Contents

Scientific environment

The present work has been conducted as part of Bergen group of Epidemiology and Biomarkers in Rheumatic Disease (BEaBiRD) at Haukeland University Hospital's Department of Rheumatology and the Norwegian Arthroplasty Register during the period 2013-2019.

The thesis is part of the PhD program at the Department of Clinical Science, Faculty of Medicine, University of Bergen.

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Bergen, January 2019

Tone W. Nystad

Abbreviations

ACPA	Anti-citrullinated protein antibodies
ACR	American College of Rheumatology
ACR EULAR criteria	Diagnostic criteria for rheumatoid arthritis
Anti-CCP	Anti-citrullinated cyclic peptide
AS	Ankylosing spondylitis
ASAS	Assessment of Spondyloarthritis international Society
ASDAS	Ankylosing spondylitis disease activity score
BASDAI	Bath ankylosing spondylitis disease activity index
bDMARD	Biologic disease modifying antirheumatic drug
BMI	Body mass index
CASPAR criteria	Classification criteria for psoriatic arthritis
CDAI	Clinical disease activity index
CI	Confidence interval
CRP	C-reactive protein
DAG	Directed acyclic graph
DAS28	Disease activity score for 28 joints
DDD	Defined daily dosage
DIP joint	Distal interphalangeal joint
DMARD	Disease modifying antirheumatic drug
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
HAQ	Health assessment questionnaire
HDS	Haraldsplass Deaconess Hospital
HLA	Human leucocyte antigen
HUS	Haukeland University Hospital
HUS-PAS	HUS patient administrative system
HUS-pf	HUS patient files

IA	Inflammatory arthritis
IL	Interleukin
IP joint	Interphalangeal joint
IS joint	Iliosacral joint
JAK	Janus kinase
KIH	The Coastal Hospital at Hagevik
LJR	Large joint replacement
MCP joint	Metacarpophalangeal joint
MRI	Magnetic resonance imaging
MTP joint	Metatarsophalangeal joint
NAR	Norwegian Arthroplasty Register
NorArthritis	Norwegian arthritis registry
NorPD	Norwegian Prescription Database
NPR	Norwegian Patient Register
NSAID	Nonsteroidal antiinflammatory drug
OA	Osteoarthritis
PAS	Patient administrative system
PIP joint	Proximal interphalangeal joint
PsA	Psoriatic arthritis
RA	Rheumatoid arthritis
RCT	Randomised clinical trial
REC	Regional committees for medical and health research ethics
RF	Rheumatoid factor
RR	Relative risk
SDAI	Simplified disease activity index
sDMARDs	Synthetic DMARDs
SpA	Spondyloarthritis
SPSS	Statistical package for the social sciences
T2T	Treat to target

THR	Total hip replacement
TICOPA	Tight control in psoriatic arthritis
TJR	Total joint replacement
TKR	Total knee replacement
TNF	Tumor necrosis factor

Abstract

Background and aim of thesis

Medical treatment of inflammatory joint disease has changed significantly in recent years. In order to see whether improved treatment has affected the long-term outcome we wished to investigate the occurrence of orthopaedic surgery in patients with ankylosing spondylitis (AS), rheumatoid arthritis (RA) and psoriatic arthritis (PsA). We also wanted to study predictive factors for surgery in RA and PsA.

Methods

In paper I, we investigated time trends in the number of hip prosthesis surgeries in patients with AS, using data from the Norwegian Arthroplasty Register (NAR).

In paper II, we investigated time trends in the incidence of orthopaedic surgery in patients with RA, using data from NAR and the Norwegian Patient Register (NPR).

In papers III and IV, we built historical cohorts of 1010 RA patients and 590 PsA patients, diagnosed 1972-2009 and 1954-2011, respectively. Patients were followed up until 2015/2017, and the incidence and risk factors for orthopaedic surgery were investigated.

Results and conclusions

For AS, mean age at hip prosthesis surgery increased significantly, and there was a declining trend of surgery, as opposed to the significant increase in hip prosthesis surgery among patients with osteoarthritis (OA). This suggests that tumour necrosis factor (TNF) alpha inhibitors inhibit or slow peripheral arthritis in AS patients.

There has been a declining incidence of surgery among patients with RA, and patients with early years of diagnosis had greatly increased risk of having orthopaedic surgery performed. This is probably due to the year of diagnosis being a proxy for the type and intensity of medical treatment.

For PsA, year of diagnosis had no effect on the risk of orthopaedic surgery. Thus, in our material, the prognosis of patients with PsA did not change, with regard to this outcome, despite the change in treatment. A possible explanation is the general increase in joint replacement surgery.

Paper	Patient group	Time period	Aim of investigation	Study design	Outcome	Results
I	AS	1988-2010	Time trends of hip prosthesis surgery in AS compared to OA	Longitudinal register study	Hip prosthesis surgery	Trend towards a reduced frequency Significant increase in mean age at surgery
II	RA	1994-2012	Time trends of orthopaedic surgery in RA compared to OA	Longitudinal register study	Arthrodesis, synovectomy and prosthesis in all peripheral joints	Decrease in synovectomies and prosthesis surgery Declining trend of arthrodeses
III	RA	1972-2015	Incidence and risk factors for orthopaedic surgery	Cohort study of 1010 patients	Arthrodesis, synovectomy and prosthesis in all peripheral joints	Incidence 31% Risk factors: -Diagnosis in 1972-1985 and 1986-1998 -Female gender -Radiographic changes at diagnosis
IV	PsA	1954-2017	Incidence and risk factors for orthopaedic surgery	Cohort study of 590 patients	Arthrodesis, synovectomy and prosthesis in all peripheral joints	Incidence 20% Risk factors: -Female gender -age≥70 at diagnosis -Maximum ESR 30-59 -Radiographic arthritis at diagnosis -Time of diagnosis had no effect

Publications

Paper I

Hip replacement surgery in patients with ankylosing spondylitis

Tone W. Nystad, Ove Furnes, Leif Ivar Havelin, Arne Kristian Skredderstuen, Stein Atle Lie and Bjørg-Tilde Svanes Fevang
Ann Rheum Dis. 2014;73(6):1194-7

Paper II

Reduction in orthopaedic surgery in patients with rheumatoid arthritis: a Norwegian register-based study

Tone W. Nystad, Anne Marie Fenstad, Ove Furnes, Leif Ivar Havelin, Arne Kristian Skredderstuen and Bjørg-Tilde Svanes Fevang
Scand J Rheumatol. 2015:1-7

Paper III

Predictors for orthopaedic surgery in patients with rheumatoid arthritis: results from a retrospective cohort study of 1010 patients diagnosed from 1972 to 2009, and followed up until 2015.

Tone W. Nystad, Anne Marie Fenstad, Ove Furnes and Bjørg-Tilde Svanes Fevang
Scand J Rheumatol. 2018:1-9

Paper IV

Incidence and predictive factors for orthopedic surgery in patients with psoriatic arthritis.

Tone W. Nystad, Yngvil S. Husum, Ove Furnes and Bjørg-Tilde Svanes Fevang
J Rheumatol. 2018;45(11):1532-40

Background

1. Prevalence of inflammatory arthritis (IA)

Ankylosing spondylitis (AS), rheumatoid arthritis (RA) and psoriatic arthritis (PsA) are the three most incident chronic inflammatory rheumatic joint diseases. AS has a prevalence of about 0.26% (1, 2) in the Norwegian population. The prevalence of RA has been found to be 0.43 -0.77% (1, 3), and the prevalence of PsA has been reported 0.2% and 0.67% in the population of western (4) and central (5) Norway, respectively.

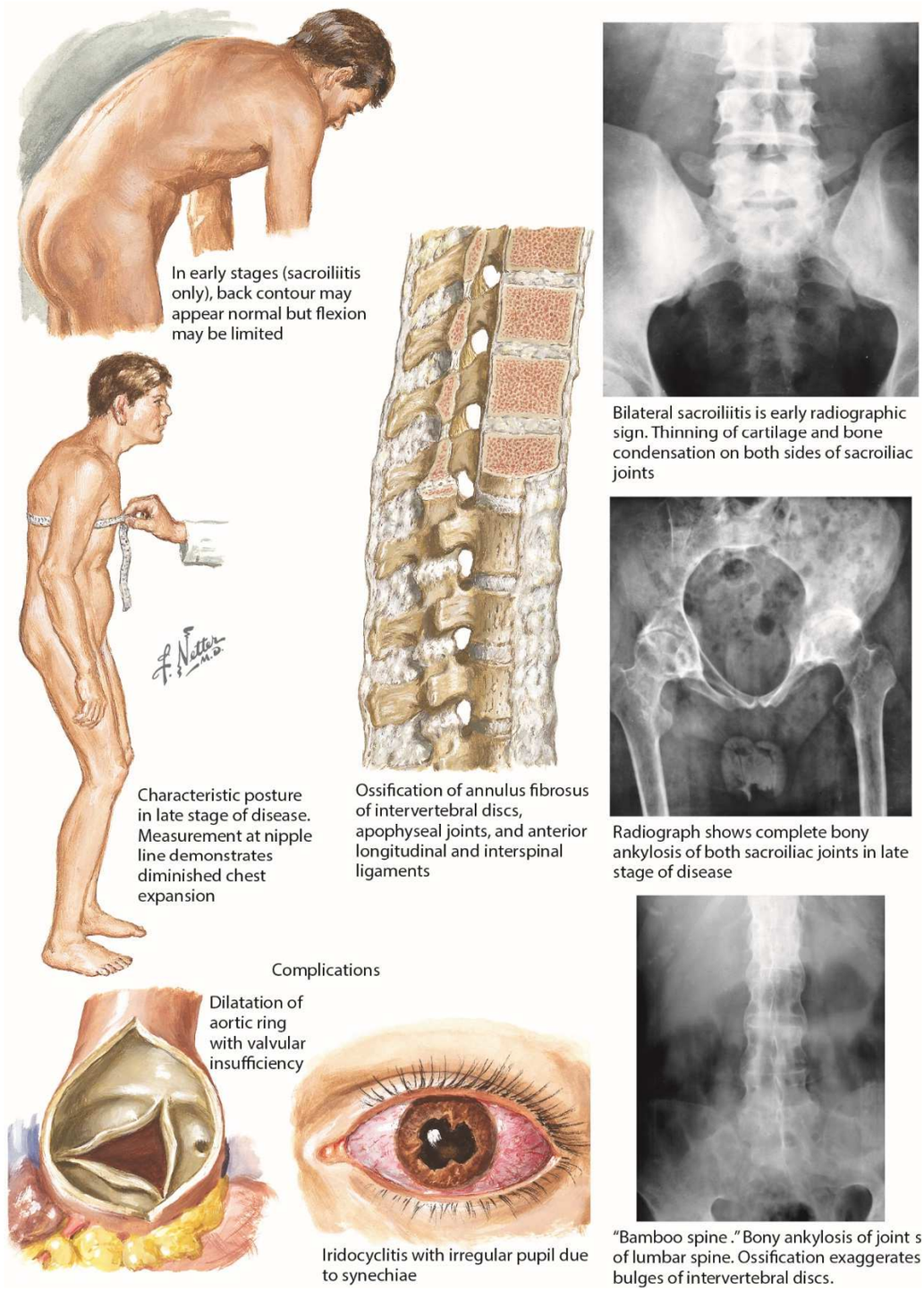
2. Ankylosing spondylitis (AS)

Although AS mainly affects axial joints, peripheral joint involvement is frequent, primarily in ankle, hip, knee, shoulder and sternoclavicular joints (6, 7). The risk of hip involvement has been estimated to 24-40% (7, 8). Diagnosis is based mainly on the history of inflammatory back pain, the presence of human leucocyte antigen (HLA)-B27, elevated inflammatory parameters and radiologic changes in iliosacral (IS)-joints. In the modified New York classification criteria of 1984, sacroiliitis on radiographs is a prerequisite for diagnosis (9).

In later years, less emphasis has been put into separating AS from the larger group of spondyloarthritis (SpA). For diagnosing SpA in patients with inflammatory back pain, sacroiliitis on magnetic resonance imaging (MRI) or HLA-B27 positivity is sufficient when accompanied by one (for sacroiliitis on MRI) or two (for HLA-B27 positivity) additional clinical features for SpA, according to the Assessment of Spondyloarthritis international Society (ASAS) criteria of 2009 (10). This takes into account that radiographic sacroiliitis may be preceded by a long period of symptoms of inflammation. The SpA features are arthritis, heel enthesitis, uveitis, dactylitis, psoriasis, inflammatory bowel disease, good response to nonsteroidal

antiinflammatory drugs (NSAIDs), family history of SpA, or elevated C-reactive protein (CRP).

Figure 1. Ankylosing spondylitis (Netter images, with permission)



3. Rheumatoid arthritis (RA)

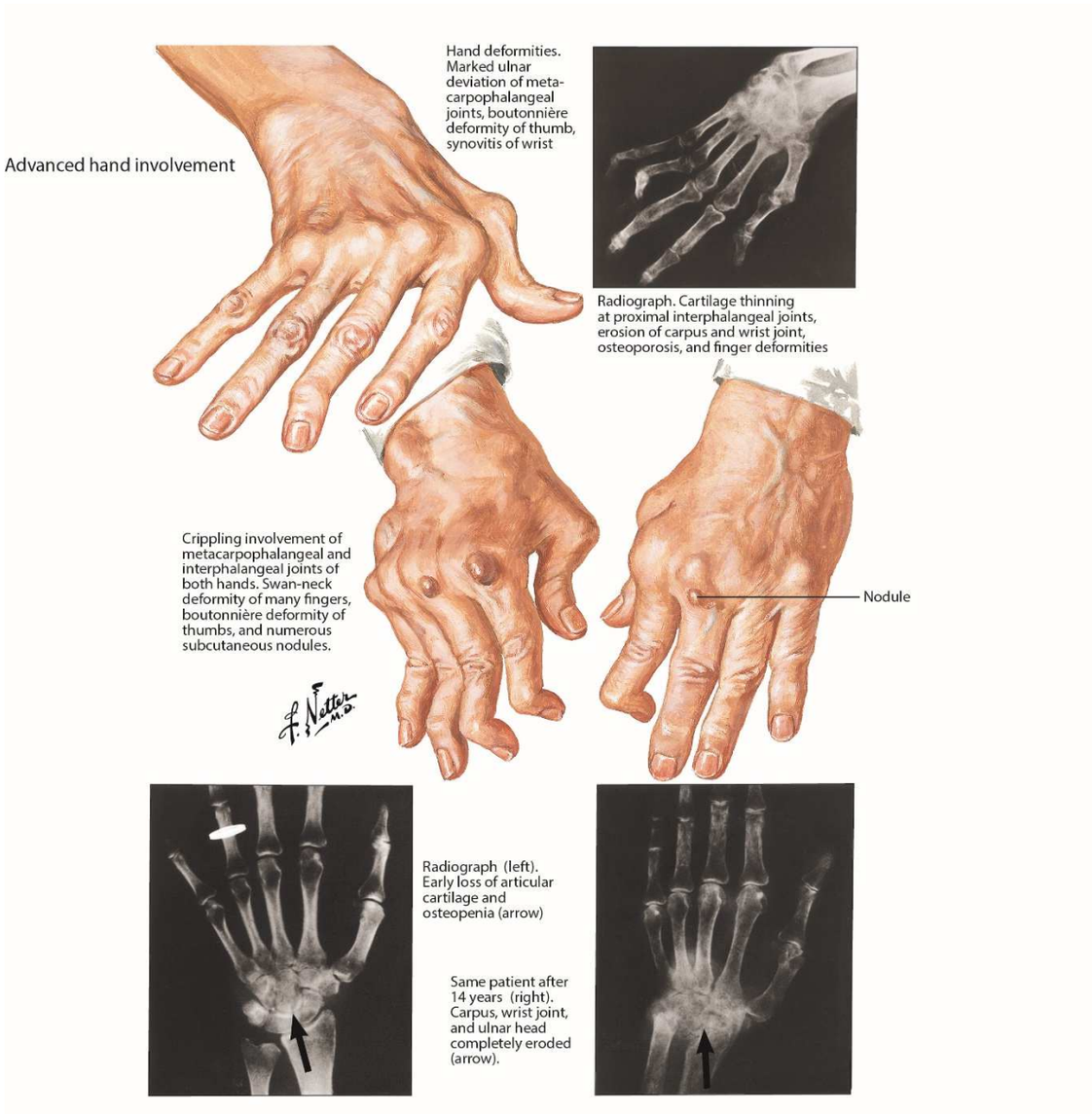
RA mainly has a symmetrical distribution of small joint arthritis. Distal joints, such as the metacarpophalangeal (MCP), metatarsophalangeal (MTP) and proximal interphalangeal (PIP) joints, as well as the wrists are most frequently affected, but RA may also affect larger joints, such as the elbow, shoulder, hip or knee. Diagnosis is based on the presence of morning stiffness, symmetrical polyarthritis and elevated inflammatory parameters, as well as the presence of rheumatoid factor (RF) and/or anti-citrullinated cyclic peptides (anti-CCP) for the subgroup seropositive RA.

In the American College of Rheumatology (ACR) classification criteria from 1987, rheumatoid nodules and radiographic changes were two of seven criteria, of which four had to be fulfilled (11). These criteria were insensitive in detecting patients with early disease, and in 2010, the revised ACR/EULAR (European League against Rheumatism) criteria were published (12). These are based on the presence of synovitis in at least one joint, the absence of an alternative probable diagnosis, and the score six out of ten points when considering four domains: number and site of involved joints, serological abnormality and elevated acute phase response and symptom duration. Patients presenting later in disease course can be classified according to previous symptoms and radiographic changes consistent with RA.

Even though classification criteria are not meant for diagnostic use, the change in criteria over time may have affected which patients were diagnosed with RA in different time periods.

The ACR/EULAR criteria for RA are provided in Appendix.

Figure 2. Joint pathology in rheumatoid arthritis (Netter images, with permission)



4. Psoriatic arthritis (PsA)

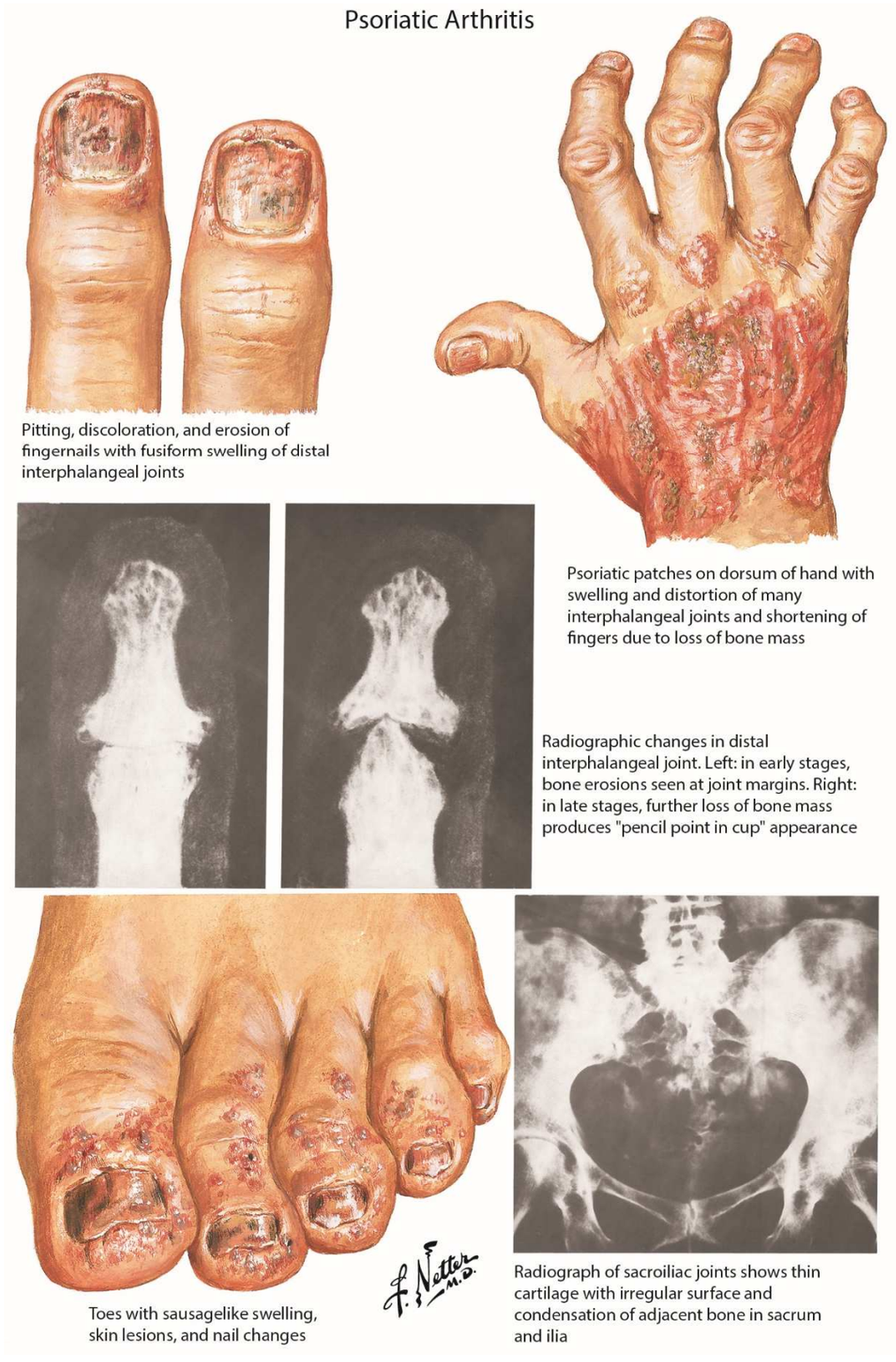
PsA mainly affects peripheral joints, with additional axial disease in 5-36% (13). Polyarticular disease, similar to RA, is the most frequent manifestation (4), but asymmetric oligoarticular arthritis is the most frequent pattern at disease onset (13). Joint affection may also be characterised by involvement of distal interphalangeal (DIP) joints, or in some cases present as a mutilating arthritis of these. Isolated axial disease is uncommon. Periarticular affection with enthesitis (30-50%) and dactylitis (40-50%) frequently occurs (14).

As PsA may be very similar to RA differential diagnosis can be difficult, but is mainly based on the presence of psoriatic skin or nail disease, specific joint patterns and absence of RF and anti-CCP.

Classification criteria for PsA (CASPAR) were published in 2006 (15), and state that patients with peripheral arthritis, enthesitis or spondylitis may be classified as suffering from PsA if accumulating at least three out of six possible points regarding the presence of skin psoriasis (present, previous or family history), nail lesions, dactylitis, negative RF or juxtaarticular bone formation on radiographs.

CASPAR criteria are provided in Appendix.

Figure 3. Psoriatic arthritis (Netter images, with permission)



5. Disease mechanisms

Inflammatory mechanisms differ between the three diseases, and may play a role in response to treatment.

5.1. Rheumatoid arthritis

The primary lesion of RA is synovitis, leading to the formation of inflammatory pannus invading cartilage and bone, causing destruction of affected joints (16). A complex and not fully understood interaction between genes and environment lead to disease development, in a combination of pre-determined and random events.

RA is a heterogeneous disease, and patients are in clinical practice divided into two subgroups based on the presence or absence of autoantibodies. RF and/or anti-CCP are found in about two thirds of patients, and these patients are more susceptible to joint destruction (17). The pathogenesis of seropositive RA is best understood. Known triggering mechanisms are smoking (18, 19) and microorganisms such as porphyromonas gingivalis involved in periodontitis (20). These factors induce peptide citrullination in the airways and oral cavity respectively. In RA, the immune system is inclined to respond to the neoepitopes created by protein citrullination, with the production of anti-citrullinated protein antibodies (ACPA) (21), that probably in some way contribute to the initiation or exacerbation of synovitis. Increasing antibody levels may be seen years before disease eruption, and presumably will not cause RA without the occurrence of one or more additional factors (16).

Macrophages, fibroblasts and lymphocytes infiltrate synovial tissue, and the inflamed synovium produces different cytokines, such as tumour necrosis factor (TNF) and interleukins (IL). This starts a process of tissue destruction by increasing the production of enzymes that increase inflammation and bone destruction. A vicious circle is thus established, leading to continued destruction of bone, cartilage and periarticular tissue (16).

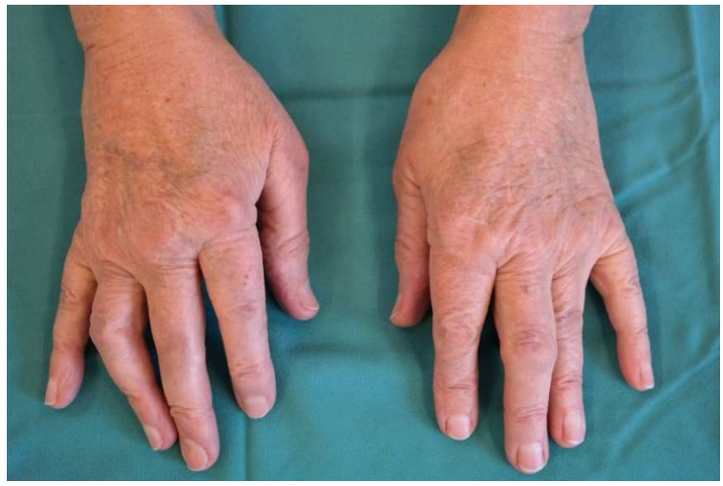


Figure 4. Hands in a patient with long-standing RA demonstrates polyarticular swelling and dislocations, preventing proper hand function.

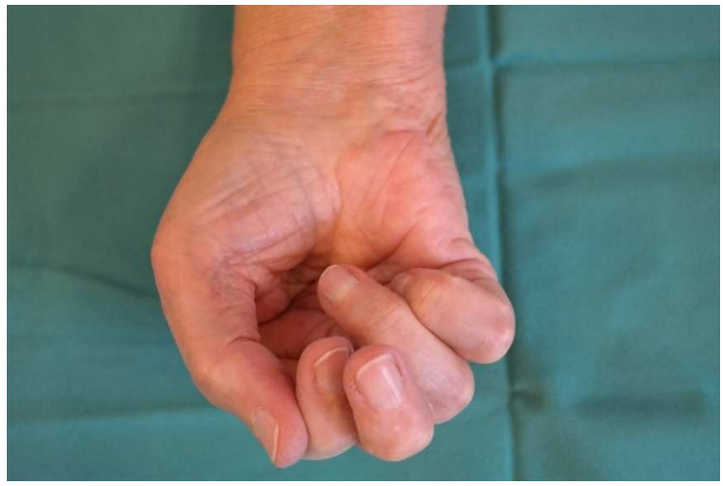


Figure 5. Rotation error inhibiting hand function

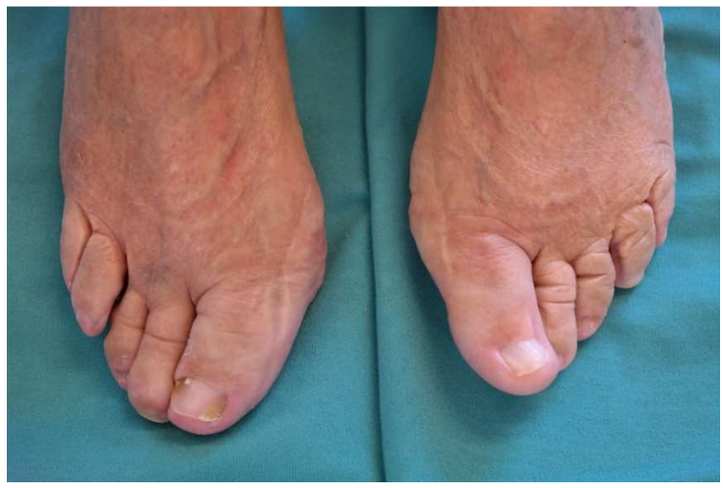


Figure 6. Feet of long-standing RA, following several surgical procedures

Photographs by TW Nystad

5.2 Spondyloarthritis

It is presumed that genetic, immunologic and environmental factors all contribute in the development of PsA and AS, and that they may differ between SpA subgroups.

Both AS and PsA (14) are linked to HLA genes. In AS HLA-B27 is particularly important, and is assumed to play a major role in the pathogenesis. The prevalence of AS corresponds closely to the prevalence of HLA-B27 in the given population (22).

Both the IL-23/IL-17 axis and the TNF pathways are believed to be implicated in disease pathogenesis (23). The autoinflammatory process may potentially be activated by mechanical stress and dysbiosis of the skin or gut (23). No specific antigen or autoantibody has been identified.

When investigating the synovium and synovial fluid in RA and SpA, several studies have found differences regarding cellularity, vascularity, the morphology of vessels and the presence of cytokines (24, 25). The level of IL-17 is higher in the synovial fluid in PsA compared to RA (26) and have in PsA been shown to correlate with disease activity (27). Contrary to RA, IL-17 is thus considered an important target in the treatment of SpA (28).

Alternate models for inflammation in SpA have been suggested, and some evidence indicate that the enthesitis is the initial site of inflammation and subsequent musculoskeletal disease (29).

6. Radiographic changes

Radiographic changes of peripheral joints differ in RA, PsA and AS. In RA, periarticular osteoporosis and soft tissue swelling are the earliest radiographic signs, followed by joint space narrowing, subchondral cysts and erosions. Early erosions have a predilection for some specific locations, such as the MCP and PIP joints. Contrary to PsA, the distal DIP joints are typically spared (30). Because of chronic

synovitis of the MCP and metatarsophalangeal (MTP) capsule and periarticular connective tissues, joints become unstable, and in turn cause palmar subluxation and ulnar drift. The boutonniere and swan neck deformities seen in RA are caused by rupture of ligaments.

Arthritis in PsA usually has an asymmetrical distribution, and erosions are located in DIP and PIP joints. Bone proliferation and enthesis involvement are present, and the bone is normally mineralized (30). Juxtaarticular bone formations, distinct from osteophytes, are a hallmark of PsA.

In AS radiographic images of hips and knees demonstrate joint space narrowing and bony proliferations, whereas hands with arthritis have smaller, shallower erosions and marginal periostitis (31).

7. Treatment

7.1 Historic treatment for IA

In the 1950ties corticosteroids were the first drugs to substantially inhibit joint inflammation, and during the 1950- and 60ties the introduction of prosthesis surgery (32) represented a revolution in treating patients with inflammatory arthritis. Up until that time, patients that suffered from severe joint destruction and ankylosis had no possibility to preserve movement, and in many cases became in need of a wheel chair or were forced to bedrest. The implantation of a prosthesis restoring joint movement, enabled patients to function in daily life, to an extent that had previously been impossible.

The treatment for joint inflammation, however, remained limited until the 1980ties, when the introduction of methotrexate represented the second revolution, at least for patients with RA. Prior to this, available treatment was mainly supportive consisting of parafango body wraps, baths and diets. Long hospital stays were common. Physiotherapists and occupational therapists gave active and passive treatment,

aiming to preserve the range of movement, and orthopaedic engineers provided custom foot orthotics. Joint destruction remained frequent, and orthopaedic corrective surgery was an important part of the treatment, to ease pain and restore function. The ideal was “the combined unit”, where the rheumatologist and the orthopaedic surgeon were mutually responsible for caring for the patient with inflammatory arthritis (33).

7.2 Medical treatment for RA and PsA

Salicylic acid has been in use for rheumatic complaints since the 1800s, first extracted by cooking willow bark, and later synthetically made in the form of acetylsalicylic acid. Paracetamol was developed in the early 1900s, and different NSAIDs have been in use since the 1950s. All provided some relief of pain and inflammation, although side effects such as gastrointestinal complaints were frequent, especially for the early preparations.

In 1949 Philip Hench published an article on “The potential reversibility of rheumatoid arthritis” (34), arguing that far too much emphasis had been put on the disease’s potential chronicity. In 1950, he received the Nobel Prize for discovering the substantial effect of cortisone in rheumatoid arthritis. Although the efficacy of short-term use of corticosteroids is undebatable, evidence is conflicting regarding chronic use. Side effects such as osteoporosis, gastrointestinal events, diabetes, infections and disturbance of the hypothalamic-pituitary-adrenal axis response limits long term use of higher doses, and the addition of a disease modifying antirheumatic drug (DMARD) is recommended (35, 36). In addition, in PsA, some studies support a more careful use of systemic corticosteroids as the psoriasis may worsen during tapering (37). Intraarticular steroid injections may temporarily resolve arthritis in the treated joint, and represent effective treatment with few side effects. For mono- and oligoarthritis in PsA, injections on demand may be the treatment of choice, in addition to the use of NSAIDs (36).

A number of DMARDs have been in use over the years. In the early 1970ties, gold preparations were the only drugs, except from steroids, demonstrating an anti-inflammatory effect (38), but although oral administration appear to have a better safety profile than parenteral preparations, many developed toxic side effects (39), and discontinuation was frequent. Antimalarials, that came in use later the same decade, had fewer side effects, but the anti-inflammatory effect was only modest (40). Azathioprine also became available, demonstrating effects superior to gold and chloroquine, but adverse reactions were reported in up to 58%, leading to discontinuation in 21% (41). The effect of cyclophosphamide might be slightly better than that of azathioprine or gold, but it has side effects comparable to these (42), in addition to the risk of developing malignancy (43). Penicillamine was prescribed for a short period from 1977, but use was limited by its toxicity. Only between 30 and 40% of patients started on penicillamine were still using the drug after two years (44).

Methotrexate was introduced in the late 1970ties, and around 1986 became part of the treatment for RA and PsA in Norway. With the introduction of sulfasalazine in 87, and leflunomide in 1995, both demonstrating effect in RA (45, 46), several efficient synthetic DMARDs (sDMARDs) were now available for treating inflammatory arthritis. Methotrexate alone or in combination with other sDMARDs assumed a dominant role in the treatment strategy, and has been prescribed increasingly early (47), and in higher doses (48), to achieve adequate disease control in RA. In 1999 treatment further improved, with the introduction of TNF alpha inhibitors that were the first of many biologic DMARDs (bDMARDs) to become available to patients for whom the synthetic DMARDs are insufficient.

Polyarticular PsA has largely been treated with the same synthetic DMARDs as RA, but for PsA there is less documentation regarding their effect (36). Some drugs are also less relevant for PsA, in example antimalarials, which carries a risk of causing exacerbation of psoriatic dermatitis in these patients (37). For biologic DMARDs evidence of effect in PsA is more convincing (49).

7.3 Medical treatment for AS

Up until etanercept became available in 1999, medical treatment for AS had been limited to NSAIDs. Sulfasalazine may have some benefit in the treatment of peripheral arthritis (50), but there is not enough evidence to support any benefit from methotrexate (51), and neither have effect on axial symptoms. TNF alpha inhibitors, however, provided a dramatic improvement, with many patients achieving symptom relief and restored function (52), and thus represent the third revolution in the treatment of inflammatory arthritis.

7.4 Recent development in medical treatment for IA

Since the introduction of etanercept several TNF alpha inhibitors, and other biologic DMARDs, including B- and T-cell as well as IL inhibitors, and recently the targeted synthetic janus kinase (JAK) inhibitors have become available for treating inflammatory arthritis. As a result, medication of inflammatory joint disease has changed significantly in the last decades.

When investigating data from the Norwegian Prescription Database (NorPD) (53), we found an increasing trend in the use of methotrexate in Norway in the years 2004-2013, both measured by number of users per 100 000 and by dose taken by each individual. The estimated number of users doubled from 4101 in 1999 to 8205 in 2004. Use of TNF alpha inhibitors also increased (own unpublished data).

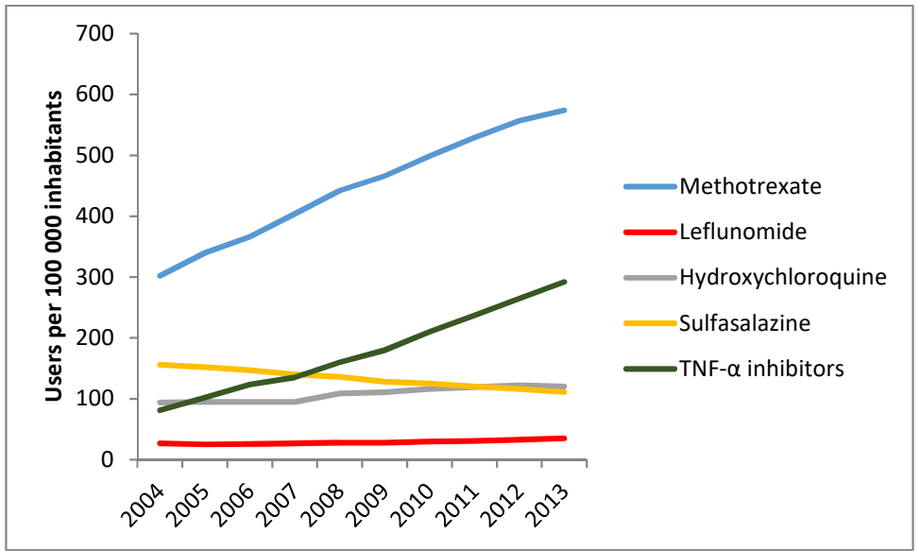


Figure 7. Use of sDMARDs and subcutaneous bDMARDs in the Norwegian population 2004-2013

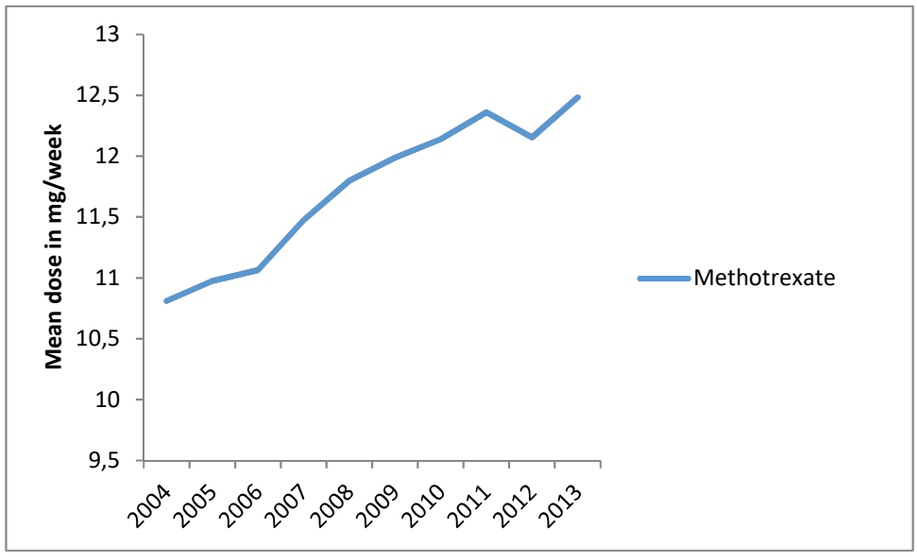


Figure 8. Mean dose of methotrexate in the Norwegian population 2004-2013

When considering the impression from clinical practice, it is somewhat surprising that mean weekly dose of methotrexate is still as low as 12.5 mg/week (own unpublished data). A Norwegian prospective longitudinal study of RA patients treated with methotrexate alone or in combination with biologic DMARDs showed that mean weekly dose had increased to 15.7mg/week and 16.3mg/week respectively from 2000 to 2010 (48). In a study from southern Norway mean weekly methotrexate was found to be 13.5mg/week in 2013 (54).

A limitation when considering data from the NorPD is that the defined daily dosage (DDD) was not registered for methotrexate administered subcutaneously, and that we do not have information on which diagnosis is being treated. The analysis of the increasing use of bDMARDs is incomplete as NorPD only provided data for preparations used subcutaneously, meaning that infliximab as well as the non-TNF biologic agents (tocilizumab, rituximab and abatacept), were incompletely or not registered, but the trend was increasing. As the database was not established until 2004, it could not give information on previous years.

7.5 Effect of present medication

That synthetic DMARDs and TNF alpha inhibitors reduce inflammation and inhibit joint destruction is well documented in patients with RA (55, 56). Data on PsA are more limited. Methotrexate probably reduce inflammation (57), but no synthetic DMARD has been shown to inhibit joint destruction. Biologic treatment gives better control of structural damage in PsA (49, 58, 59) but the role of co-medication with methotrexate has not been established (58). Evidence of any effect is scarce (58), but some studies suggest that methotrexate might increase TNF alpha inhibitor drug survival (60).

None of the synthetic DMARDs, including methotrexate, have been found to affect axial disease in AS (61). Despite the convincing clinical effect of TNF alpha inhibitors on patients with AS (62), spinal radiographic progression had not yet been

found to be inhibited or decelerated when compared to historical controls (63) when we started this study in 2012. One report showing positive results on joint space narrowing of the hip had been published in 2006 (64). Since, studies have been published, showing an association between use of TNF blockers and inhibition of spinal radiographic progression (65, 66). The effect is probably mediated by medication reducing disease activity (65), and it has been discussed whether inhibition of vertebral inflammation is what halters disease development (67). Whether co-medication with synthetic DMARDs is efficient is under debate (68). Sulfasalazine has been found beneficial in peripheral arthritis (69, 70), although its clinical effect was inferior to the effect of etanercept (71). No effect has been demonstrated for methotrexate (72).

Results from clinical trials have proved that some biologic treatments such as rituximab and abatacept are effective in RA, but not in PsA, while others, such as secukinumab, are solely effective for SpA (73). This seems to be associated with the importance of IL-17 in the pathogenesis in SpA but not in RA. Other findings also support the hypothesis that the disease mechanisms of RA and PsA are dissimilar. While results for drug free remission in RA are promising (74), the authors of a study on PsA patients published in 2015 found that chances of reaching drug free remission was low (75). Residual synovial inflammation has, in histological examination, been found to be higher in PsA patients in remission than in RA patients in remission, despite negative power doppler ultrasound findings in both groups (76).

7.6 Change in treatment regimens

Significant changes in the handling of patients with inflammatory arthritis have occurred for the last five centuries. There has been an increasing use of biologic and synthetic DMARDs in the treatment of RA (77-79), and although not to the same extent, this is also true for PsA (80).

In clinical practice the Disease activity score for 28 joints (DAS28) (81), a composite measure of tender and/or swollen joints, erythrocyte sedimentation rate (ESR) (or CRP) and patient global health (Visual analogue scale 1-100), is most commonly used for evaluating disease activity and treatment response. Others are the Clinical disease activity index (CDAI) (82) and the Simplified disease activity index (SDAI) (83).

For research purposes, the ACR/EULAR provisional definition of remission in RA was published in 2011 (84). To be defined as in remission according to these criteria, both swollen joint count, tender joint count, CRP as well as patient global assessment (0-10 scale) must be equal to or less than one, or the score on the SDAI must be equal to or less than three. Radiographic progression may however occur even in the presence of remission by any of the criteria described above (85).

In 2004, a study showing the effect of intensive step up treatment towards a predetermined goal, and how this improved disease activity and radiographic progression was published (86). Treat to target (T2T) is now a mainstay of modern RA treatment (35).

A similar approach has been suggested for PsA, but partly due to the heterogeneity of PsA, a suitable disease activity measure and treatment target have not yet been agreed on (87). Up until publication of the TICOPA (tight control of inflammation in early psoriatic arthritis) trial in 2015, there were few studies on T2T in this patient group (88). Coates et al found that tight control of PsA disease activity significantly improved joint outcomes for newly diagnosed patients (89), although at a greater economic cost and without any influence on radiographic progression.

For AS, the Bath ankylosing spondylitis disease activity index (BASDAI) is widely used to evaluate treatment response (88). BASDAI is based on the score in six subjective questions on fatigue, spinal pain, peripheral joints, entheses and intensity and duration of morning stiffness (90). A score of four or greater (1-10) is considered

consistent with active disease, and a response to treatment is defined as an absolute change of two units, or an improvement by at least 50% (91). In later years the Ankylosing spondylitis disease activity score (ASDAS)-CRP (92) has become increasingly popular as an outcome measure, as it includes CRP as an objective measure.

No data have been published showing any positive effect of a T2T strategy on physical function and radiographic progression in the treatment of SpA (88). In Norway, patients with AS are now routinely treated with biologics, if NSAIDs do not give sufficient disease control.

The impact of these significant changes in treatment strategies is an interesting research subject, in the relatively unchanged Norwegian population.

7.7 Orthopaedic procedures

Indications for rheumatic surgery may be pain relief, improvement of function, intent to prevent deterioration, cosmetics or a combination of these (93). If pain can be explained by radiographic changes, a surgical procedure may be considered. If not, one would commonly await the effect of non-surgical interventions.

When considering orthopaedic surgery in patients with rheumatic joint disease, a holistic approach is necessary. A multidisciplinary team should consider the patient's possible benefits of surgery, capability of rehabilitation and risk of complications. Patients might, especially in previous years, be in need for several procedures, and the order in which these are conducted is of importance (93).

Type of joint, the natural course of inflammation in these and grade of destruction is of importance when deciding which procedure is most expedient. Synovectomy aimed to be a preventive surgical procedure, whereas arthrodesis, prosthesis and resection surgeries are reconstructive procedures.

Preventive joint surgery

Early synovectomy can ease pain (94) and improve the range of motion (95), but whether the procedure may halter or prevent joint destruction and dislocation is doubtful (93). The procedure has been used since the 1940ties. The inflamed synovium that lines the joint is chemically or radiologically destructed, or surgically removed in an open or arthroscopic procedure. The procedure was commonly performed in the knee, shoulder, wrist/hand, elbow and ankle.

Reconstructive joint surgery

Arthrodesis, joint resection and prosthesis surgery is performed to correct dislocation, ease pain and restore function.

Arthrodesis is an artificial joint fusion that can be performed in any joint, but most commonly in the wrist, ankle and foot. The joint is denuded by removing the joint surfaces, and bones are then apposed in an optimal position and stabilised, using pins, cramps, nails, plates and screws until union is achieved. The joint should be non-weight bearing for 6-12 weeks depending on which joint and surgical technique (93).

In the ankle arthrodesis, the tibia and the talus are fused, whereas in the triple arthrodesis procedure the talonavicular, subthalar and calcaneocuboid joints are fused, to improve stability and make walking less painful. In wrist arthrodesis, the radius is fused with the carpal bones, to ease pain and provide a firm grip.

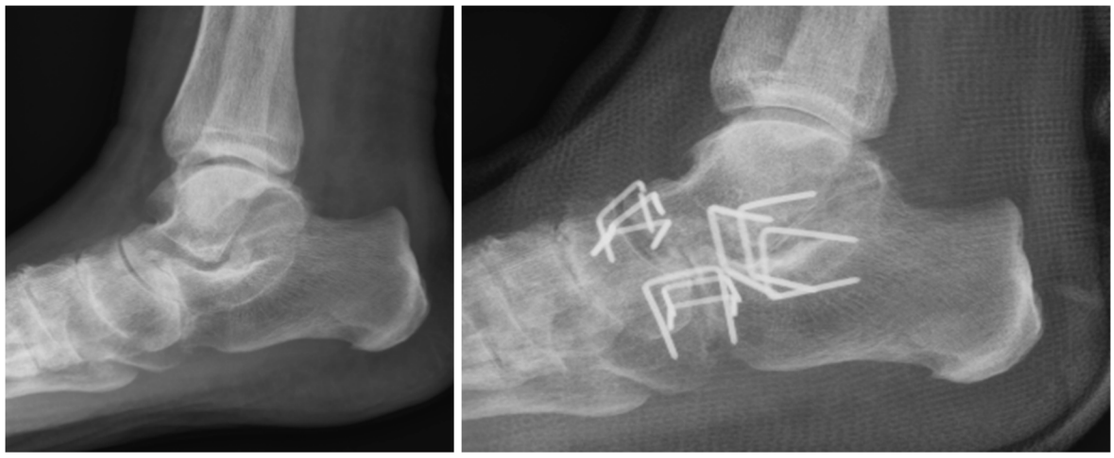


Figure 9. Foot with triple arthrodesis using cramps, and preoperative pictures

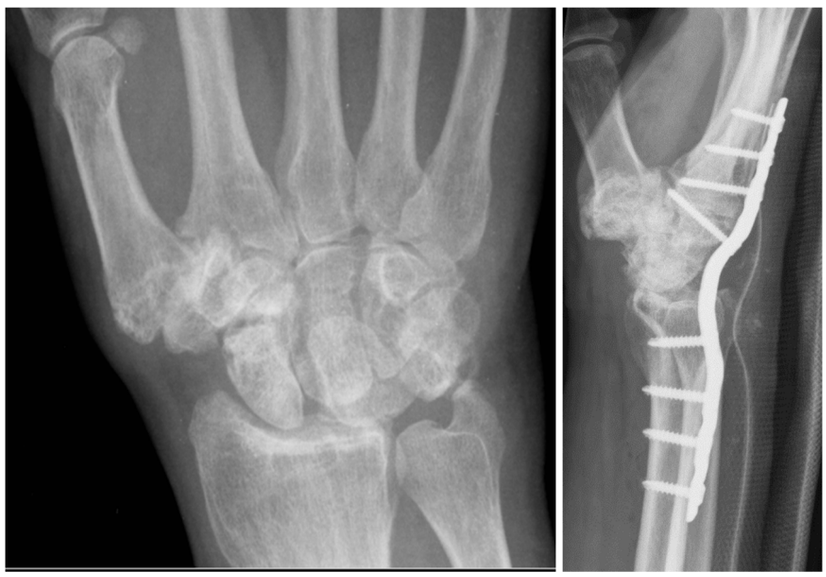


Figure 10. Wrist of patient with PsA with arthritic changes preoperative, and with performed arthrodesis with plate and screws.

Joint resections were the earliest surgical treatments, performed since the 1500s, but are now commonly part of combined procedures where arthrodesis or prosthesis surgery is also performed, such as the forefoot procedure. In this procedure a subcapital resection of metatarsus head 2-5 and an arthrodesis or prosthesis in the first MTP joint is performed.

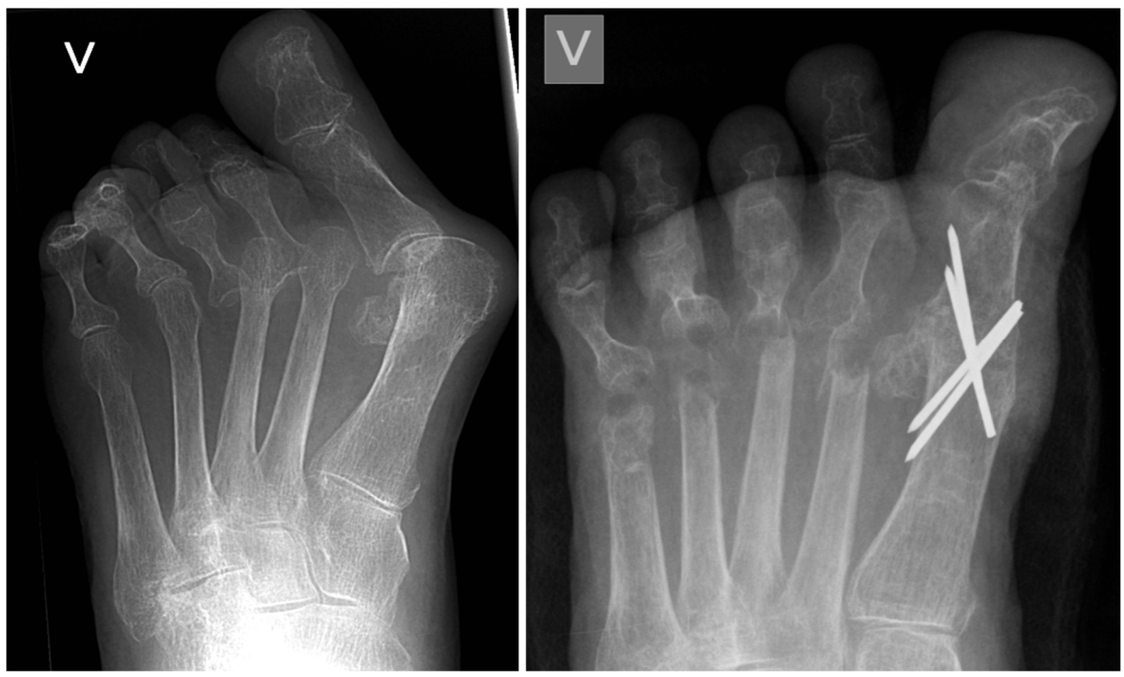


Figure 11. Foot of RA patient with arthrodesis and subluxation in the MTP joints, and performed forefoot procedure with arthrodesis of MTP-1 and resection of metatarsus heads 2-5.

In prosthesis surgery the destructed joint is replaced by an artificial joint. Prosthesis surgery is used mostly in large joints such as the hip and knee, but also in shoulder, elbow, wrist, finger joints, ankles and feet. The procedure aims to relieve pain, and improve the range of movement.

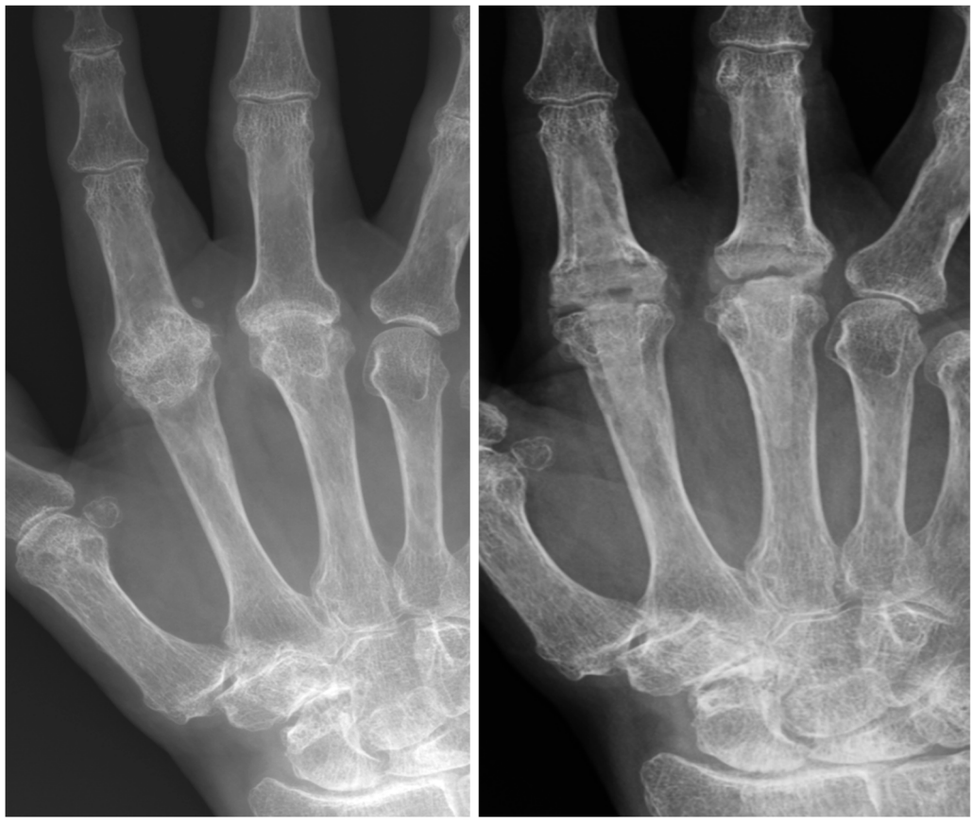


Figure 12. Arthritis in MCP joints of RA patient to the left, and with implanted silicon MCP joint prosthesis in MCP-2 and -3 to the right.

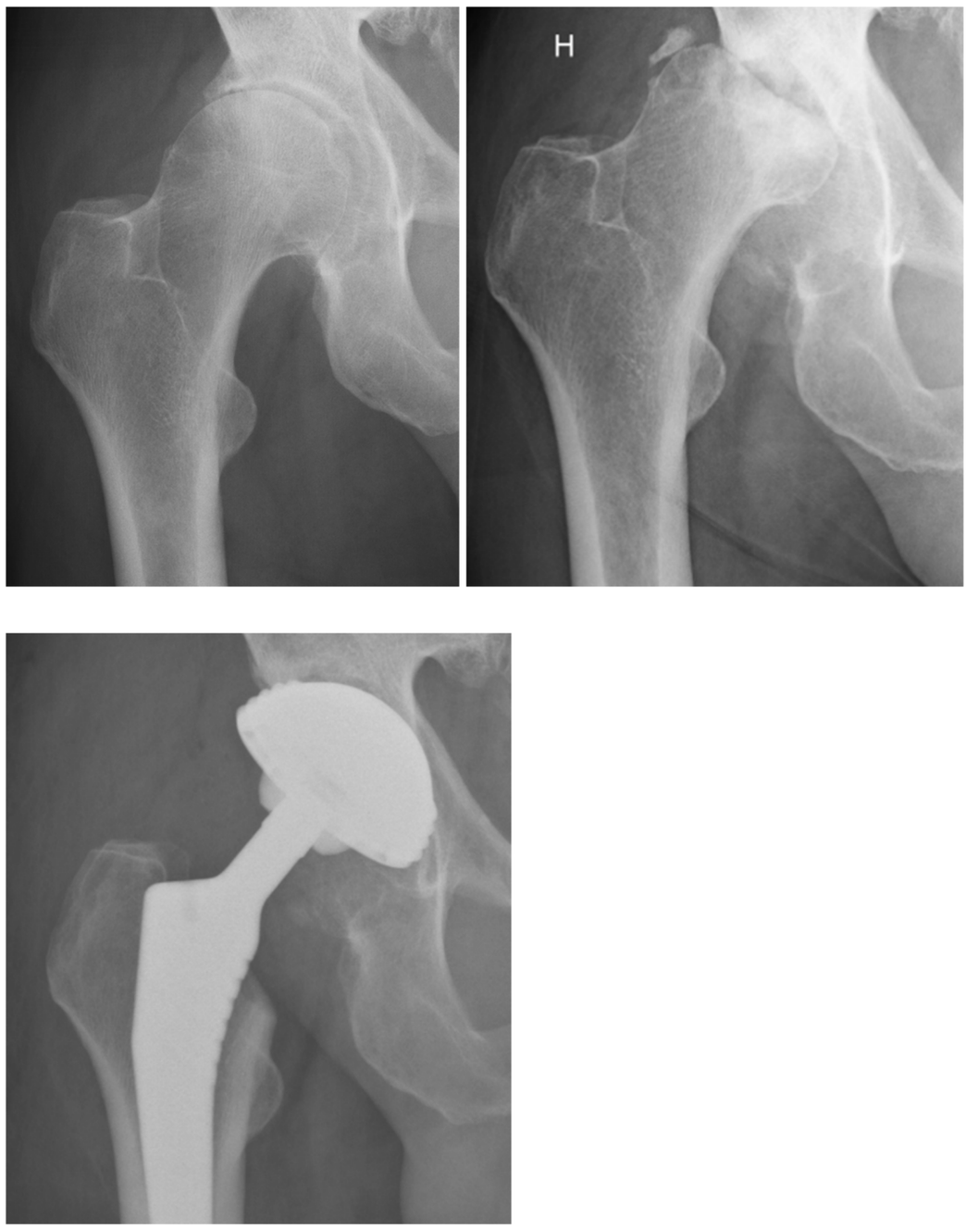


Figure 13. Hip of PsA patient showing the progression from moderate osteoarthritis to arthritic destructions and caput necrosis, and post implantation of a hip prosthesis with uncemented acetabular cup and uncemented stem in femur and a ceramic femoral head.

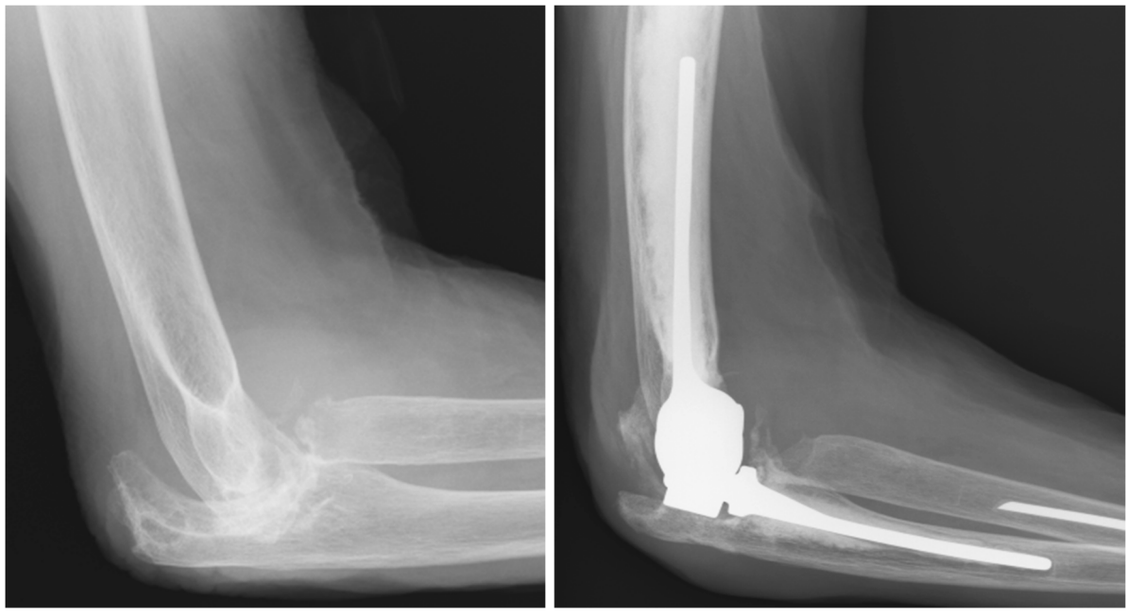


Figure 14. Elbow joint of RA patient with arthritis and post implantation of an elbow prosthesis fixated with cement. The caput radii is usually resected. The intramedullary nail is from a previous injury.

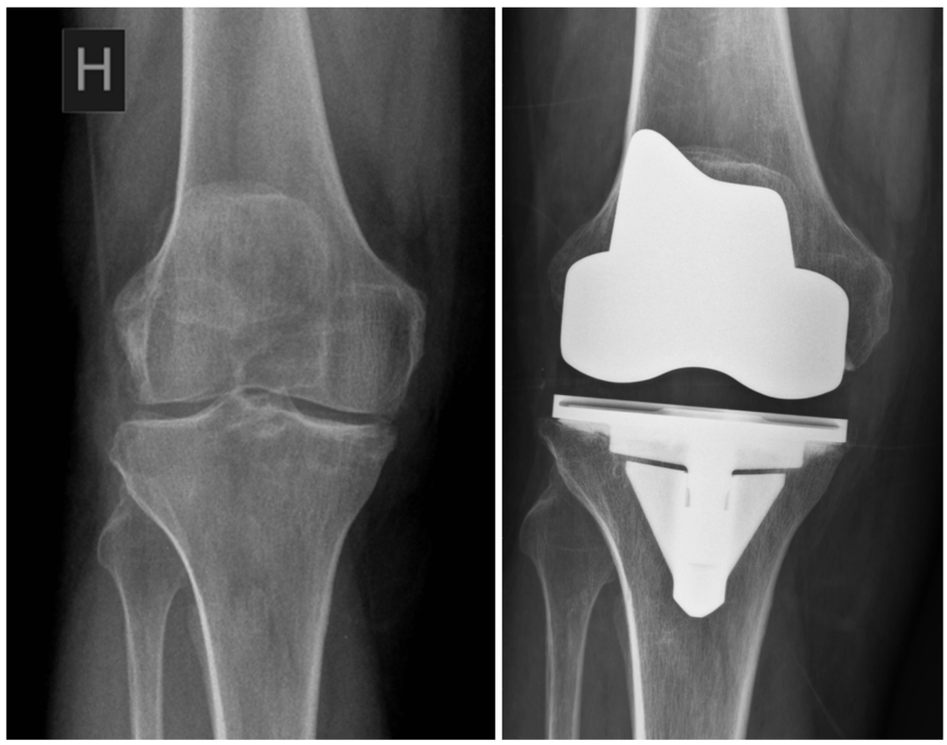


Figure 15. Knee joint arthritis in PsA patient, and the same knee with implanted cemented prosthesis.

8. Orthopaedic surgery as outcome measure

Orthopaedic surgery is an important outcome measure in inflammatory rheumatic joint disease, and gives an objective measure of inflammation not adequately handled by medical treatment. Arthrodesis and prosthesis surgery may also be considered proxies for destructed joints. Thus, the incidence of rheumatic surgery gives valuable information about the degree of joint inflammation and prognosis of patients with inflammatory joint disease.

The incidence of joint replacement surgery has increased during the last 20 to 30 years in Norway (96) as well as in Europe, Australia and the US (97-101). This can be due to an increased frequency of OA due to more elderly persons in the population

(97) and an increasing amount of overweight individuals (102), a change in the clinical criteria for performing joint replacement procedures, improved availability of prostheses and surgery, and surgery more often now than before being performed in individuals with significant comorbidities. The authors of a study published in 2014 found the growth insensitive to economic downturns and predicted a continued increase in the US (103).

8.1 Orthopaedic surgery in IA

In 2007, our group published a study on time trends in joint replacement surgery in patients with IA in the years 1994-2004. The IA group consisted of patients with RA, PsA, AS and reactive arthritis, of which RA was the most common diagnosis (86%), thus expected to have the stronger influence on the results. Among these patients, a significant decrease in joint replacement procedures was found during the entire time span. As methotrexate assumed a dominant role in the treatment of IA during the 1980s and 1990s, this is a possible explanation for the findings, although changes in the incidence or severity of IA is also possible (104). In the study from 2007 only patients operated before the year 2005 were included, and any influence of the introduction of biologic agents would be quite uncertain, as the use was limited and of short duration.

8.2 Orthopaedic surgery in AS

Hip involvement is common in AS, and hip replacement surgery is frequently performed. In a study published in 2010, 12-25% of patients had at least one replaced hip after more than 30 years' disease (105). Lu et al found that male AS patients have a significantly higher risk of osteoarthritis and for knee or hip prosthesis surgery (106). Male gender, longer disease duration, bilateral hip involvement, higher ESR, axial disease and enthesitis are considered risk factors for hip involvement and need for hip replacement surgery (7, 107-109).

To our knowledge, our study, published in 2014, was the first regarding trends in hip prosthesis surgery in patients with AS (110). In 2017, a study on trends in total hip arthroplasties due to AS in the United States population was published. Results were that the annual incidence of total hip arthroplasties due to AS per one million US adults slightly increased from 2002 to 2013. However, the proportion of total hip arthroplasties that were performed due to AS compared to other causes significantly decreased in the same time period (111). An explanation might be that factors believed to be responsible for the general increase in joint replacement surgery also apply to the AS population, but that improved medical treatment decreased the surplus joint destruction.

8.3 Orthopaedic surgery in RA

Previous studies have shown a high incidence of orthopaedic surgery in RA. In a cohort of patients, diagnosed 1974-1996 34% had a surgical procedure performed, and estimates were that 25% would undergo total joint replacement (TJR) within 22.1-years disease duration (112). Several studies have however shown that the incidence is declining (113-117). It has also been found that this declining trend coincides with an increasing use of synthetic and biologic DMARDs (77, 78). A summary of studies on orthopaedic surgery in RA, published prior to and after this work is described in table 1.

Table 1. Literature on orthopaedic surgery in RA
(TJR=Total joint replacement LJR=Large joint replacement THR= Total hip replacement TKR = Total knee replacement HAQ= Health assessment questionnaire)

Author	Location	Year	Material	Follow-up time/yrs	Incidence of orthopaedic surgery	Predictive factors
Reilly (118)	UK	1990	35 surviving from a cohort of 100 pt included 1957-63	25	62% had surgery	
Eberhardt (119)	Sweden	1996	99 pt with duration < 2 yrs included 1985-87	5	15% had TJR	
Kuper (120)	Netherlands	1997	157 pt	6	10% had TJR or arthrodesis	
Wolfe (112)	US	1998	1600 pt included 1974 onwards	mean 15.9	34% had surgery. Estimated cumulative incidence at 21.8 yrs 25% for TJR	For TJR; Disease duration. Treatment and other markers of disease severity.
Weyand (121)	US	1998	165 pt included 1970-1985	10-34	50% in women, 27% in men	Female gender
Crilly (122)	UK	1999	65 pt with TJR of hip, knee or shoulder and 65 without			High ESR more common in surgery group
Young (123)	UK	2000	732 pt with disease duration<2 yrs competed 5 yrs follow-up	5	17% had surgery. 8% had LJR	
Gordon (124)	UK	2001	289 pt with disease duration ≥1 yr included 1986-96	median 10	19% had LJR. 52% had LJR after 20yrs	Female gender, high ESR, disability and radiographic damage
Massardo (115)	US	2002	424 pt≥35yrs included 1955-85.	median 14.8	35% had surgery. Estimated cumulative incidence at 30yrs 53% for surgery, 24% for TJR	Younger age, RF and rheumatic nodules positive
Lindqvist (125)	Sweden	2002	183 pt with duration < 2 yrs included 1985-89	up to 10	17% had LJR	
Palm (126)	Finland	2002	103 RF pos pt with disease duration < 6mos included 1973-75	up to 25	27% had LJR	

Da Silva (113)	US	2003	609 pt included 1955-95	mean 13.9	Cumulative incidence of surgery at 30 years 34%. 20% had TJR	Female gender, younger age, RF and rheumatic nodules positive. Less risk of surgery when diagnosed after 1985, compared to 1965-74 and 1975-84
Ward (127)	US	2004	16 133 TKR in RA pt 1983-2001		Lower risk of TKR 1998-2001 vs 1990-1993	
Gossec (128)	France	2004	300 pt	12+/−9	24% had surgery. 7% had LJR. 13% had TJR or arthrodesis after 10 yrs	
James (129)	UK	2004	1064 pt with disease duration<2yrs	5	17% had surgery.	LJR: low hemoglobin, high ESR, DAS and Larsen x-rays. Hands/feet: female gender, DAS, HAQ.
Weiss (130)	Sweden	2005	49 802 pt with RA-related admissions included 1987-2001. 20 789 surgical procedures for RA in lower limbs		24% decrease during 1987 to 1996, and 8% decrease during 1998 to 2001	Female gender
Boonen (131)	Belgium	2006	285 pt included cross-sectionally in 2004. Compared diagnosis before and after 1990		37% had surgery. 15% had TJR	Shift towards more frequent and earlier synovectomy in pt diagnosed after 1990
Verstappen (132)	Netherlands	2006	482 pt with disease duration<1yr and follow up duration≥2yrs included 1990-98	14	27% had surgery. 10% had TJR (fingers and toes not included)	All surgeries: Delayed start and poor response to therapy. Fast radiographic progression. TJR: Radiographic changes at baseline and ESR first 2yrs.
Fevang (104)	Norway	2007	16 834 orthopaedic procedures for IA (86% RA) 1994-2004		Significant reduction in synovectomy and TJR	

Sokka (133)	Finland	2007	Cases with TJR of hip or knee in RA (317) and other diagnoses (2623) 1986-2003		Age adjusted incidence rate ratio of TJR unchanged in RA vs increase in other diagnoses	
Kapetanovic (134)	Sweden	2008	183 pt with early RA included 1985-89. Continuation of Lindqvist	up to 20 mean 16	58% had surgery. 24% had LJR	For LJR: Radiographic changes at year 1, and higher CRP, ESR and HAQ
Weiss (135)	Sweden	2008	54 579 pt included 1998-2004. 8251 procedures for RA in upper limbs.		29% decrease during 1998-2004. Stable or increasing (hand) occurrence of TJR	
Kolling (136)	Switzerland	2009	LJR or hand surgery in RA (1546) or OA (9546) 1997-2007		Stable occurrence of TJR for RA, increasing for OA. Decrease in synovectomies	
Momohara (117)	Japan	2009	201 synovectomies in 183 RA patients 2000-2007		Declining incidence	
Louie (114)	US	2009	40 743 procedures (TKR, THR, ankle or wrist surgery) in patients ≥40 yrs 1983-2007		Peak incidence in 1990s, and have since decreased in pt aged 40-60	
Momohara (116)	Japan	2010	RA outpatients (4000-5000 month) 2001-2007		Peak incidence of TJR in 2003, and then decrease	
De Piano (137)	Brazil	2010	THR and TKR in RA (116) and OA (24 119) 2007-2008		Decrease in TJR for RA patients, when compared to Kolling's numbers	
Hekmat (138)	Sweden	2011	2164 pt included 1997(prevalent)-2007	up to 10	Decreased incidence of THR in RA after 2001, TKR stable	
Jain (139)	US	2012	TJRs in RA (246 059) and general population (6482 595) 1992-2005		Increase in rate in both groups, but smaller for TJR for RA	

Shourt (140)	US	2012	813 pt diagnosed 1980-2007	mean 9.6	Cumulative incidence at 10 years 27% for pt diagnosed 1980-94 and 20% for 1995-2007 Significant reduction of soft tissue procedures	Obesity
Skyttâ (141)	Finland	2012	TKR in RA (10 739) and OA (110 048) 1980-2010		20-fold increase in TKR. For RA, incidence peaked in 1992, and has since decreased	
Dafydd (142)	UK	2012	1109 Hand/wrist surgeries in RA 1996-2009		Decrease in synovectomies, TJR and arthrodeses	
Kokkonen (143)	Finland	2013	911 ankle arthrodesis or TJR in RA pt 1997-2010		No change in incidence when procedures pooled together	
Jämsen (77)	Finland	2013	13 037 TJR in RA pt 1995-2010		Annual incidence decreased markedly. Greatest reduction for upper limb surgery	
Leon (144)	Spain	2013	1272 RA pt cross-sectionally included in 2010		7.4% had surgery. 2.25 TJR per 100 person-years, 4.5 for other surgeries	For TJR: Older age, long-term disease, biologics. For any surgery: Female gender, long-term disease, extra articular complications, NSAIDs prev 2 yrs
Pantos (145)	Greece	2013	489 pt included 1994-2008	median 4	4.3% had TKR og THR	Disease duration, high ESR at baseline and inadequate treatment response
Momohara (146)	Japan	2014	Surgery in a cohort of 5000-6000 pt 2001-2012		RA-associated surgery peaked 2002, decreased through 2007, and slight increase since 2008	
Nikiphorou (147)	UK	2014	1465 (1986-1999) and 1236 (2002-2013) early RA pt	Max 25 median 10	29% had surgery. Decline in 10yr cumulative incidence of hand/foot surgery but not of LJR	

Harty (148)	Ireland	2015	54 806 pt records 1995-2010		Substantial annual reduction in orthopaedic surgery from 1996 onwards	
Pedersen (149)	Denmark	2015	7575 pt registered 1996-2012		Decrease from 15% with THR in 1996 to 10% in 2012. Other joint procedures decrease from 29 to 23%.	
Moura (150)	Canada	2015	11333 early RA pt included 2002-2011	Median 4.6	5.3% had TJR	Longer exposure to DMARDs within first yr associated with longer time to TJR
Widdifield (151)	Canada	2016	27627 incident RA pt included 2000-2013	Median 4.5	9.5% had TJR	Same as above
Gwinnutt (152)	UK	2017	589 pt included 1990-1994	mean 12.1	17% had major surgery	HAQ score at beginning of follow-up
Stamp (153)	New Zealand	2017	1999-2015		Increase for OA. Rates of hip, knee, shoulder and ankle replacements for RA remained stable over time.	
Matsumo (154)	Japan	2017	15021 pt 2004-2014		Reduction from 72.2 to 51.5 procedures per 1000 pt during study period. Reduction of THR and TKR. Ankle, shoulder and elbow stable	

8.4 Orthopaedic surgery in PsA

In previous studies, there is a large discrepancy in the incidence of orthopaedic surgery in patients with PsA ranging from 7% (155) to 48% (156), and we have not found any data on changes over time. A summary of studies published on this subject is presented in table 2.

Table 2. Literature on orthopaedic surgery in PsA

Author	Location	Year	Material	Incidence of orthopaedic surgery
Hicken (157)	US	1994	435 pt during 15 yrs	3.9% had foot and ankle surgery
Zangger (155)	Switzerland	1998	31 operations in 444 pt	7.0% had surgery
Shbeeb (158)	US	2000	66 pt diagnosed 1982-1991	7.6% had surgery
Haque (156)	Belgium	2016	269 pt 2000-2014	48% had surgery

Although commonly used as first line treatment, or in combination with a TNF alpha inhibitor, the role of methotrexate in the treatment of PsA has not been established (159). As synthetic DMARDs may be less efficient in patients with PsA, it is uncertain whether a decline in orthopaedic surgery of the same magnitude, as seen among RA patients, can be expected. It is also possible that a change, if present, would occur later, after the introduction of TNF alpha inhibitors in this patient group, as our study on patients with AS suggests.

Information on previous knowledge and statistical methods was obtained from PubMed by free text and semi systematic searches, guided by a university librarian. Both single studies and review articles were used. Additional information came from textbooks, knowledge databases, websites and colleagues with experience in treating patients in earlier years. The study of literature was completed September 5th.

Aim of thesis

To see whether improved treatment has affected long-term outcome of inflammatory joint disease, we wished to investigate the occurrence of orthopaedic surgery in patients with AS, RA and PsA. We also wanted to study predictive factors for surgery in RA and PsA.

Paper I

Investigate time trends in hip replacement surgery in individuals with AS, to study whether the frequency has been affected by the introduction of TNF alpha inhibitors.

Paper II

Investigate time trends in the incidence of orthopaedic surgery in individuals with RA, to study whether long-term outcome of RA has changed.

Paper III

Investigate the incidence and predictive factors for orthopaedic surgery in an unselected cohort of RA patients, to study whether patient characteristics or diagnosis in different treatment eras affect the need for orthopaedic surgery in RA.

Paper IV

Investigate the incidence and predictive factors for orthopaedic surgery in an unselected cohort of PsA patients, to study whether patient characteristics or diagnosis in different treatment eras affect the need for orthopaedic surgery in PsA.

Patients and methods

1. Data sources

Several different data sources were used to establish the patient cohort and to identify outcomes. Table 3 shows the use of different sources in each paper.

The Norwegian Arthroplasty Register (NAR)

NAR was established in 1987, first as a register of hip prostheses, but from 1994, the register was expanded to include all artificial joints. Most patients receiving a primary joint arthroplasty are registered. The operating surgeon does registration. Data concerning the identity of the patient, diagnosis, date of surgery, type and brand of prosthesis and cement, whether antibiotics or thrombosis prophylaxis were used, complications, whether the operation was primary or a revision and cause of and procedure at revision, are incorporated in the database (160, 161).

The Norwegian Patient Register (NPR)

NPR was established in 1997, and receives information on diagnosis and procedure codes from all Norwegian hospitals' electronic administrative patient records.

Haukeland University Hospital's patient administrative system (HUS-PAS)

Haukeland University Hospital is responsible for providing health care to approximately 500 000 inhabitants in western Norway. The great majority of patients with inflammatory joint disease in need of treatment are cared for by the Department of Rheumatology. A random selection of these is likely to be representative for patients in the region. Computerised records containing diagnoses and procedures for all hospitalisations and outpatient clinic visits exist from 1972 for hospitals in the Hordaland County.

Haraldsplass Deaconess Hospital (HDS)

Up until the early 1990s some surgery on patients with inflammatory joint disease was conducted in Bergen's local Deaconess Hospital; HDS. To complete outcome data, we did a separate search in this hospital's system to detect performed procedures.

The Coastal Hospital at Hagevik (KiH)

Prosthesis surgery is also performed in KiH. We did a search in this hospital's records to find procedures performed prior to 1994. Later procedures would be registered in the NAR.

Patient files from Haukeland University Hospital (HUS-pf)

From 2000 onwards, patient journals are computerised. Information on prior years is found in archived paper files.

The Norwegian Arthritis Register (NorArthritis)

NorArthritis is a national quality registry, which was established in 2014 to increase the knowledge on chronic inflammatory joint diseases in Norway. Patients included are evaluated according to disease features, duration, disease subgroup (ACPA positivity), patient age and gender, smoking habits, comorbidity, body mass index (BMI), education, disease activity and treatment.

2. Outcome measures

The main outcome in this thesis is orthopaedic surgery, in terms of synovectomy, arthrodesis, prosthesis or resection surgeries, as described previously.

3. Study designs

3.1 Paper I

Prospective longitudinal study on register data

From the Norwegian Arthroplasty Register we selected hip prosthesis procedures in AS patients (n=534) from 1988 to 2010. Primary hip replacement procedures in patients with OA were included (n=95 094), and served as a control group. We analysed trends in annual frequency of such procedures in AS patients versus controls.

3.2 Paper II

Prospective longitudinal study on register data

From the Norwegian Arthroplasty Register we selected joint replacement procedures in RA patients from 1994 to 2012 (n=11 337). Procedures in OA patients (n=135 109) were included, and served as a control group. From the Norwegian Patient Register we obtained data on synovectomies (n= 4782) and arthrodeses (n=6022) performed in RA patients from 1997 to 2012.

3.3 Paper III

In the title of this paper, it was named a retrospective cohort study. However, it is actually a *prospective cohort*, although data were collected retrospectively, as patients were included at the time of diagnosis, and then prospectively followed when concerning the outcome.

We reviewed the medical history of 1544 patients with possible RA at Haukeland University hospital in Bergen, Norway. 1010 (mean age 57, 69% women) had sufficient journal information and a confirmed diagnosis of RA made between 1972 and 2009, and were included in the present study. Relevant orthopaedic procedures were obtained from the Norwegian Arthroplasty Register and HUS', HDS's and

KiH's administrative patient records. Survival analyses were completed to evaluate the impact of different factors such as year of diagnosis, age, gender, radiographic changes, disease activity and treatment, on the risk of undergoing surgery.

3.4 Paper IV

Prospective longitudinal observational cohort study

We reviewed the medical history of 1432 patients with possible PsA at Haukeland University Hospital in Bergen, Norway. 590 (mean age 49, 52% women) had sufficient journal information and a confirmed diagnosis of PsA made between 1954 and 2011, and were included in the present study. Relevant orthopaedic procedures were obtained from the Norwegian Arthroplasty Register and HUS's, HDS's and KiH's administrative patient records. Survival analyses were completed to evaluate the impact of different factors such as year of diagnosis, age, gender, radiographic changes, disease activity and treatment, on the risk of undergoing surgery.

Table 3. Data sources utilised for information extraction in papers I through IV

Study design	Paper	Data	HUS-PAS*	HDS**	KiH≠	HUS-pf***	NorArthritis†	NAR‡	NPR⁑
Prospective longitudinal study on register data	I	Prostheses						X	
	II	Prostheses						X	
		Arthrodeses							X
		Synovectomies							X
Prospective longitudinal cohort study	III and IV	Patients (Pt.)	X						
		Pt. characteristics				X	X		
		Medication				X	X		
		Prostheses	X	X	X			X	
		Arthrodeses	X	X					
		Synovectomies	X	X					

*Haukeland University Hospital's patient administrative system **Haraldsplass Deaconess Hospital ≠ The Coastal Hospital in Hagevik ***Patient files from Haukeland University Hospital †Norwegian arthritis registry ‡Norwegian Arthroplasty Register ⁑ Norwegian Patient Register

4. Statistics

For all papers, descriptive statistics were used for presentation of patient characteristics. Unpaired t-test for continuous variables and the chi-square test for categorical data were used to test for possible differences in demographic data. The level for statistical significance was set at 0.05.

4.1 Paper I

We analysed trends in the absolute number of procedures performed in patients with AS and OA. Incidences (AS patients with hip arthroplasties per 100 000 AS patients) were not evaluated since we did not have information on the annual number of patients with AS in the Norwegian population during the study period. As the number of procedures in this patient group was quite small, absolute numbers were used instead of number per 100 000 inhabitants (as was used in paper II). For statistical analysis we used Poisson regression models to test for trend, and change in trend over the years. A random effect was included in the model to account for over dispersion in the data.

4.2 Paper II

We analysed trends in the annual incidence; number of operated joints per 100 000 inhabitants in respective years, as we did not have reliable figures for the number of Norwegian patients with RA. Some analyses were also performed in different age categories (0-49, 50-59, 60-69, 70-79 and >80). Population figures were obtained from Statistics Norway (available at www.ssb.no/english). Poisson regression analysis was used to analyse trends in the incidence of the different procedures and in the different patient subgroups. As in paper I, a random effect was included to account for over dispersion in the data.

4.3 Papers III and IV

Person-time was accumulated from RA or PsA diagnosis until the first occurrence of orthopaedic surgery, death or the end of the study period (31st December 2015 or 30th July 2017 for RA and PsA, respectively). Cumulative incidence rates were calculated for the entire study period as the number of events per 100 patient-years. As follow-up duration was different for individual patients, the impact of different factors on the risk for undergoing surgery was analysed using Kaplan-Meier plots and Cox regression analyses. In paper III, where a difference in Kaplan-Meier was found, using log rank test for significance, further analyses using univariate and multivariate Cox proportional hazards regression models were performed. For paper IV, however, a directed acyclic graph (DAG) was constructed to determine which variables should be included in the multivariate Cox proportional hazards regression model to estimate the total effect of each factor. As this was a different approach, we also, post publication of paper III, reanalysed the data from the RA cohort using a DAG model.

To account for the increasing trend in arthroplasty surgery for OA (162), we also performed separate analyses for arthroplasty surgery of the hip and knee, and all other orthopaedic procedures.

For some of the variables, there were missing data. In the PsA cohort, analyses were done on the original files, as well as on files with multiple imputation of missing values (100 files). This was not done in the RA cohort before publication of the article, but was later performed (results presented on page 67).

We investigated the impact of patient characteristics such as age at diagnosis, gender, time period of diagnosis, number of affected joints, BMI ≥ 30, highest ESR within first two years of diagnosis (for RA), first ESR and ESR during disease course (for PsA), radiographic changes at diagnosis, use of methotrexate or biologic treatment and whether fulfilment of the ACR/EULAR (for RA) or CASPAR criteria (for PsA), on the risk for undergoing surgery. For the investigation of time period of diagnosis, patients were divided into three groups depending on diagnosis in different treatment

eras: diagnosis before 1986 (pre-methotrexate era), 1986-1998 (methotrexate era) and 1999-onwards (biologic era).

The impact of different treatments is subject to confounding, as the most severely affected individuals will have a propensity for receiving the most potent treatment. We therefore used time period of diagnosis as proxy, when investigating the effect of different medical treatments.

For paper III, when observing the Kaplan-Meier plot of risk of surgery according to time of diagnosis, we saw that patients diagnosed 1986-2009 had surgery performed earlier in the disease course, compared to patients diagnosed 1972-1985. The survival curves for the different time periods are not proportional, and hence the prerequisite for Cox regression is not strictly present, since use of the Cox regression model requires hazard functions that are proportional over time for all the three study periods. We therefore supplemented with Cox regression analyses of events occurring excluding the first four years after diagnosis.

In additional analyses of the RA cohort, using any procedure as outcome, we used a propensity score model to control for systematic differences and imbalance in the measured covariates. We used age, gender, radiographic changes at diagnosis, numbers of joints affected, fulfilment of the 2010 ACR/EULAR classification criteria for RA, and serologic status as covariates describing the three time periods. These covariates are all factors that affect the treatment assignment. The analyses were performed pairwise. Propensity score matching was not performed in paper IV, as it was not shown to affect the results in paper III.

Table 5. Overview of statistical methods used in papers I through IV

Papers	I	II	III	IV
Chi square	X	X	X	X
t-test	X	X	X	X
Poisson regression	X	X		
Kaplan-Meier			X	X
Cox regression			X	X
Propensity score matching			X	
Multiple imputation of missing values				X

SPSS (Statistical package for the social sciences) software versions 18, 22, 23 and 24 and the R statistical software package were used for the analyses.

5. Ethical aspects

The Regional Committee for Medical and Health Research Ethics (REC) approved all the studies (REC West Ref. no.: 2012/1852, 2014/1923 and 2016/2207). Patients registered in the NAR and NorArthritis have approved of their data being used for research purposes. Patients in NorArthritis have also given consent to journal review and the linking of data to other sources. From patients not included in NorArthritis, written consent was obtained.

It was important to include patients diagnosed in previous years, of whom many were deceased. REC approved the use of these data, and of radiographic images, without consent. All other photographs and radiographic images are presented with patient consent.

Photographs by TW Nystad. Radiographs by Department of Radiology, Haukeland University Hospital, selected in collaboration with radiologist Per Martin Kristoffersen. Illustrations by Netter Images, with permission.

Results

1. Paper I

In the years 1988-2010, 534 hip replacement procedures (74% men) were performed due to hip involvement of AS, whereas 95 094 procedures (32% men) were performed due to OA. The cases were divided into two groups according to the year of surgery (1988-2002 and 2003-2010). The segregation was based on the timing of introduction and significant use of TNF alpha inhibitors for AS in Norway.

The frequency of hip prosthesis surgery in both groups increased up until 2002 with a coefficient of 0.028 per year for OA patients ($p<0.001$), and a coefficient of 0.039 per year for AS patients ($p=0.002$) (Figure 16). Whereas the number of surgical procedures in the OA group continued to rise significantly ($p<0.001$) with a coefficient of 0.017 per year in the years 2003-2010, there was a trend towards a reduced frequency (coefficient of -0.022 per year) in the AS group, although the reduction was not statistically significant ($p=0.51$). When comparing the observed falling trend after 2002 to the expected increasing trend during the first period, the difference between the coefficients was -0.061 ($p=0.087$).

When comparing patients with AS before and after 2002, patients operated from 2003 onwards were significantly older (mean age 56.4 years compared to 49.9 years).

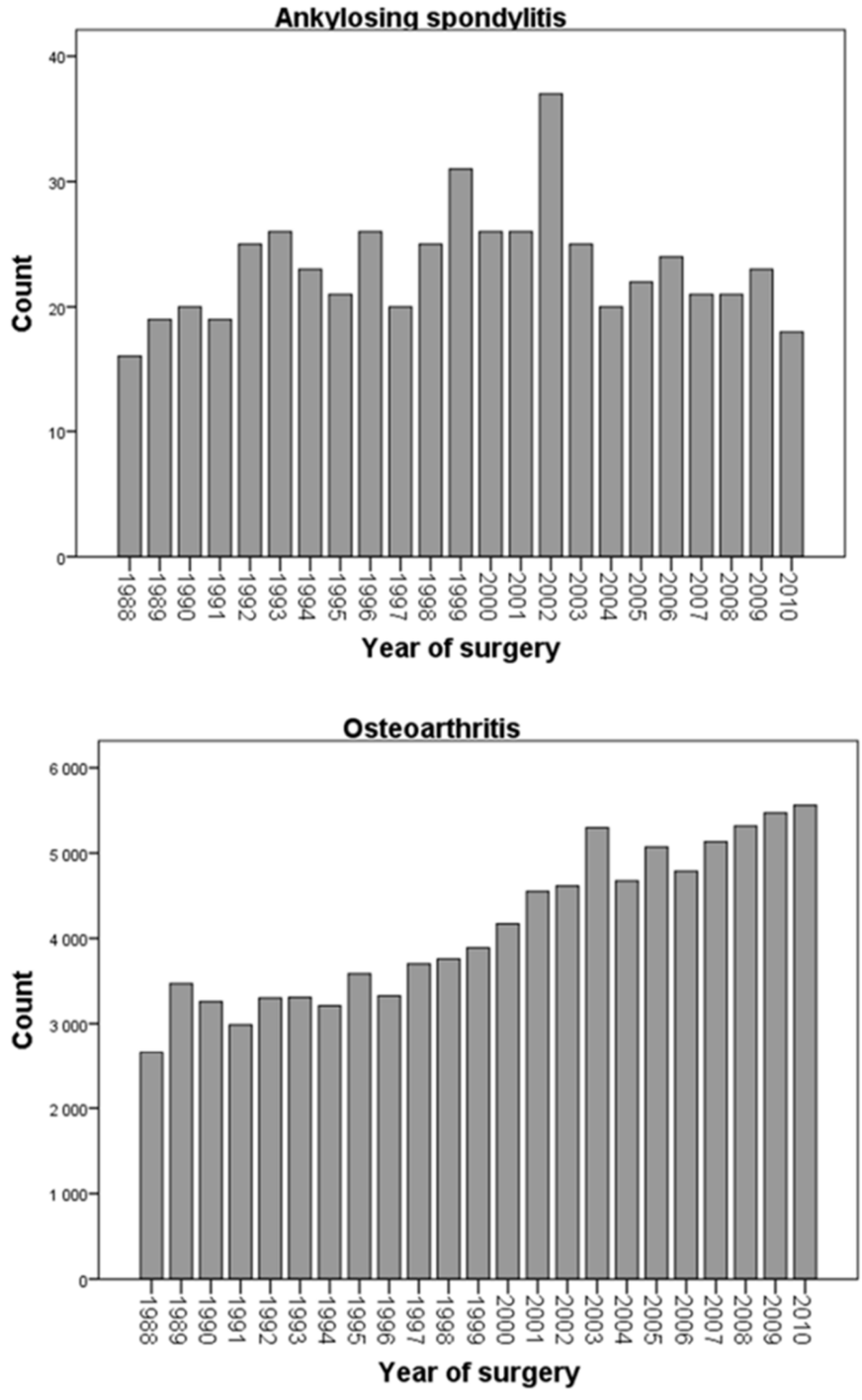


Figure 16. Annual number of hip prosthesis surgery in AS and OA

2. Paper II

11 337 joint replacement procedures were performed in 6 394 patients with RA in the study period of 1994-2012, whereas 135 109 procedures were performed in 106 008 patients with OA. 4 782 synovectomies and 6 022 arthrodeses were performed in patients suffering from RA in the years 1997-2012.

The incidence of prosthesis surgery in RA patients declined during the entire study period (coefficient of -0.050 per year, $p<0.001$), whereas the incidence in OA patients increased significantly (Figure 17). The incidence of synovectomies declined during the entire study period (coefficient of -0.10, $p<0.001$, Figure 18). There was an increase in arthrodeses of the ankle and foot from 1997 to 1999 causing the total number of arthrodeses to increase in these years (Figure 18). The incidence has since had a non-significant declining trend.

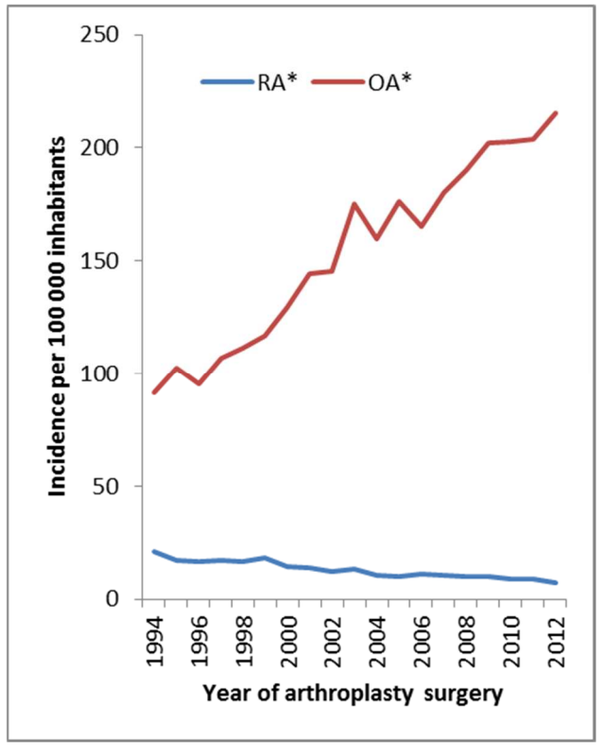


Figure 17. Incidence of arthroplasty surgery in patients with rheumatoid arthritis versus osteoarthritis (* p<0.001)

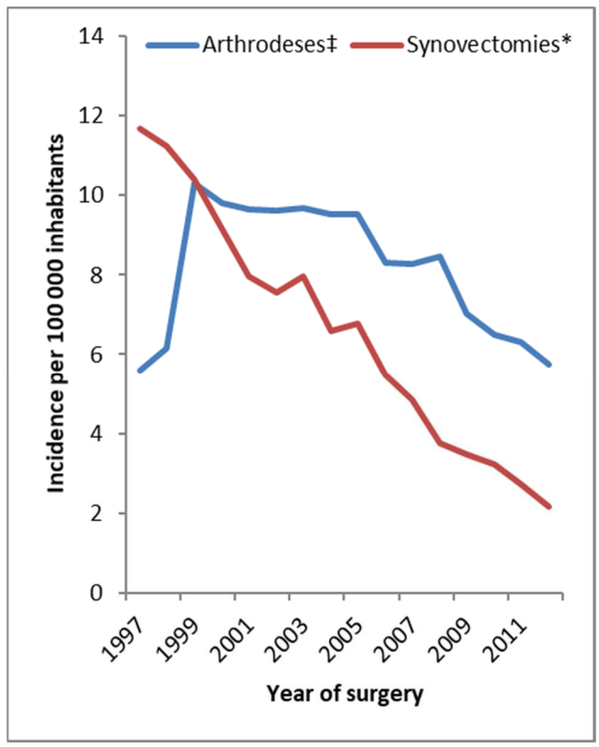


Figure 18. Incidence of arthrodeses and synovectomies in patients with RA (*p<0.001 ‡p>0.05)

3. Papers III and IV

Surgery in RA and PsA cohorts

Number of patients with surgery, and the distribution between the different procedures are presented in table 5. In general, a higher percentage of RA patients had surgery, and the frequency of events were higher. Large joint surgery was most common among PsA patients, whereas for RA patients, surgery of the hands and feet was most frequently performed.

Table 5. Surgery in RA and PsA cohorts

	RA	PsA
N	1010	590
Inclusion period	1972-2009	1954-2011
Observation period	1972-2015	1954-2017
Events per 100 patient-years	5	1.4
Patients operated (% of total)	31	20
Number of procedures	693	171
Synovectomy (% of procedures)	22	25
Arthroplasty (% of procedures)	41	53
Arthrodesis or forefoot (% of procedures)	35	15
Most frequently operated area (%)	Ankle/foot (26) Wrist/hand (23)	Knee (39) Hip (28)

Predictors for surgery

For RA (paper III), the factor with greatest impact on the risk of a surgical procedure during the course of the disease was the year of diagnosis. The effect of different time periods of diagnosis on the risk for orthopaedic surgery is shown in figure 19. Patients diagnosed 1972-1985 and 1986-1998 had a relative risk (RR) of 2.4 (95% confidence interval (CI) 1.71-3.31, p<0.001) and 2.2 (95%CI 1.62-2.87, p<0.001) respectively, of surgery compared to patients diagnosed in 1999-2009. Female gender (RR 1.35 95% CI 1.02 -1.77, p=0.035) and arthritis (RR 1.46 95% CI 1.10-1.94, p=0.008) or osteoarthritis (RR 2.81, 95% CI 1.94-4.05, p<0.001) in initial radiographs also increased the risk.

When using the propensity score model for analysing surgical interventions during the entire time span, patients diagnosed 1972-1985 and 1986-1998 had a RR of 2.1 (95% CI: 1.49-3.10, p<0.001) and a RR of 2.3 (95% CI: 1.70-3.04, p<0.001), respectively, of surgery compared to patients diagnosed 1999-2011.

When the variables in the model had been reanalysed (DAG and imputation of missing values), we found minor differences, that did not change the main findings described above.

For PsA (paper IV), factors found to affect the risk of a surgical procedure during the course of the disease were: older age at diagnosis (RR 2.4, 95% CI 1.5-4.1, p=0.001), female gender (RR 1.9, 95% CI 1.3-2.8, p=0.001), arthritis in initial radiographs (RR 2.2, 95% CI 1.3-4.0, p=0.006) and highest ESR between 30 and 59 (RR 1.6, 95% CI 1.1-2.5, p=0.026). Time period of diagnosis did not influence the risk, as shown in figure 20. Osteoarthritis in initial radiographs was borderline significant, but not significant when analysing 100 files with imputed values. For the other exposure variables, analysis of the files with imputed values did not change the significance of the above-described results.

When performing sub analyses of procedures exclusive of hip and knee prostheses (61 PsA patients had other procedures performed), we found that patients diagnosed 1954-1985 had an increased risk of surgery (RR: 2.1 95%CI: 1.03-4.18, p=0.042) compared to patients diagnosed 1999-2011. Diagnosis in the years 1986-1998 was not a significant risk factor (RR 1.5, 95% CI 0.83-2.72, p=0.18).

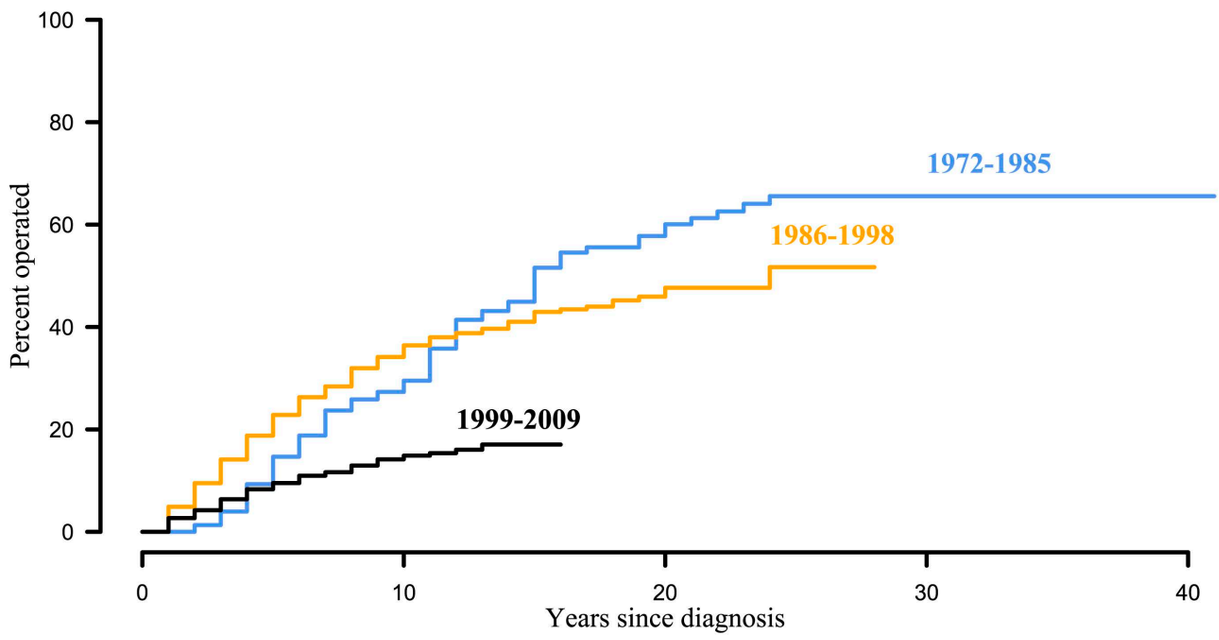


Figure 19. For patients with RA diagnosis in earlier years was a significant risk factor for surgery

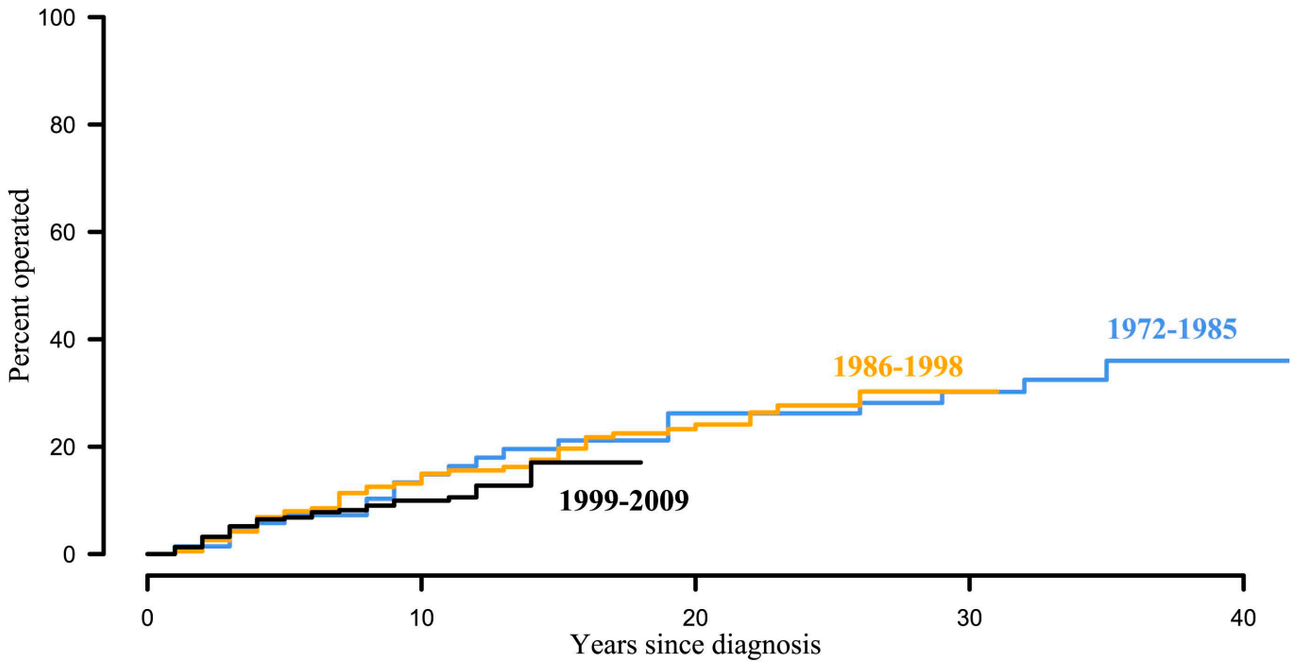


Figure 20. For patients with PsA the time period of diagnosis did not affect the outcome

Medication in RA and PsA

PsA patients consistently had less treatment than RA patients did, as described in figure 21 and 22. A comparison of the use of methotrexate and biologic drugs is presented in table 6. When analysing the impact of whether methotrexate was used for RA patients the first year of diagnosis (applicable for patients in time periods 2 and 3) in univariate Cox regression analysis, patients who were prescribed methotrexate had a significantly lower risk for later surgical procedures (RR 0.60, 95% CI: 0.46-0.76, $p<0.001$). Any use of biologic drugs during the course of the disease did not affect the outcome.

For PsA patients, we found no impact of use of methotrexate or biologic drugs, when concerning the risk of orthopaedic surgery.

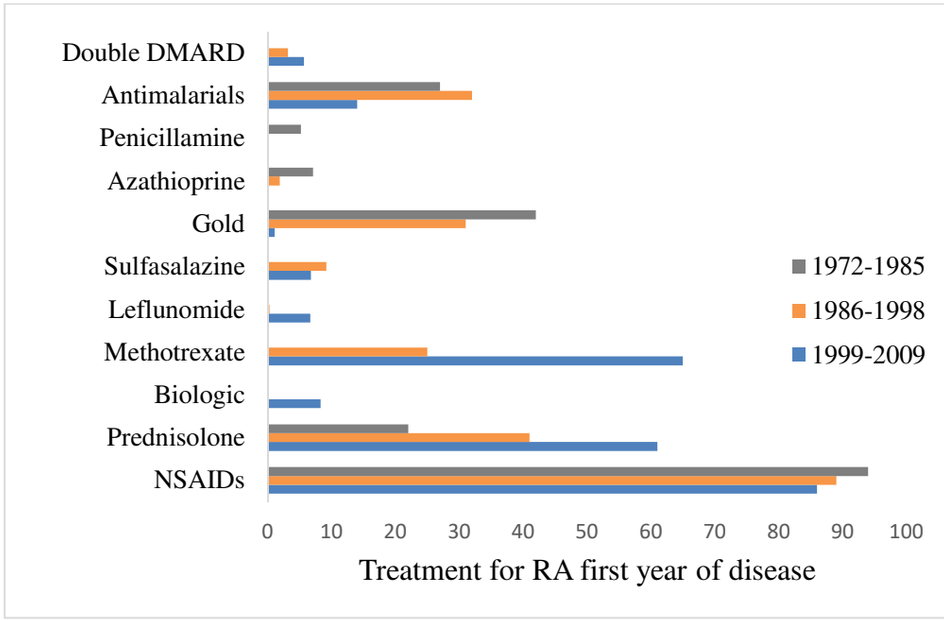
Table 6. A comparative analysis of medication used first year and during disease course for RA and PsA in total and in the three different treatment eras, given in percent within each patient group.

		RA	PsA	p
Total	n	1010	590	
	Methotrexate first year	43	30	<0.001
	Methotrexate during disease course	73	56	<0.001
	Biologic first year	4.5	4.7	0.79
	Biologic during disease course	30	25	0.021
<1986	n	154	72	
	Methotrexate first year	0	4.2*	0.011
	Methotrexate during disease course	54	36	0.013
	Biologic first year			
	Biologic during disease course	11	15	0.37
1986-1998	n	315	196	
	Methotrexate first year	25	17	0.023
	Methotrexate during disease course	71	42	<0.001
	Biologic first year			
	Biologic during disease course	29	10	<0.001
1999-2009/11	n	541	322	
	Methotrexate first year	65	43	<0.001
	Methotrexate during disease course	81	68	<0.001
	Biologic first year	8.3	8.7	0.847
	Biologic during disease course	37	36	0.87

*All PsA patients given methotrexate prior to 1986 had been prescribed this by their dermatologist

Figure 21. Percent of RA patients with given treatment first year (A) of disease and during disease course (B)

A



B

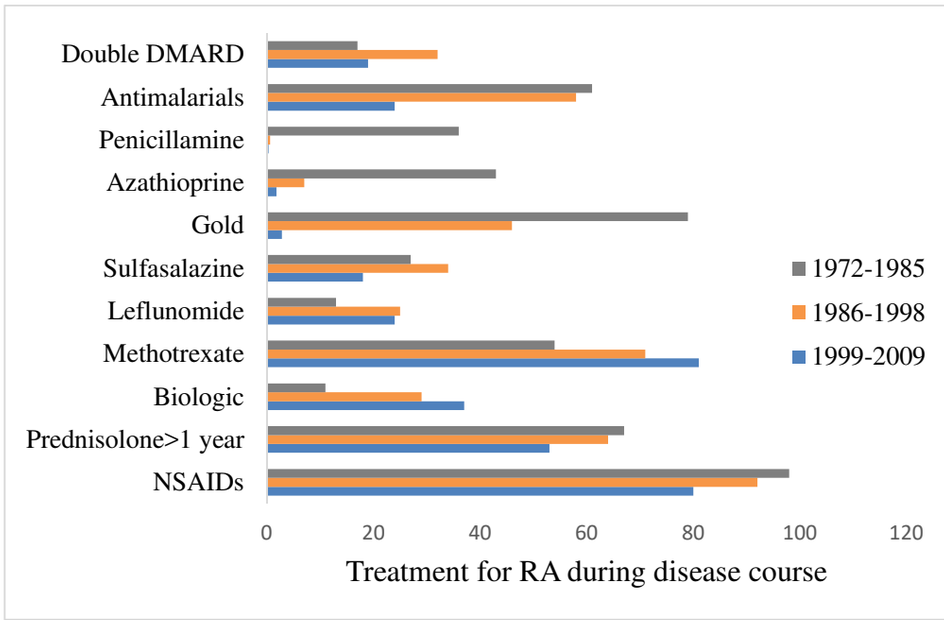
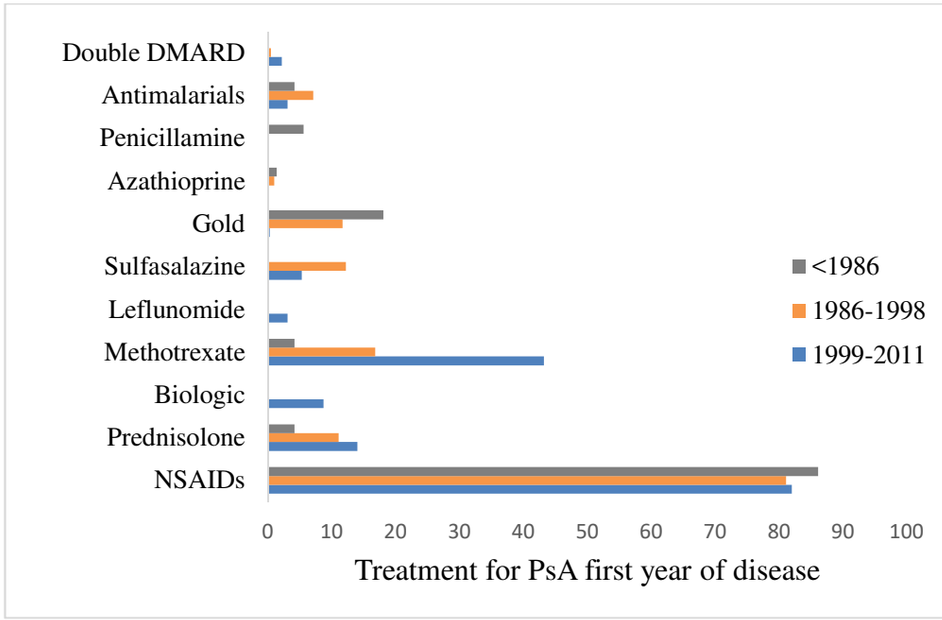
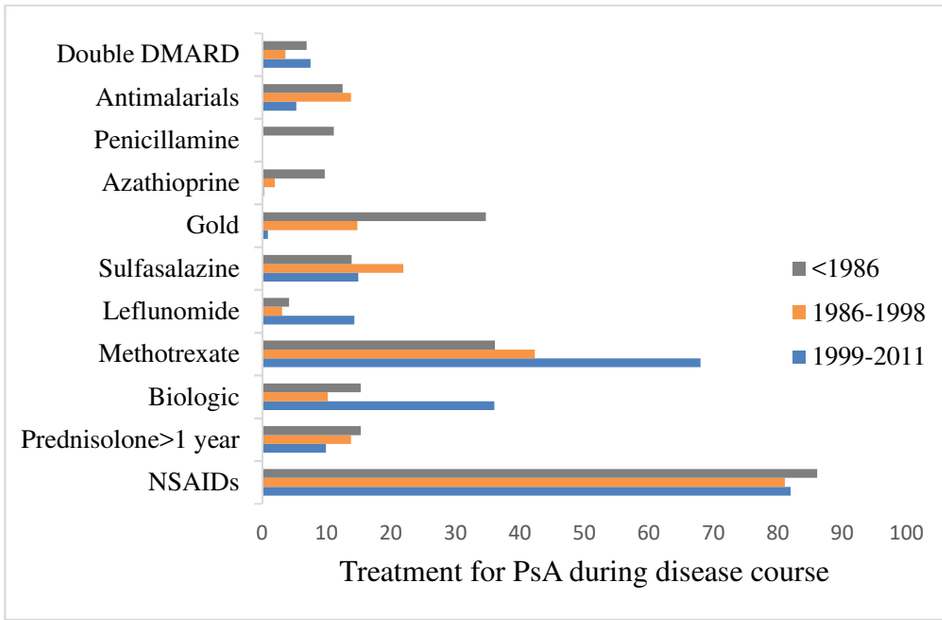


Figure 22. Percent of PsA patients with given treatment first year of disease (A) and during disease course (B)

A



B



Discussion

In the general discussion, I will first present study methods and statistics, and concerns regarding these and regarding the validity of our results. I will then discuss the results and their implications.

1. Methodological considerations

In this project, we aimed to study long-term effects by using orthopaedic surgery as an outcome reflecting failed medical treatment. The treatment of IA has changed greatly during the last 40 years, and we sought to study major effects of this treatment revolution. We chose to use observational longitudinal study designs with hard study endpoints and a long study period.

The randomised clinical trial is gold standard when investigating exposure and outcome. Interventional studies would however be impossible to perform when investigating historical treatment regimens. They are also costly, and unable to include such a large number of patients observed for a similar duration of time, as achieved in our studies.

For papers III and IV, a case control study design could have been used, selecting patients with and without surgeries, and comparing these. Using this approach could help us find predictors for surgery, but not the incidence. We would also be unable to perform survival analyses.

1.1 Study designs

Papers I-II

Observational longitudinal studies on register data enable us to study time trends in data registered, in our case orthopaedic surgery. As the registers used did not contain patient information beyond diagnosis, age, gender and date of performed procedure

(and for the NAR, technicalities regarding the procedure and implant used), these studies were of limited value in evaluating risk factors. The large number of included patients represents a major strength with this study design, enabling the detection of trends in rather seldom outcomes, such as arthroplasty surgery in AS. The study design also offered a large control population (joint replacement for OA) to control for possible time dependent effects, such as changes in indications for surgery related to age or comorbidity and changes in surgical techniques or prophylactic measures, which would presumably affect cases and controls equally.

Papers III-IV

Longitudinal cohort studies are useful for evaluating the relationship between risk factors and outcome. Using this design, incidence of orthopaedic surgery in patients with inflammatory arthritis could also be calculated.

One of the disadvantages of using a prospective cohort study design to investigate a late outcome, such as orthopaedic surgery, is that subjects need to be followed for a long time. This was not a problem in our studies, as the prospective cohorts were historical, and the outcome was found in already existing databases. Large cohorts are needed when investigating rare events. Orthopaedic surgery is however a frequent outcome in inflammatory joint disease, occurring in 31% of RA patients, and in 20% of PsA patients.

Another disadvantage is loss to follow-up. In our studies, this would only occur if the patient moved out of the region, as measurement of the outcome was not related to continued surveillance, but based on events registered in the hospital databases covering the entire region.

1.2 Study populations

The study population of paper I is Norwegian AS patients with hip prosthesis surgery. The study population of paper II is Norwegian RA patients with orthopaedic surgery. For these studies, Norwegian patients with prosthesis surgery for OA were used as a control group.

The study populations of papers III and IV are patients with respectively RA and PsA within the Bergen region. Patients were selected according to computerised records, and diagnoses were validated through journal review. Inclusion criteria was that the patients were suffering from RA or PsA in the opinion of the treating physician. 85% of included RA patients and 90% of included PsA patients fulfilled the classification criteria (ACR/EULAR and CASPAR criteria, respectively).

To account for the possibility of PsA patients in previous years being coded as other arthritis subgroups we searched not only for PsA, but also for the combination of arthritis or spondyloarthritis and psoriasis. A broader search was conducted for PsA (any contact in time period 1, or at least two contacts in time periods 2 and 3) than for RA (at least five contacts) to increase the detection rate and cohort size. Inclusion criteria were however, the same for both diagnoses, and in all time periods.

As the HUS patient administrative system goes back to 1972, we could obtain data on diagnoses and performed procedures from this year onwards. During journal review, data on patients diagnosed prior to 1972 were also found. For RA, these patients were excluded. To increase the size of the much smaller PsA cohort, we chose to include some PsA patients diagnosed as far back as 1954, provided that all information regarding patient characteristics, treatment and performed surgical procedures was available. The RA cohort was followed up until 2015 and the PsA cohort until 2017, due to the order of published papers.

Data from several sources were obtained (see table 3), to avoid bias regarding patient selection and information. This is further discussed in the chapter on validity on pages 81-84.

1.3 Statistical methods

Poisson regression

In the Poisson distribution, the expected value equals the variance. If the data has a variance much greater than the data's average, over dispersion is present. In our analysis, a random effect was included to account for this. In paper I, we analysed trends in the absolute number of procedures performed in patients with AS and OA. This was because we did not have reliable figures for the incidence of AS in Norway, and because the number of performed procedures in AS patients was too low (n=534) to compare to the general population. In paper II, the number of performed procedures was much higher (n=11 337, 4782 and 6022 for prostheses, synovectomies and arthrodeses, respectively) and we analysed trends in the annual incidence; the number of operated joints per 100 000 inhabitants at risk in respective years.

Survival analysis

Survival analyses are commonly used when investigating time from diagnosis until the occurrence of a certain event, such as death, recovery, or in our case orthopaedic surgery. In longitudinal observational studies, patients with different lengths of follow-up are included. Survival analyses takes into account that not all events of interest may have occurred before the end of the entire study period, or before the individual patient's follow-up prematurely determinates (due to death or study discontinuation). They are widely used in register studies. Survival times seldom follow the normal distribution, and linear regression cannot be used when estimating the effect of different risk factors. The most commonly used survival methods are Kaplan-Meier survival curves and Cox proportional hazards models.

Kaplan-Meier survival curves

The Kaplan-Meier estimates probabilities of occurrence of an event at a certain point of time, by multiplying the successive probabilities by any earlier computed probabilities to get the final result. It is considered one of the best options when measuring the fraction of patients reaching a certain endpoint (163).

Cox proportional hazards models

In the Cox proportional hazards models, no certain distribution is assumed, but the model requires that hazard functions are proportional over time in each group. In paper III, when estimating the effect of diagnosis in different time periods, the survival curves for the different periods were not proportional, and the prerequisite for Cox regression was not strictly present. The results showing an increased risk of surgery among patients diagnosed in earlier years could thus be questioned. We therefore also investigated events occurring later than four years since diagnosis, from which time the relative hazards were constant. In these analyses, patients diagnosed in earlier years had an even greater risk of surgery, thus confirming the results for the entire period.

Propensity score

Observational treatment studies are limited by the lack of randomisation. The propensity score is the probability of having a certain treatment conditioned on observed baseline characteristics. Propensity score models aim to perform as a random clinical trial. Propensity score matching makes it possible to estimate the average treatment effect for the treated, and thus excludes the confounding effect of the most severely affected individuals being susceptible to receive the most potent treatment. Instead of using regression adjustment, as in a Cox model, to adjust for differences in baseline characteristics, we used the propensity score model to eliminate the effect of possible known confounders (164).

In paper III, we performed analyses using a propensity score model in addition to the Cox model. We used age, sex, radiographic changes at diagnosis, numbers of joints affected, fulfilment of the 2010 ACR/EULAR classification criteria for RA, and serologic status as covariates describing the three time periods. These covariates are all factors that may affect the treatment assignment. The analyses were performed pairwise, using 1:1 matching. When a pair has been formed, based on having the same propensity score, and thus the same probability of receiving treatment based on baseline characteristics, the treatment effect can be measured directly from comparing the outcomes between the treated and the untreated subject. Using this model, we confirmed the results from fitting the traditional Cox model.

It is important to remember that propensity score matching does not replace randomisation, as propensity score matching only assures balance in the observed covariates, while randomisation provides balance in all known and unknown covariates. Cases missing one or several of the variables will be excluded, reducing the sample size.

In paper IV, the survival curves for the three different time periods were proportional, and the prerequisite for the Cox regression analysis fulfilled. During the discussion of paper III, we concluded that the most balanced measure of which treatment a patient had received was in which treatment era the patients had been diagnosed. As using the propensity score did not give additional information, besides confirming the results from the Cox model, we chose not to use this method in paper IV, which also comprised a much smaller study population (PsA).

1.4 Outcome measure

The outcome measure was the occurrence of orthopaedic surgery. Total joint arthroplasty is in particular considered a proxy for the long-term outcome of joint destruction (112, 129, 134), and synovectomies are performed when medication does not halter inflammation. When discussing the results, we interpreted orthopaedic

surgery both as a measure of long-term outcome in inflammatory joint disease, and as a surrogate measure for the degree of inflammation, and later need for joint surgery, in patients with inflammatory arthritis. A limitation to interpreting surgery as a proxy for failed treatment, and further as a measure of time trends in failed treatment is that the indication for surgery may have changed over time. A limited number of orthopaedic surgeons perform rheumatic surgery in the study hospitals, and the turnover rate of surgeons is low. One would assume that this ensures a stable surgical strategy, but we unfortunately know little about how the indication for surgery might have changed. In the first two articles, such factors were controlled for by comparing to OA patients. Improved surgical capacity and extended theatre access, as have occurred during the study period, tend to increase the number of surgeries performed.

As used in previous studies, we adopted the approach that any surgery after the diagnosis of IA was related to this disease (165). As the aetiology of joint destruction, whether degenerative or inflammatory, may be hard to distinguish, our studies share this weakness with others.

1.5 Validity

Validity, in medical research, is to what extent the results of a study are true, and can be applied to the population. Validity may be separated in an internal and an external component. Internal validity applies within the study, concerning whether the study was performed correctly regarding selection bias, information bias and confounding. External validity applies outside the study, concerning whether results can be generalised to a larger population.

External validity

In register and observational cohort studies, the external validity is generally good, as they describe the treatment and prognosis of patients in real life, instead of selected patients treated under ideal conditions. Although RCTs are considered the gold standard in research, they can be difficult to use when investigating late outcomes

such as terminal joint destruction with subsequent orthopaedic surgery. The RCT also has other limitations, particularly concerning generalisability (166), as they demonstrate the effect of treatment under ideal conditions, often within strictly selected patient groups. In papers III and IV we observed the patients for a mean time of 13.1 (0-42) and 13.8 (0-63) years respectively, which would be impossible in an RCT, as would the assignment of outdated treatment regimens to current patients.

Internal validity

Internal validity is a prerequisite for external validity, and consists of selection bias, information bias and confounding.

1.5.1 Selection bias

Selection bias occurs if the study subjects are not representative for the study population, in our case Norwegian AS patients with hip prosthesis surgery (paper I), Norwegian RA patients with orthopaedic surgery (paper II), RA patients treated in the Bergen region (paper III) and PsA patients treated in the Bergen region (paper IV).

Diagnostic criteria for RA have changed over time. This may lead to patients in later years being diagnosed with RA with less severe disease than in previous years. This could explain an improved prognosis for the entire group. However, when collecting data from patient journals, the same inclusion criteria were used for all patients, independent of time of diagnosis.

Papers I-II

The incidence of orthopaedic surgery is calculated from two large registers (NAR for paper I, and NAR and NPR for paper II), and as for all register studies some miscoding must be expected. Possible causes of selection bias in paper I and paper II, are individuals refusing to participate in the NAR, as this is based on written consent,

and surgeons not registering patients, or ascribing the surgery to a wrong diagnosis. The latter also applies to data from NPR.

The NAR has demonstrated a very high completeness (167), and as the papers describe trends, it is unlikely that patient unwillingness should have increased, or surgeon participation deteriorated during the years. In addition, if a change in patient unwillingness had indeed occurred, it would be unlikely that it should only have changed among patients with rheumatic disease and not in other patients having undergone joint replacement surgery. For arthroplasties of the hip and knee the data completeness was confirmed to be steadily high (97 and 95 percent respectively) for the years 2008-2012 in the 2014 annual report from the Norwegian Arthroplasty Register (168) as compared to the years 1999-2002 (167). The data completeness of the more uncommon arthroplasty procedures have improved when comparing the years 1999-2002 (167) to the years 2008-2014 (169). For ankle prostheses completeness improved from 82 to 91 percent, whereas wrist prostheses completeness improved from 52 to 70 percent. Improved registration completeness might make a declining incidence less evident.

Data concerning the diagnosis was derived from the inclusion form on which ankylosing spondylitis, osteoarthritis and rheumatoid arthritis are separate options. When more than one diagnosis was recorded we determined inflammatory arthritis to overrate osteoarthritis, and each joint was considered a separate case when concerning joints of the hands and feet. Psoriatic arthritis is not a tick box in these forms, and if believed to be the cause of prosthesis surgery, must be written under the category “others”. We could thus not perform a study on prosthesis surgery in patients with PsA in the way we did for AS in paper I and for RA in paper II, as the amount and quality of data would be too poor.

There is a possibility of the surgeons registering PsA patients as RA patients in the forms. As PsA is far less common than RA, we believed this to be a minor bias, and the findings from paper II, that orthopaedic surgery is diminishing, was confirmed in

paper III, where diagnoses were verified through journal review. A study from the Danish Hip Arthroplasty Registry, that have the same registration system as NAR, found that the positive predictive value of diagnoses of RA and AS were 100% (170).

Papers III-IV

In papers III and IV, study inclusion was based on patient consent. There is a possibility that patients more severely affected were more likely to participate. As deceased patients were except from consent, this would level some of that bias. Among 2679 RA patients eligible for the study, 2187 were deceased or had consented to inclusion in the study. Among the 2187 patients, we then randomly selected 1544 for journal review. Without consent, we unfortunately could not obtain information on what characterised patients that declined participation.

When comparing part of our RA cohort (patients diagnosed 1999-2009) to another Norwegian study (RA patients starting first methotrexate therapy 2000-2010) age and gender distribution was quite similar (48).

As our cohorts in papers III and IV were prospective, the possibility of selection bias towards more severely affected individuals is reduced, since the researcher did not know the outcome of interest on inclusion.

1.5.2 Information bias

Information bias occurs if information is incorrectly registered. This is most applicable for papers III and IV. The cohorts of RA and PsA patients were built during journal review performed by TW Nystad (RA and PsA) and YS Husum (PsA). For electronic patient files (available since 2000), search functions could be used to make the work easier. For paper files, however, detection of desired information depended on thorough review. This, of course, introduces the possibility of registration error or discrepancy between the two researchers. To minimise this, guidelines for registration and for interpretation of clinicians' descriptions were

made, and followed throughout the process. Files were read in a random order, so that acquired skills, that might enhance registration completeness, would be equally distributed throughout the cohort.

For the PsA cohort, two researchers contributed to the registrations. Both researchers followed the same guidelines for registration, and continuously discussed patients whenever in doubt of how to interpret clinicians' descriptions, or how to register other data. The paper files were assigned randomly to the two researchers, so that any interobserver differences would be equally distributed, and not cause a systematic error.

Information regarding the outcome was obtained from the hospitals' electronic paper records. Information might be erroneous, and might have improved over time.

1.5.3 Exposure variable selection and confounding

The objective of our papers III and IV was to find the effect of different exposures on the outcome orthopaedic surgery. We investigated both patient characteristics, diagnosis in different time periods and exposure to different treatments. As 94% of PsA patients had current or previous psoriatic dermatitis, no further analysis for this exposure variable was performed. The reason why we recorded highest ESR during disease course for PsA patients contrary to highest ESR first two years for RA patients was that the PsA patients often had a more insidious onset of disease, and we wished to record the highest degree of inflammation during disease course. We divided patients according to age above or below 70, to distinguish inflammatory arthritis of the elder versus inflammatory arthritis of the young and middle aged. We could instead have investigated age as a continuous variable, to see what effect any increase in age might have.

As each exposure variable can potentially affect both the outcome variable and the other exposure variables, a common approach is to perform multivariate analyses. Several considerations need to be taken into account when doing this. Statistical

software has an automated procedure, where the impact of each exposure variable on the outcome is tested, to determine whether it should be included in the analysis. This automated approach is often less relevant in medical research, as profound knowledge and consideration of the different variables is necessary to produce a relevant analysis.

Confounders

Confounding implies that the effect of an exposure becomes mixed with the effect of other variables. An example is the effect of use of biologic DMARDs. As biologic DMARDs inhibit joint destruction, we would expect biologic DMARDs to decrease the risk of surgery. However, it is also the most severely affected patients that are prescribed biologic DMARDs. As we would expect the most severely affected to have a higher risk of orthopaedic surgery, the number of affected joints and ESR, as measures of disease activity, are possible confounders when evaluating the effect of bDMARDs.

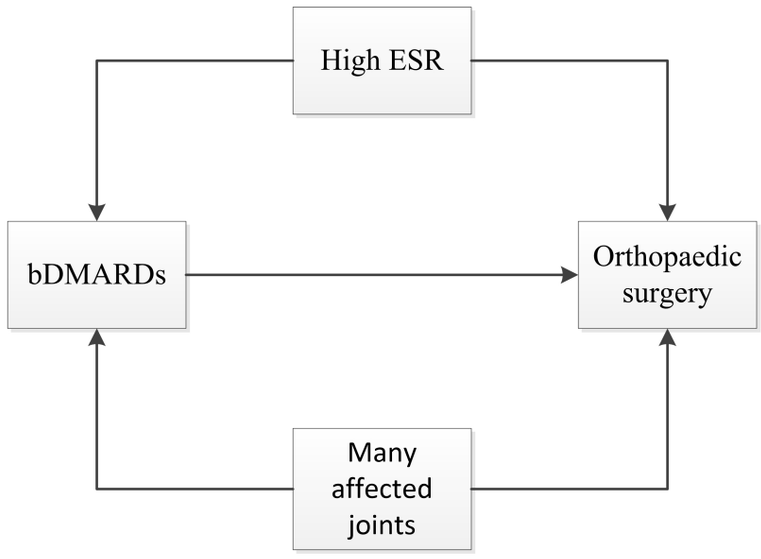


Figure 23. ESR and number of affected joints as confounders

Mediators

Other exposure variables might be mediators of an effect, in example when considering the effect of time period of diagnosis. For instance, we found that female gender was a risk factor for orthopaedic surgery. This might be mediated through women having higher inflammatory activity, as measured by ESR or number of affected joints.

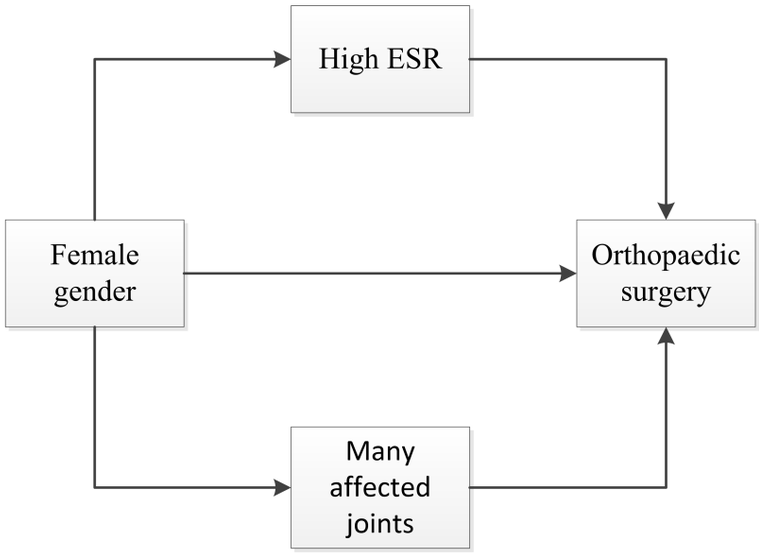


Figure 24. ESR and number of affected joints as mediators

In many cases, we assume that the effect of an exposure variable is mediated through others. We found that diagnosis in later years decreased the risk of surgery. We assume that time period of diagnosis is not a risk factor in itself, but mediated through other factors, such as medication. Patients with later years of diagnosis were more likely to be treated with methotrexate and biologic drugs, and we have mainly interpreted the effect of time period of diagnosis as mediated through drug use, and not being an effect of time period of diagnosis in itself.

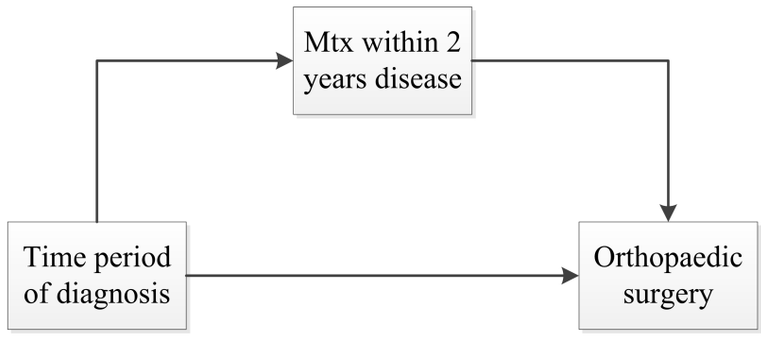


Figure 25. Methotrexate (Mtx) as mediator

Some have discussed that the decreased incidence of orthopaedic surgery might be a secular trend. In that case, the effect of time period of diagnosis could be mediated through a decrease in inflammatory activity over time.

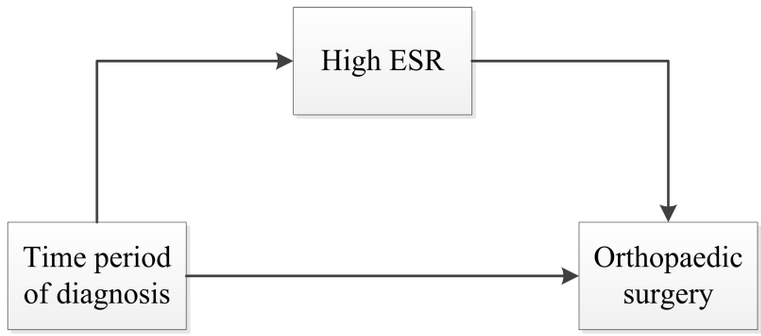


Figure 26. ESR as mediator

The main emphasis has been put on the effect of time period of diagnosis, and how this might be mediated through different exposure variables. This is further discussed in the results for each paper. The most striking change between the three time periods is however, the change in medication, and this is why we suggest that the improved prognosis for RA patients is due to treatment changes.

Selection of included variables

Different approaches to the selection of included variables, was used in paper III and paper IV. In paper III, each exposure variable was investigated with Kaplan-Meier analysis, regarding any effect on the outcome variable; orthopaedic surgery, or subgroups of procedures. Where a difference in Kaplan-Meier estimates was found, using the log rank test for significance, further analyses using univariate and multivariate Cox proportional hazards regression models were performed. For paper IV however, a DAG was constructed to determine which variables should be included in the multivariate Cox proportional hazards regression model for each factor.

A DAG is a graphic model that depicts a set of hypotheses about the causal process that generates a set of variables of interest. The intention is to minimise bias in empirical studies in epidemiology.

We considered the different exposure variables, and how they could potentially affect one another. This was plotted using the software on www.dagitty.net, with orthopaedic surgery as the outcome variable. All included exposure variables may potentially affect this outcome. Arrows are drawn according to whether the exposure variables may have an effect on other exposure variables, and visualises causal paths and biasing paths. One may thus find potential biases and which variables that need to be included in the Cox regression analyses to minimise bias, for each variable. In example; for “Time period of diagnosis”, no adjustment is necessary to estimate the total effect. When estimating the effect of first ESR, however, age, number of affected joints, gender and time period of diagnosis needs to be included in the analysis. This approach was also used post publication on the data from the RA cohort.

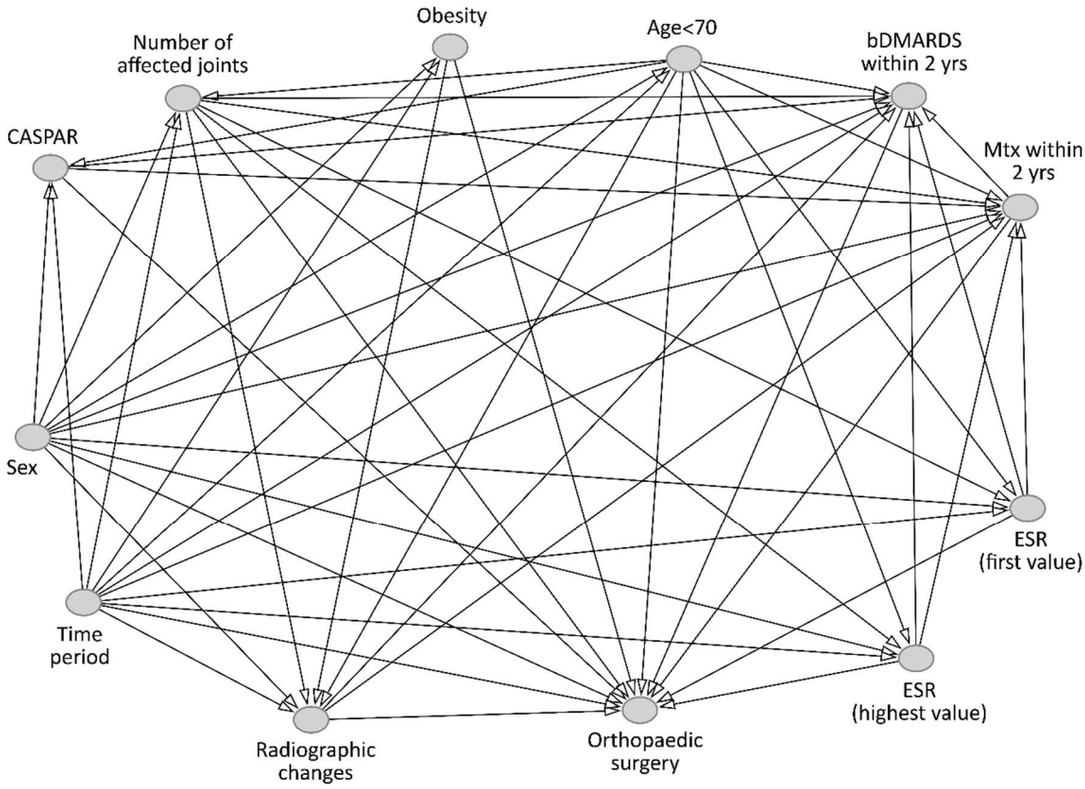


Figure 27. DAG for PsA analysis

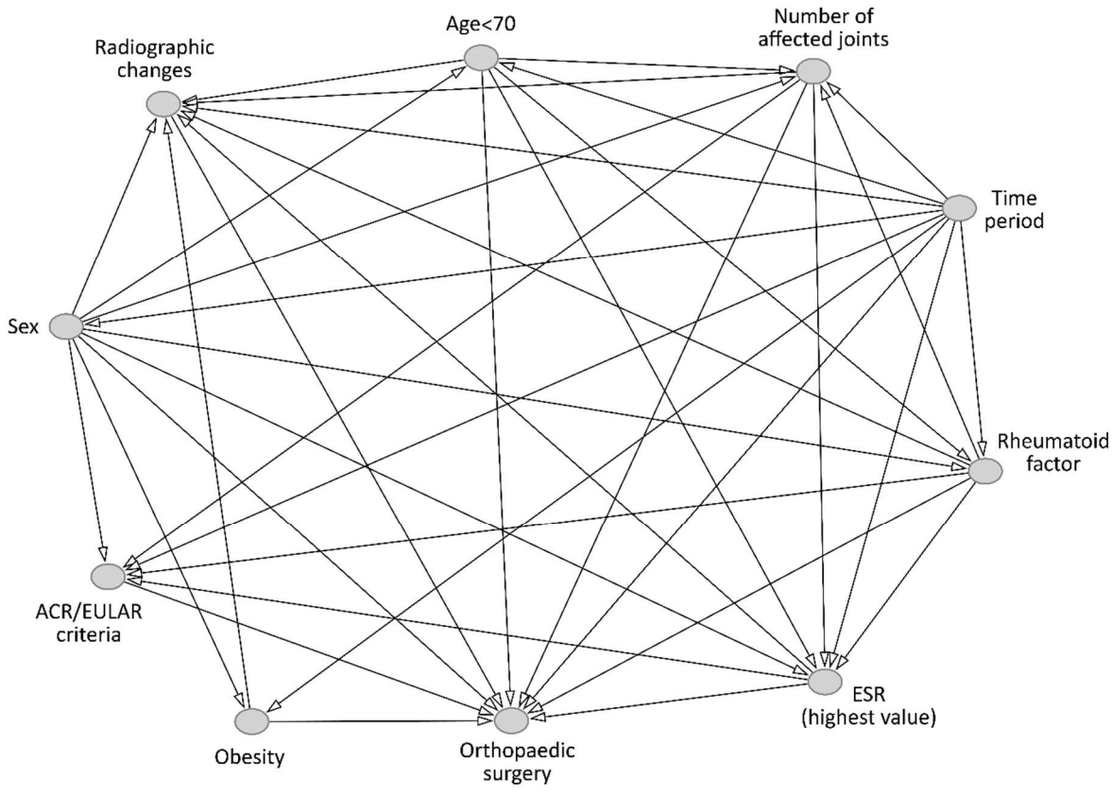


Figure 28. DAG for RA analysis

1.6 Multiple imputation of missing values

In the original analysis, we used case wise deletion of missing data, which means that only cases that do not contain any missing data for any of the variables selected for the analysis will be included. Potential problems with this approach include the possibility of a biased deletion of cases, in example; less severely affected individuals might be less likely to have radiographs taken at diagnosis, so that the final dataset had a larger proportion of individuals with higher disease activity. Another problem is less statistical power because of the exclusion of cases with multiple complete variables, because of one missing.

Multiple imputation of missing data describes the method where lacking values are imputed using a model that incorporates random variation. This is performed several times, producing any given number of complete data sets, and it is recommended to generate a large number of data sets (171). The desired statistical analysis is then performed on each set, and an average is calculated, producing a single result.

Multiple imputation of missing values was performed in paper IV, and when reconsidering the data from paper III, we applied multiple imputation of missing data to the analyses performed in the DAG directed procedure. We performed this process in SPSS, producing 100 complete data sets.

The reanalysis of the RA cohort using a DAG directed procedure and multiple imputation of missing data produced only minor differences, and none that changed main results and conclusions.

2. Results

The principal findings of this thesis were that orthopaedic surgery decreased for RA patients and showed a declining trend for AS patients, while the prognosis for PsA patients remained largely unchanged. Reasons for the discrepancy between patient groups can be discussed. The pathophysiology differs between diseases, and contrary to RA, methotrexate has not been proven efficient in inhibiting joint destruction in PsA or AS. Biologic treatment inhibits joint destruction in RA (55, 56) and PsA (58), and has been shown to be associated with inhibition of axial progression in AS (65), but as they were introduced fifteen years later than methotrexate, one has to assume that any change in prognosis would occur with a time delay in AS and PsA.

2.1 Ankylosing spondylitis, paper I

For RA patients there has been a declining incidence of orthopaedic surgery since 1994 (104), although some have suggested that this is not true for large joint replacements (147). In contrast, for AS patients the frequency of hip prosthesis surgeries continued to increase up until 2002, in accordance with the general increase in joint replacement surgery. After 2002 however, there was a tendency of a reduced frequency of hip prosthesis surgery performed in AS patients, despite the continuing rise in OA patients. This suggests that the change in this group is caused by a later event.

In 2003 etanercept was the first TNF alpha inhibitor approved for use in patients with AS when treatment with NSAIDs (and sDMARDs for peripheral arthritis), was insufficient. Local data show that TNF alpha inhibitors were introduced in some AS patients as early as 2000 (data from Haukeland University Hospital), with extended use from 2003, the same year an international ASAS consensus statement for the use of TNF alpha inhibitors in patients with AS was published (172).

Up until we conducted our study, it had been unclear whether TNF alpha inhibitors haltered joint destruction in AS (63). However, the observed change in trend in the

frequency of hip replacement procedures in patients with AS in our study indicates a recent change in the course of the disease, suggesting a reduced incidence and/or severity of large joint arthritis. The significantly higher mean age at surgery supports this, as it suggests that improved treatment of arthritis postponed orthopaedic surgery. The changes coincide with the initiation of TNF alpha inhibitor treatment in Norwegian patients with AS, and can probably be explained by it.

A recent study on the trends of hip prosthesis surgery in US found significant decrease in the share of hip arthroplasties being performed for AS patients (in percent of total number of procedures) in the years 2004-2014 (111), and there is now also evidence of inhibition of spinal radiographic progression (65) following biologic treatment. Both findings are consistent with the excellent clinical effect in this patient group.

2.2 Rheumatoid arthritis, papers II and III

For RA our analyses were consistent with previous findings.

The main finding in paper II was a significant decrease in joint replacement surgery and synovectomies in Norwegian patients with RA in the time period 1994/97-2012.

We have limited knowledge of whether the indication for surgery might have changed over time. Improved surgical capacity and extended theatre access, as have occurred during the study period, tend to increase the number of surgeries performed. A decline of procedures these years most likely represent an improved prognosis for Norwegian RA patients, and our study confirms that the trend continues into the era of biologics.

It was among that study's limitations that we could only report the general use of orthopaedic surgery in Norway, and therefore not analyse outcomes of individual patients with different patient characteristics, and diagnosed in different treatment eras. We aimed to investigate this further in paper III. The main finding from this

study was that 31% of RA patients needed surgery during disease course, and that diagnosis in earlier years increased the risk of orthopaedic surgery.

In other cohorts, the incidence of surgery has been 29% (147), 34% (112), 37% (131), 58% (134) and 62% (118). A declining incidence over the years have been found in Norway (104), Sweden (130, 135, 138), Denmark (149), Finland (77, 141), UK (142, 147), Ireland (148), Japan (116, 117, 154), and the US (113, 114, 127). Some authors have found a stable incidence of some surgeries, such as large joint replacements or knee joint replacements (133, 135, 136, 138, 147). In a New Zealand cohort, the stable rates of hip, knee, shoulder and ankle replacements were interpreted as due to biologics being introduced as late as 2006, and limited to those with erosions (153).

When performing sub analyses of the risk for hip and knee arthroplasty in our cohort, year of diagnosis was not a risk factor. One explanation might be the general increase in joint replacement surgery, which would presumably affect our patients similarly. Another might be that the inflammation process in large joint is different from that of small joints, as suggested by Nikiphorou (147). In the sub analyses of prosthesis surgery of the hip and knee, in paper II, only a modest, insignificant decline was found. However, as argued by others, compared to the increase seen in OA patients (174), no rise among arthritis patients might also be considered an improved prognosis (133, 136).

Uhlig and Kvien postulate that the incidence of RA today is lower than in the 1950s (175). A lower incidence of RA might be a reason why the incidence of surgery is diminishing, but as the decline was found to have occurred mainly in the 1970s or early 1980s (175), it does not explain the continued decrease.

RA has become a more benign disease in later years (78, 176, 177), and although some argue that this is partly a secular trend (178), most associate the improvement with the change in treatment (179, 180). A change in the diagnostic criteria for RA

towards including patients with milder disease might also explain an improved prognosis (181).

One might argue that the lower occurrence in paper II and lower risk of surgery in paper III is because of higher disease activity among patients diagnosed in earlier years. In our RA cohort, significantly more patients diagnosed 1972-1985 had ESR≥60 during disease course, more than ten joints affected, and signs of arthritis on initial radiographs. Time of diagnosis was however still a significant risk factor both in multivariate Cox analysis and in the propensity score model correcting for these factors. It might be that the higher ESR in earlier cohorts is not a sign of more aggressive disease in earlier years, but a sign of under treatment or lack of response to current medical treatment. Mean ESR at diagnosis was also significantly higher in previous years. This may reflect a more severe disease in previous years, but is equally possible the result of a delay in referral to specialist care, and the use of diagnostic criteria including features of long-standing disease, such as rheumatoid nodules or radiographic changes. Finch et al found, when adjusting for DMARD use, steroid use and baseline predictors, that the improvement in patient outcome was attributable to more effective antirheumatic treatment (179).

Medical treatment for RA changed significantly over time in our cohort, and the decreased risk of surgery coincides with an increasing use of synthetic and biologic DMARDs. The decline is seen already from 1994 (104), before the introduction of biologic agents, and is probably mainly attributable to the introduction of methotrexate (79). In paper III, patients diagnosed 1972-1985 did not have an increased risk when compared to patients diagnosed 1986-1998, whereas both groups had higher risks than patients diagnosed 1999-2014. This might be interpreted as an indication that prognosis is better after the introduction of TNF alpha inhibitors. It is however hard to separate the effect of additional treatment options from the effect of RA patients now being referred and treated earlier and more aggressively (182) with higher doses of methotrexate (48). In addition to improved medical treatment options,

two major treatment strategies have been implemented in daily clinical care of RA patients during the last 10-15 years; the tight control treatment strategy which involves frequent controls during the early stages of the disease (183, 184), and "treat to target" which means that patient and doctor agree on a prespecified goal (remission or low disease activity), and treatment is escalated until this goal is reached (35, 185).

As rheumatic surgery is a late outcome of RA, a time delay between change in treatment and change in incidence of surgery must be expected, and later studies might provide more information on the additional effect of biologic treatment.

2.3 Psoriatic arthritis, paper IV

This study's main findings were that 20% of PsA patients required orthopaedic surgery, and that time period of diagnosis did not alter the outcome.

Between patients diagnosed in the three time periods, we did not find any significant changes in the disease activity at disease onset. On the other hand, maximum ESR during disease course decreased, and more patients among those diagnosed in earlier years developed radiographic changes. This suggests that the burden of inflammation has subsided in recent years in patients followed by rheumatologists. Other authors studying differences between PsA patients operated and those not operated have found significantly more radiological damage and more actively inflamed joints at first assessment in operated patients (155), and that asymmetric mono-/oligoarticular arthritis and the combination of peripheral and axial disease was more frequent among patients with surgeries (156). Haque et al did not find differences in treatment between the groups.

One possibly confounding factor in our study is that the indication for surgery may have changed due to better access to surgeons and operating theatres. Another is that hip and knee arthroplasties may have been conducted based on coexisting osteoarthritis in patients with inflammatory arthritis. Whereas arthroplasty in joints other than hip and knee were found to be frequent in RA (18% of prosthesis

procedures), this was seldom performed in patients with PsA, where 96% of prosthesis surgeries were hip and knee procedures. The incidence of arthroplasty surgery in patients with osteoarthritis has increased significantly in later years (162), and as large joint replacements account for a greater proportion of surgery in PsA than in RA (51% versus 33% in our material) this would be expected to weaken the effect of time period of diagnosis. PsA patients are also more prone to being overweight (186) which increases the risk of osteoarthritis, especially in the knee (187, 188). After excluding prosthesis surgery of the hip and knee from the analysis, we found that diagnosis in 1954-1985 increased the risk of surgery compared to diagnosis later than 1998. However, 57% of PsA patients with knee prosthesis surgery had arthritis of the knee during disease course, and 21% of patients with hip prosthesis surgery had hip joint arthritis. One must thus suspect that inflammatory disease was a contributing factor also for large joint destruction, and that this has not been successfully treated.

As available data were not suitable to do an investigation on trends in the incidence of prosthesis surgery in PsA patients, as was performed for RA, we do not know whether there has been a stabilisation or decline, as seen for RA, and whether this, compared to the increase in the general population, might represent an improved prognosis also for PsA patients. As diagnosis in later years is not a risk factor for hip and knee prosthesis surgery, one must however suspect that any increase among PsA patients would not be of the same magnitude as for OA patients.

According to senior rheumatologists in Haukeland University Hospital's PsA patients were considered to have a greater risk of joint stiffness after surgeries such as knee synovectomy. This might have contributed to the incidence of surgery being lower among PsA patients (20%) than among RA patients (31%). If inflamed joints in PsA patients were not operated to the same extent as inflamed joints in RA patients, a decrease in inflammation might not give the same decrease in surgical procedures.

Although not to the same extent as for RA, PsA patients have, to an increasing degree, been treated with synthetic, and in later years, biologic DMARDs (80). Our comparative analysis of medical treatment show that RA patients significantly more often were prescribed methotrexate, both first year and during disease course. An exception is the years prior to 1986, when a few PsA patients had methotrexate prescribed by a dermatologist, before the drug came in use among rheumatologists. For biologic drugs, more RA patients were prescribed these during disease course when diagnosed 1986-1998, whereas for patients diagnosed 1999 onwards, there was no difference between diagnoses. This suggests a more aggressive treatment of PsA in later years, and might also reflect that treatment with methotrexate has not been sufficient. We see that for PsA mean initial ESR has not changed, while mean ESR during disease course was higher in patients diagnosed earlier.

Our patients in the cohorts of papers III and IV were all treated within the same facility, with a common treatment philosophy, by physicians following the same guidelines in providing care for the entire region of western Norway. Treatment indication may have changed over time, but there is every reason to believe that all patients in a given year were treated similarly. We therefore believe that the year of diagnosis may be considered a proxy for the treatment received. A limitation to the approach of dividing patients in three time categories is that the change in treatment came gradually, and that new treatment was made available to patients diagnosed in previous years, although later in the disease course.

In our material, the change in treatment coincides with PsA patients having a lower burden of inflammation. However, it has been shown that clinical signs of inflammation and progression of joint destruction might be dissociated (189-191), and we could not find a decrease in joint surgery, when considering all procedures, suggesting that this outcome has not been affected by the change in medication, contrary to what is found for patients with RA. This is in concordance with the

knowledge that contrary to the effect of synthetic DMARDs on structural damage in RA patients (55), the same has not been shown for PsA.

As biologic treatment has been shown to prevent joint destruction in PsA (49), we would expect that increasing use of TNF alpha inhibitors would lessen the risk of an orthopaedic procedure during the disease course. When considering all procedures, this was not the case in our material. Even though we did a broader search when including patients for the PsA cohort than for the RA cohort, we did not manage to include more than 590 patients. Not finding a difference may be caused by lack of statistical power, but the curves for surgery in PsA gives no indication that any difference is present. However, no difference may also be interpreted as an improved prognosis of PsA as the use of TKR and THR for OA increased during the study period (as shown in papers I and II). As joint surgery is a late outcome, we might see a decline in such procedures in the future.

Novelty, strengths and limitations

Our paper on hip prosthesis surgery in patients with AS was the first to indicate that biologic treatment had an effect on structural changes in this patient group. For PsA, previous knowledge on orthopaedic surgery was scarce. Our study included the largest published material to date, and gave an estimate of the incidence of surgery among PsA patients. For RA, the body of previous evidence was larger, but our studies were unique in the duration of follow-up, and our two large materials confirmed a declining trend of surgery in later years.

The greatest flaw in our study designs is probably that in papers III and IV parts of information was gathered manually. We could have done investigations of intra- and interobserver variability to assure that our efforts to avoid information bias had the desired effect.

Although longitudinal observational studies were considered the most suitable for this investigation, observational studies can only find associations between exposures and outcomes, and theories regarding causality must be discussed with caution. Considerations regarding confounding and bias have been elaborated above.

Conclusions

Paper I

We found a trend towards a reduced frequency of hip prosthesis surgery in AS patients and an increased mean age at surgery when comparing patients up until and after 2002. TNF alpha inhibitors were introduced to patients with AS in Norway in 2000-2003, and our findings suggest that they may have altered the prognosis by inhibiting or slowing large joint arthritis and thus reducing the need for hip replacement surgery.

Paper II

We found a decrease in orthopaedic surgery in patients with RA that continued into the biologic era and throughout the study period. The general increasing trend in the use of synthetic and biological DMARDs thus coincides with less joint destruction and an improved long-term prognosis of patients with RA.

Paper III

We found that 31% of RA patients had orthopaedic surgery performed. Patients with diagnosis in the early years had a greatly increased risk of having surgery. This is probably due to the year of diagnosis being a proxy for the type and intensity of medical treatment, which we found to have changed significantly during the study period.

Paper IV

We found that 20% of PsA patients had orthopaedic surgery performed. For PsA patients the prognosis did not change, regarding the risk of orthopaedic surgery, despite the change in medical treatment.

Thesis

In conclusion we believe that the validity of our study is good enough for our results to imply that the change in treatment for patients with inflammatory joint disease has had a beneficiary effect, regarding orthopaedic surgery, in patients with AS and RA. Results for patients with PsA do not show the same trend. An explanation might be that the general increase in large joint replacements have a higher impact on surgery for PsA than for RA, or that the changes in treatment so far has not affected this group to the same extent.

Future perspectives

We plan to publish a comparative investigation of the RA and PsA cohorts, regarding treatment and outcome, and have started the work of performing an updated analysis on hip prosthesis surgeries for AS patients, expanding the material from 2010 to 2018, to see whether the declining trend progresses and becomes significant.

Patients with inflammatory joint disorders have an increased risk of cardiovascular disease (192-195). The risk remains high even after correcting for traditional cardiovascular risk factors, suggesting that the inflammatory joint disease is a separate contributor (196). We aim to use the cohorts described in paper III and IV to investigate time trends in the incidence of cardiovascular disease and stroke among patients with RA and PsA, and to see what impact cardiovascular risk factors, disease characteristics and anti-rheumatic treatment has had on the risk of these outcomes. The work is already in progress.

In aiming to treat all patients with inflammatory arthritis adequately, to prevent joint destruction, we have come a long way with patients suffering from rheumatoid arthritis. Further investigations regarding the beneficial effect of biologic treatment on peripheral arthritis in ankylosing spondylitis are needed, but results are promising. For psoriatic arthritis, however, the change in treatment has not yet proven successful in preventing orthopaedic surgery. One explanation might be the general increase in joint replacement procedures. This calls for further research, and for considerations regarding the intensity of treatment and follow-up in this patient group.

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Appendix

ACR/EULAR classification criteria for rheumatoid arthritis

CASPAR classification criteria for psoriatic arthritis

NAR registration form for hip prostheses

NAR registration form for prostheses in other joints

Papers I-IV

ACR/EULAR classification criteria for rheumatoid arthritis

Joint distribution (0-5)	
1 large joint	0
2-10 large joints	1
1-3 small joints (large joints not counted)	2
4-10 small joints (large joints not counted)	3
>10 joints (at least one small joint)	5
Serology (0-3)	
Negative RF* and negative ACPA**	0
Low positive RF or low positive ACPA	2
High positive RF or high positive ACPA	3
Symptom duration (0-1)	
<6 weeks	0
≥6 weeks	1
Acute phase reactants (0-1)	
Normal CRP† and normal ESR‡	0
Abnormal CRP or abnormal ESR	1

*Rheumatoid factor **Anti-citrullinated protein antibodies †C-reactive protein
‡Erythrocyte sedimentation rate

The classification criteria are valid for patients having at least one joint (not including DIP, first MTP and first CMC joint) with definitive clinical synovitis not explained by another disease. Large joints are shoulder, elbow, hip, knee and ankle. Small joints are PIP, MCP, IP, MTP and wrist. A score of ≥6 is defined as definite RA. If the score is <6, patients may fulfil the criteria prospectively (cumulatively) over time, or retrospectively if data on all four domains have been adequately recorded in the past.

CASPAR classification criteria for psoriatic arthritis

Skin psoriasis	
Present	2
Previously present by history	1
Family history of psoriasis, if the patient is not affected	1
Nail lesions (onycholysis, pitting)	1
Dactylitis (present or past, documented by a rheumatologist)	1
Rheumatoid factor negative	1
Juxtaarticular bone formation on radiographs (distinct from osteophytes)	1

CASPAR criteria are valid for patients with established inflammatory musculoskeletal disease (joint, spine or entheseal). A patient can be classified as having psoriatic arthritis if total score is ≥3

Nasjonalt Register for Leddproteser
Ortopedisk klinikk, Helse Bergen HF
Haukeland universitetssjukehus, Postboks 1400
Møllendalsbakken 11, 5021 BERGEN
Tlf 55973742/55973743

F.nr. (11 sifre).....

Navn:.....

(Skriv tydelig ev. pasientklistrelapp – **spesifiser sykehus**.)

Sykehus:.....

HOFTEPROTESER

Alle totale hofteproteseoperasjoner og hemiproteser på annen indikasjon enn fraktur/fraktursekvele registreres her (hemiprotese for fraktur/fraktursekvele registreres på Hoftebruddskjema). Alle reoperasjoner skal registreres: skifte/fjerning av protesedeler, kantplastikk, bløtdelsdebridement, og operasjoner for protesenær fraktur eller gluteal svikt.

TIDLIGERE OPERASJON I AKTUELLE HOFTE (ev. flere kryss)
☐0 Nei
☐1 Osteosyntese for fraktur i prox. femurende
☐2 Hemiprotese pga. fraktur
☐3 Osteotomi
☐4 Artrodese
☐5 Totalprotese(r)
☐6 Annen operasjon ……

AKTUELLE OPERASJON (ett kryss)
☐1 Primæroperasjon (også hvis hemiprotese tidligere)
☐2 Reoperasjon (totalprotese tidligere)
☐3 Primær hemiprotese for annen indikasjon enn fraktur/fraktursekvele

OPERASJONSDATO (dd.mm.åå) |__|__| |__|__| |__|__|

AKTUELLE SIDE (ett kryss) (Bilateral opr.= 2 skjema)
☐1 Høyre ☐2 Venstre

ÅRSAK TIL AKTUELLE OPERASJON (KRYSS AV ENTEN I A ELLER B)

A. Primæroper. pga (ev. flere kryss)
☐1 Idiopatisk coxartrose
☐2 Rheumatoid artritt
☐3 Sekvele etter frakt. colli. fem.
☐4 Sekv. dysplasi
☐5 Sekv. dysplasi med total luksasjon
☐6 Sekv. Perthes
☐7 Sekv. epifysiolyse
☐8 Mb. Bechterew
☐9 Akutt fraktura colli femoris
☐10 Annet……..
(f.eks caputnekrose, tidl. artrodese o.l)

B. Reoper. pga (ev. flere kryss)
☐1 Løs acetabularkomponent
☐2 Løs femurkomponent
☐3 Luksasjon
☐4 Dyp infeksjon
☐5 Fraktur i acetabulum
☐6 Fraktur av femur
Vancouverklassifikasjon, se bakside.
☐A ☐B1 ☐B2 ☐B3 ☐C
☐7 Smerter
☐8 Osteolyse i acetab. uten løsning
☐9 Osteolyse i femur uten løsning
☐10 Implantatfraktur femurdel
☐11 Implantatfraktur caput
☐12 Implantatfraktur kopp
☐13 Implantatfraktur liner
☐14 Implantatfraktur annet: .....
.....
☐15 Gluteal svikt
☐16 Annet……
(f.eks Girdlestone etter tidl. infisert protese)

REOPERASJONSTYPE (ev. flere kryss)
☐1 Bytte av femurkomponent
☐2 Bytte av acetabularkomponent
☐3 Bytte av hele protesen
☐4 Fjernet protese og satt inn sementspacer
☐5 Fjernet sementspacer og satt inn ny protese
☐6 Fjernet protese (Girdlestone eller fjerning av sementspacer)
Angi hvilke deler som ble fjernet……
☐7 Bytte av plastforing
☐8 Bytte av caput
☐9 Bløtdelsdebridement
☐10 Ny protese etter Girdlestone
☐11 Resutur av muskel
☐12 Transposisjon av muskel
☐13 Osteosyntese for fraktur
☐14 Konvertering til hemiprotese
☐15 Andre operasjoner ……..

TILGANG (ett kryss)
☐1 Fremre (Mellom sartorius og tensor)
☐2 Anterolateral (Mellom glut. medius og tensor)
☐3 Direkte lateral (Transgluteal)
☐4 Bakre (Bak gluteus medius)
☐5 Annen ……

MINIINVASIV KIRURGI (MIS) ☐0 Nei ☐1 Ja
LEIE ☐0 Sideleie ☐1 Rygg
TROCHANTEROSTEOTOMI ☐0 Nei ☐1 Ja

BENTRANSPLANTASJON (ev. flere kryss)
Acetabulum ☐0 Nei ☐1 Ja ☐2 Benpakking
Femur ☐0 Nei ☐1 Ja ☐2 Benpakking a.m. Ling/Gie

BENTAP VED REVISJON (Paprosky's klassifikasjon se baksiden)
Acetabulum ☐1 I ☐2 IIA ☐3 IIB ☐4 IIC ☐5 IIIA ☐6 IIIB
Femur ☐1 I ☐2 II ☐3 IIIA ☐4 IIIB ☐5 IV

PROTESEKOMPONENTER (Bruk klistrelapp på baksiden, eller skriv REF.NR.)

Acetabulum
Navn/Type ……
ev. REF.NR. … ……..
☐ Med hydroksylapatitt ☐ Uten hydroksylapatitt
☐1 Sement med antibiotika – Navn ……
☐2 Sement uten antibiotika – Navn ……
☐3 Usementert

Femur (+ ev. trokanterdel)
Navn/Type ……..
ev. REF.NR. .. ……..
☐ Med hydroksylapatitt ☐ Uten hydroksylapatitt
☐1 Sement med antibiotika – Navn ……
☐2 Sement uten antibiotika – Navn ……
☐3 Usementert

Caput (+ ev. halsdel)
☐1 Fastsittende caput
☐2 Separat caput - Navn/Type ……
ev. REF. NR. .. ……
Diameter ……..

ANTIBIOTIKAPROFYLAKSE ☐0 Nei ☐1 Ja

	Navn	*Dosering*	*Varighet i timer*
Medikament 1	.....	.....	.....timer
Medikament 2	.....	.....	.....timer
Medikament 3	.....	.....	.....timer

TROMBOSEPROFYLAKSE
☐0 Nei ☐1 Ja: Første dose ☐1 Preoperativt ☐2 Postoperativt
Medikament 1……..Dosering opr.dag……
Dosering videre…….Varighet……døgn
Medikament 2…….. Dosering……Varighet……døgn

FAST TROMBOSEPROFYLAKSE
☐0 Nei ☐1 Ja, type: ……..

FIBRINOLYSEHEMMER
☐0 Nei ☐1 Ja, medikament: …….. Dosering…….

OPERASJONSSTUE
☐1 "Green house"
☐2 Operasjonsstue med laminær luftstrøm
☐3 Vanlig operasjonsstue

OPERASJONSTID (hud til hud) ……min

PEROPERATIV KOMPLIKASJON
☐0 Nei
☐1 Ja,hvilke(n) .....

ASA KLASSE (se baksiden for definisjon)
☐1 Frisk
☐2 Asymptomatisk tilstand som gir økt risiko
☐3 Symptomatisk sykdom
☐4 Livstruende sykdom
☐5 Moribund

Lege .....
Legen som har fylt ut skjemaet (navnet registreres ikke i databasen).

2025016 Bergen Grafisk AS 04.2016

RETTLEDNING TIL HOFTEPROTESER

Registreringen gjelder innsetting, skifting og fjerning av totalproteser i hofteledd, samt kantplastikk, bløtdelsrevisjon for infisert protese og hemiproteser på annen indikasjon enn fraktur/fraktursekvele. Hemiprotese for fraktur/ fraktursekvele registreres på Hoftebruddskjema. Ett skjema fylles ut for hver operasjon. Fødselsnummer (11sifre) og sykehusnavn må påføres. Aktuelle ruter markeres med kryss. På eget Samtykkeskjema skal pasienten gi samtykke til rapportering til Leddregisteret.

AKTUELLE OPERASJON

Primæroperasjoner: Første totalproteseoperasjon, og første hemiprotese hvis denne settes inn på annen indikasjon enn fraktur. Hemiprotese for fraktur/fraktursekvele registreres på Hoftebruddskjema.

Reoperasjon (totalprotese tidligere): Fjerning av protesedeler (f.eks. Girdlestone) må registreres. Kantplastikk (f. eks. PLAD), bløtdelsrevisjoner for infeksjon, osteosyntese, resutur av muskel og muskeltransposisjon registreres selv om protesedeler ikke skiftes.

ÅRSAK TIL AKTUELLE OPERASJON

Kryss av under A ved primæroperasjoner og under B ved reoperasjoner. I B må du krysse av for alle årsakene til reoperasjon, eller forklare med fritekst.

REOPERASJONSTYPE

Fjerning av protesedeler (f.eks. Girdlestone) må registreres. Kantplastikk (f. eks. PLAD), bløtdelsrevisjoner for infeksjon, osteosyntese, resutur av muskel og muskeltransposisjon registreres selv om protesedeler ikke skiftes.

BENTRANSPLANTASJON Benpropp som sementstopper regnes ikke som bentransplantat. Vi skiller mellom benpakking og transplantasjon.

PROTESEKOMPONENTER: Acetabulum - Femur - Caput - Trokanterdel og hals hvis disse er separate deler

Bruk klistrelappene som følger med protesen. Lim disse på baksiden av skjema. Alternativt, skriv inn protesenavn + REF.NR., materiale, overflatebelegg og design. Sementnavn må anføres (bruk klistrelapp).

KOMPLIKASJONER Også operasjoner hvor pasienter dør på operasjonsbordet eller rett etter operasjon skal meldes. Ved stor blødning, angi mengde**.**

ASA-KLASSE (ASA=American Society of Anesthesiologists)

ASA-klasse 1: Friske pasienter som røyker mindre enn 5 sigaretter daglig.

ASA-klasse 2: Pasienter med en asymptomatisk tilstand som behandles medikamentelt (f.eks hypertensjon) eller med kost (f.eks diabetes mellitus type 2) og ellers friske pasienter som røyker 5 sigaretter eller mer daglig.

ASA-klasse 3: Pasienter med en tilstand som kan gi symptomer, men som holdes under kontroll medikamentelt (f.eks moderat angina pectoris og mild astma).

ASA-klasse 4: Pasienter med en tilstand som ikke er under kontroll (f.eks hjertesvikt og astma).

ASA-klasse 5: Moribund/døende pasient.

MINIINVASIV KIRURGI (MIS = Minimally Invasive Surgery**)** når det er brukt spesialinstrument laget for MIS.

ANTIBIOTIKAPROFYLAKSE Før på antibiotikum som er benyttet i forbindelse med operasjonen, f.eks.: Medikament 1: Keflin 2g x 4, med varighet 4,5 timer.

TROMBOSEPROFYLAKSE

Medikament, dose og antatt varighet av profylaksen skal angis separat for operasjonsdagen og senere. Det skal også oppgis om pasienten står fast på tromboseprofylakse (AlbylE, Marevan, Plavix ol).

FIBRINOLYSEHEMMER Her føres det på om en benytter blødningsreduserende legemidler i forbindelse med operasjonen (f.eks. Cyklokapron).

BEINTAP VED REVISJON

Femur (Paprosky`s klassifikasjon)

Type I: Minimalt tap av metafysært ben og intakt diafyse.

Type II: Stort tap av metafysært ben, men intakt diafyse.

Type IIIA: Betydelig tap av metafysært ben uten mulighet for proximal mekanisk støtte. Over 4 cm intakt corticalis i isthmusområdet.

Type IIIB: Betydelig tap av metafysært ben uten mulighet for proximal mekanisk støtte. Under 4 cm intakt corticalis i isthmusområdet.

Type IV: Betydelig tap av metafysært ben uten mulighet for proximal mekanisk støtte. Bred isthmus med liten mulighet for cortical støtte.

Acetabulum (Paprosky`s klassifikasjon)

Type I: Hemisfærisk acetabulum uten kantdefekter. Intakt bakre og fremre kolonne. Defekter i forankringshull som ikke ødelegger subchondral benplate.

Type IIA: Hemisfærisk acetabulum uten store kantdefekter, intakt bakre og fremre kolonne, men med lite metafysært ben igjen.

Type IIB: Hemisfærisk acetabulum uten store kantdefekter, intakt bakre og fremre kolonne, men med lite metafysært ben igjen og noe manglende støtte superiort.

Type IIC: Hemisfærisk acetabulum uten store kantdefekter, intakt bakre og fremre kollonne, men med defekt i medial vegg.

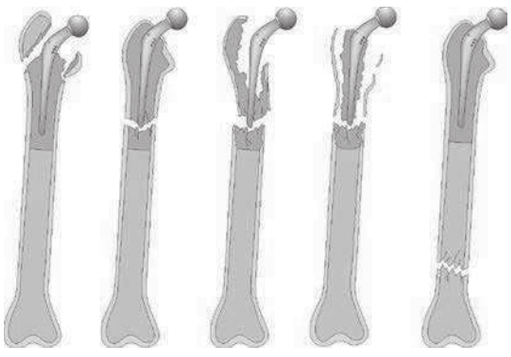
Type IIIA: Betydelig komponentvandring, osteolyse og bentap. Bentap fra kl.10 til 2.

Type IIIB: Betydelig komponentvandring, osteolyse og bentap. Bentap fra kl. 9 til 5.

Kopi beholdes til pasientjournalen, originalen sendes Haukeland universitetssjukehus.

PROTESENÆR FRAKTUR

Vancouverklassifikasjon



Type A Type B1 Type B2 Type B3 Type C

Kontaktpersoner vedrørende registreringsskjema er

Seksjonsoverlege Ove Furnes tlf. 55 97 56 90 og overlege Geir Hallan tlf. 55 97 56 87

Ortopedisk klinikk, Haukeland universitetssjukehus. Besøksadresse: Møllendalsbakken 11.

Konsulent Merete Husøy tlf. 55 97 37 43 og sekretær Randi Furnes tlf. 55 97 37 42

Nasjonalt Register for Leddproteser, Ortopedisk klinikk, Helse Bergen

Epost nrl@helse-bergen.no Internett: http://nrlweb.ihelse.net/

Skjema revidert i november 2015.

Nasjonalt Register for Leddproteser
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Haukeland universitetssjukehus, Postboks 1400
Møllendalsbakken 11, 5021 BERGEN
Tlf 55973742/55973743

F.nr. (11 sifre).....

Navn:.....

(Skriv tydelig ev. pasientklistrelapp – **spesifiser sykehus**.)

Sykehus:.....

KNEPROTESER og andre leddproteser

Innsetting, skifting eller fjerning av protese eller protesedeler, samt bløtdelsrevisjoner for infisert protese og protesenære frakturer.

LOKALISASJON, AKTUELL OPERASJON

☐1 Kne
☐2 Ankel
☐3 Tær (angi ledd) ……..
☐4 Skulder
☐5 Albue
☐6 Håndledd
☐7 Fingre (angi ledd) …….
☐8 Annet ……..
☐9 Rygg (angi nivå)……..……

AKTUELLE SIDE (ett kryss) (Bilateral opr. = 2 skjema)
☐1 Høyre ☐2 Venstre

TIDLIGERE OPERASJON I AKTUELLE LEDD (ev. flere kryss)
☐0 Nei
☐1 Osteosyntese for intraartikulær/leddnær fraktur
☐2 Osteotomi
☐3 Artrodese
☐4 Protese
☐5 Synovectomi
☐6 Annet (f.eks menisk og leddbåndsop.)……

AKTUELLE OPERASJON (ett kryss)
☐1 Primæroperasjon ☐2 Reoperasjon (protese tidligere)

OPERASJONSDATO (dd.mm.åå) |__|__| |__|__| |__|__|

ÅRSAK TIL AKTUELLE OPERASJON (KRYSS AV ENTEN I A ELLER B)

A. Primæroper. pga (ev. flere kryss)
☐1 Idiopatisk artrose
☐2 Rheumatoid artritt
☐3 Frakturseq uele……
☐4 Mb. Bechterew
☐5 Sequele ligamentskade
☐6 Sequele meniskskade
☐7 Akutt fraktur
☐8 Infeksjonssequele
☐9 Spondylose
☐10 Sequele prolaps kirurgi
☐11 Degenerativ skivesykdom
☐12 Rotarcuff artropati
☐13 Annet ……

B. Reoper. pga (ev. flere kryss)
☐1 Løs prox.protesedel
☐2 Løs distal protesedel
☐3 Løs patellaprotese
☐4 Luksasjon av patella
☐5 Luksasjon (ikke patella)
☐6 Instabilitet
☐7 Aksefeil
☐8 Dyp infeksjon
☐9 Fraktur av bein (nær protesen)
☐10 Smerter
☐11 Slitt eller defekt plastforing
Hvilken……
☐12 Progresjon av artrose
☐13 Annet (f.eks tidl fjernet protese)
……

REOPERASJONSTYPE (ev. flere kryss)
☐1 Bytte el. innsetting av distal komponent
☐2 Bytte el. innsetting av proximal protesedel
☐3 Bytte el. innsetting av hele protesen
☐4 Innsetting av patellakomp.
☐5 Bytte av patellaprotese
☐6 Bytte av plastforing
☐7 Artrodese
☐8 Amputasjon
☐9 Fjernet protesedeler (inkl. sementspacer)
Angi hvilke deler ……..
……
☐10 Bløtdelsdebridement for infisert protese
☐11 Osteosyntese av protesenær fraktur. Angi hvilket ben ……..
☐12 Annet……..

BENTRANSPLANTASJON / BENERSTATNING (ev. flere kryss)

Proximalt	☐0 Nei	☐1 Ja	☐2 Benpakking	☐3 Kjegler (cones)
Distalt	☐0 Nei	☐1 Ja	☐2 Benpakking	☐3 Kjegler (cones)

ANTIBIOTIKAPROFYLAKSE ☐0 Nei ☐1 Ja

	Navn	*Dosering*	*Varighet i timer*
Medikament 1	.....	.....	.....timer
Medikament 2	.....	.....	.....timer

TROMBOSEPROFYLAKSE
☐0 Nei ☐1 Ja: Første dose ☐1 Preoperativt ☐2 Postoperativt
Medikament 1……..Dosering opr.dag……
Dosering videre…….Varighet…….døgn
Medikament 2…….. Dosering……..Varighet…….døgn

FAST TROMBOSEPROFYLAKSE
☐0 Nei ☐1 Ja, type: ……..

FIBRINOLYSEHEMMER
☐0 Nei ☐1 Ja, medikament: …….. Dosering……

DREN ☐0 Nei ☐1 Ja. Antatt varighet ……døgn

OPERASJONSTID (hud til hud) ……minutter

BLODTOMHET ☐0 Nei ☐1 Ja **BLODTOMHETSTID**…… minutter
BLODTOMHET UNDER SEMENTERING ☐0 Nei ☐1 Ja

PEROPERATIV KOMPLIKASJON
☐0 Nei ☐1 Ja,hvilke(n): .....

MINI INVASIV KIRURGI (MIS) ☐0 Nei ☐1 Ja
COMPUTERNAVIGERING (CAOS) ☐0 Nei ☐1 Ja Type:……..
PASIENTTILPASSEDE INSTRUMENTER ☐0 Nei ☐1 Ja Type:……..

ASA KLASSE (se baksiden for definisjon)
☐1 Frisk
☐2 Asymptomatisk tilstand som gir økt risiko
☐3 Symptomatisk sykdom
☐4 Livstruende sykdom
☐5 Moribund

PROTESE KNE (Bruk klistrelapper på baksiden, eller spesifiser nøyaktig)

PROTESETYPE
☐1 Totalprot. m/patella . ☐4 Patellofemoralledd prot.
☐2 Totalprot. u/patella ☐5 Bi-compartmental ☐6 Hengslet protese
☐3 Unicondylær prot ☐ Medial ☐ Lateral ☐7 Annet ……..

FEMURKOMPONENT
Navn/Type/Str / evt. Katalognr……..
ev. katalognummer ……..
Sentral stamme ☐0 Nei ☐1 Ja, ev. lengde ……mm
Sementert stamme ☐0 Nei ☐1 Ja
Metallforing (Wedge) ☐0 Nei ☐1 Ja
Stabilisering ☐0 Nei ☐1 Ja, bakre ☐2 Ja, annen
☐1 Sement med antibiotika – Navn ……
☐2 Sement uten antibiotika – Navn ……
☐3 Usementert

TIBIAKOMPONENT (metallplatå)
Navn/Type/Str / ev. katalognummer ……
Forlenget sentral stamme ☐0 Nei ☐1 Ja, ev. lengde ……mm
Sementert stamme ☐0 Nei ☐1 Ja
Metallforing (Wedge) ☐0 Nei ☐1 Ja
☐1 Sement med antibiotika – Navn ……
☐2 Sement uten antibiotika – Navn ……
☐3 Usementert

TIBIAKOMPONENT (plastkomponent)
Navn/Type/Str / ev. katalognummer……
Tykkelse …….. mm
Stabilisering ☐0 Nei ☐1 Ja, bakre ☐2 Ja, annen

PATELLAKOMPONENT
Navn/Type/Str / ev. katalognummer……
Metallrygg ☐0 Nei ☐1 Ja
☐1 Sement med antibiotika – Navn ……
☐2 Sement uten antibiotika – Navn ……
☐3 Usementert

KORSBÅND

Intakt fremre korsbånd før operasjon	☐0 Nei	☐1 Ja
Intakt fremre korsbånd etter operasjon	☐0 Nei	☐1 Ja
Intakt bakre korsbånd før operasjon	☐0 Nei	☐1 Ja
Intakt bakre korsbånd etter operasjon	☐0 Nei	☐1 Ja

PROTESE ANDRE LEDD (Bruk klistrelapper på baksiden, eller spesifiser nøyaktig)

PROTESETYPE
☐1 Totalprotese ☐2 Hemiprotese ☐3 Enkomponentprotese ☐4 Annet …..

PROKSIMAL KOMPONENT
Navn/Type/Str / ev. katalognummer……
☐1 Sement med antibiotika – Navn ……
☐2 Sement uten antibiotika – Navn ……
☐3 Usementert

DISTAL KOMPONENT
Navn/Type/Str / ev. katalognummer……
☐1 Sement med antibiotika – Navn ……
☐2 Sement uten antibiotika – Navn ……
☐3 Usementert

INTERMEDIÆR KOMPONENT (f.eks. caput humeri)
Navn/Type/Str/Diameter / ev. katalognummer……

Lege .....
Legen som har fylt ut skjemaet (navnet registreres ikke i databasen).

RETTLEDNING KNEPROTESER og andre leddproteser

Registreringen gjelder innsetting, skifting eller fjerning av protese i kne, skuldre og andre ledd med unntak av hofter som har eget skjema. Ett skjema fylles ut for hver operasjon. Pasientens fødselsnummer (11 sifre) og sykehus må være påført. Aktuelle ruter markeres med kryss.
På eget Samtykkeskjema skal pasienten gi samtykke til rapportering til Leddregisteret.

Kommentarer til de enkelte punktene

AKTUELLE OPERASJON
Primæroperasjon: Dette er første totalproteseoperasjon.
Kryss av enten i A eller i B. Kryss av for alle årsakene til operasjonen. Bløtdelsrevisjon for infeksjon skal registreres selv om protesedeler ikke skiftes.

REOPERASJONSTYPE
Fjerning av protesedeler må spesifiseres og føres opp, også fjerning ved infeksjon.

BENTRANSPLANTASJON
Påsmøring av benvev rundt protesen regnes ikke som bentransplantat.

ANTIBIOTIKAPROFYLAKSE
Medikament, dose og varighet av profylaksen skal angis f.eks. slik: Medikament: Keflin, Dosering: 2g x 4, med varighet 4,5 timer.

TROMBOSEPROFYLAKSE
Medikament, dose og antatt varighet av profylaksen skal angis separat for operasjonsdagen og senere. Det skal også oppgis om pasienten står fast på tromboseprofylakse (AlbylE, Marevan, Plavix ol).

FIBRINOLYSEHEMMER
Her føres det på om en benytter blødningsreduserende legemidler i forbindelse med operasjonen (f.eks. Cyklokapron).

PEROPERATIV KOMPLIKASJON
Dersom det foreligger komplikasjon i form av stor blødning, må mengden angis.
Dersom pasienten dør under eller like etter operasjonen, ønsker vi likevel melding om operasjonen.

ASA-KLASSE (ASA=American Society of Anesthesiologists)
ASA-klasse 1: Friske pasienter som røyker mindre enn 5 sigaretter daglig.
ASA-klasse 2: Pasienter med en asymptomatisk tilstand som behandles medikamentelt (f.eks. hypertensjon) eller med kost (f.eks. diabetes mellitus type 2) og ellers friske pasienter som røyker 5 sigaretter eller mer daglig.
ASA-klasse 3: Pasienter med en tilstand som kan gi symptomer, men som holdes under kontroll medikamentelt (f.eks. moderat angina pectoris og mild astma).
ASA-klasse 4: Pasienter med en tilstand som ikke er under kontroll (f.eks. hjertesvikt og astma).
ASA-klasse 5: Moribund/døende pasient

PROTESETYPE
Dersom det er gjort revisjon av totalprotese uten patellakomponent og REOPERASJONSTYPE er **innsetting av patellakomponent,** skal det krysses av for pkt. 1: Totalprotese med patellakomponent (dvs. protesen har nå blitt en totalprotese med patellakomponent). Ved revisjon av unicondylær protese til totalprotese brukes enten pkt. 1 eller 2.

PROTESEKOMPONENTER
Her anføres kommersielle navn, materiale, størrelse og design. Alternativt kan en føre opp protesenavn og katalognummer eller benytte klistrelapp som følger med de fleste protesene. **Denne kan limes på baksiden av skjemaet (vennligst ikke plasser klistrelapper på markeringskryss, som brukes ved scanning av skjema).**
Navnet på sementen som evt. brukes må anføres, f.eks. Palacos R+G. (Bruk helst klistrelapp)
Under femurkomponent skal evt. påsatt **femurstamme** anføres med lengde.
Med **metallforing** under femur- og tibiakomponent menes bruk av en eller flere separate metallkiler (wedges) som erstatning for manglende benstøtte.
Stabilisering er bruk av proteser med stabilisering som kompensasjon for sviktende båndapparat.
Forlenget sentral stamme under tibiakomponent (metallplatå) skal bare anføres ved bruk av en lengre påsatt stamme enn standardkomponenten.

ANDRE LEDD. PROTESETYPE
Ved bruk av hemiprotese med bare en komponent, f.eks. resurfacing i skulder, skrives dette på DISTAL KOMPONENT. Enkomponent-protese i finger/tå, skrives på PROKSIMAL KOMPONENT.

COMPUTERNAVIGERING (CAOS = Computer Aided Orthopaedic Surgery**)**
Angi firmanavn på computersystem.

MINIINVASIV KIRURGI (MIS = Minimally Invasive Surgery**)**
Her menes at kirurgen har brukt kort snitt og at det er brukt spesialinstrument laget for MIS.

PASIENTTILPASSEDE INSTRUMENTER
Her menes kutteblokker eller instrumenter som lages etter MR eller CT bilder tatt av pasienten før operasjonen. Oppgi navn på systemet.

Kopi beholdes til pasientjournalen, originalen sendes Haukeland universitetssjukehus.

Kontaktpersoner vedrørende registreringsskjema er
Seksjonsoverlege Ove Furnes, tlf. 55 97 56 90.
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Overlege Yngvar Krukhaug, kontaktperson (albue/hånd), tlf. 55 97 56 88.
Ortopedisk klinikk, Haukeland universitetssjukehus. Besøksadresse: Møllendalsbakken 11.
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I

CONCISE REPORT

Hip replacement surgery in patients with ankylosing spondylitis

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ABSTRACT

Objectives Although TNF-α inhibitors' striking effect on clinical symptoms have revolutionised the treatment of ankylosing spondylitis (AS), no certain influence on the development of spinal ankylosis and joint destruction has been documented. We wished to investigate whether improved treatment has affected the use of hip arthroplasty surgery.

Methods Using the Norwegian Arthroplasty Register, we selected hip prosthesis procedures performed in patients with AS in 1988–2010 (n=534), and compared the trend in the number of procedures being performed annually in 1988–2002 versus 2003–2010. Patients with osteoarthritis (OA) (n=95094) were used as a control group.

Results The frequency of hip prosthesis surgery increased significantly in both groups up until 2002. In 2003–2010, although not statistically significant (p=0.087), there was a trend towards a reduced frequency in the AS group when compared with the expected continued increase as was seen among patients with OA. Mean age at surgery increased significantly (p<0.001) from 49.9 years to 56.4 years when comparing patients with AS up until and after 2002.

Conclusions TNF-α inhibitors were introduced to patients with AS in Norway in 2000–2003, and our findings suggest that they may have altered the prognosis by inhibiting or slowing large joint arthritis and thus reducing the need for hip replacement surgery.

INTRODUCTION

Of patients with ankylosing spondylitis (AS) 24–36% suffer from hip joint arthritis, and patients with severe clinical and radiological hip involvement are more prone to have severe axial disease.[1] One study showed that after more than 30 years' disease 12–25% of patients had at least one replaced hip.[1] Although the long-term results of total hip replacement in young patients with AS are good,[2] and the prosthesis survival is equivalent to the results in patients with osteoarthritis (OA),[3] hip prostheses have a limited life span, and there is a possibility of revision surgery, which carries a higher morbidity and mortality than primary procedures.[4 5] Consequently, there is a great need for treatment effective in preventing coxarthritis and subsequent need for hip prosthesis surgery. Studies on patients with AS have shown some benefit of sulfasalazine in the treatment of peripheral arthritis,[6 7] but a recent Cochrane review did not find enough evidence to support any benefit from methotrexate.[8] We have not found any studies on the effect of TNF-α inhibitors on peripheral arthritis in AS.

Histopathological investigations have suggested that hip involvement in AS is mainly caused by inflammation of the subchondral bone marrow.[9 10] Whereas AS changes of the spine lead to the formation of new bone, rheumatic inflammation of the hip results in an erosive disease which can potentially destroy the joint.[9 10] It has already been proved that TNF-α inhibitors reduce progression of erosive disease in rheumatoid arthritis,[11] but despite the convincing clinical effect of TNF-α inhibitors on patients with AS,[12] spinal radiographic progression has not been found to be inhibited or decelerated when compared with historical controls.[13] As a replaced hip is considered the most objective proxy for severe end-stage hip involvement,[1] we wished, by investigating the trends in hip replacement surgery in individuals with AS, to study whether the frequency has been affected by the introduction of TNF-α inhibitors in the treatment of this inflammatory rheumatic disease.

PATIENTS AND METHODS

Nearly all patients (98%) receiving a primary arthroplasty of the hip from 1988 until today are registered in the Norwegian Arthroplasty Register.[14 15] Data concerning the diagnosis was derived from the inclusion form on which AS as reason for hip replacement is a separate option. All patients registered in the Norwegian Arthroplasty Register having undergone a primary total hip arthroplasty due to AS from 1988 until 2010 were identified and included. Primary hip replacement procedures in patients with OA were included, and served as a control group. When more than one diagnosis was recorded we determined AS to overrate OA, and each hip was considered a separate case.

Statistical analysis

Descriptive statistics were used for presentation of the patient characteristics. For the analysis of age the student's t test was used, while χ^2 tests were used when analysing gender distribution. We analysed trends in the absolute number of procedures performed in patients with AS and OA. Incidences (patients with AS with hip arthroplasties per 100 000 patients with AS) were not evaluated since we did not have information on the annual number of patients with AS in the Norwegian population during the study period. For statistical analysis we

Table 1 Hip replacement procedures

	Ankylosing spondylitis			Osteoarthritis		
	1988–2002	2003–2010	p Value	1988–2002	2003–2010	p Value
n	360	174		53 782	41 312	
Gender (% men)	76	70	0.14	31	32	<0.001
Mean age (years)	49.9	56.4	<0.001	71.0	70.5	<0.001

used Poisson regression models to test for the trend, and change in trend over the years. A random effect was included in the model to account for overdispersion in the data. SPSS software V.18.0 and the R statistical software package were used for the analyses.

RESULTS

In the years 1988–2010, 534 hip replacement procedures (74% men) were performed due to hip involvement of AS, whereas 95 094 procedures (32% men) were performed due to OA (table 1). The cases were divided into two groups according to the year of surgery (1988–2002 and 2003–2010). The segregation was based on the timing of introduction and significant use of TNF-α inhibitors for AS in Norway.

The frequency of hip prosthesis surgery in both groups increased up until 2002 with a coefficient of 0.028/year for patients with OA ($p<0.001$) (figure 1) and a coefficient of 0.039/year for patients with AS ($p=0.002$) (figure 2). Whereas the number of surgical procedures in the OA group continued to rise significantly ($p<0.001$) with a coefficient of 0.017/year in the years 2003–2010, there was a trend towards a reduced frequency (coefficient of −0.022/year) in the AS group, although the reduction was not statistically significant ($p=0.51$). When comparing the observed falling trend after 2002 to the expected increasing trend during the first period, the difference between the coefficients was −0.061 ($p=0.087$).

When comparing patients with AS before and after 2002, patients operated from 2003 onwards were significantly older (mean age 56.4 years compared with 49.9 years), whereas among patients with OA, no relevant age difference was found.

DISCUSSION

In the present study, there were two major findings: Mean age at surgery among patients with AS increased significantly from 49.9 years to 56.4 years when comparing patients up until and after 2002, and there was a change of trend in the frequency of hip replacement procedures in patients with AS. Up until 2002 the frequency increased ($p=0.002$) in accordance with the general increase in joint replacement surgery. After 2002 however, there was a tendency of a reduced frequency, instead of the rise that would be expected when comparing with the steadily increasing number of hip prosthesis procedures in patients with OA.

A study on time trends in joint replacement surgery in the years 1994–2004 in patients with inflammatory arthritis, of which the majority (86%) suffered from rheumatoid arthritis found a significant decrease during the entire time span, possibly explained by the use of methotrexate assuming a dominant role in the treatment of inflammatory arthritis during the 1980s and 1990s.[16] In contrast, the annual frequency of hip replacement procedures in patients with AS continued to rise significantly until 2002 before the trend turned, suggesting that the change in this group is caused by a later event.

There has been constancy over time in the epidemiology of AS in a Norwegian study[17] and in a study from Minnesota, USA,[18] making it unlikely that the reduced annual frequency of

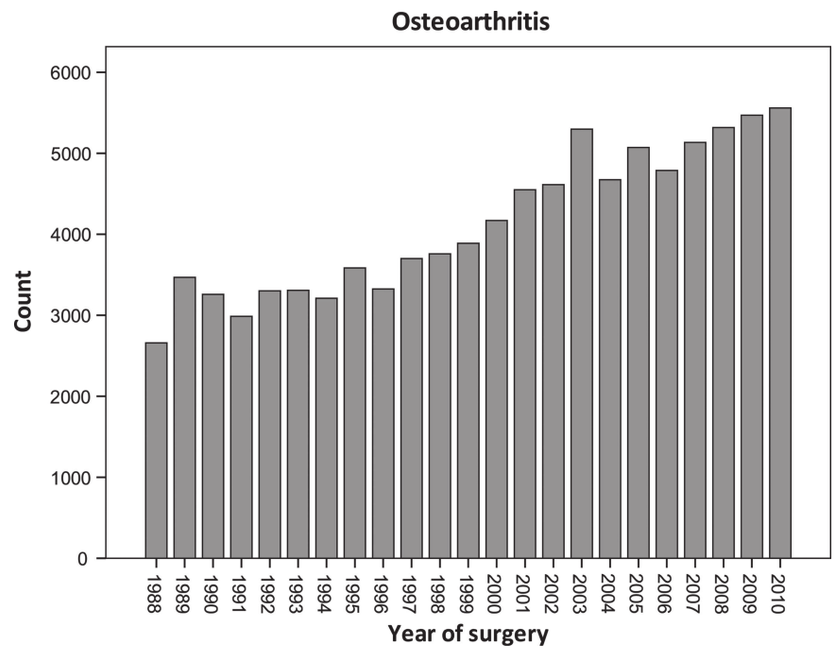

Figure 1 Frequency of hip replacement procedures in patients with osteoarthritis.

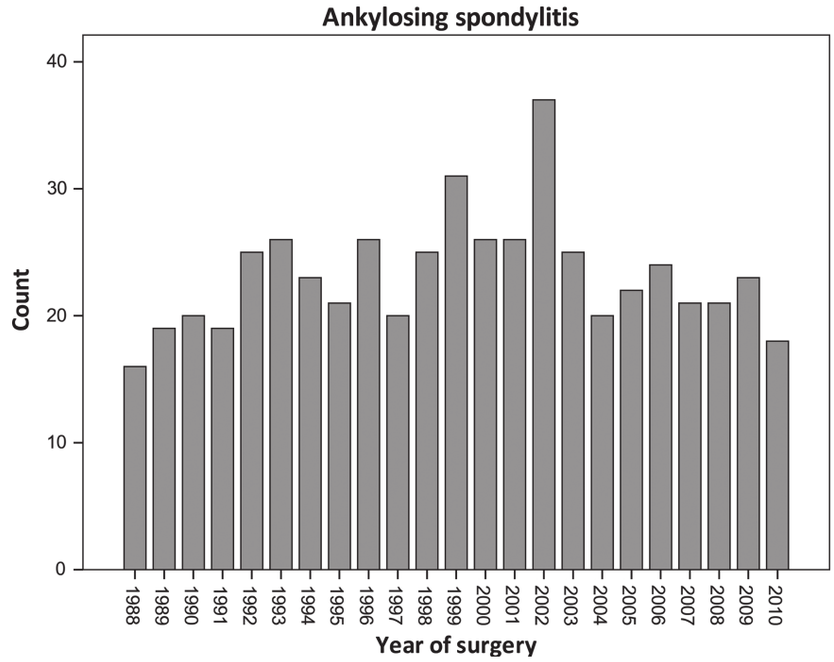

Figure 2 Frequency of hip replacement procedures in patients with ankylosing spondylitis.

surgical procedures can be explained by a reduced prevalence of AS in the Norwegian population.

The inclusion in the register has excellent completeness and coverage nationwide,[14 15] and AS from the register's beginning being an option in the inclusion form assures that the condition is recorded when present. There is no reason to believe that surgeons have become less aware of the diagnosis during this period.

We found that patients with AS since 2003 have become older when hip prosthesis surgery is being performed, indicating that they suffer from the disease for longer before hip replacement is necessary. Although a generally milder disease or onset of disease later in life during our study period cannot be excluded, environmental factors prone to change over time have not been found to influence disease activity,[19] and the age of onset in previous (1935–1989) years has shown little change.[18] In addition to better medication improving arthritis control thus inhibiting or slowing destruction, one would expect an immediate effect of less inflammation resulting in less symptoms and better function in a destructed joint. This might explain to some extent why the candidates for surgery are becoming significantly older, and also why the change of trend in the number of procedures being performed is seen so soon after the introduction of TNF-α inhibitor treatment.

Continuous use of nonsteroidal anti-inflammatory drugs (NSAIDs) has been shown to influence axial radiographic progression in AS,[20] but the inflammation of peripheral joints in AS is structurally different,[9] and we have not found literature evidence supporting that NSAIDs have any effect in preventing their destruction.

So far, it has been unclear whether TNF-α inhibitors have a prognostic effect on AS.[13] However, the observed change in trend in the frequency of hip replacement procedures in patients with AS in the present study indicates a recent change in the course of the disease, suggesting a reduced incidence and/or severity of large joint arthritis which coincides with the initiation of TNF-α inhibitor treatment in Norwegian patients with AS.

Strengths and weaknesses

We have not been able to find that others have quantified the diminishing use of prosthesis surgery among individuals with AS. As a consequence of the relatively low prevalence of AS, the number of patients in the AS group is small, making the visible change in annual frequency less statistically significant, and the results must be interpreted with caution.

CONCLUSION

We observed a significant increase in mean age at the time of surgery (56.4 years to 49.9 years) and a change of trend towards a reduced frequency of hip arthroplasty surgery among patients with AS from 2003 to 2010 which contrasts the increasing trend from 1988 to 2002 in the same diagnostic group, and the increasing trend throughout the period 1988 to 2010 for patients with OA. A possible explanation for these findings is the introduction of TNF-α inhibitors for AS from 2000, which might suggest that TNF-α inhibitors not only improve clinical symptoms, but also inhibit or slow peripheral arthritis in patients with AS.

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Contributors TWN and B-TSF conducted the project planning. TWN, B-TSF, OF, LIH and AKS did the data collection. TWN, B-TSF and SAL performed the statistical analysis. TWN wrote the manuscript, and B-TSF, OF, LIH and AKS contributed to manuscript editing and approval.

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Competing interests None.

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Data sharing statement This article is a register study on data obtained from the Norwegian Arthroplasty Register which does a continuous registration of aspects regarding prosthesis surgery in Norway. Data from this register may by application be considered available for other research projects.

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II

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Reduction in orthopaedic surgery in patients with rheumatoid arthritis: a Norwegian register-based study

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Reduction in orthopaedic surgery in patients with rheumatoid arthritis: a Norwegian register-based study

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Objectives: The disease course of patients with rheumatoid arthritis (RA) has become milder in recent years. In this study we investigated the incidence of orthopaedic surgery in patients with RA.
Method: From the Norwegian Arthroplasty Register we selected joint replacement procedures conducted during the years 1994–2012 (n = 11 337), and from the Norwegian Patient Register we obtained data on synovectomies (n = 4782) and arthrodeses (n = 6022) during 1997–2012. Using Poisson regression we analysed the time trends in the incidence of procedures performed.
Results: There was a significant decrease in the incidence of arthroplasty surgery (coefficient of −0.050 per year) and synovectomies (coefficient of −0.10) and a declining trend of arthrodeses in patients with RA in the study periods. The greatest reduction was found in procedures involving the wrist and hand.
Conclusions: We found a decrease in orthopaedic surgery in patients with RA that continued into the biologic era and throughout the study period. The general increasing trend in the use of synthetic and biological disease-modifying anti-rheumatic drugs (DMARDs) thus coincides with less joint destruction and an improved long-term prognosis of patients with RA.

There has been a growing emphasis on diagnosing and treating rheumatoid arthritis (RA) early and intensively with the aim of preventing disability and reducing mortality, and the disease course has become milder in recent years (1–3). Methotrexate alone or in combination with other disease-modifying anti-rheumatic drugs (DMARDs) has, since its introduction in the late 1970s, assumed a dominant role in the treatment strategy. DMARDs have been shown to prevent joint destruction (4), and methotrexate has been introduced increasingly earlier (5) to achieve adequate disease control. The introduction of biologics in the past decades (1999 in Norway) has further improved the treatment of RA because of their significant impact on disease signs and symptoms as well as their ability to slow radiographic progression of joint damage (6, 7), and has changed the prognosis of patients for whom other treatment modalities are not sufficient.

Joint replacement surgery can be considered an objective proxy for joint destruction, and studying time trends in prosthesis surgery gives valuable information regarding the prognosis of patients with RA. Estimates from previous years show that 25% of patients with RA would undergo total joint replacement within 22 years of disease onset (8), but the results of some studies now indicate a declining incidence of prosthesis surgery among these patients in recent years (9–14). Jämsen et al found a decline in the annual incidence of joint replacement surgery in Finland in the years 1995–2010 (15), and also showed that in the same time period the number of individuals using synthetic and biological DMARDs was increasing. Their study did not consider arthroplasties in joints distal to the elbow or knee, or arthrodeses or synovectomies. In their cohort study of 992 patients with RA, Kievit et al also found an increasing use of DMARDs in the years 1989–2008, and a trend towards a reduced incidence of orthopaedic rheumatic surgery in 2006–2008 (16).

In 2007 our group published a study describing the reduction in orthopaedic surgery among patients with chronic inflammatory joint diseases in Norway (17). The change in treatment mainly represented by methotrexate is thought to be a major contributor to this reduction (18), although it has been argued that the improved outcome in patients with RA is partly a secular trend (19). In the study from 2007, only patients operated on before the year 2005 were included, and any influence of the introduction of biological agents would be uncertain, as their use was limited and of short

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duration. We now wanted to investigate the incidence of orthopaedic surgery among RA patients from 1994/97 to 2012 to address this matter further.

Method

The present study considered arthrodeses, synovectomies, and joint replacement procedures in patients with RA. For arthroplasties, procedures in patients with osteoarthritis (OA) were included for comparison.

Most patients receiving a primary joint arthroplasty in Norway from 1994 until today are registered in the Norwegian Arthroplasty Register. Registration is carried out by the operating surgeon, and although not compulsory, there is a very high degree of registration completeness for the most frequently replaced joints (hip 97%, knee 95%) (20), and a somewhat lower degree for the less common operations (ankle 82%, wrist 52%) (21). Data concerning the diagnosis were derived from the inclusion form on which both OA and RA are separate options. When more than one diagnosis was recorded, we determined RA to overrate OA, and each joint was considered a separate case, also when concerned with joints of the hands and feet. In patients with RA, an average of 3.3 finger joints and 1.3 toe joints were replaced per patient, whereas multiple joint replacements were less common among patients with OA, with an average per patient of 1.2 finger joints and 1.0 toe joints.

The Norwegian Patient Register was established in 1997, and receives information from the hospitals' electronic administrative patient records. Using ICD-9 and ICD-10, patients with RA were identified and information regarding all synovectomies and arthrodeses in these patients could be extracted. The location of a synovectomy or an arthrodesis was given in the surgical procedure code, and unlike the arthroplasty register, where each joint is registered separately, procedures of the ankle and foot were grouped together, as were procedures of the wrist and hand. As for arthroplasties, each procedure was considered a separate case.

Statistical analysis

Descriptive statistics were used for presentation of the patient characteristics. For the analysis of age, the Student's t-test was used, while χ^2 were used when analysing gender distribution. We analysed trends in the annual incidence, that is the number of operated joints per 100 000 inhabitants in respective years, as we did not have reliable figures for the number of Norwegian patients with RA. Some analyses were also performed in different age categories (0–49, 50–59, 60–69, 70–79, and > 80 years). Population figures were obtained from Statistics Norway (available at www.ssb.no/english).

Poisson regression analysis was used to analyse trends in the incidence of the different procedures and in the different patient subgroups. The significance level was set to 5%.

Statistical analyses were performed in SPSS version 22, 2013 and the statistical program R version 3.0.2 (25 September 2013).

Results

In the study period 1994–2012, 11 337 joint replacement procedures were performed in 6394 patients with RA whereas 135 109 procedures were performed in 106 008 patients with OA. In the years 1997–2012, 4782 synovectomies and 6022 arthrodeses were performed in patients suffering from RA.

Age and sex at surgery

For arthroplasty procedures, the mean age at surgery was significantly lower among patients with RA (63 years) than among patients with OA (70 years) ($p < 0.001$). There were more women than men in

Table 1. Number of procedures and age at surgery of different joints in patients with rheumatoid arthritis (RA).

	Joint replacement		Arthrodesis		Synovectomy	
	n	Age (years)	n	Age (years)	n	Age (years)
Shoulder	855	64 (13)	12	61 (12)	433	58 (14)
Elbow	609	62 (13)	16	63 (11)	379	55 (14)
Wrist/carpus/finger*	134/99/2619	55 (13)/62 (14)/61 (12)	2191	61 (12)	1867	57 (14)
Hip	3045	64 (14)	21	74 (11)	14	52 (17)
Knee	2925	66 (12)	30	61 (16)	1133	52 (17)
Ankle/foot*	246/805	58 (14)/61 (12)	3743	62 (12)	948	54 (14)
Total†	11 337	63 (13)	6022	62 (12)	4782	55 (15)
Women/men	9330/2007		4983/1039		3546/1236	

Age given as mean (standard deviation).
*For the joint replacements, separate numbers for ankle and toes as well as wrist, carpus, and fingers were registered, whereas these were grouped together for arthrodeses and synovectomies.
†Some reports did not specify which joint was operated on, hence the total number may be larger than the sum.

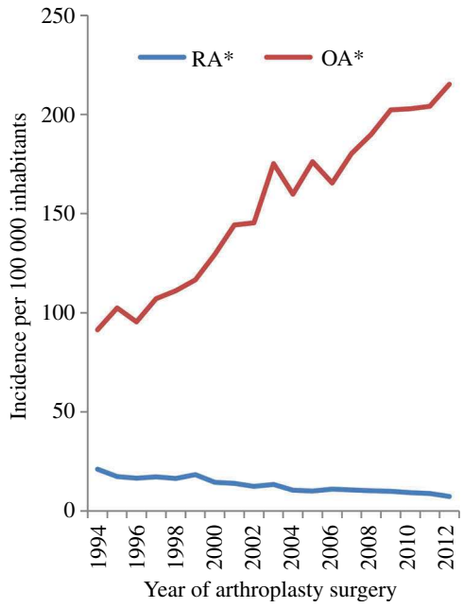

Figure 1. Incidence of arthroplasty surgery in patients with rheumatoid arthritis (RA) vs. osteoarthritis (OA). *p < 0.001.

both groups but the female count among RA patients (82%) was higher (p < 0.001) than among OA patients (68%). RA patients were younger (55 years) at synovectomy than at arthrodesis (62 years), and oldest at prosthesis surgery (63 years). We found that 74% of synovectomies and 83% of arthrodeses were performed in women. Age at surgery for each separate joint is shown in Table 1.

Distribution of procedures in different joints

Fingers, knees, and hips comprised the bulk of replaced joints, whereas arthrodeses above all were performed in the wrist/hand and ankle/foot. Synovectomies were infrequent in the hip, but otherwise performed in all joints, and most commonly in the wrist/hand. The total spread is presented in Table 1.

Arthroplasties

The incidence of prosthesis surgery in RA patients declined during the entire study period, with a coefficient of –0.050 (p < 0.001), whereas the incidence in OA patients increased significantly with a coefficient of 0.047 (p < 0.001) (Figure 1).

We also found that the mean age at surgery in patients with RA was significantly (p < 0.001) higher in 2012 (66 years) than in 1994 (62 years). Among patients with OA, the mean age at surgery in 2012 was somewhat lower than in 1994 (69 years vs. 71 years, p < 0.001). The reduction in arthroplasty surgery among RA patients

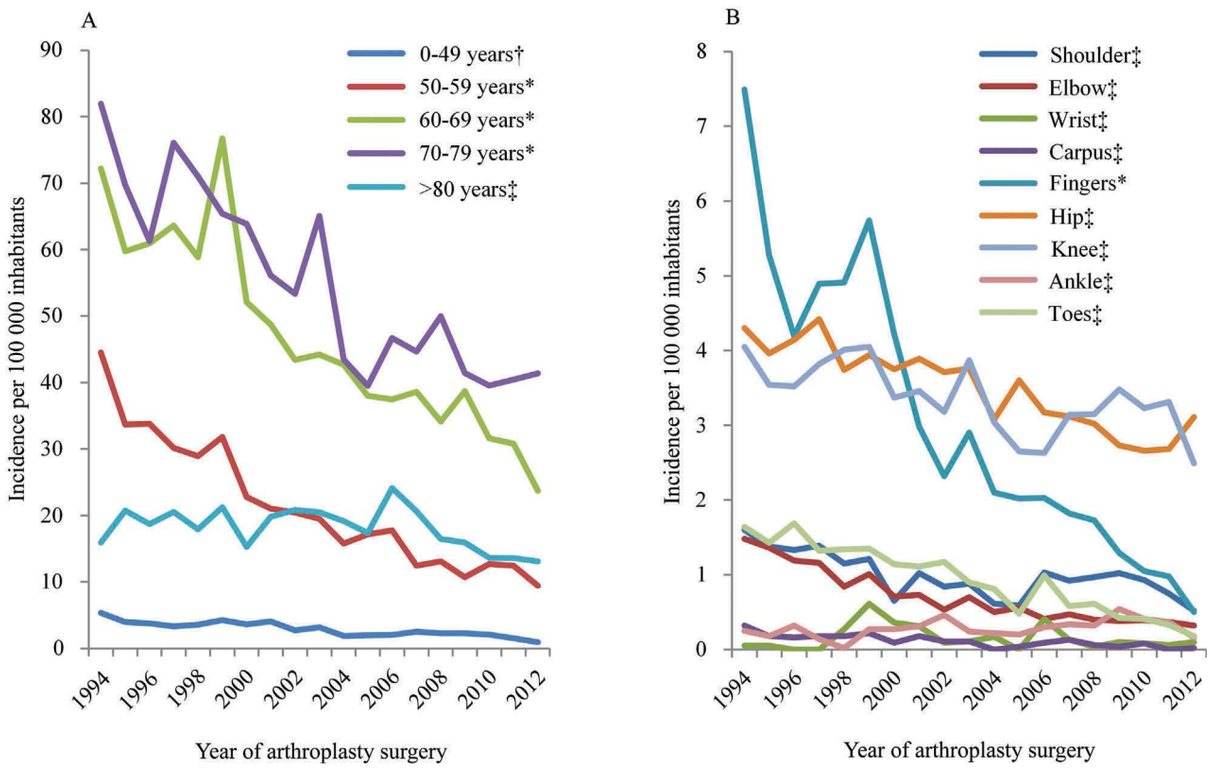

Figure 2. Joint replacement surgery (A) in different age groups and (B) in different joints in patients with rheumatoid arthritis (RA). *p < 0.001, †p < 0.05, ‡p > 0.05.

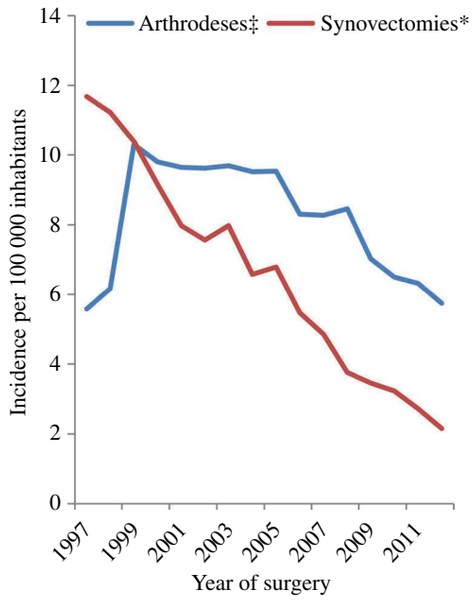

Figure 3. Incidence of arthrodeses and synovectomies in patients with rheumatoid arthritis (RA). *p < 0.001, ‡p > 0.05.

was steepest among patients between 50 and 59 years of age (coefficient of –0.079, p < 0.001) but significant in all age groups below 80 (0–49 years: –0.059, p < 0.05; 60–69 years: –0.051, p < 0.001; and 70–79 years: –0.040, p < 0.001). For patients aged > 80 years, the reduction coefficient of –0.013 was not significant (Figure 2A).

In Figure 2B the incidence of prosthesis surgery in each joint is presented separately, showing that while finger prostheses were previously the most frequently performed, their incidence has declined markedly from 7.5 to 0.5 per 100 000 inhabitants with a coefficient of –0.11 (p < 0.001). The reduced number of toe joint prostheses was borderline significant (p = 0.057), while the evident declining trends for shoulder, elbow, and hip were not statistically significant.

Synovectomies

The incidence of synovectomies declined markedly (p < 0.001) during the entire study period from 11.7 per 100 000 inhabitants in 1997 to 2.2 per 100 000 inhabitants in 2012 (Figure 3).

Synovectomies of the wrist and hand had the greatest reduction from 5.4 to 1.1 procedures per 100 000 inhabitants (coefficient of –0.12, p < 0.001) but the coefficient was also negative for all other joints but the hip, and significant in knee joints (p < 0.05), and borderline

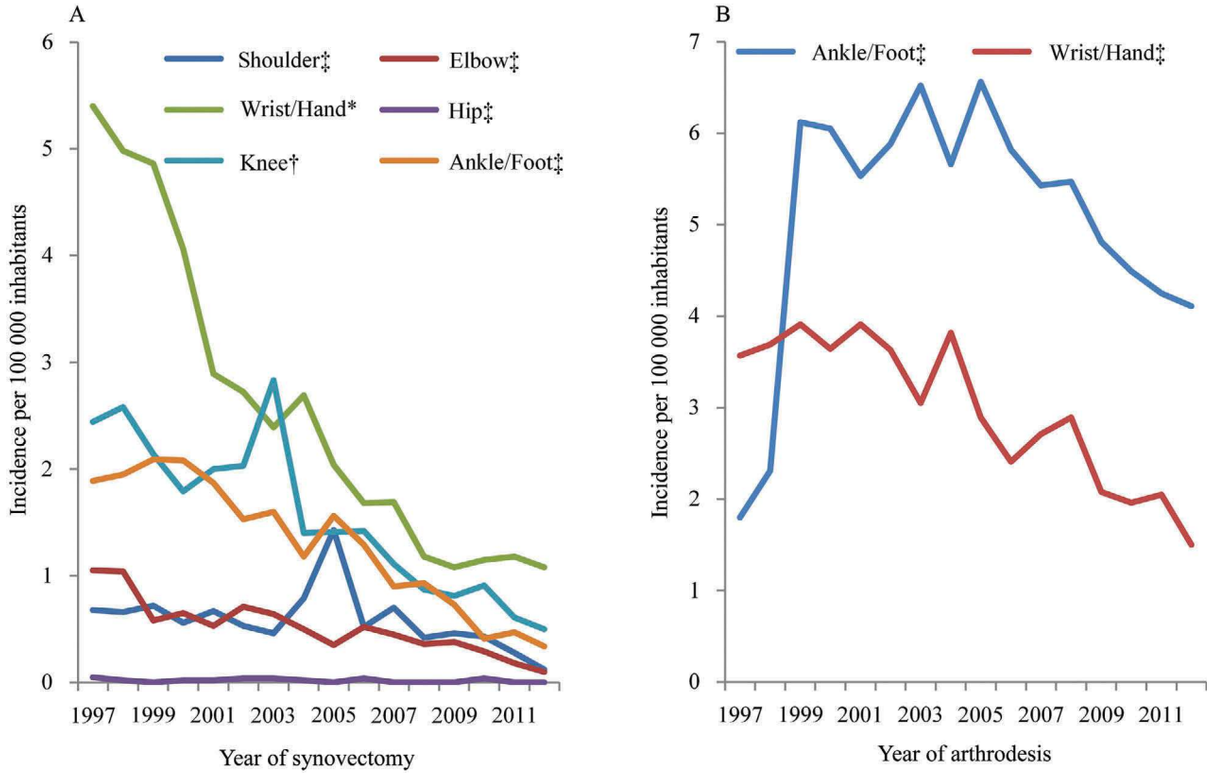

Figure 4. (A) Synovectomies and (B) arthrodeses for different joints in patients with rheumatoid arthritis (RA). The incidences of arthrodeses performed in the shoulder, elbow, hip, and knee were so low that they were excluded from the figure. Absolute numbers can be found in Table 1. *p < 0.001, †p < 0.05, ‡p > 0.05.

significant in ankle/foot joints (p = 0.052) (Figure 4A). The decrease was most evident (coefficient of –0,14, p = 0.001) among the youngest patients (age < 50 years) but also statistically significant (p < 0.05) in patients aged 50–59 years.

Arthrodeses

There was an increase in arthrodeses of the ankle and foot from 1997 to 1999 (Figure 4B) causing the total number of arthrodeses to increase in these years. The incidence has since been declining from 10.3 to 5.7 procedures per 100 000 inhabitants (coefficient of –0.042, p = 0.067) (Figure 3). When performing subgroup analyses for each joint, no significant changes were found, but for the subgroup of wrist and hand the incidence declined with a coefficient of –0.05 (p = 0.11) during the entire study period from 1997 to 2012. No decrease was seen in the eldest patient group (≥ 80 years), and for the other age groups the decline was not statistically significant.

Discussion

This study's main finding was a significant decrease in joint replacement surgery and synovectomies in Norwegian patients with RA in the time period 1994/97–2012. There was an increasing number of arthrodeses of the ankle and foot during the first 2 years from 1997 to 1999, and although the reduction in arthrodeses since 1999 was not statistically significant, there was a strong declining trend (p = 0.067).

The decreasing number of joint replacements contradicts the general increase in prosthesis surgery as seen in patients with OA. Reasons for the increasing number of arthroplasties for OA in recent years may be the increased proportion of elderly or overweight persons in the population, and a greater acceptance in general for operating on patients of advanced age and with co-morbidities. Increasing surgical capacity might also be a contributory factor. These factors should also affect the use of prosthesis surgery in patients with RA, which is nevertheless diminishing.

Studies of other cohorts have shown a similar decrease in the number of joint replacements (15–17), and the study of this large volume of material from the Norwegian Arthroplasty Register confirms that the trend continues into the era of biologics. When performing subgroup analyses, the decrease is not evident among patients above the age of 80. In addition to the increased acceptance for operating on elderly patients, an explanation for this may be that joint destruction in this age group had, to a greater extent, already occurred before the improvement in treatment of patients with RA. For arthroplasty surgery there is a significant decrease in the incidence of procedures in patients below 80 years of age. Although there is a negative coefficient in these age groups for the other procedures, the decline is statistically significant only in patients below 60 years of age for synovectomies, and for no age groups with regard to arthrodeses, probably because of the reduced number of study subjects obtained when dividing the groups.

In a review conducted in 2004, Uhlig and Kvien reported that the incidence of RA had generally declined in recent decades (22). Although this might also reflect changing methodology in classification, a true reduced incidence of RA would be expected to affect the incidence of rheumatic orthopaedic surgery. However, as this decline was found to have occurred mainly in the 1970s and early 1980s, it is unlikely to explain all of the steadily continuing decrease in surgical procedures.

We also found a significant increase in mean age at prosthesis surgery in patients with RA from 62 years in 1994 to 66 years in 2012. This might indicate that patients suffer from their disease for longer before needing joint replacement, probably because of better arthritis control inhibiting joint destruction or because of reduced inflammation resulting in less pain and improved function in a destructed joint. It can also be explained by epidemiological changes towards an older population causing the age at onset of RA to increase (19), or by our finding that the decrease in the number of procedures is not evident among the eldest patients.

Hand function is of utmost importance, and while finger joints, followed by hips and knees, were previously the most frequently replaced, these procedures have seen the greatest reduction, with an incidence of 0.5 per 100 000 inhabitants in 2012 compared to 7.5 per 100 000 inhabitants in 1994. The incidence of synovectomies and arthrodeses in the wrist and hand also declined markedly. In a recent study by Nikiphorou et al on an inception cohort of RA patients in the UK, a similarly decreased incidence of intermediate surgery (joint replacements of hands and feet as well as synovectomies and arthrodeses) was found whereas major surgery (joint replacements of the hip, knee, shoulder, and elbow) remained constant (23). The authors discuss whether this could be attributed to a different mechanism and/or a different response to treatment in larger joints. Another probable explanation discussed is that the population is ageing, with the consequent increased prevalence of OA. Increased body weight among RA patients as well as among the general population might also be relevant. The relationship between body weight and joint destruction is complex, but Shourt et al found an increased incidence of joint surgery, and particularly knee surgery, in obese RA patients (24). Our data similarly provided no evidence for a decrease in knee joint replacements.

Documented good results for new reverse prostheses of shoulder joints might have made surgeons more eager to perform this procedure, and rheumatologists more prone to recommend surgery to their patients. However, prosthesis of the elbow is a typical RA procedure, and although not strictly statistically significant (p = 0.096), there is a

declining trend for this procedure, with a coefficient of –0.09 that equals the trend for toe joint prostheses. Thus, in our study as well as that of Nikiphorou et al, the most RA-specific procedures declined the most, indicating a true change in prognosis for RA patients.

The finding of arthrodesis procedures increasing from 1997 to 1999 before declining might be related to the temporary dip in ankle replacements in Norway in 1997 and 1998 (25). In 1997/98 the Norwegian Thompson Parkridge Richards (TPR) ankle prosthesis, the most popular ankle prosthesis in Norway, stopped being produced, and more patients may in these years have had an arthrodesis performed instead. Using orthopaedic surgery as a surrogate marker for joint destruction, our results are consistent with other studies finding reduced progression in radiographic damage and functional disability (18).

The incidence of orthopaedic surgery was calculated from two large registers, and as with all register studies, some miscoding must be expected. Nevertheless, there is no reason to believe that the degree of perfection should have changed during the study period, or that the completeness of the data should have deteriorated. For arthroplasties of the hip and knee, the data completeness was confirmed to be steadily high for the years 2008–2012 in the 2014 annual report from the Norwegian Arthroplasty Register (20), compared to the years 1999–2002 (21). The data completeness of the more uncommon arthroplasty procedures such as the ankle (82%) and wrist (52%) have not been reported since 2006, and might have improved in later years following greater awareness among surgeons. If so, that would make a declining incidence less evident.

RA has become a more benign disease in later years (1, 16), and this has been postulated to be partly a secular trend (19). By contrast, Finckh et al found that, when adjusting for DMARD use, steroid use, and baseline predictors, the improvement in patient outcome was attributable to more effective anti-rheumatic treatment (18). As the decline in orthopaedic surgery in patients with RA is already evident from 1994, before the introduction of biological agents, it is probably mainly attributable to the introduction of methotrexate in the treatment of this inflammatory disease (26). Tumour necrosis factor (TNF)-α inhibitors has been shown to prevent joint destruction and radiographic damage, and their use should thereby induce a reduction in the need for orthopaedic surgery among patients with RA. Theoretically, we would expect that at some point after the introduction of methotrexate, the incidence of joint replacement surgery should stabilize at a new level, and that a further decrease would be attributable to the introduction of TNF-α inhibitors, but it is difficult to predict when this would occur, especially as RA is now being treated earlier and more aggressively with higher doses of methotrexate (27). It is also among this study's limitations that we can only report the general use of orthopaedic surgery in Norway, and therefore cannot analyse outcomes of individual patients receiving different treatment, and further studies are required to more specifically evaluate what impact biological treatment has had on the need for rheumatic orthopaedic surgery. As rheumatic surgery is a late outcome of RA, a time delay between change in treatment and change in incidence must be expected. Later studies might give results with higher significance.

Conclusions

The reduction in rheumatic surgery reported by a few previous authors is confirmed in this analysis of a large amount of material from the Norwegian Arthroplasty Register and the Norwegian Patient Register. The trend seen in earlier time periods is found to continue into the biologic era and throughout the study period from 1994/97 to 2012. The general increasing trend in the use of synthetic and biologic DMARDs thus coincides with less joint destruction and an improved long-term prognosis of patients with RA.

Acknowledgements

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Predictors for orthopaedic surgery in patients with rheumatoid arthritis: results from a retrospective cohort study of 1010 patients diagnosed from 1972 to 2009 and followed up until 2015

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Predictors for orthopaedic surgery in patients with rheumatoid arthritis: results from a retrospective cohort study of 1010 patients diagnosed from 1972 to 2009 and followed up until 2015

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Objectives: To investigate how patient characteristics, time of diagnosis, and treatment affect the need for orthopaedic surgery in patients with rheumatoid arthritis (RA).
Method: We reviewed the medical history of 1544 patients diagnosed with RA at Haukeland University Hospital in Bergen, Norway, from 1972 to 2009, of whom 1010 (mean age 57 years, 69% women) were included in the present study. Relevant orthopaedic procedures were obtained from the Norwegian Arthoplasty Register and the hospital's administrative patient records. In total, 693 procedures (joint synovectomies 22%, arthrodeses 21%, prostheses 41%, and forefoot procedures 12%) were performed in 315 patients. Survival analyses were completed to evaluate the impact of different factors such as age, gender, radiographic changes, and year of diagnosis, on the risk of undergoing surgery.
Results: Patients diagnosed in 1972–1985 and 1986–1998 had a relative risk of undergoing surgery of 2.4 and 2.2 ($p < 0.001$), respectively, compared to patients diagnosed in 1999–2009. Radiographic changes at diagnosis and female gender were also significant risk factors. Anti-rheumatic medication was significantly different in the three time periods.
Conclusion: Patients with a diagnosis in the early years had a greatly increased risk of having orthopaedic surgery performed. This is probably due to the year of diagnosis being a proxy for the type and intensity of medical treatment.

Rheumatoid arthritis (RA) causes pain, swelling, and erosions in affected joints. Medical treatment in the form of classical synthetic disease-modifying anti-rheumatic drugs (DMARDs) or newer biological treatment has been introduced increasingly earlier to achieve disease control, and many believe this to be the reason why the disease course of patients with RA has become milder in recent years (1, 2). Surgery still comprises a necessary part of treating these patients, when medication fails to prevent joint destruction. Orthopaedic corrective procedures are considered a reliable and objective proxy for a destroyed joint, and are an important outcome measure in RA (3). Studying time trends in orthopaedic surgery thus gives valuable information regarding the prognosis of RA patients.

In the past, estimates have shown that 25% of patients with RA would undergo joint replacement during the course of the disease (4), but the results of later studies indicate a declining incidence of prosthesis surgery (5–9). In 2015, our group published a study investigating the incidence of orthopaedic surgery in Norwegian patients with RA from 1994 to 2012, and found a significant decrease in performed procedures (10). As seen in other studies, this decline coincided with the increasing use of synthetic and biological DMARDs (11–13), and in our study continued into the biological era and throughout the study period. That study described only the general use of orthopaedic surgery in Norway, and therefore could not give information on the outcomes of individual patients with diverse patient characteristics receiving different treatment.

In 1998, Wolfe and Zwillich published a large study on the long-term outcomes of RA, and found that variables that indicated disease activity and severity, such as erythrocyte sedimentation rate (ESR), predicted later joint replacement (4). In a Swedish study on 183 RA patients with onset of disease in 1985–1989, the Health Assessment Questionnaire score, C-reactive protein (CRP), and ESR at disease onset, and radiographic changes in small joints after 1 year were associated with an increased risk of undergoing arthroplasty surgery of large joints (14). Concerning treatment, findings from Moura et al (15) and

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Widdifield et al (16) suggest that longer exposure to DMARDs soon after RA diagnosis is associated with longer time to joint replacement surgery.

Using Haukeland University Hospital's extensive administrative patient system, we now wished to investigate how patient characteristics, treatment, and year of diagnosis affect the need for surgical procedures in Norwegian patients diagnosed with RA in the years 1972–2009, and whether this has changed since the description of earlier cohorts.

Method

Our data originate from Haukeland University Hospital, which delivers specialist care to approximately 500 000 inhabitants in western Norway. As only two private practising rheumatologists operate in this area, the great majority of patients with rheumatic disease are cared for by the hospital's Department of Rheumatology. In general, patients are referred at the time of suspected inflammatory rheumatic disease, and a random selection of these patients is likely to be representative of patients in the region. Some patients with stable disease are later managed by their general practitioner, but most continue to be followed until death or inactive disease.

From the hospital's administrative patient records, we have data available from 1972 to the present. A search on disease codes for RA using International Classification of Diseases (ICD) revisions 8, 9, and 10 detected 6318 unique patients from 1972 to 2014. As most patients with RA are in specialist care for several years after diagnosis, we excluded patients with four or fewer hospital contacts, assuming that these patients were miscoded, initially wrongly diagnosed, or followed up at a different institution. This left us with 3053 patients. We chose to exclude patients with their first encounter later than 2009 to ensure that all patients were observed for at least 6 years, unless diseased, and selected our study subjects from the remaining 2679 patients aged 16 years or older at diagnosis.

The selection process is described in Figure 1. Each medical record was reviewed for the following information: weight, height, affected joints within 2 years of diagnosis, whether the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for RA were fulfilled, serological status, ESR, and CRP. As the medical records did not contain radiographic images, the radiologist's interpretation of these as normal or consistent with arthritis or osteoarthritis was recorded. Medication used in the first year and during the course of the disease was also registered. Supplementary data were taken from the Norwegian Arthritis Registry (http://www.norartritt.no) for patients in this register.

Patient characteristics

During the study period, there has been a great change in available medication and intensity of follow-up, and we wished to investigate the outcomes of patients diagnosed in different periods. As methotrexate was introduced to our patient group in 1986, and biological treatment in the form of tumour necrosis factor-α inhibitors in 1999, we split the group into three, depending on diagnosis in different treatment eras: time period 1 from 1972 to 1985, time period 2 from 1986 to 1998, and time

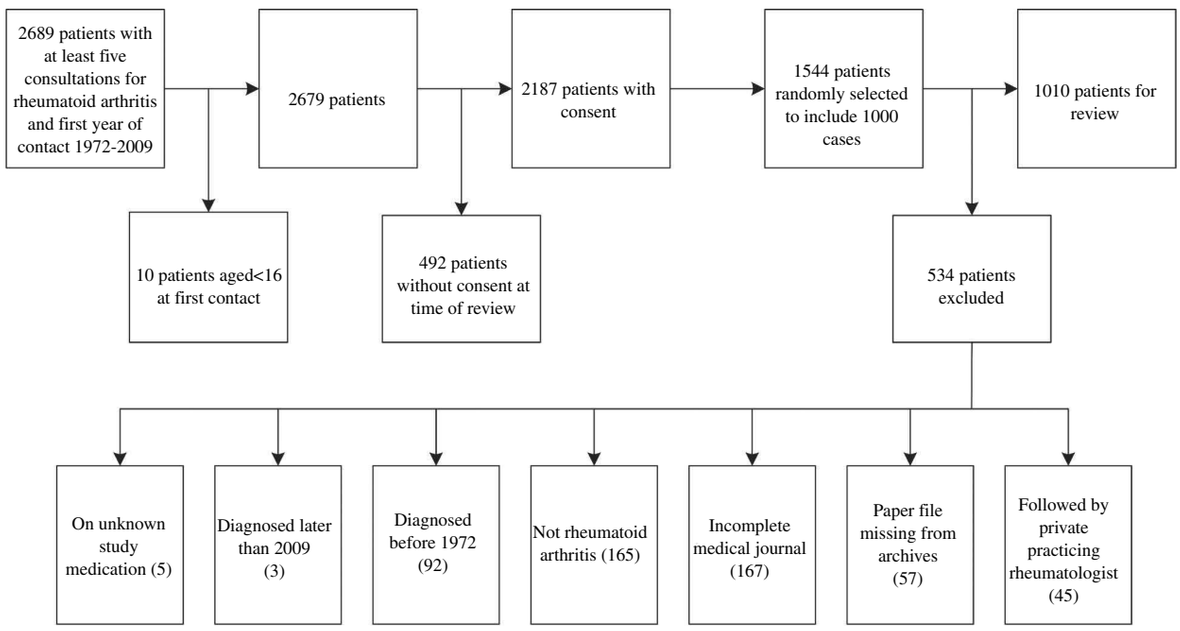


Figure 1. Selection process.

period 3 from 1999 to 2009. Patient characteristics for each group and in total are described in Table 1. Treatments used in the first year and during the course of the disease are presented in Figure 2.

In the years 1986–1998, more patients aged 70 years or above were prescribed methotrexate in the first year of the disease than patients younger than 70 years (37% vs 22%, p = 0.01). In 1999–2009, receiving methotrexate in the first year of the disease seemed to be more common in patients aged below 70 years, but this was not statistically significant (67% vs 58%, p = 0.062). The proportion of patients receiving methotrexate in the first year of the disease increased from 6.3% in 1986 to 48% in 1999 and to 78% in 2009. In 2009, there was no significant difference in prescription rates between older and younger patients.

Surgical procedures

For the selected 1010 patients, information on orthopaedic surgery was obtained from the Norwegian Arthroplasty Register (NAR) and the hospital's administrative patient records. The NAR was established in 1987, initially as a register of total hip replacements, but since 1994 it has been a register of all artificial joints in the Norwegian population. Haukeland University Hospital's administrative patient system has registered all procedures performed since 1972, and the data from NAR gave extra security for completeness of data in the years since the register's establishment. The archives of two other local hospitals which up until the early 1990s performed some surgery in this patient group were also investigated. We searched for joint synovectomies, arthrodesis, and prosthesis procedures using the coding systems NCSP (NOMESCO Classification of Surgical Procedures) and SIFF (Norwegian Institute of Public Health). When excluding surgery conducted earlier than 1 year before diagnosis, we found 693 procedures performed in 315 patients (31%). The procedures performed within 1 year before diagnosis were counted as performed at diagnosis since we had reason to assume an association between surgery and diagnosis.

Five events per 100 patient-years occurred during the whole study period. Forty-one per cent of procedures were arthroplasties, 21% were arthrodeses, 22% were joint synovectomies, and 14% were combined procedures, of which forefoot procedures were the most frequent. The distribution of different procedures in diverse joints is described in Table 2. The areas most frequently operated on were the ankle/foot and the wrist/hand, on which, respectively, 26% and 23% of procedures were performed. Eleven per cent of the 1010 patients had undergone one or more surgical procedure on the hips, 10% ankle or foot surgery, 9.1% hand or wrist surgery, and 8.5% knee surgery, whereas 2.8% and 2.5%, respectively, had undergone shoulder and elbow surgery.

The main outcome of interest was the time from RA diagnosis to the first orthopaedic procedure. The impact of patient characteristics such as age, gender, body mass index (BMI), whether the diagnostic criteria were fulfilled, level of inflammatory parameters during the first 2 years of disease, number and type of affected joints, and radiographic findings at diagnosis on the risk of undergoing surgery was investigated.

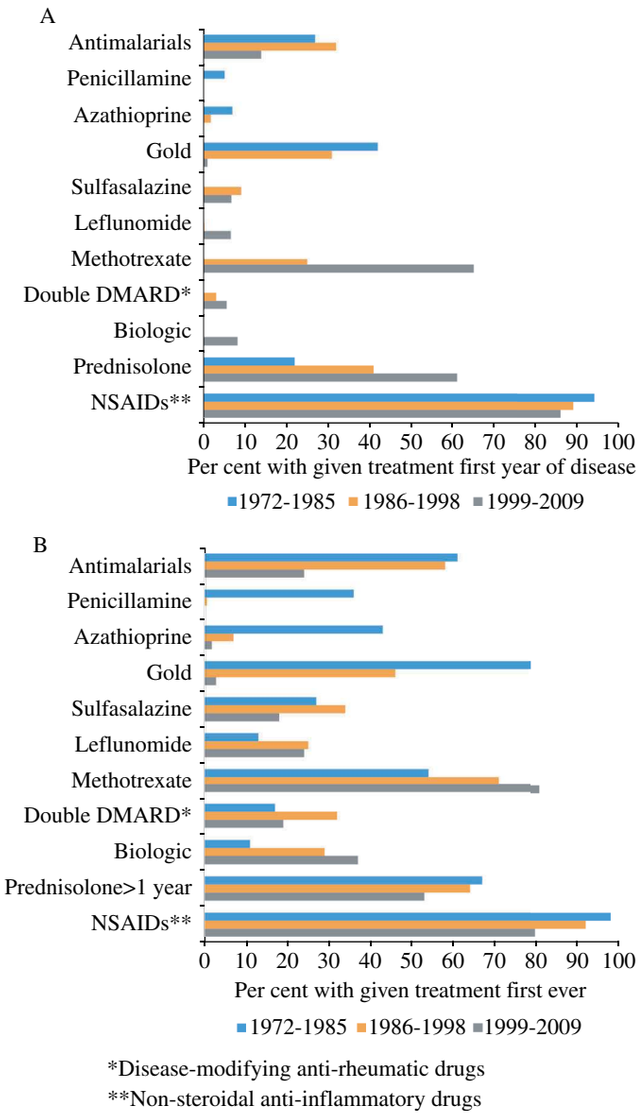
Statistical analyses

Descriptive statistics were used for the presentation of patient characteristics. The unpaired t-test was used for

Table 1. Characteristics in each time period and in total.

	1972–1985 (n = 154)	1986–1998 (n = 315)	1999–2009 (n = 541)	Total (n = 1010)	p
Observation time (years), mean ± SD	21 ± 10	17 ± 6.2	9.7 ± 3.2	14 ± 7.3	
Age (years), mean ± SD	57 ± 12	57 ± 16	58 ± 16	57 ± 15	> 0.4
Gender (% female)	73	70	68	69	0.41
Fulfilled ACR/EULAR criteria (%)*	84	84	86	85	0.74
> 10 joints affected within first 2 years (%)	63	64	52	57	0.001
Rheumatoid factor positive (%)†	71	68	59	63	0.004
ESR ≥ 60 mm/h within first 2 years (%)‡	44	40	28	34	< 0.001
Radiographic arthritis initially (%)§	43	30	17	25	< 0.001
Arthrodesis during disease course (%)	22	12	3.1	8.9	< 0.001
Prosthesis during disease course (%)	31	28	11	19	< 0.001
Synovectomy during disease course (%)	22	14	3.7	9.6	< 0.001
Combined procedure during disease course (%)	20	8.9	0.7	6.1	< 0.001

*2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for rheumatoid arthritis.
†Among available (1006).
‡Among available (1009).
§Percentage among patients with initial radiographic examination (922 in total).
ESR, erythrocyte sedimentation rate.



*Disease-modifying anti-rheumatic drugs
**Non-steroidal anti-inflammatory drugs

Figure 2. Percentage of patients with the given treatment in each time period: (A) first year of disease; (B) ever. Because of the low numbers, cyclosporine and triple synthetic disease-modifying anti-rheumatic drugs were excluded from the figure.

continuous variables and the chi-squared test for categorical data. Person-time was accumulated from RA diagnosis until the first occurrence of orthopaedic surgery, death, or the end of the study period (31 December 2015). Cumulative incidence rates were calculated for the entire study period as the number of events per 100 patient-years. As follow-up duration was different for individual patients, the impact of each factor on the risk of undergoing surgery was analysed using Kaplan–Meier plots and log-rank analyses for significance. Where a statistically significant difference was found, further analyses using univariate and multivariate Cox proportional hazards regression models were performed. Unless otherwise stated, analyses included all subjects and the outcome was the first occurrence of arthroplasty, arthrodesis, or synovectomy.

When observing the Kaplan–Meier plot of risk of surgery according to time of diagnosis, we saw that patients diagnosed in 1986–2009 had more surgery performed in the early years of disease compared to patients diagnosed in 1972–1985. We therefore supplemented the analysis with Kaplan–Meier analyses of events occurring, excluding the first 4 years.

To account for the increasing use of arthroplasty surgery for osteoarthritis (10), we also performed analyses using orthopaedic surgery exclusive of arthroplasty surgery of the hip and knee as outcome, to look only at the most RA-specific procedures. As others have found a reduction in procedures in the hands and feet, but not in large joint prosthesis surgery (12), we included separate analyses for hip and knee replacements.

We also performed subanalyses of factors affecting the risk of synovectomy, arthrodesis, and prosthesis separately.

In additional analyses using any procedure as outcome, we used a propensity score model to control for

Table 2. Type and localization of surgical interventions.

Procedure	Joint area	No.	% of total
Arthroplasties	Shoulder	20	2.9
	Elbow	9	1.3
	Wrist	4	0.6
	Fingers	8	1.2
	Hip	139	20
	Knee	93	13
	Ankle	3	0.4
	Foot	4	0.6
	Other/unknown	3	0.4
Synovectomies	Shoulder	17	2.5
	Elbow	21	3.0
	Wrist/hand	81	12
	Knee	27	3.9
	Ankle/foot	5	0.7
Arthrodeses	Wrist/hand	50	7.2
	Ankle	2	0.3
	Foot	82	12
	Other/unknown	10	1.4
Combined	Ankle	2	0.3
	Forefoot	81	12
	Hand	13	1.9
Other		19	2.7
Total		693	100

systematic differences and imbalance in the measured covariates. The propensity score is the probability of having a certain treatment conditioned on observed baseline characteristics. Propensity score models aim to perform as a randomized clinical trial (RCT). Instead of using regression adjustment, as in a Cox model, to adjust for differences in baseline characteristics, we use the propensity score model to eliminate the effects of possible known confounders (17). In this study, we used age, gender, radiographic changes at diagnosis, numbers of joints affected, fulfilment of the 2010 ACR/EULAR classification criteria for RA, and serological status as covariates describing the three time periods. These covariates are all factors that affect the treatment assignment. The analyses were performed pairwise.

Statistical analyses were performed in SPSS versions 22 and 23, and in R software version 3.3.0. The level for statistical significance was set to $p < 0.05$.

The study was approved by the regional committee for medical and health research ethics (2014/1923/REC West).

Results

The factor with the greatest impact on the risk of a surgical procedure during the course of the disease was the year of diagnosis. The effect of different time periods of diagnosis on the risk of orthopaedic surgery is shown in Figure 3. Patients diagnosed in 1972–1985 and 1986–1998 had a relative risk (RR) of surgery of 2.4 and 2.2 ($p < 0.001$), respectively, compared to patients diagnosed in 1999–2009 (Table 3).

Female gender and radiographic changes at diagnosis were also significant risk factors (Table 3). No significant effects of number or type of affected joints, rheumatoid factor, or anti-cyclic citrullinated peptide (anti-CCP) positivity, initial level of inflammatory parameters, or whether the diagnostic criteria were fulfilled at time of diagnosis were found, and their presence did not change the significance of the above-mentioned factors. Obesity, defined as BMI ≥ 30 kg/m^2, was not significantly different between the groups, and it did not affect the outcome.

When analysing the impact of whether methotrexate was used in the first year of diagnosis (applicable for patients in time periods 2 and 3) in univariate Cox regression analysis, patients who were prescribed methotrexate had a significantly lower risk of later surgical procedures, with methotrexate decreasing the risk by an RR of 0.60 [95% confidence interval (CI) 0.46 to 0.76, $p < 0.001$]. Any use of biological drugs during the course of the disease did not affect the outcome.

When considering only surgery performed later than 4 years since diagnosis, Cox regression analysis of the same parameters (age, gender, radiographic changes at diagnosis, and time of diagnosis) showed that patients diagnosed in 1986–1998 had an RR for surgery of 3.0, and patients diagnosed in 1972–1985 had an RR of 5.3.

When excluding joint replacement surgery of the hip and knee, patients diagnosed in 1972–1985 and 1986–1998 had RRs for surgical procedures of 3.6 and 2.9, respectively ($p < 0.001$), compared to patients diagnosed in 1999–2009. For prosthesis surgery of the hip and knee, the increased risk (RR 1.6 in 1972–1985 and RR 1.4 in 1986–1998, compared to 1999–2009) was not statistically significant ($p = 0.065$ and 0.067, respectively).

When using the propensity score model to analyse surgical interventions during the entire time span. We found an RR of 2.1 (95% CI 1.49 to 3.10, $p < 0.001$) for time period 1 (1972–1985) compared to time period 3 (1999–2009), and an RR of 2.3 (95% CI 1.70 to 3.04) when comparing time period 2 (1986–1998) to time period 3 (1999–2009).

When performing subanalyses of how age, gender, radiographic changes at diagnosis, and time period of

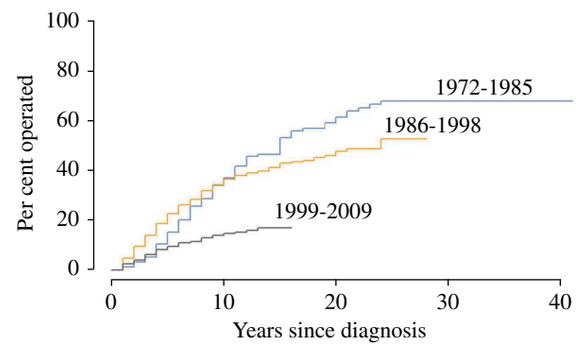


Figure 3. Percentage of patients operated on depending on the time period of diagnosis.

Table 3. Percentage of patients operated on at 5 and 10 years' duration of disease, and relative risk (RR) of surgery according to major explanatory factors.

Variable category	5 years*	10 years*	RR	95% CI	p
Age (years)					
< 70	15	27	1		
≥ 70	22	31	1.04	0.77–1.42	0.78
Gender					
Male	13	22	1		
Female	19	30	1.35	1.02–1.77	0.035
Radiographic changes at diagnosis					
No arthritis	12	21	1		
Possible arthritis, or MRI findings only	19	26	1.01	0.66–1.57	0.92
Arthritis	23	34	1.46	1.10–1.94	0.008
Osteoarthritis	35	55	2.81	1.94–4.05	< 0.001
Time period					
1999–2009	12	18	1		
1986–1998	25	38	2.16	1.62–2.87	< 0.001
1972–1985	15	37	2.38	1.71–3.31	< 0.001

*Five year and 10 year survival, in per cent.
MRI, magnetic resonance imaging; CI, confidence interval.

diagnosis affected the risk of synovectomy, arthrodesis, or prosthesis, we found that patients diagnosed in 1972–1985 had an RR of 4.4 ($p < 0.001$), and patients diagnosed in 1986–1998 an RR of synovectomy of 3.1 ($p < 0.001$) compared to patients diagnosed in 1999–2009. Younger age (< 70 years) was also a risk factor (RR 2.2, $p = 0.036$). For arthrodeses, there was an increased risk of 3.6 ($p < 0.001$) for patients diagnosed in 1972–1985 and 2.4 ($p = 0.004$) for patients diagnosed in 1986–1998 compared to patients diagnosed in 1999–2009, and female gender was a significant risk factor (RR 2.5 $p = 0.004$). For prosthesis surgery, osteoarthritis in radiographic images at diagnosis was the strongest risk factor (RR 4.2, $p < 0.001$). Time of diagnosis was also a significant risk factor; RR 1.8 ($p = 0.006$) for patients diagnosed in 1972–1985 and RR 1.7 ($p = 0.007$) for patients diagnosed in 1986–1998, compared to those diagnosed in 1999–2009. Older age (≥ 70 years) at diagnosis significantly increased the risk of prosthesis surgery (RR 1.6, $p = 0.011$).

Discussion

This study's main finding is that diagnosis in earlier years increased the risk of undergoing orthopaedic surgery. In addition, female gender and radiographic changes consistent with arthritis or osteoarthritis at diagnosis were associated with increased risk of surgery.

Although RCTs are the gold standard in research, they can be difficult to use when investigating late outcomes such as terminal joint destruction with subsequent orthopaedic surgery. RCTs also have other limitations, particularly concerning generalizability (18), as they demonstrate the effect of treatment under ideal conditions. Observational studies have other disadvantages, but describe to a greater extent the prognosis of patients in real life. In this study, we observed the patients for a mean duration of 13.1 years (range 0–42 years), which would be impossible in an RCT, as would the assignment of outdated treatment regimens to current patients.

Female gender is a known predictor of worse outcome of RA (19), and our study confirms that women are more prone to be in need of orthopaedic surgery.

When performing subanalyses for the different procedures, we found that diagnosis in the earlier time periods was a significant risk factor for all procedures, but strongest for synovectomies and weakest for prosthesis surgery. This may be because of the general increase in prosthesis surgery seen in later years. In the subgroup analyses, radiographic arthritis at diagnosis was not a significant risk factor for subsequent surgery, probably because of the reduced number of cases when splitting the cohort.

The use of synthetic and biological DMARDs changed significantly during the study period (Figure 2), with more patients receiving methotrexate and biological treatment both in the first year of disease and during the course of the disease, in later years. Whereas prednisolone is increasingly used in the first year of disease, the proportion using prednisolone for more than 1 year is diminishing. Widdifield et al studied patients aged 66 years and above, and raised the question of whether methotrexate is prescribed to a lesser extent in older patients (16). Investigation of our material did not support this.

In our study, we found the strongest risk factor to be diagnosis in earlier time periods. The survival curves for the different time periods are not proportional, and hence a prerequisite for Cox regression is not strictly present, since use of the Cox regression model requires hazard functions that are proportional over time for all three study periods. We found that the RR was even higher

when investigating events after 4 years, from which time the relative hazards were constant. It is possible that surgical intervention has become more aggressive, and that necessary procedures were performed sooner in later decades, which could explain the higher rates of surgery during the early years of diagnosis in the later cohorts. In that case, some time has to pass before the number of events in each group is comparable, when used as a proxy for joint damage. The propensity score model used does not have the same prerequisite of proportionality, and confirmed the results from fitting the traditional Cox model.

Patients diagnosed in earlier years have a longer time of observation than patients in the latest time period. This may be a confounding factor. However, all patients were included within 2009, but no later, to ensure the possibility of at least 6 years' observation time.

One could argue that the lower risk of surgery is a secular trend indicating higher disease activity among patients diagnosed in 1972–1985 and 1986–1998. Our data do indeed show that patients diagnosed in earlier years included a significantly greater proportion with ESR ≥ 60 mm/h, more than 10 joints affected, and signs of arthritis on initial radiographs. Time of diagnosis was, however, still a significant risk factor, both in multivariate Cox analysis and in the propensity score model correcting for these factors.

Previous studies claim to show that the improved prognosis of patients with RA is due not to secular changes, but to improved treatment (20). In addition, it is probable that the increased disease activity found during the first 2 years of disease among our patients diagnosed in the 1970s and 1980s was caused by later referral to specialist care, and a delay in of or lack of response to an initial treatment that was less intensive in those decades.

Our patients were all treated within the same facility, providing care for the entire region of western Norway. The indication and approval of the costly biological treatments have, since their introduction, been considered for each individual patient by a committee consisting of three rheumatologists, none of whom is the patient's physician. The indication may have changed over time, but there is every reason to believe that all patients in a given year were treated similarly. The use of the synthetic DMARDs was decided by each physician, who all worked within the same treatment tradition, following the same guidelines. We therefore believe that the year of diagnosis may be considered a proxy for the treatment received.

The type and number of affected joints within the first 2 years of diagnosis was not found to be a predictive factor. This is probably because we counted both tender and swollen joints as affected, as according to the ACR/EULAR criteria, and thus a large number (57%) of patients had more than 10 joints involved. According to clinical experience, it is also probable the patient's long-term outcome can be predicted not by initial disease activity, but by how he or she responds to treatment (21). This was confirmed in a study published in 2016 finding that < 20% improvement 1 year after baseline, but not swollen joint count at baseline, was a significant predictor of the number of joints with deformities 18 years after baseline (22). Because there was no uniform registration of clinical response in earlier years, we did not record this in the present study. In our analyses, no significant effects of other signs of initial disease activity, ESR, or fulfilment of the ACR/EULAR criteria were found, and rheumatoid factor positivity did not increase the risk. Previous studies have, however, shown variables expressing disease activity at baseline to be a predictor of poor prognosis and later surgery (4). Because of the long inclusion period of this study, data on anti-CCP were lacking for one-third of patients. Positive anti-CCP was, however, not found to be a significant risk factor among the patients tested.

In this study, 25% of patients had radiographic signs of arthritis initially, and these patients had an increased risk of subsequent surgery, as shown previously (4). The proportion of patients with radiographic arthritis at baseline decreased significantly over the years. Because our cohort went as far back as 1972, we did not have access to the radiographic images, but instead recorded the concluding remarks in the description performed by the evaluating radiologist. Pathology in any image (small or large joint) was recorded. The change may indicate more severe disease in earlier time periods, but is more probably caused by later specialist referral in previous decades.

Radiographic signs of osteoarthritis were seen in 8.6% of the patients at diagnosis. The incidence of arthroplasty surgery in patients with osteoarthritis has increased significantly in later years (10), and this is a possible confounder when considering orthopaedic surgery in patients with RA. When patients with inflammatory rheumatic joint disease develop osteoarthritis, it can be difficult to distinguish primary osteoarthritis from osteoarthritis secondary to inflammatory arthritis. Previous studies have shown that while hand and foot surgery rates in RA have declined, large joint replacements have remained unchanged (12, 23), and that the most RA-specific procedures have declined the most (10). When excluding joint replacement surgery of the hip and knee, which are the more common locations for primary osteoarthritis in need of intervention (24), earlier time of diagnosis is an even stronger risk factor for orthopaedic surgery. This confirms that treatment in later years has decreased the risk of an unfavourable outcome.

Methotrexate has, in later years, been introduced increasingly early (25) and in higher doses (26) to achieve sufficient disease control, and patients are subject to tight management. It is difficult to separate the effect of this from the effect of the introduction of biological DMARDs. In our study, the risk of surgery

was lower among patients diagnosed after the introduction of biologicals, but it is hard to say whether this indicates that biological DMARDs reduce the risk of orthopaedic surgery. Aaltonen et al did not find evidence for this in a study from 2013 (27), but in contrast to their results, we did not find that use of biological medication at any time of the disease was associated with an increased risk of surgery. As users of biologicals are probably the patients with the highest disease activity, this may be considered an indirect indication of their effect.

Conclusion

Patients with a diagnosis in the early years had a greatly increased risk of having an orthopaedic procedure performed. This could be caused by secular changes, but is most probably due to the year of diagnosis being a proxy for the type and intensity of medical treatment received, which we found to have changed significantly during our study's inclusion period.

Acknowledgement

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Supporting Information

Additional Supporting Information may be found in the online version of this article.

Supplementary table S1. Per cent operated with synovectomy at 5 and 10 years' duration of disease, and relative risk of surgery according to major explanatory factors.
Supplementary table S2. Per cent with arthrodesis at 5 and 10 years' duration of disease, and relative risk of surgery according to major explanatory factors.
Supplementary table S3. Per cent with prosthesis at 5 and 10 years' duration of disease, and relative risk of surgery according to major explanatory factors

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Supplementary table S1. Percent operated with synovectomy at five and ten years duration of disease, and relative risk of surgery according to major explanatory factors

Variable category	5 years[a]	10 years[a]	RR	95% CI	p-value
Age					
<70	5.7	9.9	1		
≥70	3.5	4.5	0.45	0.21-0.95	0.036
Gender					
Male	5.6	9.0	1		
Female	5.1	8.7	1.04	0.65-1.65	0.88
Radiographic changes at diagnosis					
No arthritis	4.5	7.8	1		
Possible arthritis, or MR findings only	2.5	6.8	0.67	0.28-1.58	0.36
Arthritis	8.1	13	1.23	0.77-1.99	0.38
Osteoarthritis	5.2	6.9	0.97	0.38-2.48	0.95
Time period					
1999-2009	3.0	4.0	1		
1986-1998	8.0	13	3.1	1.76-5.39	<0.001
1972-1985	7.3	16	4.4	2.41-8.04	<0.001

[a] 5- and 10-year survival, in percent

Supplementary table S2. Percent with arthrodesis at five and ten years duration of disease, and relative risk of surgery according to major explanatory factors

Variable category	5 years[a]	10 years[a]	RR	95% CI	p-value
Age					
<70	3.7	7.6	1		
≥70	3.1	4.2	0.56	0.26-1.20	0.14
Gender					
Male	1.3	2.6	1		
Female	4.5	8.8	2.46	1.33-4.56	0.004
Radiographic changes at diagnosis					
No arthritis	3.2	5.6	1		
Possible arthritis, or MR findings only	3.7	8.2	0.71	0.30-1.68	0.43
Arthritis	5.0	7.6	1.30	0.79-2.14	0.31
Osteoarthritis	4.0	7.6	1.03	0.40-2.67	0.95
Time period					
1999-2009	2.7	3.3	1		
1986-1998	4.8	10	2.44	1.34-4.46	0.004
1972-1985	4.0	11	3.57	1.88-6.76	<0.001

[a] 5- and 10-year survival, in percent

Supplementary table S3. Percent with prosthesis at five and ten years duration of disease, and relative risk of surgery according to major explanatory factors

Variable category	5 years[a]	10 years[a]	RR	95% CI	p-value
Age					
<70	5.5	12	1		
≥70	17	24	1.61	1.11-2.31	0.011
Gender					
Male	6.3	10	1		
Female	8.8	16	1.38	0.96-1.97	0.082
Radiographic changes at diagnosis					
No arthritis	4	10	1		
Possible arthritis, or MR findings only	10	11	0.98	0.55-1.75	0.95
Arthritis	10	17	1.38	0.96-2.00	0.084
Osteoarthritis	28	47	4.17	2.72-6.38	<0.001
Time period					
1999-2009	7.3	11	1		
1986-1998	11	20	1.66	1.15-2.40	0.007
1972-1985	4.7	14	1.85	1.19-2.87	0.006

[a] 5- and 10-year survival, in percent

IV

Incidence and Predictive Factors for Orthopedic Surgery in Patients with Psoriatic Arthritis

Tone Wikene Nystad, Yngvil Solheim Husum, Ove Nord Furnes and Bjørg-Tilde Svanes Fevang

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Incidence and Predictive Factors for Orthopedic Surgery in Patients with Psoriatic Arthritis

Tone Wikene Nystad, Yngvil Solheim Husum, Ove Nord Furnes, and Bjørg-Tilde Svanes Fevang

ABSTRACT. ***Objective.*** To investigate the incidence of orthopedic procedures in patients with psoriatic arthritis (PsA), and how patient characteristics, time of diagnosis, and treatment affect the need for surgery.

Methods. We reviewed the medical history of 1432 patients with possible PsA at Haukeland University Hospital in Bergen, Norway. There were 590 patients (mean age 49 yrs, 52% women) who had sufficient journal information and a confirmed diagnosis of PsA, and who were included in the present study. Relevant orthopedic procedures were obtained from the hospital's administrative patient records. Survival analyses were completed to evaluate the effect of different factors such as year of diagnosis, age, sex, radiographic changes, disease activity, and treatment, on the risk of surgery.

Results. There were 171 procedures (25% synovectomies, 15% arthrodesis, and 53% prostheses) performed on 117 patients. These factors all increased the risk of surgery: female sex [relative risk (RR) 1.9, p = 0.001], age ≥ 70 years at diagnosis (RR 2.4, p = 0.001), arthritis in initial radiographs (RR 2.2, p = 0.006), and maximum erythrocyte sedimentation rate 30-59 mm/h (RR 1.6, p = 0.026). Time period of diagnosis had no effect on the outcome. In a subanalysis of surgery exclusive of hip and knee arthroplasty, diagnosis in earlier years (1954–1985 vs 1999–2011) was a risk factor (RR 2.1, p = 0.042). Antirheumatic treatment changed significantly over time.

Conclusion. There were 20% of patients with PsA who needed surgery. We found that the prognosis of patients with PsA did not change regarding the risk of orthopedic surgery, despite the change in treatment. A possible explanation is the increase in large joint replacements in the general population.

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Key Indexing Terms:
PSORIATIC ARTHRITIS ORTHOPEDIC PROCEDURE PROGNOSIS EPIDEMIOLOGY

Psoriatic arthritis (PsA) develops in up to 30%[1,2] of patients with psoriasis, and the prevalence worldwide has been estimated between 0.02% and 0.25%[3,4,5,6,7]. A study of the population of Hordaland county in western Norway, which is the population we address in this study, found a prevalence of 0.2%, and polyarthritis was the most frequent subclass, documented in 68.6%[8].

PsA with peripheral joint involvement is a progressive disease in most patients[9], and erosions are seen in 47% within the first 2 years[10]. Individuals with polyarthritis are the most susceptible to bone erosions and deformities[11]. Previous studies have been conflicting regarding whether PsA is as destructive radiologically as rheumatoid arthritis (RA)[6,12].

Spontaneous remission of PsA is rare[13], and if nonsteroidal antiinflammatory drugs (NSAID) and intra-articular steroids are not sufficient, a synthetic disease-modifying antirheumatic drug (DMARD) is often prescribed to ease pain and restore function. No synthetic DMARD has, however, been proven to slow or prevent radiographic changes. Biologic treatment is recommended when other agents are not sufficient, and it has been shown to give better control of structural damage[14,15].

Orthopedic surgery has been a necessary part of treating patients with PsA when medication fails to prevent inflammation and joint destruction. Surgery can thus be considered a proxy for the degree of inflammatory activity, and studying time trends in orthopedic surgery gives valuable information regarding the prognosis of patients with inflammatory arthritis. In previous studies, there is a large discrepancy in the incidence of orthopedic surgery in patients with PsA. A study of 444 patients published in 1998 found that 7% had a musculoskeletal procedure performed[16]. In a more recent study of 269 patients published in 2016, 48.3% received orthopedic surgery[17]. This total, however, also included arthroscopies, meniscus surgery, carpal tunnel surgery, surgery of the spine, and others (205 of 280 procedures)[18]. We have not found any data on changes over time. In patients

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with RA there has been a gradual declining incidence of orthopedic interventions[19]. The change in available medical treatment is believed responsible for this[20,21]. Because synthetic DMARD may be less efficient in patients with PsA, it is uncertain whether a decline of the same magnitude can be expected among these patients. It is also possible that a change, if present, would occur later, after the introduction of tumor necrosis factor (TNF)-α inhibitors in this patient group.

We investigated the occurrence of orthopedic surgery among patients diagnosed with PsA in western Norway, and whether patient characteristics, treatment, and year of diagnosis affected the need for surgical intervention.

MATERIALS AND METHODS

Our data originate from Haukeland University Hospital, which delivers specialist care to about 500,000 inhabitants in western Norway. Because only 2 private practicing rheumatologists operate in the area, the vast majority of patients with rheumatic disease are cared for by the hospital's department of rheumatology. In general, patients are referred to specialist care at the time of suspected inflammatory rheumatic disease. Some patients with stable disease are later managed by their general practitioner, but most continue to be followed until death or inactive disease.

From the hospital's administrative patient records, we have data available from 1972 until the present, and some paper files go back even further. Using the International Classification of Diseases (ICD) 8th, 9th, and 10th revisions, we searched for disease codes for PsA (ICD-10 L40.5, ICD-9 7133), and the combination of arthritis or spondyloarthritis (SpA; ICD-10 M06, M46; ICD-8 712, 715; ICD-9 714) and psoriasis (ICD-10 L40, ICD-8/ICD-9 696). Because orthopedic surgery is a late outcome, we wished to give all patients the possibility of at least 5 years observation after the date of diagnosis and excluded patients with first hospital contact later than 2011. The number of patients with first contact in the pre-methotrexate (MTX) era (before 1985) and in the era after the introduction of MTX, but before the use of TNF-α inhibitors (1986–1998), was much lower than the number of patients with first contact from 1999 to 2011. To ensure a sufficient number of patients from the first 2 periods, we chose to evaluate all of these, to find possible subjects for inclusion. From the third period, we evaluated patients with at least 2 hospital contacts, to increase the possibility that cases evaluated had a confirmed diagnosis of PsA and could be included in the study. However, the inclusion criteria were the same for all evaluated patients. We also searched the local patient system GoTreatIt and the National Arthritis Registry (NorArthritis; helse-bergen.no/seksjon-engelsk/seksjon-avdeling/Sider/Norwegian-Arthritis-Registry-NorArthritis.aspx) for patients registered under the diagnosis psoriatic arthritis.

Using these sources, 2251 patients remained for evaluation. All of these had contacts with Haukeland University Hospital from 1972 to 2011 coded in accordance with our search, but some had no contact with the department of rheumatology prior to 2012, and others did not consent to participation. There were 819 patients excluded because of this, leaving 1432 patients available for journal review. Of these, 951 had given consent to participate and 481 had died. Following this process, we were able to include 590 patients. The selection process is described in Figure 1. The search performed was very broad, to account for the possibility that in previous years, patients with PsA were not identified and coded that way, but rather as other arthritis conditions. This proved not to be true, and the vast majority of patients included had been identified and coded as PsA.

Each medical record was reviewed for the following information: weight, height, year of diagnosis, number of joints with arthritis (evaluated by the treating rheumatologist) during disease course, whether in fulfillment of the ClASsification for Psoriatic ARthritis criteria (CASPAR), the presence of psoriatic dermatitis, and erythrocyte sedimentation rate (ESR) at diagnosis and maximal levels. The medical records did not contain radiographic images, so only the radiologist's interpretation of these as normal or consistent with arthritis or osteoarthritis (OA) was recorded, and for images of the columnar and sacroiliac joints (SIJ), whether there were signs of SpA. Medications used in the first year and during the course of the disease were also registered. Supplementary data were obtained from the Norwegian Arthritis Registry for patients herein. The study was approved by the Regional Committee for Medical and Health Research Ethics (2016/2207/REK West).

Because MTX was introduced to our patient group around 1986, and biologic treatment in the form of TNF-α inhibitors in 1999, we split the group into 3 depending on diagnosis in different treatment eras: time period 1 included patients diagnosed prior to 1986, time period 2 from 1986 to 1998, and time period 3 from 1999 to 2011. Patient characteristics for each group and in total are described in Table 1. Mean body mass index (BMI) was significantly lower in time period 1 versus time period 3 ($p = 0.033$). Mean age at disease onset was significantly older in time period 2 than in time periods 1 and 3. Mean maximum ESR during disease course was significantly higher in patients in time periods 1 and 2 versus time period 3. For 56% of patients, radiographic examination of SIJ was present, and 62% of journals contained radiographic examination of the spine. If we assume that when pictures were not taken, the patient did not have symptoms from axial joints, and presumably no axial arthritis, 19% of patients had sacroiliitis and/or SpA (radiographic SIJ arthritis 14% and radiographic SpA 9%).

Surgical procedures. For the selected 590 patients, information on orthopedic surgery was obtained from the hospital's administrative patient records and the Norwegian Arthroplasty Register (NAR). NAR was established in 1987, initially as a register of total hip replacements, but has since 1994 been a register of all artificial joints in the Norwegian population. Haukeland University Hospital's administrative patient system has registered all performed procedures since 1972, and the data from NAR gave extra security for completeness of data in the years since the register's establishment. The archives of 2 other local hospitals, which up until the early 1990s performed some surgery in this patient group, were also investigated. We searched for synovectomies, arthrodesis, and prosthesis procedures using coding systems NOMESCO Classification of Surgical Procedures, and that of the Norwegian Institute of Public Health.

Statistical analysis. Descriptive statistics were used for presentation of the patient characteristics. Unpaired t test for continuous variables and chi-square test for categorical data were used. Person-time was accumulated from PsA diagnosis until the first occurrence of orthopedic surgery, death, or the end of the study period (July 30, 2017). Cumulative incidence rates were calculated for the entire study period as the number of events per 100 patient-years. Because followup duration was different for individual patients, the effect of different factors on the risk for undergoing surgery was analyzed using Kaplan-Meier plots and Cox regression analyses. A directed acyclic graph (model code in Supplementary Data 1, available with the online version of this article)[22] was constructed to determine which variables should be included in the multivariate Cox proportional hazards regression model for each factor. Unless otherwise stated, analyses included all subjects, and the outcome was the first occurrence of arthroplasty, arthrodesis, or synovectomy. We also performed subanalysis of factors affecting the risk of surgery exclusive of hip and knee arthroplasty. All analyses were done on the original files, as well as on files with multiple imputation of missing values (100 files).

We investigated the effect of these patient characteristics on the risk for undergoing surgery: age at diagnosis, sex, time period of diagnosis, number of affected joints (< 4 vs ≥ 5), BMI ≥ 30, first ESR, highest ESR during disease course, radiographic changes at diagnosis, use of MTX within 2 years of disease onset, use of biologic treatment within 2 years of disease onset, and fulfillment of the CASPAR criteria for PsA. Because psoriatic dermatitis was present in 94% of the patients, no further analysis of this exposure variable was performed.

Statistical analyses were performed in SPSS versions 23 and 24. The level for statistical significance was set to $p < 0.05$.

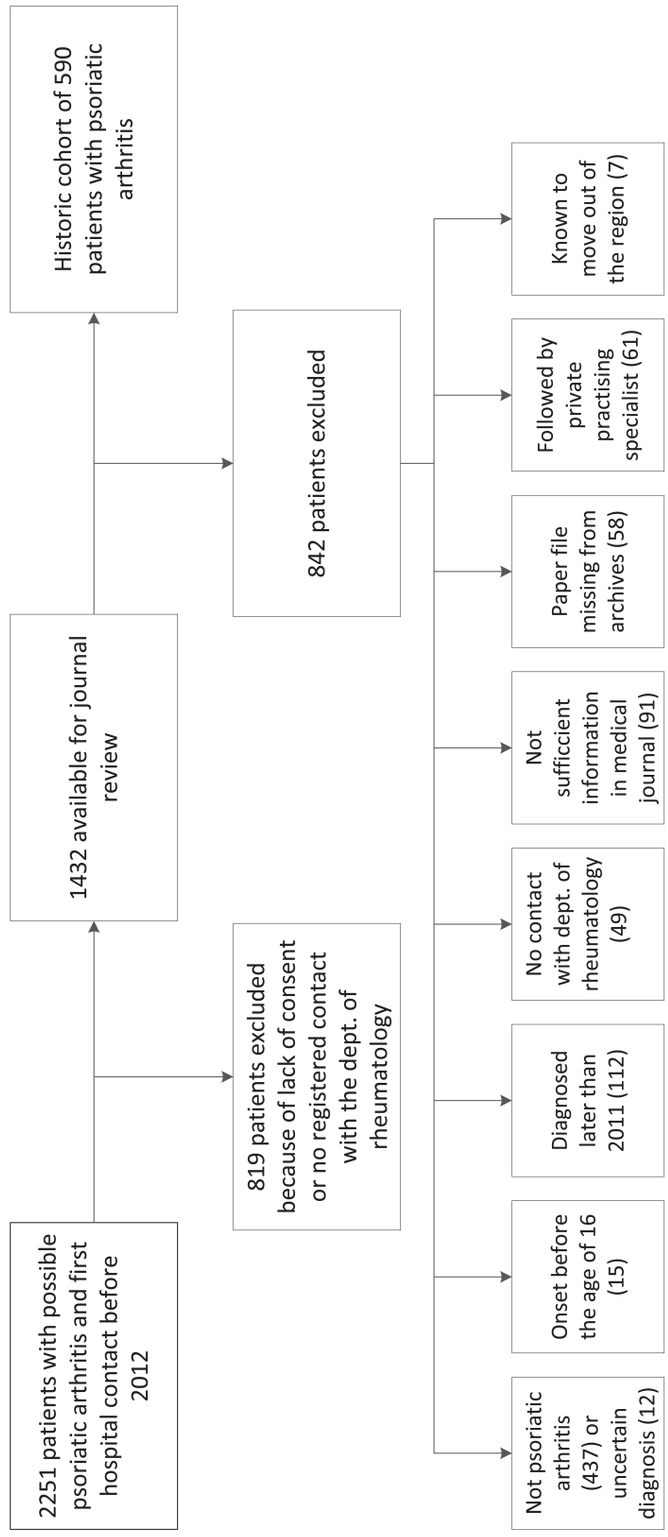

Figure 1. Selection process.

Table 1. Patient characteristics in each time period and in total.

Characteristics	< 1986, n = 72	1986–1998, n = 196	1999–2011, n = 322	Total, n = 590	p
Observation time, yrs	25 (15)	16 (8.6)	9.8 (4.5)	14 (9.3)	
Age at disease onset, yrs	47 (17)	52 (15)	49 (15)	49 (15)	
Female sex	58	46	54	52	0.14
BMI [a], kg/m^2	26 (4.8)	27 (5.0)	28 (4.8)	27 (4.9)	
Fulfilled CASPAR criteria	89	87	91	90	0.25
1 joint affected	2.8	4.1	5.0	4.4	0.24
2–4 joints affected	17	29	26	26	
≥ 5 joints affected	72	60	64	64	
No peripheral arthritis	8.3	7.7	4.3	5.9	
ESR at disease onset, mm/h	25 (28)	27 (26)	27 (23)	27 (24)	
Maximum ESR during disease course, mm/h	43 (29)	36 (31)	30 (25)	34 (28)	
ESR ≥ 60 during disease course[b], mm/h	30	30	14	21	< 0.001
Radiographic arthritis initially[c]	12	18	13	14	0.09
Radiographic arthritis during disease course[d]	49	37	30	34	< 0.001
Methotrexate within 2 yrs disease onset	4.2	22	53	37	< 0.0001
sDMARD[e]/bDMARD within 2 yrs disease onset	4.2	31	62	45	< 0.0001

Data are % or mean (SD) unless otherwise specified. [a] Available for 459 patients. [b] Among available (506). [c] Percentage among patients with initial radiographic examination (470 in total). [d] Percentage among patients with radiographic examination later in disease course (434 in total). [e] Defined as sulfasalazine, methotrexate, or leflunomide. BMI: body mass index; CASPAR: ClASsification for Psoriatic ARthritis criteria; ESR: erythrocyte sedimentation rate; sDMARD: synthetic disease-modifying antirheumatic drug; bDMARD: biologic DMARD.

RESULTS

Treatment, presented as percentage of patients given each medication in the first year and during the course of the disease is presented in Figure 2. The proportion of patients using NSAID was high in all 3 time periods, but significantly higher in time period 1, both in the first year and during the course of the disease. Within 2 years of disease duration, 37% of all patients had been prescribed MTX. There were 56% who were prescribed MTX during the course of the disease. The proportion of patients receiving MTX within the first year since diagnosis increased from 17% in time period 2 to 43% in time period 3. When looking only at patients in time period 3, 53% were prescribed MTX, and 19% biologics within 2 years of disease, and 36% had used biologic treatment during disease course. Further details are described in Table 1.

The department of dermatology seemed to start using MTX earlier than the department of rheumatology in our county, and the 3 patients in time period 1 using MTX in the first year of disease had all been prescribed this from their dermatologist.

There was no significant difference in the prescription of effective medication in patients aged ≥ 70 years versus younger patients.

Surgical procedures. There were 1.4 events per 100 patient-years over the whole study period. When excluding surgery conducted earlier than 1 year prior to diagnosis, we found 171 procedures performed in 117 patients (20%). The procedures performed within 1 year prior to diagnosis were counted as performed at diagnosis, because we had reason to assume an association between surgery and diagnosis. A single procedure was performed on 68%, and 24% who had 2 procedures performed, whereas 9.5% underwent 3–6 surgeries. Of the types of procedures, 53% of the 171 procedures were prosthetic, 25% were synovectomies, and 15% arthrodesis procedures (triple arthrodeses and forefoot procedures included). The distribution of different procedures in diverse joints is described in Table 2. The most frequently operated area was the knee, in which 38% of procedures were performed, followed by the hip (27%). Eight percent of the 590 patients had knee surgery performed, 6.4% who had hip surgery, and 6.1% who had surgery of the hands or feet. Mean time to first procedure was 8.5 years (0–52 ± SD 8.5 yrs). Mean age at surgery was 62 years. Patients were youngest at time of synovectomy (mean age 45 yrs), older at first arthrodesis procedure (mean age 55 yrs), and oldest at arthroplasty surgery (mean age 70 yrs).

Survival analyses. Results are presented in Table 3 and Figure 3. Factors found to affect the risk of a surgical procedure during the course of the disease were older age at diagnosis, female sex, arthritis on initial radiographs, and highest ESR between 30 and 59 mm/h. Time period of diagnosis did not influence the risk. No significant effects were found involving fulfillment of the CASPAR criteria, biologic treatment within 2 years of disease onset, MTX treatment within 2 years of disease onset, ESR at disease onset, ≥ 5 versus ≤ 4 joints affected, or BMI ≥ 30 kg/m^2. OA in initial radiographs was borderline significant, but not significant when analyzing 100 files with imputed values [relative risk (RR) 1.4, 95% CI 0.72–2.64, p = 0.33]. For the other exposure variables, analysis of the files with imputed values did not change the significance of the above-described results.

When performing subanalyses of procedures exclusive of

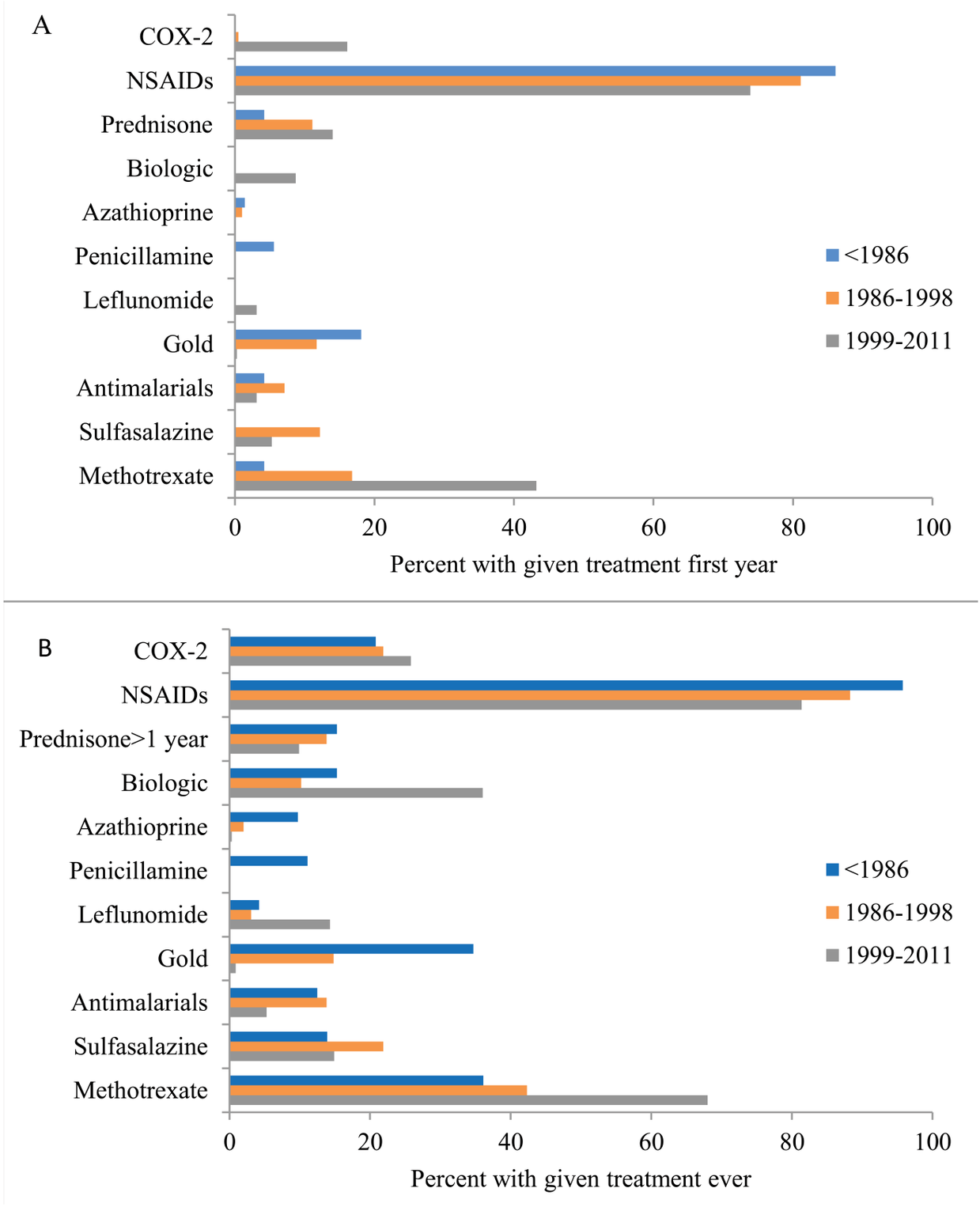

Figure 2. Medical treatment in the first year (A) and during the course of the disease (B) for patients diagnosed in 3 different time periods. COX-2: cyclooxygenase 2 inhibitors; NSAID: nonsteroidal antiinflammatory drugs.

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Table 2. Type and localization of surgical interventions.

Procedure	Joint Area	N	% of Total
Arthroplasties	Shoulder	2	1.2
	Hip	47	27
	Knee	41	24
	Foot	1	0.6
Synovectomies	Elbow	2	1.2
	Wrist/hand	10	5.8
	Knee	23	13
	Ankle/foot	7	4.1
Arthrodeses	Wrist/hand	11	6.4
	Foot	13	7.6
	Unknown (hand/foot)	1	0.6
Other/unknown	Wrist/hand	4	2.3
	Knee	2	1.2
	Ankle/foot	7	4.1
Total		171	100

hip and knee prostheses (61 patients), we found that patients diagnosed 1954–1985 had an increased risk of surgery (RR 2.1, 95% CI 1.03–4.18, p = 0.042) compared to patients diagnosed 1999–2011. Diagnosis in the years 1986–1998 was not a significant risk factor (RR 1.5, 95% CI 0.83–2.72, p = 0.18). Highest ESR 30-59 mm/h (RR 3.4, 95% CI 1.8–6.4, p < 0.001) and ESR ≥ 60 mm/h (RR 2.4, 95% CI 1.1–5.0, p = 0.025) increased the risk of surgery. Analyzing 100 files with imputed values did not change the significance of the above-described results, and we did not find other factors that significantly affected the outcome.

DISCUSSION

Our study's main findings were that 20% of patients with PsA required orthopedic surgery, and that time period of diagnosis did not affect the outcome.

Observational studies have disadvantages, compared to randomized controlled trials (RCT), but describe to a greater extent the prognosis of patients in real life instead of patients treated under ideal conditions. In this study we observed the patients for a mean time of 13.8 (0–63) years, which would be impossible in an RCT because it is less suitable for the investigation of late outcomes.

Female sex, older age, elevated ESR, and arthritis in initial radiographs increased the risk of orthopedic surgery. Others have also found that female sex predicts an unfavorable outcome[23,24], whereas in a different study, male sex was a risk factor for early radiographic damage[25]. For orthopedic surgery exclusive of hip and knee prostheses, patients diagnosed in time period 1 (1954–1985) had an increased risk of surgery compared to those with a diagnosis in time period 3 (1999–2011).

We divided patients into 3 time periods based on the availability of medical treatment at diagnosis. A limitation to this approach is that the change in treatment came gradually, and that new treatment was also made available to patients diagnosed in previous years, although later in the disease course.

Among patients diagnosed in the 3 time periods, we did not find any significant changes in the disease activity as measured by inflammatory variables or radiographic changes,

Table 3. Percent operated at 5 and 10 years disease duration, among patients at risk, and relative risk (RR) of surgery according to major explanatory factors.

Variables	5 Years	10 Years	RR	95% CI	p
Age*					
< 70	8.2	13	1		
≥ 70	22	32	2.4	1.5–4.1	0.001
Sex**					
Male	7.6	11	1		
Female	11	18	1.9	1.3–2.8	0.001
Radiographic changes at diagnosis†					
No arthritis	6.9	13	1		
Possible arthritis, or MR findings only	12	15	1.4	0.58–3.3	0.45
Arthritis	15	30	2.2	1.3–4.0	0.006
Osteoarthritis	19	19	2.0	0.999–3.9	0.050
Highest ESR, mm/h††					
< 30	7.1	10	1		
30–59	12	20	1.6	1.1–2.5	0.026
≥ 60	11	18	1.5	0.93–2.5	0.095
Time period**					
1999–2011	9.4	13	1		
1986–1998	9.4	16	1.1	0.75–1.8	0.52
< 1986	9.8	17	1.2	0.69–2.0	0.54

* Adjusted for sex and time period of diagnosis. ** Unadjusted analysis. † Adjusted for sex, age, time period of diagnosis, no. affected joints (< or ≥ 5), and BMI ≥ 30. †† Adjusted for time period of diagnosis, sex, age, and no. affected joints (< or ≥ 5). MR: magnetic resonance; ESR: erythrocyte sedimentation rate.

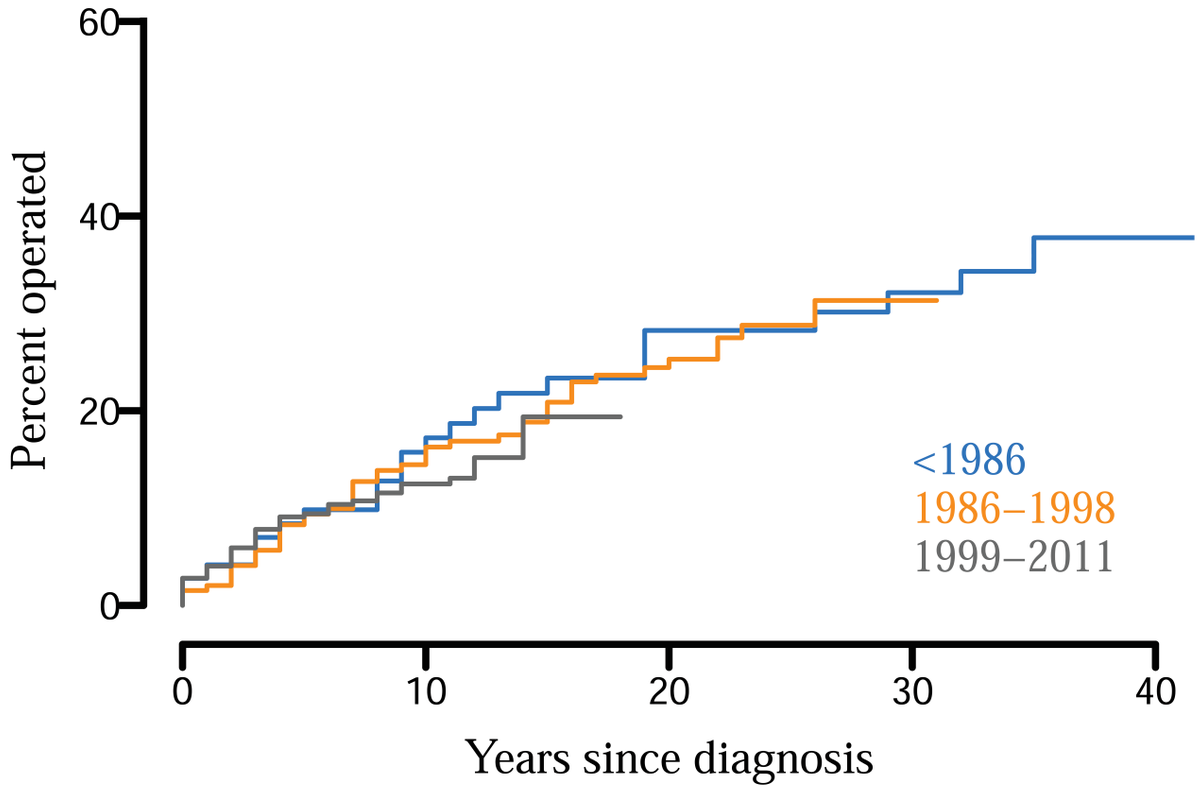

Figure 3. Cumulative percent having surgery, based on 3 different time periods of diagnosis.

at disease onset. On the other hand, maximum ESR during the disease course decreased significantly from 43 to 30, from time period 1 to time period 3, and the share with ESR ≥ 60 mm/h during the course of the disease fell from 30% in patients diagnosed before 1986 to 14% in patients diagnosed 1999–2011 ($p < 0.001$). Significantly more patients among those diagnosed in earlier years also developed radiographic changes. This suggests that the burden of inflammation has become lower in recent years. In the articles by Zangger, *et al*[16] and Haque, *et al*[17], survival analyses were not performed, but patients were divided into 2 groups according to whether they had undergone orthopedic surgery, and the groups were then compared. Zangger, *et al* found that patients who had an operation had significantly more radiological damage and more actively inflamed joints at first assessment[16]. Haque, *et al* found that asymmetric mono-/oligoarticular arthritis and the combination of peripheral and axial disease were more frequent among patients with surgeries, whereas there were no differences in treatment between the groups[17].

There has been a significant change in the prescription of medication. The share of patients receiving potent medication within 2 years of disease onset more than doubled when comparing patients diagnosed 1999–2011 to patients diagnosed 1986–1998.

When investigating surgery among patients with inflammatory arthritis in our region, we found that 31% of patients with RA underwent an orthopedic procedure[21], whereas for patients with PsA, 20% had joint surgery performed. For RA, diagnosis in earlier years was a significant risk factor for orthopedic surgery. In PsA, however, this did not affect the outcome.

When analyzing only hip and knee arthroplasty, the time period of diagnosis was not a significant risk factor for surgery in patients with RA[21]. This supports the findings from other studies, that while hand and foot surgery in RA has declined, large joint replacements remain unchanged[26]. A possible explanation for this might be the general increase seen in joint replacement surgery in later years[27,28,29], but it has also been discussed whether the inflammation process is different in small joints compared to larger joints, and that the latter could be less affected by antirheumatic therapy[26,30,31]. Whereas arthroplasty in joints other than hip and knee were found to be frequent in RA (18% of prosthesis procedures), this was seldom performed in patients with PsA, where 96% of prosthesis surgery were hip and knee procedures. Because large joint replacements account for a greater proportion of surgery in patients with PsA than those with RA (51% vs 33%), this would be expected to weaken the effect of time period of diagnosis. After excluding prosthesis surgery of the hip and knee from the analysis, we find that diagnosis in 1954–1985 increased the risk of surgery compared to diagnosis later than 1998.

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A possible confounding factor is that hip and knee arthroplasties may have been conducted on the basis of coexisting OA in patients with PsA. The etiology of joint destruction and the subsequent need for joint replacement surgery in patients with inflammatory arthritis may be hard to detect. This is especially the case for the hip joint, particularly before the use of ultrasound. We found that 57% of patients with knee prosthesis surgery had had arthritis of the knee during disease course, and that 21% of patients with hip prosthesis surgery had had hip joint arthritis, as detected by the treating rheumatologist. One must thus suspect that inflammatory disease was a contributing factor also for large-joint destruction.

Although not to the same extent as for RA, patients with PsA have, to an increasing degree, been treated with synthetic, and in later years, biologic DMARD[32]. In our study, this change coincides with patients having a lower burden of inflammation, as measured by ESR. Others have found that early referral to an arthritis clinic[33] and tight disease control[34] give a better outcome[34]. However, it has been shown that clinical signs of inflammation and progression of joint destruction might be dissociated[25,30,31], and we could not find a decrease in joint surgery, suggesting that this outcome has not been affected by the change in medication, contrary to what is found for patients with RA. This is in concordance with the knowledge that contrary to the effect of synthetic DMARD on structural damage in patients with RA[35], the same has not been shown for PsA.

Because biologic treatment has been shown to prevent joint destruction in PsA[15], it is possible that increasing use of TNF-α inhibitors would lessen the risk of an orthopedic procedure during the disease course. When considering all procedures, this was not the case in our material. Among the 25% of patients prescribed biologic treatment during the course of the disease, only 42% started treatment within 2 years of diagnosis. It might thus be that damage, predicting later orthopedic surgery, had already occurred when treatment was initiated[17].

We found that 20% of patients with PsA underwent orthopedic surgery. The maximum disease activity seems to have decreased over time, but the risk of surgery was not affected by year of diagnosis. The unchanged prognosis regarding joint surgery in patients diagnosed from 1985 to 1998, compared to those with disease onset in the pre-MTX era, might indicate that MTX and other synthetic DMARD do not prevent joint damage. However, because biologic treatment has been shown to prevent joint damage[15], one would expect the risk of orthopedic surgery to decline following its introduction, in patients diagnosed from 1999 onward. It is possible that the improved treatment is too recent for a change in prognosis to have become evident. But one must also consider whether the use of biologic treatment might be too infrequent and initiated too late if we seek optimal treatment of patients with PsA.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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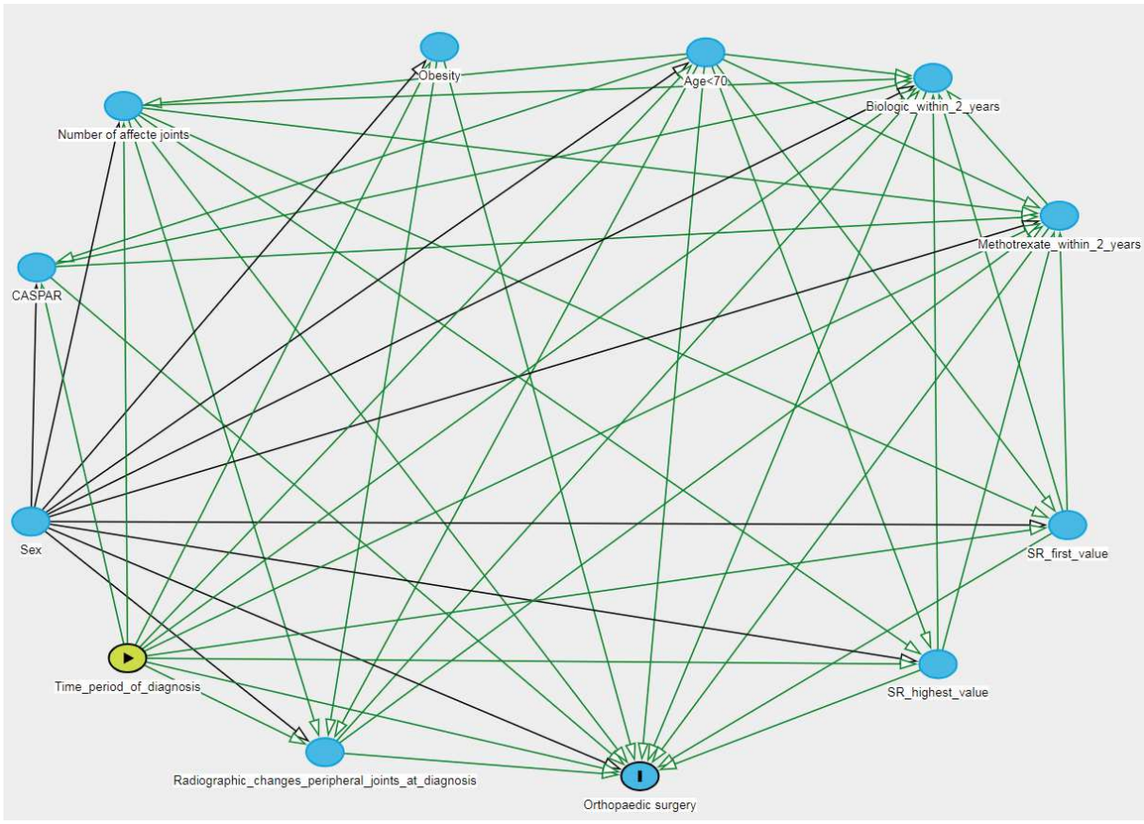
ONLINE SUPPLEMENTARY DATA

A Directed Acyclic Graph (DAG) is a graphic model that depicts a set of hypotheses about the causal process that generates a set of variables of interest. The intention is to minimise bias in empirical studies in epidemiology.

We considered the different exposure variables, and how they could potentially affect one another. This was plotted using the software on www.dagitty.net with the following result (1).



Orthopaedic surgery is the outcome variable. All included exposure variables may potentially affect this outcome. Arrows are drawn according to whether the exposure variables may have an effect on other exposure variables, and visualises causal paths and biasing paths. One may thus find potential biases and which other variables that needs to be included in the Cox regression analyses to minimise bias, for each variable. In example; for “Time period of diagnosis”, no adjustment is necessary to estimate the total effect.

The complete model code is included below.

Model code

Age%3C70 1 @0.600,-0.114

Biologic_within_2_years 1 @0.873,-0.084

CASPAR 1 @-0.071,0.243

Methotrexate_within_2_years 1 @0.990,0.352

Number%20of%20affecte%20joints 1 @0.016,-0.025

Obesity 1 @0.333,-0.123

Orthopaedic%20surgery O @0.534,1.088

Radiographic_changes_peripheral_joints_at_diagnosis 1 @0.218,1.048

SR_first_value 1 @0.963,0.671

SR_highest_value 1 @0.833,0.902

Sex 1 @-0.077,0.665

Time_period_of_diagnosis 1 @0.020,0.892

Age%3C70 Biologic_within_2_years CASPAR Methotrexate_within_2_years Number%20of%20affecte%20joints Orthopaedic%20surgery Radiographic_changes_peripheral_joints_at_diagnosis SR_first_value SR_highest_value

Biologic_within_2_years Orthopaedic%20surgery

CASPAR Biologic_within_2_years Methotrexate_within_2_years Orthopaedic%20surgery

Methotrexate_within_2_years Biologic_within_2_years Orthopaedic%20surgery

Number%20of%20affecte%20joints Biologic_within_2_years Methotrexate_within_2_years Orthopaedic%20surgery Radiographic_changes_peripheral_joints_at_diagnosis SR_first_value SR_highest_value

Obesity Orthopaedic%20surgery Radiographic_changes_peripheral_joints_at_diagnosis

Radiographic_changes_peripheral_joints_at_diagnosis Biologic_within_2_years Methotrexate_within_2_years Orthopaedic%20surgery

SR_first_value Biologic_within_2_years Methotrexate_within_2_years Orthopaedic%20surgery

SR_highest_value Biologic_within_2_years Methotrexate_within_2_years Orthopaedic%20surgery

Sex Age%3C70 Biologic_within_2_years CASPAR Methotrexate_within_2_years Number%20of%20affecte%20joints Obesity Orthopaedic%20surgery Radiographic_changes_peripheral_joints_at_diagnosis SR_first_value SR_highest_value

Time_period_of_diagnosis Age%3C70 Biologic_within_2_years CASPAR Methotrexate_within_2_years Number%20of%20affecte%20joints Obesity Orthopaedic%20surgery Radiographic_changes_peripheral_joints_at_diagnosis SR_first_value SR_highest_value

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