.3)	32 (61.5)	30 (63.8)	27 (65.9)	16 (61.5)	15 (62.5)
CRP (mg/L) median (IQR)	<9.0 (<9.0; 22.0)	<9.0 (<9.0; 17.3)	<9.0 (<9.0; 20.5)	<9.0 (<9.0; 16.0)	<9.0 (<9.0; 16.0)	13.0 (<9.0; 33.0)	11.5 (<9.0; 33.3)	13.0 (<9.0; 34.0)	10.0 (<9.0; 34.5)	14.0 (<9.0; 35.0)
ESR (mm) median (IQR)	21.0 (10.0; 43.0)	20.0 (10.0; 34.3)	21.0 (10.8; 39.3)	20.0 (10.0; 32.0)	18.0 (10.0; 30.0)	22.0 (10.0; 46.0)	20.0 (10.0; 46.5)	24.0 (11.0; 52.0)	18.0 (10.0; 43.0)	18.0 (10.0; 46.0)
Erosions n (%)	21 (13.4)	20 (14.5)	18 (14.8)	14 (15.7)	14 (16.9)	11 (17.5)	12 (20.7)	12 (23.5)	10 (30.3)	9 (29.0)
HAQ median (IQR)	0.75 (0.38; 1.25)	0.75 (0.38; 1.25)	0.82 (0.38; 1.25)	0.75 (0.38; 1.13)	0.75 (0.38; 1.13)	0.63 (0.13; 1.13)	0.75 (0.25; 1.13)	0.75 (0.25; 1.13)	0.75 (0.25; 1.13)	0.75 (0.25; 1.13)
DAS28 mean (SD)	4.63 (1.37)	4.55 (1.40)	4.59 (1.35)	4.48 (1.38)	4.37 (1.35)	4.57 (1.48)	4.66 (1.49)	4.70 (1.52)	4.61 (1.54)	4.63 (1.59)
VAS global (mm) mean (SD)	43.3 (27.1)	41.1 (26.9)	43.2 (27.0)	41.4 (25.2)	40.0 (25.2)	43.3 (26.1)	44.8 (26.4)	43.0 (25.6)	42.8 (26.6)	44.7 (26.2)
VAS pain (mm) mean (SD)	40.3 (25.6)	38.4 (25.6)	39.3 (25.9)	37.9 (24.9)	36.6 (24.8)	42.9 (28.7)	44.3 (28.7)	42.8 (29.0)	41.1 (28.6)	42.7 (28.7)
sDMARDs n (%)	128 (81.5)	115 (83.3)	102 (83.6)	75 (84.3)	69 (83.1)	54 (85.7)	49 (84.5)	45 (88.2)	29 (87.9)	28 (90.3)
bDMARDs n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Corticosteroids n (%)	57 (36.3)	49 (35.5)	39 (32.0)	31 (34.8)	27 (32.5)	31 (49.2)	26 (44.8)	24 (47.1)	14 (42.4)	14 (45.2)
Calcium and D-vitamin n (%)	50 (33.1)	47 (34.8)	36 (30.3)	26 (30.2)	24 (30.0)	16 (26.7)	16 (28.1)	14 (28.6)	10 (31.3)	10 (33.3)
Bisphosphonates n (%)	5 (3.3)	6 (4.4)	5 (4.2)	2 (2.3)	2 (2.5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0.0)
HRT n (%)	24 (15.8)	23 (17.0)	20 (16.8)	19 (22.1)	18 (22.5)	NA	NA	NA	NA	NA
Missing n (%)	0–19 (0–12.1)	0–14 (0–10.1)	0–12 (0–9.8)	0–10 (0–11.2)	0–8 (0–9.6)	0–11 (0–17.5)	0–11 (0–19.0)	0–10 (0–19.6)	0–7 (0–21.2)	0–7 (0–22.6)

Data at inclusion were complete for age, symptom duration, RF status, CRP, ESR, occurrence of erosions and treatment with sDMARDs and corticosteroids. Missing data for HAQ, DAS28 and VAS global and pain were 0.6% for women and none for men. 12.1% of the women and 17.5% of the men had missing data for anti-CCP. 3.2% of both women and men had missing data on BMI, 5.1% and 1.6%, respectively, on smoking history and 3.8% and 0%, respectively, on treatment with calcium, D-vitamin and bisphosphonates. 1.9% of the women had missing data on menopausal status and 3.2% on treatment with HRT.
anti-CCP, anticyclic citrullinated protein; bDMARDs, biological disease-modifying antirheumatic drugs; BMI, body mass index; CRP, C reactive protein; DAS28, Disease Activity Score-28 Joints; DXA, dual-energy X-ray absorptiometry; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; HRT, hormone replacement therapy; NA, not applicable; RF, rheumatoid factor; sDMARDs, synthetic disease-modifying antirheumatic drugs; VAS, Visual Analogue Scale.

Table 2 Clinical characteristics, treatment and BMD at each time point for those with available DXA data

Clinical characteristics	Women				Men			
	Inclusion	2 years	5 years	10 years	Inclusion	2 years	5 years	10 years
Number	157	138	122	89	63	58	51	33
Age (years) mean (SD)	58.5 (15.6)	60.8 (15.7)	64.1 (15.2)	66.9 (14.4)	63.2 (11.1)	64.9 (11.3)	66.5 (11.2)	69.3 (11.5)
BMI (kg/m^2) mean (SD)	24.9 (3.9)	25.6 (4.3)	NA	NA	25.3 (3.6)	25.8 (4.1)	NA	NA
CRP (mg/L) median (IQR)	<9.0 (<9.0; 22.0)	<9.0 (<9.0; 10.0)	<9.0 (<9.0; 9.0)	<9.0 (<9.0; 9.0)	13.0 (<9.0; 33.0)	<9.0 (<9.0; 15.0)	<9.0 (<9.0; 12.0)	<9.0 (<9.0; 23.0)
ESR (mm) median (IQR)	21.0 (10.0; 43.0)	15.0 (8.0; 24.0)	15.0 (9.0; 24.0)	15.5 (11.0; 26.0)	22.0 (10.0; 46.0)	15.5 (9.0; 30.5)	16.0 (9.0; 25.3)	18.5 (10.3; 31.8)
Erosions n (%)	21 (13.4)	37 (28.5)	41 (35.7)	25 (37.3)	11 (17.5)	28 (49.1)	27 (57.4)	16 (69.6)
HAQ median (IQR)	0.75 (0.38; 1.25)	0.63 (0.13; 1.06)	0.75 (0.38; 1.25)	0.75 (0.38; 1.19)	0.63 (0.13; 1.13)	0.32 (0.00; 0.91)	0.25 (0.00; 0.88)	0.57 (0.13; 1.00)
DAS28 mean (SD)	4.63 (1.37)	3.75 (1.39)	3.69 (1.41)	3.24 (0.96)	4.57 (1.48)	3.39 (1.40)	3.25 (1.31)	3.01 (1.09)
VAS global (mm) mean (SD)	43.3 (27.1)	36.6 (27.3)	36.2 (25.2)	31.6 (23.4)	43.3 (26.1)	26.6 (21.9)	29.9 (23.7)	28.9 (25.7)
VAS pain (mm) mean (SD)	40.3 (25.6)	35.2 (28.3)	32.4 (24.5)	29.9 (23.3)	42.9 (28.7)	24.8 (20.3)	25.1 (21.8)	26.4 (21.6)
sDMARDs n (%)	128 (81.5)	110 (82.7)	93 (76.9)	57 (70.4)	54 (85.7)	48 (82.8)	41 (80.4)	26 (81.3)
bDMARDs n (%)	0 (0)	9 (6.5)	21 (17.2)	21 (23.6)	0 (0)	4 (6.9)	8 (15.7)	7 (21.2)
Corticosteroids n (%)	57 (36.3)	44 (33.1)	38 (31.4)	20 (22.5)	31 (49.2)	15 (25.9)	12 (23.5)	8 (25.0)
Corticosteroids dose (mg/d) mean (SD)	8.0 (4.3)	5.2 (2.2)	5.0 (2.7)	6.4 (8.1)	11.1 (6.3)	5.3 (3.3)	5.8 (5.0)	6.6 (3.0)
Calcium and D-vitamin n (%)	50 (33.1)	87 (66.9)	74 (69.2)	34 (51.5)	16 (26.7)	29 (55.8)	21 (58.3)	14 (66.7)
Bisphosphonates n (%)	5 (3.3)	33 (25.4)	38 (35.5)	17 (25.8)	0 (0)	9 (17.3)	6 (16.7)	7 (33.3)
HRT n (%)	24 (15.8)	20 (15.4)	15 (14.1)	0 (0)	NA	NA	NA	NA
BMD femoral neck (g/cm^2) mean (SD)	0.85 (0.17)	0.83 (0.17)	0.82 (0.18)	0.82 (0.15)	0.88 (0.16)	0.87 (0.14)	0.86 (0.15)	0.86 (0.13)
BMD lumbar spine (g/cm^2) mean (SD)	1.07 (0.20)	1.08 (0.19)	1.10 (0.20)	1.14 (0.18)	1.16 (0.20)	1.16 (0.20)	1.15 (0.20)	1.18 (0.22)
Z-score femoral neck mean (SD)	−0.04 (1.03)	−0.09 (0.98)	−0.07 (1.11)	0.11 (0.92)	−0.27 (1.10)	−0.37 (0.99)	−0.38 (1.09)	−0.30 (0.91)
Z-score lumbar spine mean (SD)	−0.02 (1.04)	0.06 (0.99)	0.26 (1.05)	0.58 (0.99)	−0.12 (1.06)	−0.07 (1.07)	−0.15 (1.02)	−0.01 (1.13)

bDMARDs, biological disease-modifying antirheumatic drugs; BMD, bone mineral density (g/cm^2); BMI, body mass index; CRP, C reactive protein; DAS28, Disease Activity Score-28 Joints; DXA, dual-energy X-ray absorptiometry; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; HRT, hormone replacement therapy; NA, not available/not applicable; sDMARDs, synthetic disease-modifying antirheumatic drugs; VAS, Visual Analogue Scale.

Table 3 Z-scores in the lumbar spine and the femoral neck over 10 years of time*

	Mean Z-score		Intercept		Change/year	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
Lumbar spine women	0.057	−0.100 to 0.213	−0.043	−0.205 to 0.119	**0.039**	**0.025 to 0.053**
Lumbar spine men	−0.053	−0.294 to 0.187	−0.094	−0.365 to 0.176	**0.023**	**0 to 0.045**
Femoral neck women	−0.073	−0.222 to 0.076	−0.082	−0.593 to 0.429	0.003	−0.012 to 0.017
Femoral neck men	**−0.327**	**−0.570 to −0.085**	**−0.352**	**−0.614 to −0.090**	0.004	−0.014 to 0.023

Bold text indicates significant associations.
*Mixed linear effect models.

Despite being a significant predictor of reduced BMD in women, age was not included in the multivariate analyses due to high correlation with menopausal status (r 0.67, p<0.001). In these models, BMI had a positive association with BMD Z-scores for men and women in both locations (table 5). In women, postmenopausal status (femoral neck only) and positive anti-CCP (lumbar spine only) were significantly associated with lower mean Z-scores over the 10-year period in the adjusted analyses (table 5).

Neither treatment with calcium and vitamin D, bisphosphonates or glucocorticosteroids at baseline had a significant impact on the mean Z-scores over 10 years in the femoral neck or the lumbar spine (table 4). Treatment with HRT at baseline predicted higher Z-scores over time in the lumbar spine in women in univariate (table 4) and multivariate analyses (table 5).

DISCUSSION

In this study of repeated BMD measurements in patients with recent onset of RA, men had reduced BMD in the femoral neck already at diagnosis, with significant but marginal further decline during the first 5 years of follow-up. This pattern was not seen in women, whose BMD in the femoral neck did not differ significantly from healthy women of the same age. The average cumulative decline of BMD in men during the first 5 years was −6.9% (95% CI −4.5 to −9.3). Previous studies of repeated BMD measurements in men and women with early RA conducted in the early 1990's before the current practice of treat to target was implemented, have reported average annual rates of bone loss between −0.28% and −1.2% except for those with disease duration <6 months,[8 9 28] whereas studies conducted after the introduction of the biological DMARDs report annual rates between −0.5% and −1% per year.[10 29]

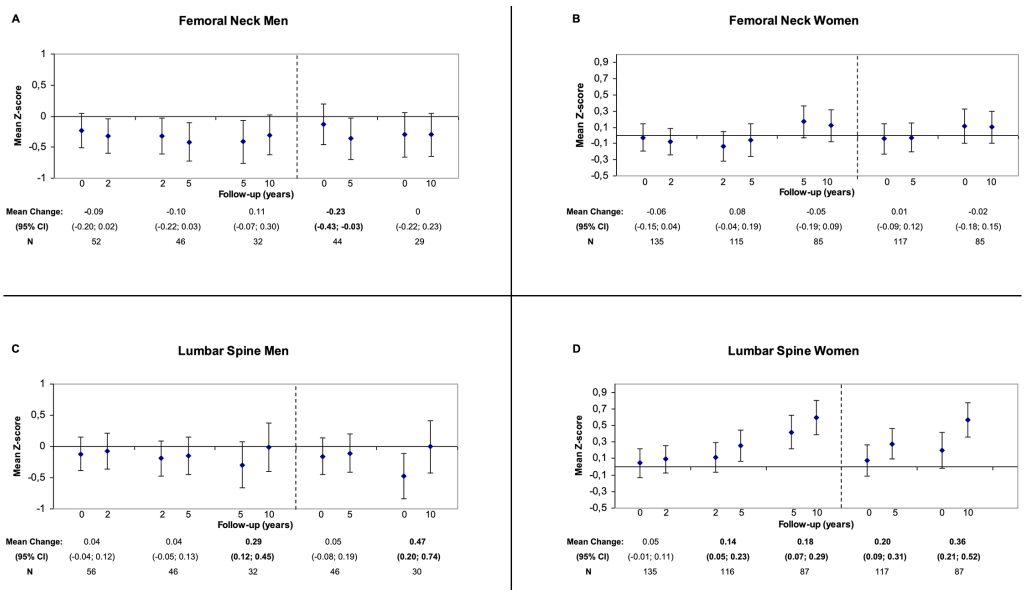

Figure 1 Pairwise comparisons of mean Z-scores between different follow-up visits, with mean changes of Z-scores.

Table 4 Relation between baseline characteristics and bone mineral density over the 10-year study period*

	Women				Men			
	Femoral neck		Lumbar spine		Femoral neck		Lumbar spine	
	Mean difference	95% CI	Mean difference	95% CI	Mean difference	95% CI	Mean difference	95% CI
Age	**−0.16**	**−0.31 to −0.02**	−0.10	−0.25 to 0.05	−0.22	−0.57 to 0.13	−0.06	−0.40 to 0.28
Postmenopausal	**−0.40**	**−0.76 to −0.04**	−0.06	−0.43 to 0.32	NA		NA	
BMI	**0.21**	**0.05 to 0.38**	**0.32**	**0.16 to 0.49**	**0.68**	**0.45 to 0.91**	**0.46**	**0.21 to 0.70**
Smoking (ever)	−0.22	−0.56 to 0.11	**−0.35**	**−0.69 to −0.01**	0.08	−0.67 to 0.84	0.25	−0.45 to 0.96
Symptom duration	−0.12	−0.27 to 0.04	−0.11	−0.27 to 0.06	0.01	−0.26 to 0.28	0.11	−0.15 to 0.37
Positive RF	−0.17	−0.49 to 0.15	−0.13	−0.46 to 0.20	0.25	−0.31 to 0.81	0.05	−0.49 to 0.58
Positive anti-CCP	−0.22	−0.56 to 0.13	**−0.35**	**−0.70 to 0.00**	0.27	−0.34 to 0.87	0.21	−0.33 to 0.75
DAS28	0.08	−0.08 to 0.24	−0.03	−0.20 to 0.14	−0.18	−0.42 to 0.06	−0.09	−0.33 to 0.14
HAQ	−0.02	−0.18 to 0.14	−0.08	−0.24 to 0.08	−0.14	−0.42 to 0.13	−0.08	−0.34 to 0.19
ESR	−0.03	−0.18 to 0.13	−0.03	−0.20 to 0.13	−0.15	−0.41 to 0.11	−0.11	−0.36 to 0.13
CRP >median	−0.12	−0.44 to 0.19	−0.11	−0.44 to 0.21	−0.03	−0.55 to 0.50	0.02	−0.48 to 0.52
VAS pain	0.08	−0.09 to 0.24	−0.02	−0.19 to 0.15	−0.07	−0.31 to 0.18	−0.02	−0.25 to 0.21
VAS global	0.03	−0.13 to 0.19	−0.06	−0.22 to 0.10	−0.17	−0.44 to 0.09	−0.17	−0.42 to 0.08
Erosions	−0.34	−0.80 to 0.12	−0.29	−0.76 to 0.18	0.33	−0.35 to 1.01	−0.32	−0.96 to 0.32
Corticosteroids	0.13	−0.20 to 0.46	0.12	−0.22 to 0.46	−0.04	−0.57 to 0.49	0.13	−0.36 to 0.63
Calcium & D-vitamin	−0.02	−0.37 to 0.32	−0.16	−0.51 to 0.18	0.25	−0.38 to 0.88	−0.09	−0.69 to 0.51
Bisphosphonates	−0.36	−1.17 to 0.45	−0.39	−1.20 to 0.42	NA		NA	
HRT	0.41	−0.03 to 0.85	**0.62**	**0.18 to 1.06**	NA		NA	

There were no men with treatment with bisphosphonates (or HRT) at baseline. Bold text indicates significant associations.
*Mixed linear effect models; estimated mean differences over time (Z-scores), per SD or positive versus negative.
anti-CCP, anticyclic citrullinated protein; BMI, body mass index; CRP, C reactive protein; DAS28, Disease Activity Score-28; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; NA, not applicable; RF, rheumatoid factor; VAS, Visual Analogue Scale.

Table 5 Multivariate analyses of the relation between baseline characteristics and BMD over the study period*

	Women				Men			
	Femoral neck		Lumbar spine		Femoral neck		Lumbar spine	
	Mean difference	95% CI	Mean difference	95% CI	Mean difference	95% CI	Mean difference	95% CI
Postmenopausal	**–0.50**	**–0.88 to –0.11**	–0.33	–0.74 to 0.08	NA		NA	
BMI	**0.24**	**0.07 to 0.41**	**0.40**	**0.23 to 0.57**	**0.70**	**0.46 to 0.95**	**0.48**	**0.23 to 0.74**
Smoking (ever)	–0.09	–0.44 to 0.26	–0.13	–0.49 to 0.23	0.38	–0.25 to 1.02	0.50	–0.16 to 1.17
Positive anti-CCP	NI		**–0.39**	**–0.75 to –0.03**	NI		NI	
HRT	NI		**0.67**	**0.23 to 1.11**	NA		NA	

Bold text indicates significant associations.
*Mixed linear effect models; estimated mean differences over time (Z-scores), per SD or positive versus negative. Adjusted for all variables in the table.
anti-CCP, anticyclic citrullinated protein; BMD, bone mineral density; BMI, body mass index; HRT, hormone replacement therapy; NA, not applicable; NI, not included.

The early loss of bone mass found in men in this study is in line with previous studies where reduction in BMD has been most pronounced in the first years after RA diagnosis.[8–10] Accelerated bone loss in men with RA has also been reported previously.[7 30 31] Potential explanations for the reduced BMD in men could include exposures that may predispose to both RA and low BMD in men, such as smoking[32] and low androgen levels,[33] although the importance of low androgen levels for bone mass is debated,[34 35] and there are limited data on their impact in men with RA.[4] Men also had more treatment with glucocorticosteroids, received antiosteoporotic treatment to a lesser extent and later and had more erosions at study start, although in this cohort none of these factors were significantly associated with Z-scores over time in neither the femoral neck nor lumbar spine.

Erosive disease has been presented as a risk factor for general osteoporosis in patients with RA,[4–6] while associations with other markers of disease severity have been reported with inconsistent results.[2 3 6 9 30 31 36] In this study, none of the disease-related factors had a significant effect on BMD in men, whereas positive anti-CCP antibodies were associated with lower Z-scores in the lumbar spine in women, after adjustment for postmenopausal status, BMI and smoking. The inconsistent reports of associations with RA severity may be due to difficulties in obtaining a robust marker for cumulative disease activity and severity over time. The limited number of male patients at the 10-year follow-up, and the modest average change in Z-score over time, may contribute to the lack of significant associations of disease severity measures and BMD in this study. Furthermore, ongoing treatment with both antirheumatic and antiosteoporotic drugs and changes in therapy and disease course over time may limit long-term prediction of BMD. In this study, low BMI was the only risk factor that predicted low BMD at both locations in both men and women. In women, postmenopausal status was associated with lower Z-scores in the femoral neck after adjustment for BMI and smoking, whereas treatment with HRT at baseline was associated with higher Z-scores in the lumbar spine.

Although osteoporosis, spinal osteoporosis and vertebral fractures in particular, is a well-established side-effect of glucocorticosteroids, there are ongoing discussions on the topic of the potential positive effects on BMD due to the anti-inflammatory effects of glucocorticosteroids in RA.[37] As with other disease related factors, there are conflicting results on the impact of glucocorticosteroids in patients with RA.[1 3 5 28 37] In this study, we did not find a significant association between baseline glucocorticosteroid treatment and BMD over time. The use of glucocorticosteroids was recorded at every follow-up visit but since treatment with Prednisone often varies over time, even in between follow-up visits, we decided against time-dependent analyses in this study.

In the lumbar spine, Z-scores in both men and women increased over the study period. Divergence in bone loss between the hip and spine is often reported, and the main

explanation for the higher BMD in the lumbar spine is the masking of bone loss by vertebral compression fractures, spinal degenerative changes and aortic calcifications.[6 10 38 39] In this study, spinal radiographs were not included and therefore we cannot evaluate such factors. Osteoarthritis in the lumbar spine is usually not considered to be a feature of RA, although we are not aware of any studies comparing osteoarthritis in the lumbar spine in patients with RA to healthy individuals. The increasing use of antiosteoporotic medication during the study period may also be part of the explanation for increasing Z-scores in the lumbar spine. Furthermore, the setting in which the study was performed, with regular DXA measurements, where antiosteoporotic treatment likely was changed based on DXA results, is favourable for preventing osteoporosis and may blunt or erase BMD changes during the course of the disease and limit long-term prediction of BMD. Such regular follow-up with DXA may likely contribute to a better BMD outcome in this study.

Limitations in this study are mainly due to the relatively small sample size and loss of patients for DXA follow-up measurements during the study period. Possibly, rapid bone loss during the last years before death could affect the estimated change in BMD in this study. Except for higher age, baseline characteristics of patients overall were not substantially different compared with the group with DXA data at all evaluations. Due to decreasing numbers with longer follow-up, power was limited for the predictor analyses, especially in men. A high prevalence of low D-vitamin levels has been observed in patients with RA,[40] which is an aspect that may be relevant in this context. However, levels of D-vitamin were not available in this study. Furthermore, the results of this study, where patients were included between 1995 and 2005, may not apply to patients treated with bDMARDs in early disease. Further studies of such patients would be of interest. Finally, exposure during the period from symptom onset to inclusion in the study may influence BMD in this study.

Strengths in this study include the longitudinal design with a follow-up period of 10 years and the structured programme in which patients were examined. The fact that our patients were treated according to the general recommendations suggests that the results are highly representative to clinical practice. Overall, women with RA retained their BMD fairly well. In men with RA, however, early intervention with antiosteoporotic treatment could be beneficial and should be further studied.

CONCLUSION

This study indicates that femoral neck BMD is reduced at diagnosis of RA in men but not in women. The lower femoral neck BMD in men was sustained over the first 5 years with a statistically significant but marginal further decline. In the lumbar spine, BMD Z-scores increased over the observation period. Taken together, low bone mass in early RA may be a greater problem in men than in women.

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Contributors LT participated in the study design and the data collection, performed the statistical analyses and wrote the first draft of the manuscript. MW managed the major part of the organisation of data for statistical analysis and participated in the analysis and interpretation of data. JÅN participated in the study design, the development of the patient questionnaires and the statistical analysis and in the analysis and interpretation of data. MK and KEÅ participated in the study design and in the analysis and interpretation of data. LJ participated in the study design, the design of the patient questionnaires and in the analysis and interpretation of data. CT conceived of the study, supervised the data management and the statistical analysis and helped draft the manuscript. All the authors helped in the revision of the manuscript and read and approved the final version.

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Supplementary Table 1. Relation between baseline characteristics and changes in BMD over the 10 year study period*

	Women				**Men**			
	Femoral Neck		Lumbar Spine		Femoral Neck		Lumbar Spine	
	Change/year	95% CI	Change/year	95% CI	Change/year	95% CI	Change/year	95% CI
Age	0.01	0.00; 0.03	**0.02**	**0.01; 0.03**	0.00	-0.02; 0.03	0.00	-0.03; 0.03
Post-menopausal	0.03	0.00; 0.06	**0.04**	**0.01; 0.07**	NA		NA	
BMI	0.00	-0.01; 0.02	0.00	-0.02; 0.01	-0.01	-0.03; 0.01	0.00	-0.03; 0.02
Smoking (ever)	-0.02	-0.06; 0.01	0.00	-0.03; 0.03	-0.01	-0.06; 0.04	-0.01	-0.08; 0.05
Symptom duration	0.01	0.00; 0.03	0.00	-0.01; 0.02	0.00	-0.02; 0.02	0.00	-0.03; 0.02
Positive RF	0.01	-0.02; 0.04	0.02	-0.01; 0.04	-0.04	-0.08; 0.00	-0.04	-0.09; 0.01
Positive anti-CCP	0.01	-0.03; 0.04	0.01	-0.02; 0.04	-0.03	-0.07; 0.01	**-0.07**	**-0.12; -0.01**
DAS28	-0.01	-0.03; 0.00	0.00	-0.02; 0.01	0.00	-0.02; 0.01	-0.02	-0.04; 0.00
HAQ	-0.01	-0.02; 0.01	0.01	-0.01; 0.02	0.00	-0.02; 0.02	0.01	-0.01; 0.04
ESR	-0.01	-0.02; 0.01	0.01	-0.01; 0.02	-0.01	-0.02; 0.01	-0.01	-0.03; 0.02
CRP>median	-0.01	-0.04; 0.02	0.01	-0.02; 0.04	-0.01	-0.05; 0.02	-0.03	-0.07; 0.02
VAS pain	-0.01	-0.03; 0.00	0.00	-0.02; 0.01	0.00	-0.02; 0.01	-0.01	-0.04; 0.01
VAS global	-0.01	-0.02; 0.01	0.00	-0.02; 0.01	-0.01	-0.03; 0.01	-0.02	-0.04; 0.00
Erosions	0.00	-0.04; 0.04	**0.05**	**0.01; 0.09**	-0.02	-0.06; 0.02	-0.01	-0.05; 0.06
Corticosteroids	-0.03	-0.06; 0.00	-0.01	-0.04; 0.02	-0.01	-0.05; 0.02	0.02	-0.03; 0.06
Calcium & D-vitamin	-0.01	-0.04; 0.03	0.00	-0.03; 0.03	-0.03	-0.07; 0.01	0.03	-0.02; 0.08
Bisphosphonates	0.00	-0.09; 0.09	0.05	-0.03; 0.14	NA		NA	
HRT	-0.01	-0.05; 0.03	**-0.04**	**-0.07; 0.00**	NA		NA	

* Mixed linear effect models; differences in change per year (Z-scores), per standard deviation or positive vs negative.
BMI: Body Mass Index. RF: Rheumatoid Factor. anti-CCP: anti-cyclic citrullinated protein. DAS28: Disease Activity Score-28. HAQ: Health Assessment Questionnaire. ESR: Erythrocyte Sedimentation Rate. CRP: C-reactive Protein. VAS: Visual Analogue Scale. CI: Confidence Interval. NA: not applicable.
There were no men with treatment with bisphosphonates (or HRT) at baseline. Bold text indicates significant associations.

Supplementary Table 2. Multivariate analyses of the relation between baseline characteristics and changes in BMD during the study *

	Women				**Men**			
	Femoral Neck		Lumbar Spine		Femoral Neck		Lumbar Spine	
	Change/year	95% CI	Change/year	95% CI	Change/year	95% CI	Change/year	95% CI
Postmenopausal	0.04	0.00; 0.07	0.04	0.00; 0.08	NA		NA	
BMI	0.00	-0.01; 0.02	-0.01	-0.03; 0.00	-0.01	-0.03; 0.01	0.00	-0.03; 0.02
Smoking (ever)	-0.03	-0.06; 0.00	-0.01	-0.04; 0.02	-0.02	-0.06; 0.03	-0.01	-0.07; 0.05
Positive anti-CCP	NI		0.01	-0.02; 0.04	NI		NI	
HRT	NI		-0.04	-0.07; 0.00	NA		NA	

* Mixed linear effect models; differences in change per year (Z-scores), per standard deviation or positive vs negative. Adjusted for all variables in the table.
BMD: bone mineral density. BMI: body mass index. anti-CCP: anti-cyclic citrullinated protein. HRT: hormone replacement therapy. CI: Confidence Interval. NA: not applicable. NI: not included.

Paper III

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Osteoporosis-related fractures in men and women with established and early rheumatoid arthritis: predictors and risk compared with the general population

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Abstract

Objectives To study the risk of osteoporosis-related fractures in a community-based sample of men and women with rheumatoid arthritis (RA) overall, as well as early (< 1 year of disease duration, follow-up time maximum 10 years) and established (RA diagnosis since ≥ 5 years on July 1, 1997) RA, compared with the general population. To study potential risk factors for fractures in patients with RA from baseline questionnaire data.

Methods A community-based cohort of patients with RA (n = 1928) was studied and compared to matched general population controls. Information on osteoporosis-related fractures (hip, proximal upper arm, distal forearm and vertebral fractures) during the period July 1, 1997 to December 31, 2017 was obtained by linkage to the Swedish National Inpatient Register and the Cause of Death Register. The incidence of fractures was estimated in patients and controls. Cox regression models were used to assess the relation between RA and the risk of fractures and to assess potential predictors of fractures in RA patients. Analyses were stratified by sex, and performed in all patients with RA, and in subsets with early and established RA.

Results The overall incidence of osteoporosis-related fractures in the RA cohort was 10.6 per 1000 person-years (95% CI 9.31; 12.0). There was an increased risk of fractures overall in both men (hazard ratio (HR) 1.55, 95% CI 1.03; 2.34) and women (HR 1.52; 95% CI 1.27; 1.83) with RA compared to controls, with significantly increased risk also in the hip. No increased risk of osteoporosis-related fractures overall was seen in patients with early RA (HR 1.01, 95% CI 0.69; 1.49). Higher age, longer duration of RA, higher HAQ scores and higher scores in the visual analogue scale for global health were predictors of fractures.

Conclusion Both men and women with RA were at increased risk of osteoporosis-related fractures. Patients with early RA did not have significantly increased risk during the first 10 years of disease in this study.

Keywords Rheumatoid arthritis, Fractures, Osteoporosis

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Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease associated with many comorbidities including osteoporosis and fragility fractures. Clinical evident osteoporosis (bone mineral density T-score<-2.5) has been observed in a substantial proportion of RA patients and has been viewed partly as a result of chronic inflammation, treatment with glucocorticosteroids, D-vitamin deficiency and immobility [1, 2]. In addition to risk factors of osteoporosis, patients with RA also have an increased risk of falling [3, 4], which predisposes them for fractures. Earlier studies and meta-analyses have shown that RA patients have about doubled risk for fractures compared to control populations [2, 5–7]. In studies comparing the incidence of fractures over time, no obvious reduction has been seen during recent years [5, 8, 9] despite better availability of treatment for both RA and osteoporosis. Indeed the "treatment gap" – i.e. the proportion of individuals with high risk of fracture with adequate treatment vs. the proportion of individuals with high risk of fracture without adequate treatment, for RA patients is getting increasing attention in literature [1, 2, 7, 10]. RA-related factors that have been associated with increased fracture risk are high disease activity, long disease duration and disability measured by the Health Assessment Questionnaire (HAQ) scores [2, 5, 6]. These are factors that reflect the effects of both chronic inflammation and level of physical activity on bone health. Established predictors of fractures in the general population, such as high age, low BMI, postmenopausal status in women, and prior fractures, also apply to patients with RA [5]. Loss of bone mass has been seen soon after RA diagnosis [11–13], but less is known about the risk of fractures in the early years after RA diagnosis. Nyhäll-Wåhlin et al. found an increased risk of fractures in patients followed from the time of diagnosis to a maximum of 8 years later [8]. Van Staa et al. found a significantly increased risk already during the first 2 years, although the risk increased with disease duration [14]. As data on risk of fracture in early RA is limited, this needs further investigation.

Men and women are affected by osteoporosis in different ways. Women typically experience bone loss earlier in life and at a faster rate than men due to hormonal changes at the time of menopause. Osteoporosis in men on the other hand is often overlooked and undertreated [15]. By examining the risks of fractures separately in men and women it is possible to find and highlight potential differences in risk and risk factors between men and women.

The aims of this study were (1) to examine the incidence of osteoporosis-related fractures (hip, proximal upper arm, distal forearm and vertebral fractures) in men and women with RA and compare it to that of the general population, with subanalyses of patients with a short disease duration, and (2) to investigate potential baseline predictors of such fractures in patients with RA. As hip fractures lead to a greater morbidity burden and are more reliably captured in the inpatient register than other osteoporosis-related fractures, we also investigated incidence and predictors of hip fractures separately.

Patients and methods

Patients and controls A community-based cohort of patients with RA (n=1928) was investigated. The cohort was based on a register of all known patients with RA in Malmö, Sweden, established in 1997. The patients were recruited from the rheumatology outpatient clinic of Malmö University Hospital and from all rheumatologists in private practice in Malmö. At the time of establishment, the register covered about 95% of all patients with RA in the area [16]. The register was extended with newly diagnosed patients until the year of 2006, as previously described [17, 18]. All patients were seen by a rheumatologist and diagnosed after fulfilment of the 1987 American College of Rheumatology criteria for RA.

Four controls without RA diagnosis per patient, individually matched for age at inclusion of the case in the register (+/- 1 year), sex and residential area were identified using the national census register from the general population. Retrieval of matched controls was performed by Statistics Sweden.

Clinical characteristics of patients In 1997, 2002, 2005, and 2009, the patients received questionnaires including the Health Assessment Questionnaire (HAQ), visual analogue scales (VAS) for current pain and global health, and questions on current and previous antirheumatic treatment. At least one completed questionnaire was obtained from 1523 (79%) of the included patients after one reminder during the study period. Information on treatment with biologic Disease-modifying Antirheumatic Drugs (bDMARDs) from study start to December 31, 2016 was obtained from the South Swedish Arthritis Treatment Group (SSATG) regional register on bDMARD treatment [19] and the Swedish Rheumatology Quality register [20], which includes national data on bDMARDs. Data on Rheumatoid Factor (RF) tests were retrieved from the databases of the two clinical immunology laboratories in the area. Patients with ≥1 positive RF test at any time were considered positive.

Identification of fractures Information on fractures in patients and controls during the period July 1, 1997 to December 31, 2017 was obtained by linkage to the Swedish National Inpatient Register and the Cause of Death Register. Fractures of the hip, proximal upper arm, distal forearm and vertebra were identified based on ICD-9 and ICD-10 diagnostic codes from in-patient care (Supple-

mentary Tables 1, Additional file 1). High-energy traumatic fractures during the study period were identified using ICD-10 external cause codes [21].

Statistics

Comparison of fracture rates in patients with RA and controls – main analyses Patients and controls with identified fractures before study start (1. July 1997 or date of RA diagnosis/corresponding index date for controls) were excluded from the analyses described below. Only the first incident fracture of the corresponding analysis was used in this study. In all analyses patients and controls were censored for death, emigration or end of study, 31 December 2017. The incidence of osteoporosis-related fractures in total (hip, proximal upper arm, distal forearm and vertebral fractures) and hip fractures specifically was estimated in RA patients and controls, overall and stratified by sex. The 95% confidence intervals (CI) for incidence rates and incidence rate ratios (IRRs) were estimated using the Poisson distribution ratio. For subsets with <5 events in RA patients, IRRs were not estimated.

The relation between RA and the risk of osteoporosis-related fractures in total and hip fractures was also assessed using Cox regression models and presented as hazard ratios. In order to take the matched design into account, the group variable identifying each case and its matched controls was entered as a stratum variable. Separate analyses for the 10 first years of disease in patients that were included in the register with <1 year of disease duration in 1997–2006 were performed to examine fracture incidence and hazard ratios in early RA. For comparison, the same analyses were performed in patients with RA diagnosis for ≥5 years on July 1, 1997. Early and established disease was also studied in a multivariable model where the interaction between RA and the status of disease (early vs. established) was analysed. For subsets with <10 events in RA patients no Cox regression analyses were performed. Although the expected numbers of fractures were lower, these analyses were also performed for the subsets of vertebral, proximal upper arm and distal forearm fractures.

Sensitivity analyses We performed Cox regression analyses where fractures with external cause ICD-10 codes for high-energy trauma during the study period were excluded [21]. In further sensitivity analyses for the risk of osteoporosis-related fractures overall in RA patients compared to matched controls, patients with osteoporosis-related fractures occurring before study start were not excluded. Instead, such fractures were adjusted for as a covariate in cox regression models.

Prediction of fractures in patients with RA The impact of baseline characteristics (age, duration of RA, RF status, HAQ score, VAS for current pain and patient's assessment of global health and treatment with Methotrexate, bDMARDs and Prednisolone at the date of the first answered questionnaire) on the risk of fractures in RA patients was examined in bivariate and age-adjusted Cox regression models. In these analyses the date of the first answered questionnaire was used as start of follow-up and the time to first fracture was investigated. Patients with fractures before start of follow-up were excluded. For all models proportional hazards assumptions were evaluated using log-minus-log plots and Schoenfeld residuals. The analyses were performed using SPSS version 25.

Ethics This study was approved by the Regional Ethical Review Board for southern Sweden (Lund, Sweden, LU 336-01, LU 2016/923). Informed consent was waived by the Regional Ethical Review Board for southern Sweden and was not obtained for the present study. The study was conducted according to the principles of the Helsinki Declaration.

Results

Patients and baseline characteristics Of the 1928 patients included in the study, 1401 (73%) were women. Mean age at inclusion was 60.5 (standard deviation (SD) 14.7) years in men and 59.5 (SD 15.9) years in women (age range 19–89 years and 16–93 years respectively). Median duration of disease was 3 (interquartile range 0–14) years in both men and women at inclusion. A total of 13 (2.5%) of the included men and 81 (5.8%) of the women with RA had had at least one of the studied fractures before study start. The corresponding numbers for controls was 33 (1.6%) in men and 186 (3.3%) in women. A total of 1022 (53.0%) of the included patients and 3649 (47.7%) of the controls were censored for death or emigration before December 31, 2017 (end of study). Of the men with RA, 105 (26%) and of the women, 273 (25%) reported treatment with glucocorticosteroids at the time of their first answered questionnaire. A total of 585 RA patients (30.3%) were treated with biologic DMARDs at any time during the study period, up to December 31, 2016. Further demographic and clinical baseline characteristics of the study cohort are shown in Table 1. Patients with newly diagnosed RA (RA duration <1 year at baseline, n=738) were on average younger and less frequently RF positive, had lower HAQ scores and were more often treated with methotrexate and biologic DMARDs at the time of their first answered questionnaire (Table 1). In the group of patients with fractures before study start both men and women were older, had longer duration of disease, a somewhat higher proportion with positive RF and scored higher in disease activity measures than patients without previous fractures (Supplementary Tables 2, Additional file 1). Patients who had not returned any completed questionnaires during

Table 1 Baseline characteristics for patients in the total cohort, with early and established RA

Total cohort	**Men**	**Women**	**All**
Number	527	1401	1928
Age (years) mean (SD)	60.5 (14.7)	59.5 (15.9)	59.8 (15.6)
RA duration at inclusion (years), median (IQR)	3 (0–14)	3 (0–14)	3 (0–14)
RA duration at first questionnaire (years), median (IQR)	7 (4–17)	7 (4–17)	7 (4–17)
RF-positive n (%)	322 (73.5)	855 (73.3)	1177 (73.3)
HAQ mean (SD)*	0.75 (0.68)	1.1 (0.76)	0.97 (0.75)
VAS pain (mm) mean (SD)*	37.9 (27.4)	44.5 (26.5)	42.7 (26.9)
VAS global health (mm) mean (SD)*	38.2 (26.4)	42.7 (26.2)	41.5 (26.3)
Methotrexate n (%)*	189 (46.1)	479 (43.0)	668 (43.9)
csDMARDs other than Methotrexate n (%)*	114 (27.8)	321 (28.8)	435 (28.6)
bDMARDs n (%)*	42 (10.2)	121 (10.9)	163 (10.7)
Prednisolone n (%)*	105 (25.6)	273 (24.5)	378 (24.8)
Previous osteoporosis-related fracture n (%)	13 (2.5)	81 (5.8)	94 (4.9)
Early RA¶	**Men**	**Women**	**All**
Number	211	527	738
Age (years) mean (SD)	57.9 (14.7)	55.4 (16.8)	56.1 (16.3)
RA duration at inclusion (years), median (IQR)	< 1 (< 1-<1)	< 1 (< 1-<1)	< 1 (< 1-<1)
RA duration at first questionnaire (years), median (IQR)	4 (2–5)	4 (2–5)	4 (2–5)
RF-positive n (%)	127 (67.7)	303 (66.3)	430 (66.7)
HAQ mean (SD)*	0.63 (0.59)	0.77 (0.57)	0.73 (0.58)
VAS pain (mm) mean (SD)*	37.3 (27.1)	40.1 (24.9)	39.4 (25.5)
VAS global health (mm) mean (SD)*	38.1 (26.6)	39.1 (24.4)	38.9 (25.0)
Methotrexate n (%)*	101 (67.3)	256 (62.6)	357 (63.9)
csDMARDs other than Methotrexate n (%)*	41 (27.3)	105 (25.7)	146 (26.1)
bDMARDs n (%)*	26 (17.3)	72 (17.6)	98 (17.5)
Prednisolone n (%)*	37 (24.7)	94 (23.0)	131 (23.4)
Previous osteoporosis-related fracture n (%)	1 (0.5)	12 (2.3)	13 (1.8)
Established RA¶¶	**Men**	**Women**	**All**
Number	237	638	875
Age (years) mean (SD)	64.1 (13.3)	63.4 (13.9)	63.6 (13.7)
RA duration at inclusion (years), median (IQR)	14 (9–22)	15 (9–26)	15 (9–25)
RA duration at first questionnaire (years), median (IQR)	18 (11–25)	18 (11–27)	18 (11–27)
RF-positive n (%)	141 (79.2)	402 (80.9)	543 (80.4)
HAQ mean (SD)*	0.96 (0.74)	1.35 (0.80)	1.24 (0.80)
VAS pain (mm) mean (SD)*	41.1 (27.7)	48.7 (27.2)	46.6 (27.6)
VAS global health (mm) mean (SD)*	41.3 (27.0)	46.5 (27.2)	45.0 (27.2)
Methotrexate n (%)*	62 (32.3)	157 (30.8)	219 (31.2)
csDMARDs other than Methotrexate n (%)*	52 (27.1)	149 (29.3)	201 (28.7)
bDMARDs n (%)*	13 (6.8)	38 (7.5)	51 (7.3)
Prednisolone n (%)*	56 (29.2)	130 (25.5)	186 (26.5)
Previous osteoporosis-related fracture n (%)	10 (4.2)	61 (9.6)	71 (8.1)

*At the date of the first available questionnaire

In the total cohort at least one questionnaire was answered by 1523 patients. Of these 10 were missing HAQ, 50 missing VAS pain and 52 missing VAS global health

SD: Standard Deviation; IQR: Interquartile Range; RA: Rheumatoid Arthritis; RF: Rheumatoid Factor; HAQ: Health Assessment Questionnaire; VAS: Visual Analogue Scale; csDMARDs: conventional synthetic Disease-modifying Antirheumatic Drugs; bDMARDs: biologic Disease-modifying Antirheumatic Drugs

¶Early RA: newly diagnosed (within 1 year) patients in 1997 or later, with follow-up time maximal 10 years

¶¶Established RA: patients with RA diagnosis for ≥5 years at study start (1997)

the study period were older and had had more fractures before study start (Supplementary Tables 3, Additional file 1).

Incidence and risk of fractures in RA patients without previous fractures compared with controls A total of 51 (10.2%) men and 202 (15.8%) women with RA suffered from at least one of the studied fractures during the study period, compared with 118 (6.6%) male and 602 (12.3%)

Table 2 Number and incidence of osteoporosis-related fractures in RA patients and matched controls

		Men		Women		All	
Fracture	**Total cohort**	**RA patients**	**Controls**	**RA patients**	**Controls**	**RA patients**	**Controls**
Hip	n (%)	43 (8.5)	92 (5.1)	147 (11.2)	463 (9.3)	190 (10.5)	555 (8.2)
	Incidence/1000 PY (95% CI)	6.56 (4.75; 8.84)	3.63 (2.93; 4.45)	8.16 (6.89; 9.59)	6.21 (5.66; 6.81)	7.73 (6.67; 8.91)	5.56 (5.11; 6.04)
Fractures in total	n (%)	51 (10.2)	118 (6.6)	202 (15.8)	602 (12.3)	253 (14.2)	720 (10.8)
	Incidence/1000 PY (95% CI)	7.86 (5.85; 10.33)	4.70 (3.89; 5.62)	11.58 (10.04; 13.29)	8.27 (7.62; 8.95)	10.57 (9.31; 11.96)	7.35 (6.82; 7.91)
Fracture	**Early RA***	**RA patients**	**Controls**	**RA patients**	**Controls**	**RA patients**	**Controls**
Hip	n (%)	6 (3.0)	24 (3.0)	16 (3.2)	68 (3.4)	22 (3.1)	92 (3.3)
	Incidence/1000 PY (95% CI)	3.41 (1.25; 7.43)	3.51 (2.25; 5.22)	3.48 (1.22; 5.64)	3.73 (2.90; 4.73)	3.46 (2.17; 5.24)	3.67 (2.96; 4.50)
Fractures in total	n (%)	7 (3.4)	33 (4.2)	29 (5.8)	101 (5.1)	36 (5.1)	134 (4.8)
	Incidence/1000 PY (95% CI)	4.00 (1.61; 8.25)	4.89 (3.36; 6.86)	6.40 (4.29; 9.19)	5.64 (4.60; 6.86)	5.73 (4.02; 7.94)	5.44 (4.55; 6.44)
Fracture	**Established RA****	**RA patients**	**Controls**	**RA patients**	**Controls**	**RA patients**	**Controls**
Hip	n (%)	31 (14.0)	39 (5.4)	82 (14.0)	257 (12.2)	113 (14.0)	296 (10.5)
	Incidence/1000 PY (95% CI)	11.35 (7.71; 16.11)	3.65 (2.60; 4.99)	10.79 (8.58; 13.40)	7.84 (6.91; 8.86)	10.94 (9.02; 13.15)	6.81 (6.06; 7.63)
Fractures in total	n (%)	34 (15.5)	46 (6.4)	106 (18.9)	324 (15.6)	140 (17.9)	370 (13.3)
	Incidence/1000 PY (95% CI)	12.55 (8.69; 17.53)	4.32 (3.16; 5.76)	14.64 (11.99; 17.71)	10.15 (9.07; 11.32)	14.07 (11.84; 16.60)	8.69 (7.83; 9.62)

RA: Rheumatoid Arthritis; n: Number; PY: Person Years; CI: Confidence Interval

*Early RA: newly diagnosed (within 1 year) patients in 1997 or later with follow-up time maximal 10 years

**Established RA: patients with RA diagnosis for ≥ 5 years at study start (1997)

Table 3 IRR and HR for osteoporosis-related fractures in RA patients compared with matched controls

	INCIDENCE RATE RATIO (95% CI)			HAZARD RATIO (95% CI)		
Total cohort	**Men**	**Women**	**All**	**Men**	**Women**	**All**
Hip fracture	**1.81 (1.23; 2.61)**	**1.31 (1.08; 1.58)**	**1.39 (1.17; 1.64)**	**1.68 (1.05; 2.68)**	**1.41 (1.14; 1.75)**	**1.46 (1.20; 1.77)**
Fractures in total	**1.67 (1.18; 2.33)**	**1.40 (1.19; 1.64)**	**1.44 (1.24; 1.66)**	**1.55 (1.03; 2.34)**	**1.52 (1.27; 1.83)**	**1.53 (1.29; 1.81)**
Early RA*						
Hip fracture	0.97 (0.33; 2.46)	0.93 (0.50; 1.61)	0.94 (0.56; 1.50)	NA	0.85 (0.49; 1.49)	0.81 (0.50; 1.33)
Fractures in total	0.82 (0.31; 1.88)	1.13 (0.72; 1.72)	1.05 (0.71; 1.53)	NA	1.14 (0.74; 1.75)	1.01 (0.69; 1.49)
Established RA**						
Hip fracture	**3.11 (1.88; 5.06)**	**1.38 (1.06; 1.77)**	**1.61 (1.28; 2.00)**	**3.77 (1.79; 7.96)**	**1.76 (1.31; 2.38)**	**1.97 (1.50; 2.59)**
Fractures in total	**2.90 (1.81; 4.58)**	**1.44 (1.15; 1.80)**	**1.62 (1.32; 1.97)**	**2.99 (1.57; 5.70)**	**1.77 (1.36; 2.30)**	**1.91 (1.50; 2.43)**

Bold text indicates statistically significant results. IRR: Incidence Rate Ratio; HR: Hazard Ration; RA: Rheumatoid Arthritis; CI: Confidence Interval; NA: Not applicable due to < 10 events in patients with RA

*Early RA: newly diagnosed (within 1 year) patients from the year of 1997 with follow-up time maximal 10 years

**Established RA: patients with RA diagnosis for ≥ 5 years at study start (1997)

female controls (Table 2). The mean period of follow-up was 12.7 years in men and 13.6 years in women with RA, and 12.2 and 13.8 years in male and female controls respectively. The corresponding incidence rates per 1000 person-years at risk (PYR) were 7.86 in men with RA compared to 4.70 in male controls and 11.6 in women with RA compared to 8.27 in female controls (Table 2). The overall incidence of fractures in the RA cohort was 10.6 per 1000 PYR (95% CI 9.31; 12.0).

Both men and women with RA had increased risk of fractures overall (hazard ratio (HR) 1.55, 95% CI 1.03; 2.34 and HR 1.52, 95% CI 1.27; 1.83, respectively) and of fractures in the hip (HR 1.68, 95% CI 1.05; 2.68 and HR 1.41, 95% CI 1.14; 1.75, respectively) (Table 3). In analyses only including newly diagnosed patients from the year of 1997

or later, with a maximum follow-up time of 10 years, no increased risk of fractures overall or in the hip was seen compared to the matched control population (Table 3). The number of fractures in men with early RA (in total 7 fractures) was too low to be sufficient for Cox regression analyses. Results of patients with more established disease were similar to the results of the total cohort, with exception for the association between RA and hip fractures in men, which was stronger in patients with RA duration of ≥5 years at study start (HR 3.77, 95% CI 1.79; 7.96) (Table 3).

In supplementary multivariable cox regression models analysing the risk of fractures, the interaction between RA and the status of early or established disease did not reach statistical significance for fractures in total (p=0.13) or hip fractures specifically (p=0.07).

Considering other subtypes of fractures (vertebral, proximal upper arm and distal forearm fractures), numbers were lower (Supplementary Tables 4, Additional file 1), but there was a higher rate of proximal upper arm fractures in patients with RA, with similar patterns in the early and established RA subsets. (Supplementary Tables 5, Additional file 1).

In men with RA there were 5 fractures with external cause ICD-10 codes for high-energy trauma during the study period and in women with RA there were 7 (compared to 8 and 27 traumatic fractures in male and female controls respectively). In analyses excluding fractures caused by high-energy trauma, hazard ratios were generally somewhat lower. Although the results in men in the total cohort were no longer significant, the overall trends were similar (Supplementary Tables 6, Additional file 1).

In sensitivity analyses for the risk of osteoporosis-related fractures overall in RA patients compared to matched controls, not excluding patients with osteoporosis-related fractures before study start, but adjusted for such fractures in cox regression models, the results were similar to the main analyses (HR 1.62 (95% CI 1.08; 2.42) in men, HR 1.44 (95% CI 1.21; 1.72) in women and HR 1.47 (95% CI 1.25; 1.72) in the total cohort). In this analysis, previous fracture was significantly associated with further fractures overall after study start in the total cohort (HR 2.10, 95% CI 1.48; 2.98) and in women (HR 2.08, 95% CI 1.45; 2.98). In men there was a similar trend but no statistically significant association (HR 2.64, 95% CI 0.61; 11.45).

Predictors of fractures in RA patients Proportional hazards assumptions were fulfilled for most models but not for some of the predictor analyses (Tables 4 and 5 and supplementary Tables 7 and 8, Additional file 1). In unadjusted analyses higher age, longer duration of RA disease, higher HAQ scores and higher scores in the VAS for global health were significantly associated with fractures overall (Table 4). The associations with HAQ scores and VAS for global health reached statistical significance in

Table 4 Baseline predictors of osteoporosis-related fractures overall in the full RA cohort*

Fractures overall	Men (n 391)		Women (n 1008)		All (n 1399)	
	HR (95% CI)	Age-adjusted HR (95% CI)	HR (95% CI)	Age-adjusted HR (95% CI)	HR (95% CI)	Age-adjusted HR (95% CI)
Age, per 10 years	**3.59 (2.52; 5.12)**	NA	**2.32 (1.99; 2.71)**	NA	**2.51 (2.18; 2.90)**	NA
RA duration, per 10 years	**1.49 (1.19; 1.87)**	1.23 (0.99; 1.51)	**1.23 (1.09; 1.39)**	1.08 (0.96; 1.21)	**1.28 (1.15; 1.43)**	1.11 (1.00; 1.22)
RF-positive	1.02 (0.46; 2.23)	1.76 (0.79; 3.90)	NA[1]	NA[1]	1.07 (0.74; 1.53)	1.34 (0.93; 1.93)
HAQ, per SD	**1.68 (1.20; 2.34)**	1.40 (0.99; 1.96)	**1.36 (1.14; 1.63)**	1.11 (0.93; 1.33)	**1.45 (1.24; 1.69)**	**1.20 (1.03; 1.40)**
VAS pain, per SD	1.19 (0.86; 1.65)	1.31 (0.96; 1.80)	1.07 (0.90; 1.27)	1.01 (0.85; 1.20)	1.11 (0.96; 1.29)	1.10 (0.94; 1.28)
VAS global health, per SD	1.36 (0.98; 1.89)	**1.55 (1.11; 2.15)**	**1.20 (1.01; 1.43)**	1.10 (0.93; 1.32)	**1.25 (1.08; 1.46)**	**1.20 (1.03; 1.40)**
Methotrexate	NA[1]	NA[1]	0.84 (0.60; 1.17)	0.93 (0.66; 1.30)	NA[1]	NA[1]
bDMARDs	0.24 (0.03; 1.77)	0.65 (0.09; 4.85)	0.47 (0.22; 1.01)	1.01 (0.46; 2.19)	**0.41 (0.20; 0.85)**	0.90 (0.44; 1.85)
Prednisolone	1.68 (0.84; 3.34)	1.78 (0.88; 3.61)	**1.56 (1.09; 2.23)**	1.24 (0.86; 1.77)	**1.58 (1.16; 2.17)**	1.31 (0.95; 1.80)

* Unadjusted and age-adjusted Cox regression analyses

At the date of the first available questionnaire. Bold text indicates statistically significant results

n: number of patients with at least one answered questionnaire after exclusion of patients with fractures before baseline; HR: Hazard Ratio; CI: Confidence Interval; RA: Rheumatoid Arthritis; RF: Rheumatoid Factor; HAQ: Health Assessment Questionnaire; VAS: Visual Analogue Scale; bDMARDs: biologic Disease-modifying Antirheumatic Drugs; SD: Standard Deviation; NA: Not Applicable; NA[1]: Not Applicable since proportional hazards assumptions were not fulfilled

Table 5 Baseline predictors of hip fractures in the full RA cohort*

Hip fractures	Men (n 394)		Women (n 1036)		All (n 1430)	
	HR (95% CI)	Age-adjusted HR (95% CI)	HR (95% CI)	Age-adjusted HR (95% CI)	HR (95% CI)	Age-adjusted HR (95% CI)
Age, per 10 years	**5.02 (3.23; 7.82)**	NA	**2.51 (2.09; 3.03)**	NA	**2.85 (2.39; 3.40)**	NA
RA duration, per 10 years	**1.64 (1.29; 2.08)**	1.23 (0.99; 1.54)	NA[1]	NA[1]	**1.27 (1.12; 1.43)**	1.08 (0.96; 1.21)
RF-positive	1.33 (0.51; 3.50)	2.59 (0.98; 6.88)	NA[1]	NA[1]	1.18 (0.77; 1.82)	**1.55 (1.01; 2.39)**
HAQ, per SD	**1.72 (1.18; 2.51)**	1.38 (0.93; 2.06)	**1.29 (1.05; 1.59)**	1.03 (0.84; 1.27)	**1.40 (1.17; 1.67)**	1.13 (0.94; 1.34)
VAS pain, per SD	1.14 (0.79; 1.65)	1.26 (0.87; 1.81)	1.10 (0.90; 1.34)	1.03 (0.84; 1.25)	1.12 (0.94; 1.34)	1.09 (0.92; 1.30)
VAS global health, per SD	**1.46 (1.01; 2.12)**	**1.63 (1.13; 2.36)**	1.20 (0.99; 1.47)	1.09 (0.89; 1.33)	**1.27 (1.07; 1.52)**	**1.20 (1.00; 1.43)**
Methotrexate	**0.26 (0.10; 0.69)**	0.49 (0.18; 1.33)	0.70 (0.47; 1.04)	0.78 (0.52; 1.16)	NA[1]	NA[1]
bDMARDs	0.33 (0.05; 2.45)	1.23 (0.16; 9.49)	**0.18 (0.04; 0.73)**	0.42 (0.10; 1.71)	**0.21 (0.07; 0.66)**	0.52 (0.16; 1.66)
Prednisolone	1.94 (0.90; 4.19)	2.21 (0.99; 4.94)	**1.54 (1.02; 2.32)**	1.19 (0.79; 1.81)	**1.62 (1.12; 2.32)**	1.30 (0.90; 1.87)

* Unadjusted and age-adjusted Cox regression analyses

At the date of the first available questionnaire. Bold text indicates statistically significant results

n: number of patients with at least one answered questionnaire after exclusion of patients with fractures before baseline; HR: Hazard Ratio; CI: Confidence Interval; RA: Rheumatoid Arthritis; RF: Rheumatoid Factor; HAQ: Health Assessment Questionnaire; VAS: Visual Analogue Scale; bDMARDs: biologic Disease-modifying Antirheumatic Drugs; SD: Standard Deviation; NA: Not Applicable; NA[1]: Not Applicable since proportional hazards assumptions were not fulfilled

age-adjusted analyses for all patients, but not when stratified by sex. The results were similar in analyses of hip fractures only (Table 5). There were no consistent associations between treatment with methotrexate, bDMARDs or glucocorticosteroids and fracture risk (Tables 4 and 5).

Since there was no excess risk of fractures in newly diagnosed RA patients compared with controls, no predictor analyses were performed for this group. In patients with RA since five or more years at study start, the results of predictor analyses were largely similar to the results of the total cohort (Supplementary Tables 7 and 8, Additional file 1). In this group, there were too few fractures in patients with bDMARDs for meaningful analyses.

Discussion

The estimated incidence of fractures in this community-based cohort of patients with RA was just over 1 per 100 person-years, which is within the range of what earlier RA studies have found [5]. As expected women had higher incidences of fractures in general but both men and women with RA had increased risk of fractures compared with the general population. The association between hip fractures and RA was strongest in men, especially in analyses of patients with established RA only. This pattern was also indicated in a Spanish study from 2018, where the female to male ratio of hip fractures in RA patients was almost 1:1 at the end of the study period, in contrast to the general population where the ratio was about 3.6:1. The authors of this study also noted that men with RA suffered from their first hip fracture at the same age as women in contrast to men without RA who had fractures on average 5–10 years later than the corresponding women [9]. A somewhat stronger association between hip fractures and RA in men was also seen in a large cohort study based on administrative claims data from the United States [22].

There have been a number of attempts to assess differences in disease characteristics, treatment choices and treatment outcomes in men and women with RA, but the interpretation of the results is complex. Consistent with the literature [23–26], women with RA in this study scored somewhat higher in HAQ and VAS for pain and global health, but the differences in other baseline characteristics were not striking. More women than men both with and without RA had had fractures before study start and were excluded from the statistical analyses. Since this could have led to underestimation of the long term fracture risk in women with RA, sensitivity analyses where patients with previous osteoporosis-related fractures were not excluded, but instead such fractures were adjusted for, were performed, but the results did not change substantially, neither in men nor in women.

Studies of bone mass in RA patients have shown accelerated bone loss not only in women but also in men with RA [11, 13], starting already early in disease [12]. This could be an explanation for the higher risk of fractures in RA patients of both sexes. Men are generally examined and treated for osteoporosis to a lesser extent than women [15], and this is also true for men with RA [27]. In the light of the doubled mortality rates after hip fractures in men compared with women [9, 15], osteoporosis in men (with and without RA) is in need of more attention. Falls are important risk factors of fractures and RA patients have been reported to have high risk of falling [4, 28, 29]. In contrast to the general population, studies of patients with RA have not reported any major influence of age or sex on the risk of falls [29], indicating that men with RA may fall as much as women with RA do. This could be part of the explanation for the limited difference in the rate of hip fractures between men and women with RA.

The risk of fractures early in disease has not been extensively evaluated before, although there are two studies finding a high risk of osteoporosis-related fractures the first years after disease onset [8, 14]. In this study we had the opportunity to follow 738 patients from their first year of diagnosis to a maximum of 10 years later and compare the risk of fractures to matched general population controls. In this subcohort, there was no statistically significant excess risk of fractures, except for fractures in the proximal upper arm. On the other hand, risk estimates were higher in the substudy of patients with more than 5 years disease duration of RA in 1997, suggesting that increased risk of fractures is in particular seen in patients with established disease. As a statistical measure of this, there was a trend towards an interaction between RA and early/established subcohort status, in particular for hip fractures, although it did not reach statistical significance. Patients with early RA (and their controls) were younger and had substantially less fractures than the patients with established disease. This could result in low power in the statistical analyses on early RA. Nevertheless, the results on early RA patients could also be partly due to the different inclusion period (1997 to 2006) compared to patients with established RA already at study start. The early RA patients had been differently treated both for their RA (with earlier and more extensive use of methotrexate and bDMARDs) and potentially also for the risk of osteoporosis. Although there most likely were many different changes in clinical practice over time during the study period, the organization of the tax funded health care system in the area was essentially unchanged, with a single hospital providing most secondary out-patient and all in-patient care. However, it should be noted that the present findings of no increased risk of fractures in patients diagnosed with RA after 1996 contrast with the lack of obvious reduction of the incidence of fractures over time in RA patients in earlier studies [5, 8].

In an attempt to come closer to the definition of fragility fractures, supplementary analyses, in which fractures with external cause ICD-10 codes for high-energy trauma during the study period were excluded, were performed. However, the traumatic fractures were few and the results turned out similar, except for the results in men, which were no longer significant. In men with RA there were just 51 fractures in total during the study period and likely, when 5 of these were classified as traumatic, the analyses of this subset became underpowered. In men with established disease there was again a strong association between RA and fractures, especially in the hip.

When examining potential baseline predictors of fractures in the RA patients, as expected age was the most important predictor of fractures. In accordance with the results of enhanced associations between established RA and fractures, longer RA duration was associated with higher risks of fractures, as well as higher scores for HAQ and VAS global health. These results are in line with observations in earlier studies [5, 14] although disease duration and HAQ scores may be partly influenced by age which has also been the case in earlier studies [30]. Treatment with glucocorticosteroids at baseline on the other hand did not show a statistically significant association with fractures after adjustment for age. There are ongoing discussions of the benefits and harms of glucocorticosteroids on bone health, and a common opinion is that it is a question of dose, length of treatment and underlying indication [2]. In this study information on daily doses of Prednisolone was unavailable (although common practice at the time was to use doses of 5 to 7.5 mg, as shown in a report on an early RA inception cohort [13]), which is a major limitation. Dose variation between patients and over time could be a reason for lack of association with fractures. Additional limitations apply. First, baseline data in this cohort was limited. Other variables that would have been interesting to include, but were unavailable, were for instance anti-citrullinated peptide antibody (ACPA) status and composite disease activity scores, as well as several established risk factors for fractures in the general population (e.g. smoking, alcohol use, body mass index, menopause and comorbidities), prevalent osteoporosis diagnosis and anti-osteoporotic treatment. Also, information on socioeconomic status and ethnicity would have been valuable since these factors covary with both RA severity and the risk of osteoporosis-related fractures [31, 32]. Although the study was performed in a single city, some variability in ethnicity and socioeconomic status was likely present in this study, and may have affected the results. Second, the method of detecting fractures, from

registry databases on inpatient care, with no verification with radiographic documentation, constitutes a limitation. Radiographic examination is especially important for detecting vertebral fractures, but we cannot for certain rule out misclassification of other fractures as well. The Swedish National Patient Register has been validated several times, both through reviews of patient records and by comparison with the Swedish quality register for hip fractures (the Swedish Hip Fracture Register), showing consistently good results regarding the validity of hip fracture diagnoses [33, 34]. However, other fracture types may be managed in outpatient care to a greater extent, and not captured in this study. Third, the number of men with early RA was limited and the number of fractures was insufficient for further analyses of fracture risk in this group of patients. Further studies on this specific patient group would be valuable since information is lacking and there is a risk that these patients are missed in fracture prevention work.

A strength of this study is the use of a community-based cohort with all known RA patients in the area, including all types of patients seen in clinical practice. The patients were treated according to the general recommendations during the studied time period, and the cohort should be representative for most other patients with similar health care opportunities and living conditions during the study period. The subanalyses of the patients with short disease duration gave us the opportunity to look into the risk of fractures in early RA and compare the results to those of more established RA patients.

Conclusions

Both men and women with RA had increased risk of osteoporosis-related fractures compared with the general population. Men with established disease had particularly high risk of hip fractures, and more focus on fracture prevention in this patient group would likely be beneficial. Patients with new onset of disease between 1997 and 2006 were not at significantly increased risk of fractures overall or hip fractures during the first ten years after diagnosis, but no conclusions on fracture risk in men with early RA could be drawn, and this should be further studied.

Abbreviations

RA	Rheumatoid arthritis
CI	Confidence intervals
HR	Hazard ratio
HAQ	Health assessment questionnaire
BMI	Body mass index
VAS	Visual analogue scale
bDMARDs	Biologic disease-modifying antirheumatic drugs
ICD	International Classification of Diseases
RF	Rheumatoid factor
PYR	Person years of risk

Supplementary Information

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Supplementary Material 1

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Authors' contributions

LT participated in the study design, performed the major part of the organization of data for statistical analysis, performed the statistical analyses and wrote the first draft of the manuscript. LJ participated in the study design and the development of the local RA register, the design of the patient questionnaires, and in the analysis and interpretation of data. CT has made substantial contributions to study design and acquisition, analysis and interpretation of data. All the authors helped in the revision of the manuscript, read and approved the final version.

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Data Availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

The study was approved by the Regional Ethical Review Board for southern Sweden (Lund, Sweden, LU 336-01, LU 2016/923) and conducted according to the principles of the Helsinki Declaration. Patient consent was not required by the ethical review board for the present study.

Consent for publication

Not applicable.

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Publisher's Note

Supplementary table 1. ICD codes for osteoporosis-related fractures used in this study.

Fracture site	**ICD 9**	**ICD 10**
Hip	820	S720, S721, S722
Vertebral column	805C, 805D, 805E, 805F	S220, S221, S320, S327
Proximal upper arm	812A, 812B	S422
Distal forearm	813E, 813F	S525, S526, S528

Supplementary table 2. Baseline characteristics of patients with osteoporosis-related fractures before study start.

Patients with previous fractures	**Men**	**Women**	**All**
Number	13	81	94
Age (years) mean (SD)	76.9 (8.3)	75.2 (7.7)	75.4 (7.7)
RA duration at inclusion (years), median (IQR)	14 (5-22)	14 (5-28)	14 (5-27)
RA duration at first questionnaire (years), median (IQR)	17 (7-27)	15 (7-28)	17 (7-28)
RF-positive n (%)	9 (81.8)	52 (82.5)	61 (82.4)
HAQ mean (SD)*	1.44 (0.92)	1.72 (0.89)	1.69 (0.90)
VAS pain (mm) mean (SD)*	39.5 (25.6)	53.0 (29.5)	51.3 (29.2)
VAS global health (mm) mean (SD)*	41.0 (30.5)	49.1 (29.6)	48.1 (29.5)
Methotrexate n (%)*	2 (25.0)	20 (32.3)	22 (31.4)
csDMARDs other than Methotrexate n (%)*	2 (25.0)	12 (19.4)	14 (20.0)
bDMARDs n (%)*	0 (0.0)	1 (1.6)	1 (1.4)
Prednisolone n (%)*	4 (50.0)	14 (22.6)	18 (25.7)

* At the date of the first available questionnaire.

SD: Standard Deviation; IQR: Interquartile Range; RA: Rheumatoid Arthritis; RF: Rheumatoid Factor; HAQ: Health Assessment Questionnaire; VAS: Visual Analogue Scale; csDMARDs: conventional synthetic Disease-modifying Antirheumatic Drugs; bDMARDs: biologic Disease-modifying Antirheumatic Drugs.

Supplementary table 3. Baseline characteristics in patients not returning any baseline questionnaire during the study period.

	Men (n 117)	Women (n 288)	All (n 405)
Age (years) mean (SD)	61.2 (17.9)	63.5 (16.5)	62.8 (16.9)
RA duration at inclusion (years), median (IQR)	0 (0; 13)	3 (0; 14)	2 (0; 14)
RF-positive n (%)	60 (65.9)	179 (72.2)	239 (70.5)*
bDMARDs n (%)	0 (0.0)	1 (0.3)	1 (0.2)
Previous osteoporosis-related fracture n (%)	5 (4.3)	19 (6.6)	24 (5.9)

n: Number; SD: Standard Deviation; RA: Rheumatoid Arthritis; IQR: Interquartile Range; RF: Rheumatoid Factor; bDMARDs: biologic Disease-modifying Antirheumatic Drugs.

*66 patients had missing information on RF

Supplementary table 4. Number and incidence of vertebral, proximal upper arm and distal forearm fractures in patients and controls.

Fracture		Patients			Controls		
Total cohort		**Men**	**Women**	**All**	**Men**	**Women**	**All**
Vertebral column	n (%)	5 (0.98)	16 (1.19)	21 (1.13)	12 (0.66)	50 (0.99)	62 (0.91)
	Incidence/1000 PY (95% CI)	0.75 (0.24; 1.74)	0.85 (0.49; 1.38)	0.82 (0.51; 1.26)	0.47 (0.24; 0.82)	0.65 (0.48; 0.86)	0.60 (0.46; 0.77)
Proximal upper arm	n (%)	5 (0.98)	46 (3.42)	51 (2.75)	11 (0.61)	107 (2.13)	118 (1.72)
	Incidence/1000 PY (95% CI)	0.75 (0.24; 1.75)	2.46 (1.80; 3.28)	2.01 (1.50; 2.64)	0.43 (0.21; 0.77)	1.40 (1.15; 1.69)	1.16 (0.96; 1.38)
Distal forearm	n (%)	4 (0.78)	27 (1.99)	31 (1.66)	14 (0.77)	105 (2.10)	119 (1.75)
	Incidence/1000 PY (95% CI)	0.60 (0.16; 1.53)	1.43 (0.94; 2.08)	1.21 (0.82; 1.72)	0.55 (0.30; 0.92)	1.38 (1.13; 1.67)	1.17 (0.97; 1.40)
Early RA*							
Vertebral column	n (%)	0 (0.00)	5 (0.98)	5 (0.70)	3 (0.37)	8 (0.39)	11 (0.39)
	Incidence/1000 PY (95% CI)	0 (-)	1.06 (0.34; 2.48)	0.77 (0.25; 1.80)	0.43 (0.09; 1.27)	0.43 (0.19; 0.85)	0.43 (0.22; 0.77)
Proximal upper arm	n (%)	1 (0.49)	10 (1.96)	11 (1.54)	5 (0.62)	17 (0.84)	22 (0.78)
	Incidence/1000 PY (95% CI)	0.57 (0.01; 3.15)	2.13 (1.02; 3.92)	1.70 (0.85; 3.05)	0.72 (0.23; 1.69)	0.92 (0.54; 1.47)	0.87 (0.54; 1.31)
Distal forearm	n (%)	0 (0.00)	5 (0.98)	5 (0.70)	6 (0.74)	22 (1.09)	28 (0.99)
	Incidence/1000 PY (95% CI)	0 (-)	1.06 (0.35; 2.48)	0.77 (0.25; 1.80)	0.87 (0.32; 1.89)	1.20 (0.75; 1.82)	1.11 (0.74; 1.60)
Established RA**							
Vertebral column	n (%)	4 (1.77)	8 (1.32)	12 (1.44)	5 (0.69)	28 (1.31)	33 (1.15)
	Incidence/1000 PY (95% CI)	1.42 (0.39; 3.63)	0.99 (0.43; 1.95)	1.10 (0.57; 1.92)	0.46 (0.15; 1.08)	0.82 (0.55; 1.19)	0.73 (0.51; 1.03)
Proximal upper arm	n (%)	1 (0.44)	24 (3.96)	25 (2.99)	3 (0.41)	59 (2.76)	62 (2.17)
	Incidence/1000 PY (95% CI)	0.35 (0.01; 1.96)	3.01 (1.93; 4.48)	2.31 (1.50; 3.41)	0.28 (0.06; 0.81)	1.74 (1.32; 2.24)	1.39 (1.06; 1.78)
Distal forearm	n (%)	3 (1.31)	10 (1.61)	13 (1.53)	2 (0.28)	54 (2.54)	56 (1.96)
	Incidence/1000 PY (95% CI)	1.06 (0.22; 3.11)	1.23 (0.59; 2.26)	1.19 (0.63; 2.03)	0.19 (0.02; 0.67)	1.60 (1.20; 2.09)	1.26 (0.95; 1.63)

RA: Rheumatoid Arthritis; n: Number; PY: Person Years; CI: Confidence Interval.

*Early RA: newly diagnosed (within 1 year) patients from the year of 1997 with follow-up time maximal 10 years.

**Established RA: patients with RA diagnosis for ≥5 years at study start (1997).

Supplementary table 5. IRR and HR for vertebral, proximal upper arm and distal forearm fractures in RA patients compared with matched controls.

	INCIDENCE RATE RATIO (95% CI)			HAZARD RATIO (95% CI)		
Total cohort	**Men**	**Women**	**All**	**Men**	**Women**	**All**
Vertebral column	1.60 (0.44; 5.10)	1.31 (0.69; 2.32)	1.36 (0.79; 2.25)	NA[2]	1.55 (0.85; 2.83)	1.48 (0.86; 2.53)
Proximal upper arm	1.74 (0.74; 5.75)	**1.76 (1.22; 2.50)**	**1.74 (1.23; 2.42)**	NA[2]	**2.11 (1.43; 3.12)**	**2.12 (1.46; 3.08)**
Distal forearm	NA[1]	1.04 (0.65; 1.59)	1.04 (0.67; 1.54)	NA[2]	1.10 0.69; 1.75)	1.05 (0.68; 1.62)
Early RA*						
Vertebral column	NA[1]	2.46 (0.63; 9.60)	1.79 (0.49; 5.90)	NA[2]	NA[2]	NA[2]
Proximal upper arm	NA[1]	2.32 (0.95; 5.39)	1.97 (0.86; 4.22)	NA[2]	**2.47 (1.09; 5.57)**	**2.35 (1.09; 5.08)**
Distal forearm	NA[1]	0.89 (0.26; 2.43)	0.70 (0.21; 1.84)	NA[2]	NA[2]	NA[2]
Established RA**						
Vertebral column	NA[1]	1.21 (0.48; 2.72)	1.50 (0.70; 2.96)	NA[2]	NA[2]	1.76 (0.84; 3.70)
Proximal upper arm	NA[1]	**1.73 (1.03; 2.80)**	**1.67 (1.00; 2.67)**	NA[2]	**2.26 (1.28; 3.99)**	**2.32 (1.32; 4.07)**
Distal forearm	NA[1]	0.77 (0.35; 1.52)	0.94 (0.47; 1.74)	NA[2]	0.81 (0.39; 1.68)	0.93 (0.48; 1.81)

Bold text indicates statistically significant results. IRR: Incidence Rate Ratio; HR: Hazard Ration; RA: Rheumatoid Arthritis; CI: Confidence Interval; NA[1]: Not applicable due to <5 events in patients with RA in the IRR analysis. NA[2]: Not applicable due to <10 events in patients with RA in the Cox regression analysis.

*Early RA: newly diagnosed (within 1 year) patients from the year of 1997 with follow-up time maximal 10 years.

**Established RA: patients with RA diagnosis for ≥5 years at study start (1997).

Supplementary table 6. Hazard ratios for osteoporosis-related fractures in RA patients compared with matched controls, fractures with external cause ICD-10 codes for high-energy trauma during the study period excluded.

	HAZARD RATIO (95% CI)		
Total cohort	**Men**	**Women**	**All**
Hip fracture	1.49 (0.90; 2.46)	**1.38 (1.11; 1.72)**	**1.40 (1.15; 1.71)**
Fractures in total	1.41 (0.92; 2.16)	**1.53 (1.27; 1.84)**	**1.51 (1.27; 1.79)**
Early RA*			
Hip fracture	NA	0.76 (0.42; 1.38)	0.72 (0.42; 1.21)
Fractures in total	NA	1.10 (0.71; 1.72)	0.97 (0.65; 1.45)
Established RA**			
Hip fracture	**3.20 (1.48; 6.92)**	**1.73 (1.28; 2.35)**	**1.88 (1.42; 2.49)**
Fractures in total	**2.60 (1.34; 5.05)**	**1.81 (1.38; 2.37)**	**1.90 (1.48; 2.44)**

Bold text indicates statistically significant results. RA: Rheumatoid Arthritis; CI: Confidence Interval; NA: Not applicable due to <10 events in patients with RA.

*Early RA: newly diagnosed (within 1 year) patients from the year of 1997 with follow-up time maximal 10 years.

**Established RA: patients with RA diagnosis for ≥5 years at study start (1997).

Supplementary table 7. Baseline predictors of osteoporosis-related fractures overall in established RA patients. Unadjusted and age-adjusted Cox regression analyses.

Fractures overall	**Men**		**Women**		**All**	
	HR (95% CI)	Age-adjusted HR (95% CI)	HR (95% CI)	Age-adjusted HR (95% CI)	HR (95% CI)	Age-adjusted HR (95% CI)
Age, per 10 years	**5.78 (3.34; 10.01)**	NA	**2.23 (1.79; 2.76)**	NA	**2.64 (2.15; 3.23)**	NA
RA duration, per 10 years	1.28 (0.94; 1.75)	0.95 (0.71; 1.27)	**1.20 (1.02; 1.42)**	1.00 (0.85; 1.18)	**1.22 (1.05; 1.41)**	0.99 (0.86; 1.14)
RF-positive	1.27 (0.44; 3.69)	1.52 (0.52; 4.46)	NA[1]	NA[1]	NA[1]	NA[1]
HAQ, per SD	1.20 (0.81; 1.78)	1.03 (0.70; 1.53)	**1.36 (1.07; 1.73)**	1.12 (0.88; 1.43)	**1.31 (1.07; 1.60)**	1.08 (0.88; 1.32)
VAS pain, per SD	1.04 (0.72; 1.50)	1.41 (0.96; 2.06)	1.01 (0.81; 1.27)	0.91 (0.72; 1.15)	1.02 (0.84; 1.24)	0.98 (0.81; 1.20)
VAS global health, per SD	1.17 (0.81; 1.69)	1.46 (0.98; 2.18)	1.09 (0.87; 1.38)	0.98 (0.77; 1.25)	1.12 (0.92; 1.36)	1.05 (0.86; 1.28)
Methotrexate	0.51 (0.19; 1.34)	0.64 (0.24; 1.70)	0.89 (0.55; 1.44)	1.02 (0.63; 1.66)	0.78 (0.51; 1.20)	0.91 (0.59; 1.40)
bDMARDs	NA[2]	NA[2]	NA[2]	NA[2]	NA[2]	NA[2]
Prednisolone	2.05 (0.95; 4.43)	**2.36 (1.05; 5.29)**	1.51 (0.92; 2.47)	1.15 (0.70; 1.90)	**1.62 (1.08; 2.45)**	1.31 (0.87; 1.99)

At the date of the first available questionnaire. Bold text indicates statistically significant results.

HR: Hazard Ratio; CI: Confidence Interval; RA: Rheumatoid Arthritis; RF: Rheumatoid Factor; HAQ: Health Assessment Questionnaire; VAS: Visual Analogue Scale; bDMARDs: biologic Disease-modifying Antirheumatic Drugs; SD: Standard Deviation; NA: Not Applicable. NA[1]: Not Applicable since proportional hazards assumptions were not fulfilled; NA[2]: Not applicable due to less than 5 events in patients with established RA on bDMARDs.

Supplementary table 8. Baseline predictors of hip fractures in established RA patients. Unadjusted and age-adjusted Cox regression analyses.

Hip fractures	**Men (n 183)**		**Women (n 463)**		**All (n 646)**	
	HR (95% CI)	Age-adjusted HR (95% CI)	HR (95% CI)	Age-adjusted HR (95% CI)	HR (95% CI)	Age-adjusted HR (95% CI)
Age, per 10 years	**5.51 (3.17; 9.56)**	NA	**2.27 (1.76; 2.91)**	NA	**2.74 (2.18; 3.46)**	NA
RA duration, per 10 years	1.30 (0.93; 1.81)	0.88 (0.64; 1.21)	1.10 (0.90; 1.34)	0.93 (0.76; 1.13)	1.14 (0.96; 1.35)	0.93 (0.79; 1.09)
RF-positive	2.38 (0.56; 10.2)	**3.36 (0.77; 14.69)**	NA[1]	NA[1]	**2.34 (1.07; 5.11)**	**2.79 (1.28; 6.11)**
HAQ, per SD	1.19 (0.78; 1.83)	1.01 (0.66; 1.56)	1.23 (0.94; 1.60)	1.00 (0.76; 1.31)	1.20 (0.96; 1.50)	0.98 (0.78; 1.23)
VAS pain, per SD	1.02 (0.68; 1.52)	1.27 (0.84; 1.91)	1.04 (0.80; 1.34)	0.93 (0.71; 1.21)	1.03 (0.83; 1.27)	0.98 (0.78; 1.21)
VAS global health, per SD	1.22 (0.82; 1.81)	1.34 (0.90; 2.01)	1.05 (0.80; 1.36)	0.93 (0.71; 1.22)	1.09 (0.88; 1.36)	1.01 (0.80; 1.26)
Methotrexate	0.46 (0.16; 1.37)	0.66 (0.22; 1.97)	0.92 (0.53; 1.59)	1.04 (0.60; 1.80)	0.78 (0.48; 1.26)	0.90 (0.56; 1.47)
bDMARDs	NA[2]	NA[2]	NA[2]	NA[2]	NA[2]	NA[2]
Prednisolone	1.91 (0.82; 4.42)	2.03 (0.84; 4.91)	1.54 (0.88; 2.70)	1.19 (0.67; 2.09)	**1.64 (1.03; 2.60)**	1.31 (0.82; 2.09)

At the date of the first available questionnaire. Bold text indicates statistically significant results.

HR: Hazard Ratio; CI: Confidence Interval; RA: Rheumatoid Arthritis; RF: Rheumatoid Factor; HAQ: Health Assessment Questionnaire; VAS: Visual Analogue Scale; bDMARDs: biologic Disease-modifying Antirheumatic Drugs; SD: Standard Deviation; NA: Not Applicable; NA[1]: Not Applicable since proportional hazards assumptions were not fulfilled; NA[2]: Not applicable due to less than 5 events in patients with established RA on bDMARDs.

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Risk and predictors of fractures in early rheumatoid arthritis – A long term follow up study of an inception cohort

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ABSTRACT

Objectives: To examine the risk of fractures in a cohort of patients with newly diagnosed rheumatoid arthritis (RA), compared to the background population, and predictors of fractures detectable early in RA.
Methods: An inception cohort of patients with RA (N = 233; 164 women/69 men, recruited 1995–2005) was evaluated according to a structured program, including repeated clinical assessments and measures of bone mineral density (BMD), from diagnosis to 10 years later. Matched population controls were identified using the national census register. Fractures through 2019 were identified based on ICD codes. Cox regression models were used to assess the risk of fractures in RA patients compared with controls, and for assessment of potential predictors for fractures in the RA population.
Results: RA patients had an increased risk of fractures (fully adjusted hazard ratio (HR) 1.52, 95 % CI 1.13; 2.06). In the RA cohort, high age, low body mass index, and low BMD were significant baseline predictors of future fractures in multivariate analyses, but baseline RA disease characteristics were not. Worse disability (i.e. higher Health Assessment Questionnaire (HAQ) scores) over time was significantly associated with increased risk of fractures (age-sex-adjusted HR 1.33 per SD, 95 % CI 1.09; 1.63) and there was an inverse association between BMD Z-scores over time and fractures.
Conclusion: Patients with RA had higher risk of fractures than controls. Fracture risk was related to BMD at baseline and over time in patients with RA. In addition, worse disability (measured by HAQ) over time was associated with higher risk of fractures.

Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease typically featuring symmetric synovitis, but also frequently extraarticular inflammation resulting in high risk of many comorbidities including osteoporosis and fractures [1]. We have previously presented results on repeated bone mineral density (BMD) measurements in patients with early RA, where males had reduced femoral neck BMD at diagnosis, with a further significant but marginal decline during the first 5 years compared to healthy men of the same age, whereas BMD in the femoral neck of women with early RA did not differ significantly from healthy women of the same age [2]. BMD in the lumbar spine was not reduced in either men or women with RA compared to the healthy control population [2]. The results of lower BMD Z-scores in the femoral neck in men were in line with previous studies showing decreased bone mass already early in the course of RA [3–5]. Other studies have reported decreasing BMD with longer disease duration, although tight disease control might reduce bone loss to some extent [6–8]. Several surveys indicate that there is still an unmet need when it comes to adequate treatment of patients with RA and high risk of fractures [9–11]. Osteoporosis is an important risk factor for fractures and RA patients have been reported to have high risk of fractures compared to the background population [12, 13]. The risk of fractures seems to increase with disease duration [12, 14], but the risk of fractures in early RA inception cohorts is less well

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studied.

The association between low bone mass and subsequent fractures in RA patients has been examined in different settings with variable results [15–19]. Through the years it has been suggested that there is a discrepancy between levels of BMD and fracture risk in RA [20,21] leading to the search for supplementary explanations and risk factors that may need more attention, before we can successfully prevent fractures related to RA. Such risk factors may be falls [22] and predictors of falls, including muscle weakness, poor balance and impaired function in lower extremities due to swollen or tender joints [23,24], but also impaired bone quality, which is getting increasing attention in literature [20,25].

The aims of this study were 1). To compare the incidence of fractures in this RA cohort (with previously described bone mineral density levels) to that in the general population, 2). To investigate the relation between BMD at diagnosis and over the first 10 years with fractures in RA, and 3). To examine other potential predictors of future fractures in early RA through baseline- and time dependent analyses of clinical parameters and upper and lower extremity functional tests.

Materials and methods

Patients and controls

Between 1995 and 2005, a total of 233 patients (164 women, 69 men) with early rheumatoid arthritis (symptom duration <12 months) were recruited from the rheumatology outpatient clinic of Malmö University Hospital (the only hospital serving the catchment area Malmö, Sweden) or from the four rheumatologists in private practice in the area. All included patients were diagnosed by a rheumatologist and fulfilled the 1987 American College of Rheumatology criteria for RA [26].

Four controls without RA diagnosis per patient were identified (n = 932; 656 women, 276 men) using the national census register from the general population. The controls were individually matched for age at inclusion of the case in the register (±1 year), sex and residential area at the time of inclusion. Retrieval of matched controls was performed by Statistics Sweden. One patient and one control were excluded because they were not registered in Sweden at the time of study start.

Clinical assessment of patients

The patients were evaluated at inclusion and after 0.5, 1, 2, 5 and 10 years by the same rheumatologist according to a structured protocol, as previously described [2]. At inclusion, and after 1, 2, 5 and 10 years, grip force (Newton) was measured using the electronic Instrument Grippit (AB Detektor, Gothenburg, Sweden). Average grip force during 10 s uninterrupted grip in the dominant hand was compared to the expected grip force, based on age- and sex-specific reference values [27,28]. A subset of patients (n 105) was also assessed according to the Index of Muscle Function (IMF) [29,30] by a physiotherapist, as previously described [31]. Information on treatment with biologic disease modifying antirheumatic drugs (bDMARDs) from study start to December 31, 2017, was obtained from the South Swedish Arthritis Treatment Group register [32] and the Swedish Rheumatology Quality Register[33]. All patients were managed according to standard care during the study period, without any prespecified protocol for antirheumatic treatment and without any restrictions for anti-osteoporotic treatment. Results on other outcomes in this cohort have been reported previously[2,27,34].

Laboratory investigations and imaging

Rheumatoid factor (RF) and antibodies to cyclic citrullinated peptides (anti-CCP) were analyzed at inclusion using standard ELISA methods, as previously described[2]. Radiographs of hands and feet were obtained at inclusion and after 2, 5 and 10 years of follow-up, and at every occasion, except at the 10 year follow up, scored according to the Sharp/van der Heijde score (SHS)[35], with sub-scores on erosion score and joint space narrowing score (JSNS). This was done by the same trained evaluator, who was unaware of the clinical status of the patient. Based on results of repeated readings of a subset of radiographs [36], a single reading in chronologic order was performed.

The patients were examined with dual-energy X-ray absorptiometry (DXA) at the left femoral neck and second to fourth lumbar spine vertebrae (L2-L4) at inclusion and after 2, 5 and 10 years, as described in a previous article [2]. From the BMD values (g/cm^2), Z-scores (number of standard deviations (SD) above or below the mean BMD for the given age and sex) were calculated using a reference population consisting of a cohort of healthy individuals (146 men and 178 women, age 20–87) from the same area as the patients [37]. Gender- and age-specific reference values were estimated using piecewise linear regression, stratified by age and sex, as previously described [2]. BMD values exceeding ±3 SD from the mean for the given age and sex were considered outliers and excluded from the analyses.

Identification of fractures and comorbidities in patients and controls

Information on fractures and comorbidities in patients and controls during the period January 1, 1987 to December 31, 2019 was obtained by linkage to the Swedish National Patient Register, which contains mandatory reports on diagnoses in inpatient care, and in specialized outpatient care from 2001, and the Cause of Death Register. Fractures of the hip, proximal upper arm, distal forearm, vertebra, and pelvis, as well as predefined comorbidities were identified based on ICD-9 and ICD-10 diagnostic codes (Supplementary Table 1). High-energy traumatic fractures during the study period were identified using ICD-10 external cause codes [38]. Comorbidities were defined and retrieved from the register based on an original research plan. However, it was later decided to instead use a multimorbidity index for the analyses (see Statistics).

Socioeconomic characteristics of patients and controls

Information on level of formal education and country of birth was obtained from Statistics Sweden[39].

Statistics

Comparison of fracture rates in patients with RA and controls

Patients and controls with registered ICD codes for the studied fractures before inclusion (date of RA diagnosis/corresponding index date for controls) were excluded from the analyses in this study. Only the first upcoming fracture after inclusion for the corresponding analysis was used. Both patients and controls were censored for death, emigration from Sweden or end of study (December 31, 2019).

The incidence of fractures (hip, proximal upper arm, distal forearm, vertebral and pelvic fractures) was estimated in RA patients and controls. The 95 % confidence intervals (CI) for incidence rates and incidence rate ratios were estimated using the Poisson distribution ratio. The relation between RA and the risk of fractures was also assessed using univariate and multivariate Cox regression models and presented as crude and adjusted hazard ratios (HR). The group variable identifying each case and its matched controls was entered as a stratum variable, to take the matched design into account. To address potential confounding by socio-economic factors, models were adjusted for level of formal education and country of birth. To adjust for comorbidities, a modified Charlson Comorbidity Index (CCI) [40,41] was created (Supplementary Table 2) and patients and controls categorized into three groups with 0, 1 or ≥2 wt. For subsets with < 10 registered fractures in RA patients no Cox regression analyses were performed.

In sensitivity analyses, fractures with external cause ICD-10 codes for high-energy trauma [38] during the study period were excluded, and

analyses for the risk of fractures in RA patients compared to matched controls were performed, where patients with fractures occurring before study start were not excluded. Instead, previous fractures were adjusted for by including it as a covariate in the Cox regression models.

In exploratory analyses, patients and controls were divided into three groups based on inclusion year (1995–1998, 1999–2001 and 2002–2005) and the risk of fractures in RA patients compared with controls analyzed separately in the three groups. In further exploratory models, patients with RA and their matched controls were stratified for treatment of the case with corticosteroids at study start or not, and for registered or no registered treatment of the case with corticosteroids at any of the follow-up visits.

Predictors of fractures in patients with RA

The impact of baseline characteristics on the risk of fractures overall in patients with RA was analyzed in unadjusted and age- and sex adjusted Cox regression models. HR for continuous variables were estimated per SD. The impact of baseline bone mineral density Z-scores in the femoral neck and the lumbar spine (L2-L4) on the risk of fractures in total and, in the femoral neck and lumbar spine/pelvis for the respective location, was analyzed in Cox regression models. To further assess the potentially independent effects of bone mineral density Z-scores on fractures in RA, the Cox regression models were adjusted for CCI and baseline characteristics that were significant predictors in the univariate models of fracture risk in RA. To assess collinearity, correlations between parameters were analyzed using Spearman's test and if a significant correlation with $r > 0.3$ was found, the parameter that had strongest association with fractures was chosen for the multivariate models. Finally, for variables assessed at multiple times during the study time, time dependent Cox regression analyses were performed. Analyses were adjusted for sex and age, and multivariate analyses were performed for variables that were significantly associated with fractures in the sex- and age-adjusted analyses. Again, Spearman's test was used to assess collinearity at each follow-up visit, and covariates that were collinear at several visits were handled as described above.

In sensitivity analyses of baseline and time-dependent predictors, fractures with external cause ICD-10 codes for high-energy trauma [38] during the study period were excluded.

For all models including baseline covariates, proportional hazards assumptions were evaluated using visual inspection of log-minus-log plots for dichotomous variables, and Schoenfeld residuals for continuous variables. A cut off of $r > 0.3$ with $p < 0.05$ for correlations of residuals with the rank of the follow-up time was used for exclusion. The analyses were performed using SPSS version 25.

Ethics

All patients gave written informed consent to participate, and the study was approved by the Regional Ethical Review Board for southern Sweden (Lund, Sweden, LU 410–94, LU 311–02, 2021–01878). The study was conducted according to the principles of the Helsinki Declaration.

Results

Study population – baseline characteristics and follow-up

A total of 232 patients (n = 163 (70.3 %) women; mean age 60.5 years) and 931 age- and sex-matched controls (n = 656 (70.5 %) women, mean age 60.5 years) were included in the study. There were 199 (85.8 %) patients and 780 (83.8 %) controls with a CCI of 0 at inclusion. Proportions with upper-secondary education or higher, as well as of individuals born in Sweden, were slightly higher among patients with RA compared to controls (Table 1). From inclusion to December 31, 2019 (end of study), 4 (1.7 %) patients and 29 (3.1 %) controls were censored due to emigration and 120 (51.5 %) patients and 409 (43.9 %) controls were censored due to death. Mean follow-up time to censoring was 14.7 (SD 6.4) years in patients and 15.3 (SD 6.4) years in controls.

Table 1
Baseline characteristics in RA patients and controls.

	Patients (n 232)	Controls (n 931)
Age (years) mean (SD)	60.5 (14.6)	60.5 (14.6)
Women n (%)	163 (70.3)	656 (70.5)
Level of formal education[a]		
≤ Lower secondary education, n (%)	83 (35.8)	403 (43.9)
Upper-secondary/short-cycle tertiary, n (%)	105 (45.3)	347 (37.8)
≥ Bachelor's degree or equivalent, n (%)	42 (18.1)	168 (18.3)
Country of birth		
Sweden n (%)	203 (87.5)	743 (81.6)
Other country in Europe n (%)	23 (9.9)	132 (14.5)
Country outside Europe n (%)	6 (2.6)	36 (4.0)
Fracture before study start n (%)	4 (1.7)	31 (3.3)
Modified Charlson Comorbidity Index n (%)		
0	199 (85.8)	780 (83.8)
1	23 (9.9)	68 (7.3)
≥2	10 (4.3)	83 (8.9)

2 patients and 13 controls had missing information on level of formal education. 20 controls had missing information on country of birth.
[a] Original variable translated according to ISCED 2011 categorization.

At baseline patients with RA had a mean duration of symptoms of 7.4 (SD 2.9) months. Of the women, 73.8 % (n = 118) were postmenopausal. Mean BMI was 25.1 kg/m^2 and 25.8 kg/m^2 in women and men respectively and 48 (30.8 %) women and 31 (46.3 %) men with RA reported current smoking at inclusion. Further baseline characteristics for patients are shown in Table 2. At inclusion, 220 patients were examined with DXA of the spine, and 217 patients with DXA of the femoral neck. Results of these measurements showed that 42 (27.1 %) women and 22 (34.9 %) men had osteoporosis (T-score<-2.5) in either the femoral neck or spine at baseline (Table 2). Over the 10 years of follow-up, 58 (36.5 %) women and 27 (40.3 %) men had osteoporosis by DXA at at least one point of measurement. The number of patients who attended and were assessed at the follow up visits was as follows: 212 at 0.5 years of follow up, 219 at 1 year, 208 at 2 years, 179 at 5 years and 123 at 10 years and clinical characteristics at each follow-up visit are shown in Supplementary Table 3.

Treatment in RA patients

Of the women with RA, 58 (35.6 %), and of the men, 32 (46.4%), were treated with glucocorticosteroids (Prednisolone) at baseline, and during the 10 first years 84 (51.5 %) women and 38 (55.1 %) men had treatment with glucocorticosteroids at at least one follow-up visit. Average daily dose at baseline was 8.0 mg and 11.1 mg in women and men respectively and ranged from 5.0 to 6.4 mg in women and 5.2 to 6.6 mg in men at follow-ups between the second and 10th year after study start. Conventional synthetic DMARDs (csDMARDs) were used in over 80 % of women and men at baseline. Although none of the patients had biologic DMARDs at study start, a total of 61 (26.3 %) were treated with bDMARDs at some point during the study period up to December 31, 2017. Calcium and vitamin D were taken by 52 (33.8 %) women and 16 (25.0 %) men. At baseline, 6 (3.9 %) women but no men were on bisphosphonates. At the 10 year follow up 53 (34.2 %) women and 13 (19.7 %) men had been treated with bisphosphonates at any point of follow-up. Of the women with RA 24 (15.5 %) received treatment with hormone replacement therapy at baseline.

Fractures

Four (1.7 %) of the included patients with RA and 31 (3.3 %) of the controls had been diagnosed with at least one of the studied fractures before study start. These patients were excluded from further analyses of

Table 2
Baseline characteristics in patients with early RA.

	All (n 232)	Women (n 163)	Men (n 69)
Age (years) mean (SD)	60.5 (14.6)	59.3 (15.7)	63.4 (11.1)
BMI (kg/m^2) mean (SD)	25.3 (4.1)	25.1 (4.2)	25.8 (3.9)
Smoking ever n (%)	154 (69.1)	97 (62.2)	57 (85.1)
Current smoking n (%)	79 (35.4)	48 (30.8)	31 (46.3)
Postmenopausal n (%)	NA	118 (73.8)	NA
Duration of symptoms (months) mean (SD)	7.4 (2.9)	7.6 (2.9)	7.0 (2.9)
RF positive n (%)	144 (62.1)	97 (59.5)	47 (68.1)
Anti-CCP positive n (%)	116 (57.4)	82 (56.6)	34 (59.6)
CRP (mg/l) median (IQR)	9.0 (<9.0; 26.8)	<9.0 (<9.0; 22.0)	10.0 (<9.0; 33.5)
ESR (mm) median (IQR)	21.0 (10.0; 43.0)	21 (10.0; 43.0)	22.0 (10.5; 44.5)
HAQ median (IQR)	0.75 (0.38; 1.25)	0.88 (0.47; 1.25)	0.75 (0.19; 1.13)
DAS28 mean (SD)	4.64 (1.40)	4.66 (1.36)	4.58 (1.49)
VAS global health (mm) mean (SD)	43.3 (26.8)	43.7 (27.1)	42.4 (26.2)
VAS pain (mm) mean (SD)	41.2 (26.7)	40.4 (25.8)	42.7 (29.0)
csDMARDs n (%)	191 (82.3)	134 (82.2)	57 (82.6)
bDMARDs n (%)	0 (0)	0 (0)	0 (0)
Corticosteroids n (%)	90 (38.8)	58 (35.6)	32 (46.4)
Corticosteroids dose (mg/day) mean (SD)	9.1 (5.2)	8.0 (4.3)	11.1 (6.2)
Calcium and vitamin D n (%)	68 (31.2)	52 (33.8)	16 (25.0)
Bisphosphonates n (%)	6 (2.6)	6 (3.9)	0 (0)
HRT n (%)	NA	24 (15.5)	NA
Index of muscle function median (IQR)	11.0 (5.0; 17.0)	10.0 (4.3; 18.8)	11.5 (6.0; 14.0)
Grip force in dominant hand (% of expected value) mean (SD)	40 (26)	39 (27)	41 (24)
Osteoporosis (T-score <−2.5)* n (%)	64 (29.4)	42 (27.1)	22 (34.9)
Osteopenia (T-score −1 to −2.5) * n (%)	65 (29.8)	49 (31.6)	16 (25.4)

Anti-CCP: anticyclic citrullinated protein; bDMARDs: biologic disease-modifying antirheumatic drugs; BMI: body mass index; CRP: C-reactive protein; csDMARDs: conventional synthetic disease-modifying antirheumatic drugs; DAS28: Disease Activity Score-28; ESR: erythrocyte sedimentation rate; HAQ: Health Assessment Questionnaire; HRT: hormone replacement therapy; IQR: interquartile range; RA: rheumatoid arthritis; RF: rheumatoid factor; SD: standard deviation; VAS: visual analogue scale.
Data at inclusion were complete for age, symptom duration, RF status, CRP, ESR and treatment with csDMARDs, bDMARDs and corticosteroids. Ten patients had missing data on BMI, 9 patients on smoking history and 30 patients on anti-CCP. One patient had missing values on HAQ, DAS28 and VAS global and pain. Fourteen patients had missing data on treatment with calcium, vitamin D and bisphosphonates and on T-scores at baseline. Of the women, 3 had missing data on menopausal status and 8 on treatment with HRT. 126 patients had missing data on index of muscle function and 32 on grip force in dominant hand.
* in the femoral neck or in the lumbar spine (L2L4).

corresponding fractures during the study period.

Seventy-eight (33.6 %) patients (60 (36.8 %) women; 18 (26.1 %) men) and 218 (23.4 %) controls (170 (25.9 %) women; 48 (17.5 %) men) had their first incident fracture during the study period. The mean time to first fracture was 9.6 (SD 5.7) years in patients and 10.0 (SD 5.2) years in controls. The incidence per 1000 person years at risk was 26.5 (95 % CI 20.9; 33.1) in patients and 17.4 (95 % CI 15.1; 19.8) in controls, giving an incidence rate ratio of 1.53 (95 % CI 1.16; 1.98). Further details on numbers of fractures, incidences, and incidence ratios, stratified by sex, and at different fracture sites, are shown in Table 3.

In Cox regression analyses the risk of vertebral and pelvic fractures and of all fractures combined was significantly higher in RA patients than in controls (HR 1.71, 95 % CI 1.07; 2.76 for vertebral and pelvic fractures, and HR 1.51, 95 % CI 1.13; 2.02 for fractures in total). Estimates were similar for hip fractures and when stratified for sex, although the associations did not reach statistical significance in men (Table 3). Adjustment for level of education, country of birth or the Charlson Comorbidity Index did not have a major impact on the results (Supplementary Table 4), and in multivariate analyses of fracture risk in RA compared to controls, with adjustments for all three factors, RA patients had still a significantly higher risk of fractures in total compared with controls (Table 3). In sensitivity analyses, where fractures registered together with an ICD-10 code for high energy trauma were excluded, the results were similar to those of the main analyses (Supplementary Table 5), and so were results in Cox regression models for the risk of fractures in RA patients compared to controls, where individuals with fractures occurring before study start were not excluded (HR 1.52, 95 % CI 1.14; 2.03, adjusted for previous fracture). In exploratory cox regression analyses, with patients and controls divided into three groups based on inclusion year, there was no obvious trend of a change of the risk of fractures in RA patients compared to controls over the years (Supplementary Table 6). Patients included in the later years had a somewhat higher disease activity than patients included during the first part of the recruitment period (Supplementary Table 7). Finally, in additional exploratory cox regression analyses, patients with corticosteroids at baseline had higher risk of fractures than patients who reported no such treatment (HR 1.64, 95 % CI 1.02; 2.62 vs HR 1.44, 95 % CI 0.99; 2.09). Although not statistically significant, there was a trend towards higher fracture risk also in patients without treatment with corticosteroids at inclusion. The pattern was similar when comparing patients who did and did not report treatment with corticosteroids at any of the follow-up visits during the first 10 years (HR 1.56, 95 % CI 1.05; 2.32 vs HR 1.46, 95 % CI 0.95; 2.24). Patients with corticosteroids at inclusion had higher disease activity than patients not treated with corticosteroids at inclusion (Supplementary Table 8 and 9).

Predictors of fractures in RA patients

There was a significant association between high age and fractures in patients with RA (HR per SD 2.20, 95 % CI 1.64; 2.94). There was an association between BMI and risk of fractures (sex- and age-adjusted HR per SD 0.58, 95 % CI 0.44; 0.77). An index of muscle function (IMF) score above median, indicating reduced muscle function in the lower extremities, was associated with increased fracture risk in the unadjusted analysis. None of the studied RA characteristics or treatment at baseline were associated with the risk of fractures after adjustment for age and sex in this study (Table 4). The modified Charlson Comorbidity Index did not predict future fractures in RA patients in this cohort (Table 4).

There were significant associations between increasing Z-scores in the femoral neck and in the lumbar spine and lower risk of fractures overall, as well as for hip, and vertebral and pelvic fractures (Table 5). When adjusting the analyses for age, BMI, CRP>median, and CCI, the negative associations with BMD remained. In the multivariate analyses the hazard ratios for BMD were somewhat attenuated and no longer statistically significant, except for the association between lumbar spine Z-scores and vertebral/pelvic fractures (Table 5). In women, when adjusting for menopausal status the associations between BMD Z-scores and fractures remained statistically significant in all analyses except for the analysis of Z-scores in the lumbar spine in relation to fractures overall, in which there was a significant correlation between the Schoenfeld residuals and length of follow-up, indicating that the proportional hazards assumption was violated for this model.

In time dependent analyses of predictors for fractures overall, there were again inverse associations between Z-scores in the femoral neck and lumbar spine and risk of fractures. Higher HAQ-scores were associated with higher risk of fractures after adjustment for age and sex (Table 6). Also, treatment with calcium and vitamin D was associated with higher risk of fractures after adjustment, whereas treatment with bisphosphonates were associated with higher risk of fractures only in crude analyses. The association seen between glucocorticosteroids and

Table 3
Number of individuals with fractures, incidence per 1000 person years at risk (pyr) and incidence ratios in patients with RA and controls, and risk of fractures in patients with RA vs controls: crude and adjusted cox regression models.

		All		Women		Men	
Fracture site		Patients	Controls	Patients	Controls	Patients	Controls
Any	n (%)	78 (33.6)	218 (23.4)	60 (36.8)	170 (25.9)	18 (26.1)	48 (17.5)
	Incidence per 1000 pyr	26.5	17.4	27.9	18.7	22.6	13.8
	(95 % CI)	(20.9; 33.1)	(15.1; 19.8)	(21.3; 35.9)	(16.0; 21.8)	(13.4; 35.8)	(10.2; 18.3)
	Incidence ratio (95 % CI)	**1.53 (1.16; 1.98)**		**1.49 (1.09; 2.00)**		1.64 (0.90; 2.85)	
	Hazard ratio, crude (95 % CI)	**1.51 (1.13; 2.02)**		**1.50 (1.07; 2.09)**		1.55 (0.84; 2.84)	
	Hazard ratio adjusted for education, country of birth, modified CCI (95 % CI)	**1.52 (1.13; 2.06)**		**1.53 (1.09; 2.15)**		ND	
Hip	n (%)	30 (12.9)	69 (7.4)	23 (14.1)	51 (7.8)	7 (10.1)	18 (6.5)
	Incidence per 1000 pyr	9.22	5.01	9.63	5.09	8.08	4.81
	(95 % CI)	(6.22; 13.2)	(3.90; 6.34)	(6.10; 14.5)	(3.79; 6.69)	(3.25; 16.7)	(2.85; 7.60)
	Incidence ratio (95 % CI)	**1.84 (1.16; 2.84)**		**1.89 (1.10; 3.13)**		1.68 (0.59; 4.26)	
	Hazard ratio, crude (95 % CI)	1.59 (0.97; 2.59)		1.76 (1.00; 3.11)		NA	
	Hazard ratio adjusted for education, country of birth, modified CCI (95 % CI)	ND		ND		NA	
Vertebral/ pelvic	n (%)	31 (13.4)	79 (8.5)	25 (15.3)	60 (9.1)	6 (8.7)	19 (6.9)
	Incidence per 1000 pyr	9.46	5.74	10.5	5.96	6.75	5.13
	(95 % CI)	(6.42; 13.4)	(4.54; 7.15)	(6.78; 15.5)	(4.55; 7.67)	(2.48; 14.7)	(3.09; 8.01)
	Incidence ratio (95 % CI)	**1.65 (1.05; 2.51)**		**1.76 (1.06; 2.82)**		1.32 (0.43; 3.47)	
	Hazard ratio, crude (95 % CI)	**1.71 (1.07; 2.76)**		**2.01 (1.18; 3.44)**		NA	
	Hazard ratio adjusted for education, country of birth, modified CCI (95 % CI)	**1.78 (1.09; 2.90)**		**2.14 (1.22; 3.73)**		NA	
Upper arm	n (%)	23 (9.9)	70 (7.5)	17 (10.4)	57 (8.7)	6 (8.7)	13 (4.7)
	Incidence per 1000 pyr	7.03	5.10	7.05	5.71	6.98	3.48
	(95 % CI)	(4.46; 10.6)	(3.98; 6.44)	(4.11; 11.3)	(4.32; 7.40)	(2.56; 15.2)	(1.85; 5.94)
	Incidence ratio (95 % CI)	1.38 (0.82; 2.22)		1.23 (0.67; 2.14)		2.01 (0.63; 5.85)	
	Hazard ratio, crude (95 % CI)	1.44 (0.87; 2.38)		1.31 (0.74; 2.33)		NA	
	Hazard ratio adjusted for education, country of birth, modified CCI (95 % CI)	ND		ND		NA	
Forearm	n (%)	25 (10.8)	78 (8.4)	21 (12.9)	70 (10.7)	4 (5.8)	8 (2.9)
	Incidence per 1000 pyr	7.70	5.76	8.81	7.17	4.64	2.13
	(95 % CI)	(4.98; 11.4)	(4.56; 7.20)	(5.45; 13.5)	(5.59; 9.06)	(1.26; 11.9)	(0.92; 4.19)
	Incidence ratio (95 % CI)	1.34 (0.82; 2.11)		1.23 (0.72; 2.01)		2.18 (0.48; 9.29)	
	Hazard ratio, crude (95 % CI)	1.30 (0.81; 2.09)		1.13 (0.68; 1.88)		NA	
	Hazard ratio adjusted for education, country of birth, modified CCI (95 % CI)	ND		ND		NA	

CCI: Charlson Comorbidity Index; CI: confidence interval; NA: not applicable due to less than 10 fractures in male RA patients; ND: not done due to lack of association in crude analysis or too few fractures for multi-adjusted analysis; Pyr: person years at risk.
Bold text indicates statistically significant results.

fractures was not statistically significant after adjustment for age and sex (Table 6).

In multivariate time dependent analyses (excluding treatment with calcium and vitamin D due to strong collinearity with age), higher HAQ scores were independently associated with increased fracture risk (HR 1.41 per SD, 95 % CI 1.12; 1.79 after adjustments for Z-scores in the femoral neck, sex and age, and HR 1.48 per SD, 95 % CI 1.17; 1.86 after adjustments for Z-scores in the lumbar spine, sex and age). Z-scores in the femoral neck and lumbar spine also remained inversely associated with risk of fractures independently of HAQ scores (HR 0.77, 95 % CI 0.60; 0.97 and HR 0.67, 95 % CI 0.53; 0.85, respectively, adjusted for time dependent HAQ, sex and age).

All analyses of predictors of fractures in RA patients were also performed after exclusion of fractures registered together with an ICD-10 code for high energy trauma, with similar results (Supplementary Table 10, 11 and 12).

Discussion

In this study, fracture risk in RA patients from diagnosis to a mean follow-up of 15 years was examined and compared to the background population. Patients with RA had a significantly higher risk of fractures than controls, which is in line with previous findings [12,13]. As it has previously been shown that women in this cohort have BMD comparable to healthy controls from the time of diagnosis and up to 10 years of follow-up [2], the results suggest that factors beyond BMD may contribute to the difference in fracture risk between RA patients and controls. Adjustments for country of birth, level of formal education and a modified Charlson Comorbidity Index did not affect the association.

Prediction of fractures is complex and there are many risk factors with multiple potential interactions. Inflammation and the reduced physical activity that often comes with it, declining muscle mass [23] and low levels of vitamin D [1,42], but also treatment with glucocorticoids, might not only lead to reduced bone mass but also to impaired bone quality in RA patients. The possibility of impaired bone quality in RA has been discussed since decades [15], but is still not commonly considered in clinical practice, although trabecular bone score (TBS) has recently been recommended in addition to DXA and FRAX-score assessment, to enhance fracture risk prediction [25]. Results of TBS are associated with fracture risk and this is partly independent of BMD [20]. Indeed, results in some studies suggest that many vertebral fractures in RA affect patients with normal or just subnormal BMD [20,21], and impaired bone architecture measured by for instance TBS could be an explanation for higher risk of fractures in patients with normal BMD

Table 4
Baseline predictors of fractures in RA patients. Crude and adjusted cox regression models.

	HR (95 % CI)	Sex- and Age-adjusted HR (95 % CI)
Age (per SD)	**2.20 (1.64; 2.94)**	NA
Female	1.20 (0.70; 2.03)	NA
BMI (per SD)	**0.67 (0.52; 0.86)**	**0.58 (0.44; 0.77)**
Smoking ever[1]	1.14 (0.70; 1.86)	1.22 (0.74; 2.01)
Current smoking[1]	1.19 (0.67; 2.09)	1.59 (0.88; 2.87)
Postmenopausal (only women)	**3.92 (1.78; 8.63)**	NA
Duration of symptoms (per SD)	1.02 (0.82; 1.28)	1.16 (0.91; 1.46)
RF positive	0.83 (0.53; 1.30)	0.98 (0.62; 1.56)
Anti-CCP positive	1.08 (0.68; 1.71)	1.24 (0.78; 1.98)
CRP >median	**1.77 (1.13; 2.77)**	1.35 (0.85; 2.14)
ESR (per SD)	1.23 (0.99; 1.52)	1.09 (0.88; 1.35)
Erosion score >0	1.35 (0.86; 2.14)	1.01 (0.63; 1.62)
JSN score >0	1.44 (0.91; 2.27)	0.99 (0.62; 1.59)
Total SHS >0	1.10 (0.69; 1.75)	0.81 (0.51; 1.31)
HAQ (per SD)	1.23 (0.98; 1.53)	1.09 (0.87; 1.35)
DAS28 (per SD)	1.25 (0.99; 1.58)	1.16 (0.93; 1.46)
VAS global health (per SD)	1.05 (0.83; 1.31)	1.07 (0.85; 1.34)
VAS pain (per SD)	1.06 (0.85; 1.33)	1.16 (0.93; 1.44)
csDMARDs	1.34 (0.71; 2.55)	1.21 (0.66; 2.30)
Corticosteroids (yes/no)	1.28 (0.82; 2.02)	1.16 (0.73; 1.83)
Corticosteroids, dosage (per SD)	1.05 (0.85; 1.30)	1.08 (0.86; 1.36)
Calcium and D-vitamin	1.37 (0.84; 2.24)	1.11 (0.68; 1.82)
Bisphosphonates	2.44 (0.76; 7.78)	1.10 (0.34; 3.61)
HRT (only women)	0.54 (0.24; 1.19)	NA
Index of muscle function >median	**2.35 (1.22; 4.52)**	1.19 (0.56; 2.53)
Grip force in dominant hand (% of expected value) (per SD)	0.88 (0.69; 1.12)	NA
Modified Charlson Index		
1[2]	1.34 (0.61; 2.93)	0.94 (0.43; 2.08)
≥2[2]	1.42 (0.44; 4.51)	1.06 (0.33; 3.40)
Level of formal education		
Upper-secondary/short-cycle tertiary[3]	1.17 (0.71; 1.93)	1.64 (0.99; 2.72)
≥ Bachelor's degree or equivalent[3]	0.90 (0.46; 1.76)	1.75 (0.88; 3.54)
Country of birth		
Other country in Europe[4]	1.05 (0.51; 2.19)	0.88 (0.42; 1.85)
Country outside Europe[4]	0.42 (0.06; 3.03)	0.88 (0.12; 6.53)

Anti-CCP: anticyclic citrullinated protein; BMI: body mass index; CI: confidence interval; CRP: C-reactive protein; csDMARDs: conventional synthetic disease-modifying antirheumatic drugs; DAS28: Disease Activity Score-28; ESR: erythrocyte sedimentation rate; HAQ: Health Assessment Questionnaire; HR: hazard ratio; HRT: hormone replacement therapy; JSN: joint space narrowing; NA: not applicable; RA: rheumatoid arthritis; RF: rheumatoid factor; SD: standard deviation; SHS: Sharp van der Heijde Score; VAS: visual analogue scale.
Bold text indicates statistically significant results.
No analyses were done for biologic DMARDs due to no patients treated with bDMARDs at study start.
[1] Reference: never smoking.
[2] Reference: 0.
[3] Reference: ≤ Lower secondary education (original variable translated according to ISCED 2011 categorization).
[4] Reference: born in Sweden.

[20]. RA patients have a high risk of falling, partly due to joint inflammation (especially in the lower extremities), pain, impaired balance and muscle strength [23,24] and this could be another reason for higher fracture risk among RA patients.

In this cohort 36 % of the women with RA and 40 % of the men had osteoporosis (T-score<−2.5) at at least one DXA measurement during the first 10 years of disease. In relation to this, 34 % of the women, but only 20 % of the men had been treated with bisphosphonates at any point of the first ten years of follow-up. Unfortunately, information on osteoporosis treatment in the control group was unavailable, which is a limitation of this study. The setting of this study though, including RA patients that had been repeatedly assessed with DXA, and probably treated according to the results, makes it unlikely that these RA patients received less osteoporosis treatment than the controls, although men with RA in this cohort seem to have been undertreated, which has previously been seen in both men in general [43] and men with RA [9]. About 35 % of the patients with RA in this cohort reported current smoking at baseline which is more than the reported smoking prevalence in the general Swedish population around the time of start of this study [44,45]. Smoking is an established predictor for developing RA [46], and smokers with RA are at increased risk of progressive joint damage [34]. Furthermore, smoking is associated with osteoporosis and a well-established risk factor of fractures [47], and could be part of the explanation for a higher fracture risk in RA patients.

The risk of fractures in the distal forearm was not increased in RA patients the way hip-, vertebral and pelvic fractures were. This has been seen previously in several studies [13,14,48], where explanations like RA patients protecting their hands when falling, or the incompleteness of register data due to less need of in-patient care with this type of fracture, have been proposed [14]. Specialized outpatient care (including emergency clinics where most fractures are assessed) was included in the Swedish National Patient register from 2001, and patients with fractures not in need of inpatient care before that may have been missed in this study.

In analyses of potential predictors of fractures in the RA cohort, high age and low BMI were significant predictors of fractures after adjustment for sex and age. These are well-known risk factors for fractures [12, 47]. None of the measures of disease activity, whether assessed at baseline or time-dependently, had a significant effect on the risk of fractures in this cohort of RA patients, except higher HAQ scores over time, which was associated with higher risk of fractures in the time-dependent analyses after adjustment for sex, age and BMD Z-scores. Associations between HAQ and fractures have been described before [12], and may reflect impaired muscle function, as high HAQ has been shown to predict development of sarcopenia and at least in some studies predict falls [23,24]. Few studies have evaluated the effect of disease related factors in early RA in this context. Ajeganova et al. found an association between DAS-28 at diagnosis and fracture risk, and also an association between positive RF-status and risk of fractures [49]. These findings were not confirmed by this study, perhaps because of smaller patient numbers, although there was a similar trend for the impact of DAS-28 at baseline. Many disease severity markers may fluctuate from time to time, especially after treatment, contributing to difficulties in assessing them as predictors at baseline or at cross sectional time points. This may be the case also in our study, since the periods between follow-up points are long enough to permit variations not captured by our assessments, especially after the first two years. The use of corticosteroids was not significantly associated with higher risk of fractures after adjustment for sex and age, which could similarly be explained by potential varying doses in between follow-up points, but may also be explained by the relatively moderate average doses from the 2nd to the 10th year of follow up. In exploratory stratified analyses, patients reporting no use of corticosteroids at baseline or at any of the follow-up visits the first 10 years, had slightly lower risk of fractures compared to patients with such treatment, but had still a clear trend towards a higher risk of fractures than the controls. It cannot be ruled out that patients without treatment at the follow-up visits had corticosteroids in between or after the 10 first years of follow-up. Further, it should be mentioned that the two patient groups were not fully comparable regarding disease activity, and that the numbers of fractures in each stratum was lower.

Higher BMD Z-scores in the femoral neck and spine were significantly associated with lower risk of fractures in total and in the hip and vertebra/pelvis respectively, at baseline and in time-dependent analyses. The results were similar when stratified for sex. The associations were still significant after adjustment for baseline age, BMI, CRP above the median and CCI and after adjustment for sex, age and HAQ in time-dependent analyses. The relationship between BMD and fractures in RA patients has been described in various studies of selected populations [15–19] and our results confirm earlier results in a broader setting. The higher risk for fractures in patients treated with bisphosphonates and

Table 5
Bone mineral density (Z-score) as predictors of fractures in RA patients. Crude and adjusted cox regression models.

	Women	Men	All					
	Crude Hazard Ratio (HR) (95 % confidence interval (CI))			Age-adjusted HR (95 % CI)	BMI-adjusted HR (95 % CI)	CRP-adjusted HR (95 % CI)	Modified CCI-adjusted HR (95 % CI)	Multivariate adjusted* HR (95 % CI)
Fractures overall								
Z-score femoral neck	**0.69 (0.53; 0.90)**	**0.46 (0.25; 0.85)**	**0.64 (0.50; 0.81)**	**0.71 (0.56; 0.90)**	**0.66 (0.51; 0.85)**	**0.63 (0.49; 0.80)**	**0.62 (0.49; 0.79)**	0.78 (0.59; 1.02)
Z-score spine (L2-L4)	**0.78 (0.60; 1.00)**	0.68 (0.42; 1.09)	**0.75 (0.60; 0.93)**	**0.76 (0.60; 0.95)**	0.79 (0.62; 1.01)	**0.74 (0.59; 0.93)**	**0.74 (0.59; 0.93)**	0.84 (0.65; 1.09)
Hip fractures								
Z-score femoral neck	**0.52 (0.34; 0.79)**	0.63 (0.26; 1.49)	**0.53 (0.37; 0.78)**	**0.63 (0.43; 0.93)**	**0.56 (0.37; 0.85)**	**0.52 (0.35; 0.76)**	**0.52 (0.35; 0.77)**	0.69 (0.44; 1.10)
Vertebral/pelvic fractures								
Z-score spine (L2-L4)	**0.62 (0.40; 0.95)**	0.66 (0.29; 1.51)	**0.62 (0.43; 0.92)**	**0.61 (0.41; 0.92)**	**0.63 (0.43; 0.94)**	**0.62 (0.42; 0.91)**	**0.62 (0.42; 0.91)**	**0.64 (0.41; 0.99)**

CCI: Charlson Comorbidity Index.
Bold text indicates statistically significant results.
* Adjusted for Age, BMI, CRP>median and modified CCI.

Table 6
Predictors of fractures in RA patients, crude and adjusted time dependent cox regression analyses.

	Crude HR (95 % CI)	Sex- and age-adjusted HR (95 % CI)
RA characteristics		
ESR (per SD)	1.17 (0.96; 1.42)	1.20 (0.97; 1.48)
Erosion score >0	1.39 (0.77; 2.51)	1.24 (0.69; 2.24)
JSN score >0	1.55 (0.84; 2.84)	1.26 (0.68; 2.34)
Total SHS >0	1.20 (0.61; 2.36)	0.83 (0.42; 1.65)
HAQ (per SD)	**1.50 (1.24; 1.81)**	**1.33 (1.09; 1.63)**
DAS28 (per SD)	1.04 (0.82; 1.30)	1.05 (0.82; 1.35)
VAS global health (per SD)	1.21 (0.98; 1.50)	1.23 (0.99; 1.52)
VAS pain (per SD)	1.18 (0.96; 1.47)	1.20 (0.98; 1.48)
Grip force in the dominant hand (% of expected value) (per SD)	0.98 (0.79; 1.23)	NA
BMD		
Z-score femoral neck	**0.67 (0.52; 0.87)**	**0.75 (0.59; 0.95)**
Z-score lumbar spine	**0.75 (0.60; 0.93)**	**0.69 (0.54; 0.88)**
RA treatment		
csDMARDs, yes/no	1.18 (0.69; 2.03)	0.94 (0.54; 1.62)
Corticosteroids, yes/no	**1.76 (1.09; 2.84)**	1.50 (0.92; 2.42)
Corticosteroids, dosage (per SD)	**1.18 (1.02; 1.37)**	1.11 (0.96; 1.28)
Osteoporosis treatment		
Bisphosphonates, yes/no	**1.80 (1.09; 2.98)**	1.46 (0.88; 2.44)
Calcium and D-vitamin yes/no	**3.13 (1.78; 5.50)**	**2.56 (1.45; 4.53)**
HRT (only women) yes/no	0.78 (0.11; 5.63)	0.90 (0.12; 6.59)

BMD: bone mineral density; CI: confidence interval; csDMARDs: conventional synthetic disease-modifying antirheumatic drugs; DAS28: Disease Activity Score-28; ESR: erythrocyte sedimentation rate; HAQ: Health Assessment Questionnaire; HR: hazard ratio; HRT: hormone replacement therapy; JSN: joint space narrowing; NA: not applicable; RA: rheumatoid arthritis; SD: standard deviation; SHS: Sharp van der Heijde Score; VAS: visual analogue scale.
Bold text indicates statistically significant results.

calcium and vitamin D likely reflects confounding by indication.

Low grip force has previously been described as a risk factor for fractures in patients with RA [50] and in the general population [51], but this was not confirmed in the present study. A high IMF score, indicating worse lower extremity function and possibly related to increased risk of falls, was associated with higher fracture risk in unadjusted analyses. The lack of significant association in age-sex-adjusted models should be interpreted with caution since only a subset of the patients had been assessed with IMF and the number of fractures was smaller. The low number of patients assessed with IMF is a limitation of this study. Like DXA is well-established for diagnosing osteoporosis, and FRAX is a valuable tool for predicting fractures, further studies on an easily performed test for the risk of falls in RA and its' relation to fracture risk would be beneficial to fully assess the risk of fractures in RA.

Except low number of patients taking part in assessments of IMF, other limitations apply in this study. The patients in this cohort were diagnosed 1995–2005, before early treatment with biologic DMARDs was common, and hence results of this study may not apply to patients treated with bDMARDs in early disease. The division of the cases and controls into groups based on inclusion year was an attempt to explore whether there was any trend of a change in fracture risk between patients included in the beginning or end of the inclusion period, but no such pattern was seen. However, these analyses should be interpreted with caution, due to small numbers of fractures and differences in baseline characteristics between the groups. There was insufficient information on baseline characteristics of the control population, and especially information on smoking, BMI and medications would have been useful. Also, the fairly small size of the RA cohort, making analyses of subsets or stratified analyses difficult, is a limitation. Missing information on alcohol intake, family history of fractures and osteoporosis as well as vitamin D-status and information on history of falls for the RA patients constitutes a limitation, and so does the method of detection of fractures from registry databases, with no verification with radiographic documentation. The Swedish National Patient Register has been validated both by comparison with the Swedish Hip Fracture Register (a Swedish quality register for hip fractures) and through reviews of patient records, showing consistently good results regarding the validity of hip fracture diagnoses [52,53]. However, radiographic examination is especially important for detecting vertebral fractures, and if RA patients in this cohort had more subclinical vertebral fractures than the background population, or the threshold for obtaining radiographs was different for patients with RA, this might affect the results. Finally, FRAX and TBS were not used at the time of study start, but would have enriched this study.

The longitudinal design with long term structured follow up and repeated assessment with DXA is a major strength of this study. Furthermore, patients with early RA were consecutively included in the cohort and the patients were treated according to the general recommendations throughout the study period, making them representative to other patients with similar health care opportunities.

In conclusion, RA patients included at diagnosis and followed up to 15 years had higher risk of fractures than controls from the background

population, despite the fact that women in this cohort have previously been shown to have comparable bone mass with healthy controls. Prediction and prevention of fractures is complex and further studies are needed to decide which risk factors of fractures are detectable already early in RA. A combination of optimal treatment of arthritis, anti-osteoporosis therapy and, assessment of risk of falls followed by other relevant preventive measures, is probably needed to successfully prevent fractures in RA.

Declaration of competing interest

Kristina E Åkesson has received consulting fees from Astellas Pharma, and has received honoraria for lectures from Amgen and UCB. Lennart TH Jacobsson has received consulting fees from Abbvie, Eli Lilly, Janssen, Novartis and Pfizer, and honoraria for lectures from Abbvie, Janssen and Novartis. Carl Turesson has received consulting fees from Abbvie, and honoraria for lectures from Abbvie, Nordic Drugs and Pfizer.

The other authors declare that they have no competing interests.

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Authors' contributions

LT participated in the study design, performed a major part of the organization of data for statistical analysis, performed the statistical analyses and wrote the first draft of the manuscript. AS helped in the management of the organization of data for statistical analysis and participated in the analysis and interpretation of data. MKK and KEÅ participated in the study design, data acquisition and in the analysis and interpretation of data. LTHJ participated in the study design, the design of the patient questionnaires and in the analysis and interpretation of data. CT conceived of the study, supervised the data management and the statistical analysis and helped draft the manuscript. All the authors helped in the revision of the manuscript and read and approved the final version.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2024.152497.

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Supplementary table 1. ICD codes for identification of fractures and comorbidities

	ICD 10	ICD 9
Hip fractures	S720-S722	820
Vertebral and pelvic fractures	S22, S32, M485	805, 808
Forearm fractures	S52	813
Upper arm fractures	S42	812
Hypertension	I10-I15	401-405
Diabetes mellitus	E10-E14, O24	250
Ischaemic heart disease	I20-I25	410-414
Heart failure	I50	428
Cerebrovascular disease	I60-I69	430-438
Peripheral vascular disease	I70-I79	440-448
Renal failure	N17-N19	584-586
Thyroid disease	E03, E05, E06	242-245
Airway disease	J40-J47, J60-J64, J66-J67, J82, J84	490-496, 500-508, 515-516, 518D
Liver disease	K70-K77	570-573
Gastric ulcer	K25-K27	531-533
Inflammatory bowel disease	K50, K51	555, 556
Psoriasis	L40	696
Anterior uveitis	H20, H221	364
Multiple sclerosis	G359	340
Parkinson disease	G209	332A
Epilepsy	G40, G41	345
Hemiplegia	G81	342
Dementia	F00-F03	290, 294B
Anxiety and depressive disorder	F32-F39, F41	311, 300
Diagnoses related to alcohol misuse	F10	303, 305, 291
Malignancy	C00-C97	140-208
Obesity	E66	278A
Malnutrition	E40-E46	260-263
Anorexia nervosa	F500, F501	307B
Testicular hypofunction or ovarian failure	E291, E895, E283, E894	257B-C, 256B-C
Osteogenesis imperfecta	Q780	756F
Osteoporosis	M80, M81, M82	733A

Supplementary table 2. ICD codes included in the modified Charlson comorbidity index, and weighted index of every comorbidity

Conditions	ICD 9-codes	ICD 10-codes	Assigned weights for diseases
Myocardial infarct	410, 412	I21, I22, 125	1
Congestive heart failure	428	I50	1
Peripheral vascular disease	440, 441, 443, 471	I70, I71, I73, I77, I79	1
Cerebrovascular disease	430-438	I60-I69	1
Dementia	290, 294	F00-F03	1
Chronic pulmonary disease	490-496, 500-506, 508	J40-J47, J60-J64, J66-J67, J68	1
Connective tissue disease	446		1
Ulcer disease	531-533	K25-K27	1
Mild liver disease	570, 571, 573	K70, K71, K73, K74, K76	1
Diabetes	250	E10, E11, E12, E13, E14	1
Hemiplegia or paraplegia	342	G81	2
Renal disease	585, 586	N18, N19	2
Any tumor, leukemia or lymphoma	140-172, 174-195, 200-208	C00-C26, C30-C34, C37- C41, C43, C45-C58, C60- C76, C81-C85, C88, C90-C97	2
Moderate or severe liver disease	572	K72	3
Metastatic solid tumor	196-199	C77-C80	6

Supplementary table 3. Number of patients examined and clinical characteristics, by follow-up visit, over the first 10 years of follow-up

	Inclusion	1 year	2 years	5 years	10 years
n	232	219	208	179	123
Women n (%)	163 (70.3)	154 (70.3)	146 (70.2)	127 (70.9)	90 (73.2)
Age (years) mean (SD)	60.5 (14.6)	61.1 (14.6)	62.1 (14.8)	64.3 (14.5)	67.4 (13.7)
BMI (kg/m^2) mean (SD)	25.3 (4.1)	NA	25.8 (4.4)	NA	NA
CRP (mg/l) median (IQR)	9.0 (<9.0; 26.8)	<9.0 (<9.0; 18.2)	<9.0 (<9.0; 11.0)	<9.0 (<9.0; 9.25)	<9.0 (<9.0; 10.8)
ESR (mm) median (IQR)	21.0 (10.0; 43.0)	15.0 (8.0; 27.8)	15.0 (8.0; 26.3)	15.0 (9.0; 24.0)	16.5 (11.0; 29.0)
Erosion score median (IQR)	0.0 (0.0; 2.0)	1.0 (0.0; 4.0)	2.0 (0.0; 6.0)	5.0 (1.0; 10.0)	NA
JSN score median (IQR)	2.0 (0.0; 6.0)	4.0 (0.0; 11.5)	6.0 (2.0; 15.0)	12.0 (3.0; 23.0)	NA
Total SHS median (IQR)	3.0 (0.0; 8.0)	6.0 (1.0; 15.5)	10.0 (3.0; 21.0)	18.0 (6.0; 31.0)	NA
HAQ median (IQR)	0.8 (0.4; 1.3)	0.5 (0.1; 1.0)	0.5 (0.0; 1.0)	0.8 (0.1; 1.1)	0.8 (0.4; 1.1)
DAS28 mean (SD)	4.6 (1.4)	3.7 (1.4)	3.6 (1.4)	3.6 (1.4)	3.2 (1.1)
VAS global health (mm) mean (SD)	43.3 (26.8)	30.6 (23.9)	33.6 (26.5)	34.5 (24.7)	31.2 (24.7)
VAS pain (mm) mean (SD)	41.2 (26.7)	30.1 (24.1)	32.1 (27.0)	30.3 (23.8)	29.4 (23.8)
csDMARDs n (%)	191 (82.3)	191 (87.2)	172 (82.7)	137 (76.5)	89 (72.4)
bDMARDs n (%)	0 (0)	12 (5.5)	17 (8.2)	32 (17.9)	28 (22.8)
Corticosteroids n (%)	90 (38.8)	69 (31.5)	62 (30.0)	52 (29.1)	30 (12.9)
Corticosteroids dose mean (SD)	9.1 (5.2)	5.8 (3.5)	5.2 (2.4)	5.2 (3.4)	6.4 (6.8)
Calcium and vitamin D n (%)	68 (31.2)	124 (59.0)	122 (62.6)	99 (67.3)	50 (56.2)
Bisphosphonates n (%)	6 (2.6)	43 (20.5)	43 (22.1)	44 (29.9)	24 (27.0)
HRT n (%) (only women)	24 (15.5)	25 (16.9)	20 (14.3)	16 (14.5)	0 (0.0)
Grip force in dominant hand (% of expected value) mean (SD)	40 (26)	52 (27)	54 (29)	57 (30)	66 (28)
Osteoporosis (T-score <-2.5)* n (%)	64 (29.4)	NA	52 (27.1)	43 (25.4)	27 (22.7)
Missing values n (%)	0-18 (0-7.8)	0-21 (0-9.5)	0-16 (0-7.7)	0-32 (0-17.9)	0-34 (0-27.6)

* in the femoral neck or in the lumbar spine (L2L4).

bDMARDs: biologic disease-modifying antirheumatic drugs; BMI: body mass index; CRP: C-reactive protein; csDMARDs: conventional synthetic disease-modifying antirheumatic drugs; DAS28: Disease Activity Score-28; ESR: erythrocyte sedimentation rate; HAQ: Health Assessment Questionnaire; HRT: hormone replacement therapy; IQR: interquartile range; JSN: joint space narrowing; NA: not available; SD: standard deviation; SHS: Sharp van der Heijde Score; VAS: visual analogue scale.

Supplementary table 4. Risk of fractures in patients with RA vs controls, crude and adjusted cox regression models, hazard ratio (95% confidence interval).

Fracture site	Crude	Adjusted for level of education	Adjusted for country of birth[1]	Adjusted for modified CCI
All	**1.51 (1.13; 2.02)**	**1.50 (1.12; 2.01)**	**1.54 (1.15; 2.07)**	**1.56 (1.20; 2.02)**
Hip	1.59 (0.97; 2.59)	ND	ND	ND
Vertebral/pelvic	**1.71 (1.07; 2.76)**	**1.76 (1.09; 2.85)**	**1.68 (1.05; 2.71)**	**1.72 (1.13; 2.60)**
Upper arm	1.44 (0.87; 2.38)	ND	ND	ND
Forearm	1.30 (0.81; 2.09)	ND	ND	ND

[1]Born in Europe or other parts of the world vs born in Sweden.

CCI: Charlson Comorbidity Index; ND: Not done due to lack of association in crude analysis or too few fractures for multi-adjusted analysis

Bold text indicates statistically significant results.

Supplementary table 5. Number of individuals with fractures, incidence per 1000 person years at risk (pyr) and incidence ratios in patients with RA and controls, and risk of fractures in patients with RA vs controls: crude and adjusted cox regression models after exclusion of fractures with ICD-10 external cause codes for high energy trauma.

Fracture site		All		Women		Men	
		Patients	Controls	Patients	Controls	Patients	Controls
Any	n (%)	76 (32.8)	207 (22.2)	59 (36.2)	163 (24.8)	17 (24.6)	44 (16.0)
	Incidence per 1000 pyr (95% CI)	26.1 (20.6; 32.7)	16.7 (14.5; 19.1)	27.9 (21.3; 35.9)	18.7 (16.0; 21.8)	21.9 (12.8; 35.1)	12.8 (9.30; 17.2)
	Incidence ratio (95% CI)	**1.57 (1.19; 2.04)**		**1.49 (1.09; 2.00)**		1.71 (0.92; 3.04)	
	Hazard ratio, crude (95% CI)	**1.51 (1.12; 2.04)**		**1.49 (1.07; 2.09)**		1.59 (0.85; 2.97)	
	Hazard ratio adjusted for education, country of birth, modified CCI (95% CI)	**1.54 (1.14; 2.09)**		**1.53 (1.08; 2.15)**		ND	
Hip	n (%)	28 (12.1)	69 (7.4)	21 (12.9)	51 (7.8)	7 (10.1)	18 (6.5)
	Incidence per 1000 pyr (95% CI)	8.70 (5.78; 12.6)	5.10 (3.97; 6.45)	8.84 (5.47; 13.5)	5.17 (3.85; 6.80)	8.29 (3.33; 17.1)	4.91 (2.91; 7.76)
	Incidence ratio (95% CI)	**1.71 (1.06; 2.66)**		1.71 (0.98; 2.87)		1.69 (0.60; 4.29)	
	Hazard ratio, crude (95% CI)	1.48 (0.89; 2.45)		1.56 (0.86; 2.80)		NA	
	Hazard ratio adjusted for education, country of birth, modified CCI (95% CI)	ND		ND		NA	
Vertebral/pelvic	n (%)	29 (12.5)	70 (7.5)	24 (14.7)	55 (8.4)	5 (7.2)	15 (5.5)
	Incidence per 1000 pyr (95% CI)	8.98 (6.01; 12.9)	5.16 (4.02; 6.51)	10.2 (6.50; 15.1)	5.54 (4.17; 7.21)	5.78 (1.88; 13.5)	4.12 (2.30; 6.79)
	Incidence ratio (95% CI)	**1.74 (1.09; 2.70)**		**1.83 (1.09; 2.99)**		1.40 (0.40; 4.18)	
	Hazard ratio, crude (95% CI)	**1.73 (1.05; 2.83)**		**2.04 (1.18; 3.53)**		NA	
	Hazard ratio adjusted for education, country of birth, modified CCI (95% CI)	**1.84 (1.10; 3.06)**		**2.23 (1.26; 3.96)**		NA	
Upper arm	n (%)	23 (9.9)	66 (7.1)	17 (10.4)	56 (8.5)	6 (8.7)	10 (3.6)
	Incidence per 1000 pyr (95% CI)	7.17 (4.55; 10.8)	4.89 (3.78; 6.22)	7.17 (4.18; 11.5)	5.69 (4.30; 7.39)	7.17 (2.63; 15.6)	2.73 (1.31; 5.02)
	Incidence ratio (95% CI)	1.47 (0.87; 2.37)		1.26 (0.69; 2.19)		2.63 (0.78; 8.49)	
	Hazard ratio, crude (95% CI)	1.52 (0.92; 2.53)		1.34 (0.75; 2.39)		NA	
	Hazard ratio adjusted for education, country of birth, modified CCI (95% CI)	ND		ND		NA	
Forearm	n (%)	25 (10.8)	74 (7.9)	21 (12.9)	66 (10.1)	4 (5.8)	8 (2.9)
	Incidence per 1000 pyr (95% CI)	7.85 (5.08; 11.6)	5.57 (4.37; 6.99)	8.96 (5.54; 13.7)	6.86 (5.30; 8.72)	4.76 (1.30; 12.2)	2.18 (0.94; 4.29)
	Incidence ratio (95% CI)	1.41 (0.86; 2.23)		1.31 (0.76; 2.15)		2.18 (0.48; 9.29)	
	Hazard ratio, crude (95% CI)	1.41 (0.87; 2.27)		1.23 (0.73; 2.06)		NA	
	Hazard ratio adjusted for education, country of birth, modified CCI (95% CI)	ND		ND		NA	

CCI: Charlson Comorbidity Index; CI: confidence Interval; NA: not applicable due to less than 10 fractures in male RA patients; ND: not done due to lack of association in crude analysis or too few fractures for multi-adjusted analysis; Pyr: person years at risk

Supplementary table 6. Number of individuals with fractures, incidence per 1000 person years at risk (pyr), incidence ratios in patients with RA and controls, and risk of fractures in patients with RA vs controls. Patients divided into groups based on inclusion year.

	1995-1998		1999-2001		2002-2005	
	Patients	Controls	Patients	Controls	Patients	Controls
Fractures n (%)	38 (40.0)	93 (24.9)	25 (32.1)	80 (25.8)	15 (27.3)	45 (20.8)
Incidence per 1000 pyr (95% CI)	29.1 (20.6; 39.9)	16.9 (13.6; 20.7)	26.6 (17.2; 39.2)	19.0 (15.1; 23.7)	21.5 (12.1; 35.5)	15.9 (11.6; 21.2)
Incidence ratio (95% CI)	**1.72 (1.15; 2.52)**		1.40 (0.85; 2.20)		1.36 (0.70; 2.47)	
Hazard ratio (95% CI)	1.46 (0.93; 2.27)		1.60 (0.97; 2.63)		1.49 (0.80; 2.77)	

Supplementary table 7. Baseline characteristics in patients divided into groups based on inclusion year.

	1995-1998	1999-2001	2002-2005
Number (% of total cohort)	97 (41.8)	80 (34.5)	55 (23.7)
Women n (%)	64 (66.0)	61 (76.3)	38 (69.1)
Age (years) mean (SD)	61.0 (14.3)	62.5 (13.9)	56.8 (15.8)
BMI (kg/m^2) mean (SD)	25.8 (4.5)	24.7 (3.5)	25.6 (4.2)
Smoking ever n (%)	68 (70.1)	54 (68.4)	32 (68.1)
Current smoking n (%)	33 (34.0)	27 (34.2)	19 (40.4)
Duration of symptoms (months) mean (SD)	8.0 (2.8)	7.7 (2.9)	6.0 (2.8)
RF positive n (%)	61 (62.9)	45 (56.3)	38 (69.1)
Anti-CCP positive n (%)	59 (62.8)	40 (50.0)	17 (60.7)
CRP (mg/l) median (IQR)	<9.0 (<9.0; 18.5)	9.5 (<9.0; 33.3)	14.0 (<9.0; 37.0)
ESR (mm) median (IQR)	20.0 (11.0; 35.5)	20.0 (10.0; 36.8)	27.0 (11.0; 61.0)
HAQ median (IQR)	0.63 (0.25; 1.13)	0.75 (0.25; 1.22)	1.00 (0.63; 1.50)
DAS28 mean (SD)	4.45 (1.33)	4.62 (1.46)	5.20 (1.30)
VAS global health (mm) mean (SD)	37.9 (27.3)	43.6 (24.6)	52.4 (26.7)
VAS pain (mm) mean (SD)	36.3 (27.1)	40.4 (25.7)	50.5 (25.5)
csDMARDs n (%)	72 (74.2)	66 (82.5)	53 (96.4)
bDMARDs n (%)	0 (0)	0 (0)	0 (0)
Corticosteroids n (%)	35 (36.1)	26 (32.5)	29 (52.7)
Corticosteroids dose (mg/day) mean (SD)	2.8 (4.4)	2.6 (4.9)	6.3 (7.0)
Calcium and vitamin D n (%)	12 (13.3)	31 (41.9)	25 (46.3)
Bisphosphonates n (%)	2 (2.1)	3 (4.1)	1 (1.9)
Index of muscle function median (IQR)	9.0 (4.0; 14.8)	14.5 (7.8; 21.3)	NA
Grip force in dominant hand (% of expected value) mean (SD)	41 (28)	41 (24)	35 (23)
Osteoporosis (T-score <-2.5)* n (%)	30 (35.3)	24 (32.0)	10 (18.9)
Osteopenia (T-score -1 to -2.5)* n (%)	21 (23.3)	23 (30.7)	21 (39.6)

*in the femoral neck or in the lumbar spine (L2L4).

Anti-CCP: anticyclic citrullinated protein; bDMARDs: biologic disease-modifying antirheumatic drugs; BMI: body mass index; CRP: C-reactive protein; csDMARDs: conventional synthetic disease-modifying antirheumatic drugs; DAS28: Disease Activity Score-28; ESR: erythrocyte sedimentation rate; HAQ: Health Assessment Questionnaire; IQR: interquartile range; RA: rheumatoid arthritis; RF: rheumatoid factor; SD: standard deviation; VAS: visual analogue scale.

Supplementary table 8. Number of individuals with fractures, incidence per 1000 person years at risk (pyr), incidence ratios in patients with RA and controls, and risk of fractures in patients with RA vs controls. Patients divided into groups based on registered treatment with corticosteroids at baseline or at follow-up visits.

	No cortiocosteroids at baseline		**Cortiocosteroids at baseline**		**No corticosteroids registered during first 10 years of follow-up**		**Corticosteroids registered during first 10 years of follow-up**	
	Patients	Controls	Patients	Controls	Patients	Controls	Patients	Controls
Fractures n (%)	46 (32.9)	131 (23.9)	32 (36.4)	87 (24.9)	35 (32.4)	97 (23.0)	43 (35.8)	121 (25.5)
Incidence per 1000 pyr (95% CI)	24.4 (17.9; 32.6)	16.9 (14.2; 20.1)	30.2 (20.6; 42.6)	18.3 (14.6; 22.6)	24.2 (16.8; 33.6)	16.8 (13.6; 20.5)	28.8 (20.8; 38.7)	18.0 (14.9; 21.5)
Incidence ratio (95% CI)	**1.44 (1.01; 2.02)**		**1.65 (1.06; 2.49)**		1.44 (0.95; 2.12)		**1.60 (1.10; 2.27)**	
Hazard ratio (95% CI)	1.44 (0.99; 2.09)		**1.64 (1.02; 2.62)**		1.46 (0.95; 2.24)		**1.56 (1.05; 2.32)**	

Supplementary table 9. Baseline characteristics in patients divided into groups based on registered treatment with corticosteroids at baseline or at follow-up visits.

	No corticosteroids at baseline	**Corticosteroids at baseline**	**No corticosteroids registered during first 10 years of follow-up**	**Corticosteroids registered during first 10 years of follow-up**
Number (% of total cohort)	142	90	110	122
Women n (%)	105 (73.9)	58 (64.4)	79 (71.8)	84 (68.9)
Age (years) mean (SD)	59.4 (15.2)	62.3 (13.6)	60.5 (15.0)	60.6 (14.3)
BMI (kg/m^2) mean (SD)	25.4 (4.2)	25.2 (3.9)	25.4 (4.3)	25.2 (3.9)
Smoking ever n (%)	94 (68.6)	60 (69.8)	74 (68.5)	80 (69.6)
Current smoking n (%)	44 (32.1)	35 (40.7)	34 (31.5)	45 (39.1)
Duration of symptoms (months) mean (SD)	7.9 (2.8)	6.7 (3.0)	8.0 (2.9)	6.9 (2.9)
RF positive n (%)	91 (64.1)	53 (58.9)	67 (60.9)	77 (63.1)
Anti-CCP positive n (%)	71 (50.0)	45 (50.0)	50 (45.5)	66 (54.1)
CRP (mg/l) median (IQR)	<9.0 (<9.0; 17.3)	14.0 (<9.0; 37.0)	<9.0 (<9.0; 14.3)	12.5 (<9.0; 37.0)
ESR (mm) median (IQR)	18.0 (9.8; 35.8)	27 (14.8; 44.0)	17.0 (9.0; 31.3)	27.0 (15.0; 52.0)
HAQ median (IQR)	0.75 (0.25; 1.13)	1.00 (0.47; 1.50)	0.63 (0.25; 1.00)	1.00 (0.47; 1.50)
DAS28 mean (SD)	4.51 (1.38)	4.83 (1.42)	4.39 (1.32)	4.86 (1.44)
VAS global health (mm) mean (SD)	41.9 (26.7)	45.5 (26.9)	39.3 (25.8)	46.9 (27.2)
VAS pain (mm) mean (SD)	39.4 (26.0)	43.8 (27.8)	37.0 (25.5)	44.8 (27.4)
csDMARDs n (%)	110 (77.5)	81 (90.0)	83 (75.5)	108 (88.5)
bDMARDs n (%)	0 (0)	0 (0)	0 (0)	0 (0)
Calcium and vitamin D n (%)	16 (12.1)	52 (60.5)	15 (15.0)	53 (44.9)
Bisphosphonates n (%)	3 (2.3)	3 (3.3)	2 (2.0)	4 (3.4)
Index of muscle function median (IQR)	10.0 (4.0; 17.0)	13.0 (7.0; 17.0)	11.0 (5.0; 17.0)	11.0 (5.0; 17.0)
Grip force in dominant hand (% of expected value) mean (SD)	43 (27)	35 (23)	42 (25)	38 (27)
Osteoporosis (T-score <-2.5)* n (%)	41 (31.8)	23 (27.4)	36 (36.4)	28 (24.6)
Osteopenia (T-score -1 to -2.5)* n (%)	36 (27.5)	29 (33.3)	27 (27.0)	38 (32.2)

*in the femoral neck or in the lumbar spine (L2L4).

Anti-CCP: anticyclic citrullinated protein; bDMARDs: biologic disease-modifying antirheumatic drugs; BMI: body mass index; CRP: C-reactive protein; csDMARDs: conventional synthetic disease-modifying antirheumatic drugs; DAS28: Disease Activity Score-28; ESR: erythrocyte sedimentation rate; HAQ: Health Assessment Questionnaire; IQR: interquartile range; RA: rheumatoid arthritis; RF: rheumatoid factor; SD: standard deviation; VAS: visual analogue scale.

Supplementary table 10. Baseline predictors of fractures in RA patients, after exclusion of fractures with ICD-10 external cause codes for high energy trauma. Crude and adjusted cox regression models.

	HR (95% CI)	Sex- and Age-adjusted HR (95% CI)
Age (per SD)	**2.27 (1.68; 3.07)**	NA
Female	1.22 (0.71; 2.09)	NA
BMI (per SD)	**0.67 (0.52; 0.87)**	**0.59 (0.44; 0.78)**
Smoking ever[1]	1.20 (0.73; 1.98)	1.32 (0.79; 2.20)
Current smoking[1]	1.27 (0.71; 2.25)	1.76 (0.96; 3.22)
Postmenopausal (only women)	**3.81 (1.73; 8.39)**	NA
Duration of symptoms (per SD)	1.02 (0.81; 1.28)	1.15 (0.91; 1.47)
RF positive	0.84 (0.53; 1.33)	1.02 (0.64; 1.62)
Anti-CCP positive	1.11 (0.70; 1.77)	1.30 (0.81; 2.10)
CRP >median	**1.84 (1.17; 2.92)**	1.38 (0.86; 2.21)
ESR (per SD)	**1.25 (1.01; 1.54)**	1.11 (0.89; 1.37)
Erosion score >0	1.35 (0.85; 2.15)	1.01 (0.63; 1.63)
JSN score >0	1.43 (0.90; 2.28)	0.99 (0.62; 1.59)
Total SHS >0	1.11 (0.69; 1.79)	0.83 (0.51; 1.34)
HAQ (per SD)	**1.26 (1.01; 1.58)**	1.12 (0.90; 1.39)
DAS28 (per SD)	**1.28 (1.02; 1.61)**	1.19 (0.94; 1.49)
VAS global health (per SD)	1.08 (0.86; 1.36)	1.11 (0.88; 1.39)
VAS pain (per SD)	1.09 (0.87; 1.36)	1.19 (0.95; 1.48)
csDMARDs	1.26 (0.67; 2.40)	1.11 (0.59; 2.11)
Corticosteroids (yes/no)	1.25 (0.80; 1.98)	1.13 (0.71; 1.80)
Corticosteroids, dosage (per SD)	1.03 (0.83; 1.27)	1.05 (0.83; 1.33)
Calcium and D-vitamin	1.29 (0.78; 2.11)	1.02 (0.62; 1.68)
Bisphosphonates	2.41 (0.76; 7.70)	1.05 (0.32; 3.45)
HRT (only women)	0.56 (0.25; 1.24)	NA
Index of muscle function >median	**2.78 (1.41; 5.50)**	1.41 (0.65; 3.07)
Grip force in dominant hand (% of expected value) (per SD)	0.86 (0.66; 1.10)	NA
Modified Charlson Index		
1 [2]	1.39 (0.63; 3.06)	0.97 (0.44; 2.14)
≥2 [2]	1.49 (0.47; 4.75)	1.14 (0.36; 3.66)
Level of formal education		
Upper-secondary/short-cycle tertiary[3]	1.11 (0.67; 1.84)	1.59 (0.95; 2.65)
≥ Bachelor's degree or equivalent[3]	0.91 (0.47; 1.79)	1.83 (0.91; 3.69)
Country of birth		
Other country in Europe[4]	1.09 (0.53; 2.28)	0.91 (0.44; 1.91)
Country outside Europe[4]	0.45 (0.06; 3.27)	1.00 (0.13; 7.43)

1. Reference: never smoking
2. Reference: 0
3. Reference: ≤ Lower secondary education (original variable translated according to ISCED 2011 categorization)
4. Reference: born in Sweden

Anti-CCP: anticyclic citrullinated protein; BMI: body mass index; CI: confidence interval; CRP: C-reactive protein; csDMARDs: conventional synthetic disease-modifying antirheumatic drugs; DAS28: Disease Activity Score-28; ESR: erythrocyte sedimentation rate; HAQ: Health Assessment Questionnaire; HR: hazard ratio; HRT: hormone replacement therapy; JSN: joint space narrowing; NA: not applicable; RA: rheumatoid arthritis; RF: rheumatoid factor; SD: standard deviation; SHS: Sharp van der Heijde Score; VAS: visual analogue scale.

Bold text indicates statistically significant results.
No analyses were done for biologic DMARDs due to no patients treated with bDMARDs at study start.

Supplementary table 11. Bone mineral density (Z-score) as predictors of fractures in RA patients, after exclusion of fractures with ICD-10 external cause codes for high energy trauma. Crude and adjusted cox regression models.

	Women	**Men**	**All**					
	Crude Hazard Ratio (HR) (95% confidence interval (CI))			Age-adjusted HR (95% CI)	BMI-adjusted HR (95% CI)	CRP-adjusted HR (95% CI)	Modified CCI-adjusted HR (95% CI)	Multivariate adjusted* HR (95% CI)
Fractures overall								
Z-score femoral neck	**0.70 (0.54; 0.92)**	**0.46 (0.24; 0.87)**	**0.65 (0.51; 0.82)**	**0.72 (0.57; 0.92)**	**0.67 (0.52; 0.87)**	**0.64 (0.50; 0.81)**	**0.63 (0.50; 0.81)**	0.80 (0.61; 1.06)
Z-score spine (L2-L4)	0.78 (0.61; 1.01)	0.71 (0.44; 1.16)	**0.76 (0.61; 0.95)**	**0.77 (0.61; 0.97)**	0.81 (0.63; 1.03)	**0.75 (0.60; 0.95)**	**0.75 (0.60; 0.95)**	0.86 (0.67; 1.12)
Hip fractures								
Z-score femoral neck	**0.47 (0.30; 0.73)**	0.64 (0.28; 1.50)	**0.49 (0.33; 0.73)**	**0.61 (0.41; 0.91)**	**0.51 (0.33; 0.78)**	**0.47 (0.31; 0.71)**	**0.48 (0.32; 0.72)**	0.66 (0.41; 1.07)
Vertebral/pelvic fractures								
Z-score spine (L2-L4)	**0.64 (0.41; 1.00)**	0.75 (0.30; 1.86)	**0.66 (0.44; 0.97)**	**0.65 (0.43; 1.00)**	**0.66 (0.44; 0.99)**	**0.65 (0.43; 0.97)**	**0.65 (0.44; 0.97)**	0.67 (0.43; 1.06)

CCI: Charlson Comorbidity Index

*Adjusted for Age, BMI, CRP>median and modified CCI.

Bold text indicates statistically significant results.

Supplementary table 12. Predictors of fractures in RA patients after exclusion of fractures with ICD-10 external cause codes for high energy trauma, crude and adjusted time dependent cox regression analyses

	Crude HR (95% CI)	Sex- and age-adjusted HR (95% CI)	Multivariate adjusted* HR (95% CI)
RA characteristics			
ESR (per SD)	1.18 (0.97; 1.44)	1.21 (0.98; 1.50)	Not included
Erosion score >0	1.34 (0.74; 2.42)	1.20 (0.67; 2.18)	Not included
JSN score >0	1.47 (0.80; 2.71)	1.21 (0.65; 2.23)	Not included
Total SHS >0	1.15 (0.59; 2.26)	0.78 (0.40; 1.56)	Not included
HAQ (per SD)	**1.55 (1.28; 1.88)**	**1.37 (1.12; 1.68)**	**1.46 (1.15: 1.85)[1]** **1.52 (1.21; 1.92)[2]**
DAS28 (per SD)	1.05 (0.83; 1.33)	1.07 (0.83; 1.37)	Not included
VAS global health (per SD)	1.20 (0.97; 1.50)	1.21 (0.98; 1.51)	Not included
VAS pain (per SD)	1.15 (0.93; 1.43)	1.16 (0.94; 1.43)	Not included
Grip force in the dominant hand (% of expected value) (per SD)	0.95 (0.76; 1.20)	NA	Not included
BMD			
Z-score femoral neck	**0.68 (0.52; 0.88)**	**0.76 (0.60; 0.97)**	**0.78 (0.61; 0.99)**
Z-score lumbar spine	**0.76 (0.60; 0.95)**	**0.70 (0.55; 0.89)**	**0.67 (0.53; 0.85)**
RA treatment			
csDMARDs, yes/no	1.35 (0.76; 2.39)	1.08 (0.61; 1.92)	Not included
Corticosteroids, yes/no	**1.67 (1.03; 2.71)**	1.42 (0.87; 2.31)	Not included
Corticosteroids, dosage (per SD)	**1.18 (1.01; 1.37)**	1.10 (0.95; 1.28)	Not included
Osteoporosis treatment			
Bisphosphonates, yes/no	1.64 (0.99; 2.74)	1.31 (0.78; 2.20)	Not included
Calcium and D-vitamin yes/no	**2.93 (1.66; 5.15)**	**2.36 (1.33; 4.18)**	Not included
HRT (only women) yes/no	0.75 (0.10; 5.45)	0.89 (0.12; 6.48)	Not included

*Adjusted for age, sex, HAQ and [1]Z-score in the femoral neck or [2]Z-score in the lumbar spine
BMD: bone mineral density; CI: confidence interval; csDMARDs: conventional synthetic disease-modifying antirheumatic drugs; DAS28: Disease Activity Score-28; ESR: erythrocyte sedimentation rate; HAQ: Health Assessment Questionnaire; HR: hazard ratio; HRT: hormone replacement therapy; JSN: joint space narrowing; NA: not applicable; RA: rheumatoid arthritis; SD: standard deviation; SHS: Sharp van der Heijde Score; VAS: visual analogue scale.

Bold text indicates statistically significant results.