Elective orthopaedic surgery in patients with inflammatory arthropathies

Hanne Osnes Ringen

Faculty of Medicine
University of Oslo
Department of Surgery, Diakonhjemmet Hospital, Oslo
2010
Acknowledgements

The work with this thesis has required input from a large number of individuals and there are many to thank.

First of all I would like to thank Ludvig Fjeld Solheim, head of the Department of Surgery at Diakonhjemmet Hospital, for giving me the opportunity and time to do this work beside surgical practice. I owe him thank for his always positive attitude, his support and encouragement and for believing in me, despite a number of childbirths.

Hanne Dagfinrud, senior researcher at NRRK, has been my main supervisor during the project, and I owe her a great thank for support, good advice, and for her always positive attitude and her great availability. Her input has been substantial and important, and she has been an excellent mentor through all phases of the work with this thesis.

I also owe a thank to Tore K. Kvien, professor and head of the Department of Rheumatology at Diakonhjemmet Hospital, who has contributed with his large experience and advise. He has been one of my supervisors during the project and has given important contributions and made the project possible both with the planning and executing the project.

Special thanks go to my co-authors Petter Mowinckel for statistical advice, Maria Knoph Kvamme and Ivar Sonbø Kristiansen (Department of Health Economics, University of Oslo) for their substantial contribution concerning health economics, Marianne Thingstad for her contributions and calculations concerning costs and Jan Egil Henriksen for advice concerning the surgical approach.

Thanks also to Elisabeth Hope, nurse and consultant who has posted and arranged most of the patients’ questionnaire concerning paper II-IV, and also the other nurses and physiotherapists at the Rheumasurgical division.

I also owe a thank to my colleagues Espen Haukeland, Jan Mjørud, Kari Eikvar, Jan Egil Henriksen, Marianne Lund Eriksen, Lars Eilertsen, Terje Ugland and Tarjei Lona for making this field exciting to study and the department a pleasant and interesting place to work, and also for contribution concerning the data collection.

I also owe thank to my office fellowship who in many ways have contributed to cheerful days at work. Chief physician Kari Eikvar, head of the Rheumasurgical division at the Department of Surgery, for her professional advice, positive attitude and for being a good conversation partner. Chief physicians Willhelm Bugge and Jan Egil Henriksen, I owe them both thanks for sharing of their philosophic vision and wisdom of life in a sort of positive melancholy way.

Finally, I am grateful to my family, the dearest ones in my life; my great love and husband Øyvind for always being there for me and my dear children Christina, Filip, William and Aksel.

Oslo, April 2010
Hanne Osnes Ringen
Contents
Acknowledgements
Abbreviations
List of papers
1. Introduction and background ................................................................. 5
   1.1 Diseases .................................................................................................. 7
       1.1.1. Inflammatory arthropathies ................................................................. 7
       1.1.2 Rheumatoid arthritis ............................................................................. 7
       1.1.3 Ankylosing spondylitis .......................................................................... 10
       1.1.4 Psoriatic arthritis .................................................................................. 12
       1.1.5 Juvenile idiopathic arthritis .................................................................. 13
       1.1.6 Other arthritides .................................................................................. 14
   1.2 Treatment of patients with inflammatory arthropathies ....................... 14
       1.2.1 Pharmacological treatment .................................................................... 14
       1.2.2 Surgical treatment ................................................................................. 15
       1.2.3 Non-pharmacological, non-surgical treatment ........................................ 17
   1.3 Measures of disease status .................................................................... 18
2. General aim and specific research questions ............................................ 19
   2.1 General aim .............................................................................................. 19
   2.2 Specific research questions ...................................................................... 19
3. Material and methods ............................................................................ 20
   3.1 Study designs ............................................................................................ 20
   3.2 Data sources ................................................................................................ 20
   3.3 Study populations ...................................................................................... 21
       3.3.1 The Oslo Rheumatoid Arthritis Register ............................................... 22
       3.3.2 Patients undergoing surgical procedures 2005-2006 ............................. 22
   3.4 Assessments ............................................................................................. 22
       3.4.1 Demographic and disease related variables ......................................... 22
       3.4.2 Patient-reported measures .................................................................... 23
           3.4.2.1 The Health Assessment Questionnaire and the Modified Health Assessment Questionnaire .................................................. 23
           3.4.2.2 The Arthritis Impact Measurement Scales ...................................... 24
           3.4.2.3 The Short Form 36 .......................................................................... 24
           3.4.2.4 Visual analogue scales ................................................................. 25
       3.4.3 Utility scores ....................................................................................... 26
           3.4.3.1 SF-6D .......................................................................................... 26
           3.4.3.2 EQ-5D ......................................................................................... 27
       3.4.4 Costs .................................................................................................. 27
       3.4.5 Cost per QALY ................................................................................... 28
       3.4.6 Economic model .................................................................................. 28
       3.4.7 Surgical procedures .......................................................................... 28
   3.5 Statistics .................................................................................................... 29
   3.6 Legal and ethical aspects ......................................................................... 31
4. Summary of results .............................................................................. 31
   4.1 Paper I ..................................................................................................... 31
   4.2 Paper II .................................................................................................... 32
   4.3 Paper III ................................................................................................. 33
   4.4 Paper IV ................................................................................................. 33
5. Discussion ............................................................................................... 34
5.1 Methodological aspects ........................................................................................................... 35
  5.1.1 Study samples .................................................................................................................. 35
    5.1.1.1 The Oslo Rheumatoid Arthritis Register .............................................................. 35
    5.1.1.2 Patients undergoing surgical procedures .............................................................. 36
    5.1.1.3 The KOSPA database ......................................................................................... 37
  5.1.2 Study designs and data collection .................................................................................... 38
  5.1.3 Assessment ....................................................................................................................... 39
    5.1.3.1 Patient-reported outcome measures ................................................................ 39
    5.1.3.2 Cost analyses ..................................................................................................... 41
  5.1.4 Data analyses .................................................................................................................... 45
  5.2 Results .................................................................................................................................. 46
    5.2.1 Physical function and surgical treatment of the upper and lower limb .................. 46
    5.2.2 Patient-reported- and cost-effectiveness outcomes after surgical intervention .... 49
  6. Conclusions .......................................................................................................................... 53
  7. Clinical implications .............................................................................................................. 54
  8. Reference List ........................................................................................................................ 55
# Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>15D</td>
<td>15-dimensional (a health state descriptive system)</td>
</tr>
<tr>
<td>ACR</td>
<td>American College of Rheumatology</td>
</tr>
<tr>
<td>AIMS2</td>
<td>Arthritis Impact Measurement Scales 2</td>
</tr>
<tr>
<td>ANCOVA</td>
<td>Analysis of Covariance</td>
</tr>
<tr>
<td>Anti-CCP</td>
<td>Antibodies to Cyclic Citrullinated Peptide</td>
</tr>
<tr>
<td>AS</td>
<td>Ankylosing Spondylitis</td>
</tr>
<tr>
<td>CASPAR</td>
<td>Classification of Psoriatic Arthritis</td>
</tr>
<tr>
<td>CCP</td>
<td>Cyclic Citrullinated Peptide</td>
</tr>
<tr>
<td>CIA</td>
<td>Chlamydia induced Reactive Arthritis</td>
</tr>
<tr>
<td>DAS 28</td>
<td>Disease Activity Score (28 joint counts)</td>
</tr>
<tr>
<td>EQ-5D</td>
<td>Euro Quality of Life group 5 dimensions</td>
</tr>
<tr>
<td>HAQ</td>
<td>Health Assessment Questionnaire</td>
</tr>
<tr>
<td>HLA</td>
<td>Human Leukocyte Antigen</td>
</tr>
<tr>
<td>HRQoL</td>
<td>Health Related Quality of Life</td>
</tr>
<tr>
<td>HUI</td>
<td>Health Utility Index</td>
</tr>
<tr>
<td>IL-1</td>
<td>Interleukin 1</td>
</tr>
<tr>
<td>IL-6</td>
<td>Interleukin 6</td>
</tr>
<tr>
<td>JIA</td>
<td>Juvenile Idiopathic Arthritis</td>
</tr>
<tr>
<td>KOSPA</td>
<td>Cost per patient accounting system</td>
</tr>
<tr>
<td>LOCF</td>
<td>Last Observation Carried forward</td>
</tr>
<tr>
<td>MCP</td>
<td>Metacarpophalangeal (joint)</td>
</tr>
<tr>
<td>MHAQ</td>
<td>Modified Health Assessment Questionnaire</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>MTP</td>
<td>Metatarsophalangeal (joint)</td>
</tr>
<tr>
<td>NOK</td>
<td>Norwegian Kroner</td>
</tr>
<tr>
<td>NPV</td>
<td>Net Present Value</td>
</tr>
<tr>
<td>ORAR</td>
<td>Oslo Rheumatoid Arthritis Register</td>
</tr>
<tr>
<td>PIP</td>
<td>Proximal Interphalangeal (joint)</td>
</tr>
<tr>
<td>PROM</td>
<td>Patient-reported Outcome Measurement</td>
</tr>
<tr>
<td>PsA</td>
<td>Psoriatic Arthritis</td>
</tr>
<tr>
<td>QALY</td>
<td>Quality Adjusted Life Years</td>
</tr>
<tr>
<td>RA</td>
<td>Rheumatoid Arthritis</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised Controlled Trials</td>
</tr>
<tr>
<td>RS</td>
<td>Rating Scales</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SF-36</td>
<td>Short Form- 36</td>
</tr>
<tr>
<td>SG</td>
<td>Standard Gamble</td>
</tr>
<tr>
<td>SMR</td>
<td>Standardized Mortality Rate</td>
</tr>
<tr>
<td>SpA</td>
<td>Spondyloarthopathies</td>
</tr>
<tr>
<td>SPSS</td>
<td>Statistical Package for the Social Sciences</td>
</tr>
<tr>
<td>SRM</td>
<td>Standardized Response Mean</td>
</tr>
<tr>
<td>THA</td>
<td>Total Hip Replacement</td>
</tr>
<tr>
<td>TNF-alpha</td>
<td>Tumour Necrosis Factor-alpha</td>
</tr>
<tr>
<td>TTO</td>
<td>Time Trade Off</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual Analogue Scale</td>
</tr>
</tbody>
</table>
List of papers


II. Osnes-Ringen H, Kvien TK, Henriksen JE, Dagfinrud H. Patients with inflammatory arthropathies undergo feet surgery later in the disease course than hand surgery. [Submitted]


Elective orthopaedic surgery in patients with inflammatory arthropathies

1. Introduction and background

*Inflammatory arthropathy* is an umbrella term for rheumatic diseases which causes inflammation of the joints, with joint destruction as one of the most serious consequences. Early systemic pharmacological treatment is the main and first choice of therapy, but when pharmacological treatment no longer provides adequate disease control, orthopaedic surgery is an option. The main goals of surgical interventions in inflammatory arthropathies are pain relief and preserved or improved function (1).

During the past decades, modern surgical care has improved patients’ quality and length of life. However, formal and comparative assessment of procedures have been given minor attention, and only scant attention has been paid to patient and societal inconvenience or costs related to surgical interventions (2;3). Procedure-oriented evaluation has historically been the most common way of evaluating different surgical procedures, e.g. with revision of a prosthesis as the endpoint (4), but patient-oriented evaluations of pain and function are also important for assessing the impact of different surgical procedures and for evaluating whether treatment goals have been achieved (5). Functional impairment, pain, and the subsequent loss of quality of life and work ability are the main considerations for surgical treatment (6). A study of patients with RA reported that pain is the factor most patients would like to see improved (7), and it is known that complications of different surgical procedures may have serious impact on patients’ quality of life. Therefore, when evaluating results of surgery,
patient-reported measures are needed to capture a wide range of relevant and important aspects and domains of health and functioning.

The potential chronic and fluctuating course of the inflammatory arthropathies is a challenge with regard to decision-making and evaluation of effects of specific surgical procedures (5). Additionally, many patients with inflammatory arthropathies also have multiple joint involvements and suffer from co-morbidities. Due to the complex, chronic and progressive nature of the disease, thorough monitoring of patients is important, in order to make reasonable clinical decisions at the right time and in right order. For patients in need of long-term care, a treatment plan should be established, based on information from patient-reported measures of symptoms, function and disease impact, patient priorities and clinical considerations.

Recent studies have demonstrated declining use of orthopaedic surgical treatment in patients with inflammatory arthropathies, as a result of the new and more aggressive medical treatment and the possibility of a milder disease (8-12). However, data registers of patients with total joint replacements include a large proportion of patients with inflammatory arthropathies, with cases ranging from 3-6 % of the total hip arthroplasty patients to more than 90% of patients receiving hand, elbow and ankle replacements (4;13-19). Further, several studies have shown that some patients do not respond to, or tolerate the new pharmacological treatment, and that progression of radiological damage may occur despite clinical remission (20-22). The importance of early diagnosis and treatment is generally accepted and delayed treatment will increase the risk of irreversible damage (23). However, despite the new era of modern biological medication, elective orthopaedic surgery will still be an important and necessary treatment alternative for patients with inflammatory arthropathies.
The increasing success rate of total replacement surgery has resulted in a shift towards surgical interventions in younger populations (4;24). There has been a trend towards a more aggressive rehabilitation phase, with earlier mobilisation and shorter hospital stay, indicating that surgical interventions will influence patients’ health and daily life to a lesser degree than earlier (25). When evaluating surgical interventions also socio-economic evaluation is of importance, e.g. considering the cost-effectiveness of the different procedures (5). Patient-reported outcome measures (PROMs) can provide information on the results after surgical interventions. Some of these measures may be used for calculation of gained quality adjusted life years (QALYs), based on the length of life and the quality of the life years. QALYs are frequently used to elicit patients’ preferences for health states, and the cost-effectiveness of an intervention can be evaluated by relating the costs to the changes in QALYs. When considering different treatment options available for the patients, cost analyses and QALYs are important in priority discussions and clinical decision-making.

1.1 Diseases

1.1.1. Inflammatory arthropathies

There are three main categories of rheumatic diseases: inflammatory conditions (arthritic diseases, systemic connective tissue diseases etc), degenerative arthropathies (osteoarthritis) and soft tissue rheumatism (fibromyalgia). In this thesis, only patients with inflammatory arthropathies were included. Rheumatoid arthritis (RA), psoriatic arthritis (PsA), juvenile idiopathic arthritis (JIA) and ankylosing spondylitis (AS) are the most frequent inflammatory joint diseases. The majority of the patients in the current studies had RA.

1.1.2 Rheumatoid arthritis
RA is a chronic systemic autoimmune inflammatory disease and the most frequent disorder affecting diarthrodial joints. The most common mode of onset is symmetric involvement of the small joints of the hands and the feet, but also larger weight-bearing and unilateral joints can be involved (26).

RA affects all ethnic groups throughout the world (26). The prevalence is estimated to be about 0.5-1.0 % among Caucasians (27;28) and the total annual incidence rate is about 25-50/100 000. The onset of disease peaks at about 60 years of age (29;30) and females are 2.5 times more likely to be affected than males (29;31).

Extra-articular manifestations can be seen in almost 50 % of all RA patients and consist of arteriosclerosis, pericarditis, pleuritis, major cutaneous vasculitis, Felty´s syndrome, neuropathy, anemia, ophthalmological manifestations, glomerulonephritis and other types of vasculitis (32). Systemic symptoms may also occur, such as myalgia, fatigue, malaise, stiffness and fever.

Patients with RA suffer from pain and reduced physical function, caused by both inflammation and structural damage (33;34) as well as impairment of other dimensions of quality of life (29). The working ability is reduced among patients with RA (35;36) which is an important socio-medical impact because of the significant financial and psychosocial losses for the patients (37). The rheumatic diseases are the single most costly group of disorders, measured in terms of hospital costs, medication costs and costs of lost days at work (38). In addition, the disease imposes a considerable economic burden on the patients (39;40). RA is diagnosed according to a set of criteria. The American College of Rheumatology (ACR) 1987 revised criteria for the classification of RA is the most widely used (41). RA is defined by the presence of at least 4 of the 7 items listed in Table 1. Antibodies to cyclic
citrullinated peptides (anti-CCP) are widely used for RA diagnosis, but are not included in the 1987 ACR criteria for RA classification. Studies have shown that cyclic citrullinated peptides (CCP) improved the sensitivity of the ACR criteria most for patients with early symptoms and could be used for the classification of subjects of RA in the clinical studies (42;43). New criteria focusing on early diagnosis will be published in the near future.

Table 1
1987 Criteria for the Classification of Acute Arthritis of Rheumatoid Arthritis

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

Criteria 1 through 4 must have been present for at least 6 weeks.

The aetiology is largely unknown, but many factors contribute to the risk of developing RA, such as genetic factors, including human leukocyte antigen (HLA) shared epitope, hormonal factors, and environmental exposures such as tobacco smoking or infectious agents (44).
The primary target organ in RA is the synovial membrane. The normal synovium consists of an intimal lining layer, only one to tree cell levels thick. In RA changes include increased cellularity, increased vascularity, and infiltration with immune inflammatory cells which lead to a marked increase in tissue volume (45). Autoantibodies in RA include rheumatoid factor and anti CCP. Importance of humoral immunity is demonstrated by the efficacy of anti-B lymphocyte treatment strategies. T cells are involved in RA pathogenesis due to their presence in the synovium, association with HLA, presence of T-cell cytokines, and efficacy of anti-T lymphocyte treatment strategies. Cytokines are critical to RA pathogenesis and an imbalance between pro- and anti-inflammatory cytokine activities favours the induction of autoimmunity, chronic inflammation and thereby joint damage (46). Mechanisms that result in destruction of cartilage and bone lead to joint deformities and disability (26;47). There is a relation between long standing inflammation, pathology of RA, disability, radiographic progression and joint damage (48). The proinflammatory cytokines tumour necrosis factor alpha (TNF-alpha), interleukin 1 (IL-1) and interleukin 6 (IL-6) have proved to be important targets for treatments.

1.1.3 Ankylosing spondylitis

Ankylosing spondylitis (AS) is the major subtype among the spondyloarthritides (SpA). The main characteristics of AS are chronic inflammation of the sacroiliac joints, spine and entheses. Some patients also have peripheral arthritis and also lesions from other organs, e.g. iridocyclitis, bowel disease and heart involvement (26).

AS affects about 0.1-2 % across different populations, most populations near the lower end of the range, but varies across ethnic groups and is correlated to the prevalence of human leukocyte antigen (HLA-B27). AS usually presents in young adulthood with a male: female ratio of approximately 2-3:1 (28;49;50).
The 1984 modified New York criteria is most widely used for the classification of AS (51). The diagnosis of AS is defined by the presence of criteria 4 or 5 and at least one of the clinical criterion 1-3 (Table 2). The modified New York criteria is useful in established disease, but is less applicable in patients with early disease. As the presence of x-ray confirmed sacroiliitis is essential for the diagnosis of AS, there is currently a delay between the first symptoms and the establishment of diagnosis of more than 5 years. However, chronic radiological changes are the consequence of inflammation and not the inflammation itself, and MRI may therefore contribute to confirm the diagnosis earlier. On this background, new classification criteria for axial SpA has been developed (52).

**Table 2 Modified New York criteria for AS**

| 1. Low back pain for at least three months duration improved by exercise and some relieved by rest |
| 2. Limitation of lumbar spine motion in sagital and frontal planes |
| 3. Chest expansion decreased relative to normal values for age and sex |
| 4. Unilateral sacroiliitis grade 3-4 |
| 5. Bilateral sacroiliitis grade 2-3 |

AS is largely determined by genetics and associated to HLA-B27 (53). About 90-95% of all patients with AS are HLA-B27 positive as compared to 7-8% of the general population, and the risk of developing AS is about 5% in HLA-B27 positive individuals. However there are other genetic markers than HLA-B27 which are also associated with AS (54-57). No environmental triggers have been identified in AS, but several studies support the hypothesis
that bacterial antigens, especially from the gut flora, play a central role in AS pathogenesis (58). Several studies indicate that CIA (Chlamydia induced reactive arthritis) and enterobacteria induced reactive arthritis may develop into AS. In arthritis induced by chlamydial species, organisms are viable and metabolically active in the synovium (59). 65-85% of patients with reactive arthritis classified as a type of seronegative spondyloarthropathy are HLA-B27 positive (60). The pathology in AS is characterised by bony formation with fusion of joints and intervertebral spaces (61). The disease may have a substantial impact on physical function, health related quality of life and work disability (62). The only known predictor of radiographic progression is structural damage on radiographs at baseline (63).

### 1.1.4 Psoriatic arthritis

PsA has been defined as an inflammatory arthritis associated with psoriasis. Radiographic damage has been reported to develop in near half of the patients within 2 years after disease onset (64). There are multiple clinical subsets of PsA reflecting variable clinical patterns including: distal joint disease, arthritis mutilans, oligoarthritis (less than or equal to four joints), RA-like polyarthritis and spondylitis (26).

PsA occurs in approximately 25% of patients with psoriasis leading to prevalence in the population of 0.3% to 1%, mean age of disease onset is 40-50 years (65). The genders are equally represented.

The Classification of Psoriatic Arthritis group (CASPAR) developed classification criteria for PsA in 2006 (Table 3). These CASPAR criteria for classification of PsA is 99% specific and 92% sensitive for PsA (66).

### Table 3 CASPAR criteria
<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
</table>
| 1. | Evidence of psoriasis (one of a, b, c) | a. current psoriasis  
b. personal history of psoriasis  
c. family history of psoriasis  
   |
| 2. | Psoriatic nail dystrophy |   |
| 3. | A negative test for rheumatoid factor |   |
| 4. | Dactylitis (one of a, b) | a. current  
b. history  
   |
| 5. | Radiological evidence of juxta-articular new bone formation |   |

PsA is triggered by a complex interaction between genetic and environmental factors.

Patients with PsA are usually seronegative for RF. Various susceptibility genes to PsA have been identified. HLA-B27 is strongly associated with axial disease, whereas HLA-B38 and HLA-B39 are of more importance in peripheral disease (67). The environmental factors include trauma and infection (26). PsA histopathology differs from RA with the most striking difference in the characteristics of the synovial vasculature. Cellular immunity and cytokines, including TNF-alpha, are important mediators of PsA. Osteoclasts are important mediators of dysregulated bone remodelling in PsA. The burden of disease in PsA has been shown to be comparable with RA and AS (68;69).

### 1.1.5 Juvenile idiopathic arthritis

JIA is an umbrella term referring to a group of disorders that has in common chronic arthritis with onset during childhood, and is also one of the more common chronic childhood illnesses (26). 5-10% of those with JIA have a disease that resembles adult-onset RA much more than other types of JIA.

The prevalence of JIA is estimated to be 57-220 per 100 000 children younger than 16 years and about half the JIA patients have active disease that persists to adulthood (70;71).

JIA is an inflammatory disease with variations in genes within the inflammation networks that predispose the patients to disease. T-cell and cytokine profiles vary according to the JIA subtype and gene variations in the HLA region of chromosome 6 are associated with different
subtypes of JIA, except systemic onset JIA. In the current studies, only patients above 16 years with persistent and symptomatic JIA in need of treatment were included.

1.1.6 Other arthritides

Some patients with other arthritides than those mentioned above were also included in this project. These patients had an arthritic disease which could not be classified according to one of the above mentioned criteria, e.g. undifferentiated arthritis. Patients with osteoarthritis were not included.

1.2 Treatment of patients with inflammatory arthropathies

The overall treatment goal for patients with inflammatory arthropathies is to reduce pain, minimize loss of function, preserve health-related quality of life (HRQoL) and prevent bone damage (72). HRQoL represents the patient's evaluation of the impact of a health condition and its treatment on daily life. Optimal treatment includes both pharmacologic and non-pharmacologic interventions such as surgical treatment, exercise, physiotherapy and patient education, as emphasized in the ACR and EULAR recommendations (73;74).

1.2.1 Pharmacological treatment

Early diagnosis and intervention are important since disability and damage increase rapidly during the first year of the disease (75). During the last years, there has been a tremendous increase in pharmacological treatments available for patients with inflammatory arthropathies. The use of expensive medication have expanded (76;77), but patient’s response to therapy has been shown to vary considerably (20-22;78). Pharmacological interventions for patients with inflammatory arthropathies consist of symptom-modifying and disease-modifying drugs (Table 4).
### Table 4 Main pharmaceutical interventions in inflammatory arthropathies

<table>
<thead>
<tr>
<th>Classification</th>
<th>Types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesics</td>
<td>Paracetamol, Codeine, Tramadol, Opioids</td>
</tr>
<tr>
<td>Non-steroidal antiinflammatory drug (NSAIDs)</td>
<td>Non-selective and COX2 selective</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Local and systemic</td>
</tr>
<tr>
<td>Conventional Disease-Modifying Antirheumatic Drugs (DMARDs)</td>
<td>Methotrexate, Sulfasalazine, Leflunomide, Gold, Antimalarial drugs</td>
</tr>
<tr>
<td>Biological drugs (cytokine inhibitors)</td>
<td>Adalimumab, Etanercept, Infliximab, Golimumab, Certolizumab, Anakinra, Tocilizumab</td>
</tr>
<tr>
<td>Biological drugs (B and T cell targeted therapies)</td>
<td>Rituximab, Abatacept</td>
</tr>
</tbody>
</table>

#### 1.2.2 Surgical treatment

Joint destruction is one of the most important consequences of inflammatory arthropathies and orthopaedic surgery is a treatment alternative expected to preserve or improve joint function and also to provide pain relief (1;79). Once it has been established that a patient’s symptoms in a specific joint are related primarily to underlying structural damage, one should assume that the lesion is fundamentally irreversible and that orthopaedic surgery is the major therapeutic option (79). Patients with multiple joint involvements may need multiple surgical procedures over time, and it is therefore important to make a treatment plan. A thorough monitoring and a treatment plan will also contribute to good timing of surgical interventions, before joint destruction is too severe. Although there is available treatment for patients also with total destructed joints, it is more beneficial to maintain than to regain joint function (79;80). Distortion of the joint anatomy with accompanying soft tissue problems including tendon ruptures and osteoporosis, are factors that limit the choice of surgical procedures and
may have a negative impact on the results of surgical treatment. Timely referral for surgery is therefore important, and several studies underline that the pre-operative status is highly correlated with the post-operative gain in function and pain (5;61;80-85).

A number of different surgical treatment options are available for patients with inflammatory arthropathies. Orthopaedic surgery for this patient group is mainly elective treatment, with a few exceptions: instability of the cervical spine with resultant myelopathy and neurologic symptoms, rupture of the ulnar extensor tendons at the wrist and removal of the prosthesis from an infected joint (86).

The most common procedures are listed in Table 5. Procedures not performed at Diakonhjemmet Hospital are not mentioned or included in the papers (e.g. spine surgery). The different surgical procedures can be categorized according to location (upper and lower limb or specific joints) or according to the different procedures like replacement and non-replacement surgery. Further, differentiation of surgical procedures may also include surgery involving joints or soft-tissue.
### Table 5

**Elective surgical procedures available for patients with inflammatory arthropathies**

<table>
<thead>
<tr>
<th>Joint</th>
<th>Replacement surgery (types of prosthesis*)</th>
<th>Non replacement surgery (different types of surgery)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shoulder</td>
<td>Total replacement</td>
<td>Arthroscopy / synovectomy</td>
</tr>
<tr>
<td></td>
<td>Cement / cementless fixation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Normal / reversed</td>
<td></td>
</tr>
<tr>
<td>Hemi prosthesis</td>
<td>Cement / cementless fixation</td>
<td>Subacromial bursectomy</td>
</tr>
<tr>
<td></td>
<td>Cement / cementless fixation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Surface / with stem</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bi / unipolar</td>
<td></td>
</tr>
<tr>
<td>Elbow</td>
<td>Cement / cementless fixation</td>
<td>Arthroscopy / synovectomy</td>
</tr>
<tr>
<td></td>
<td>Non constrained (sloopyhinge)/</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Semi-constrained prosthesis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Open synovectomy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Resection of noduli/bursa olecrani</td>
<td></td>
</tr>
<tr>
<td>Hand/fingers</td>
<td>Cementless wrist total arthroplasty</td>
<td>Arthrodesis</td>
</tr>
<tr>
<td></td>
<td>Silicone prosthesis for the MCP joints</td>
<td>Open synovectomy</td>
</tr>
<tr>
<td></td>
<td>One component</td>
<td></td>
</tr>
<tr>
<td>Elbow</td>
<td>Two component prosthesis for the finger</td>
<td>Arthroscopy / synovectomy</td>
</tr>
<tr>
<td></td>
<td>joints</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Surgery on ligaments and tendons</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Resection of noduli</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nerve decompression (Carpal tunnel syndrome (CTS))</td>
<td></td>
</tr>
<tr>
<td>Hip</td>
<td>Total hip arthroplasty</td>
<td>Arthroscopy / synovectomy</td>
</tr>
<tr>
<td></td>
<td>Cement / cementless fixation</td>
<td></td>
</tr>
<tr>
<td>Hemiprosthesis</td>
<td>Cement / cementless fixation</td>
<td></td>
</tr>
<tr>
<td>Knee</td>
<td>Total knee arthroplasty</td>
<td>Arthroscopy / synovectomy</td>
</tr>
<tr>
<td></td>
<td>Cement / cementless fixation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>With or without the patella component</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ankle/foot</td>
<td>Uncemented 3 component ankle replacement</td>
<td>Arthrodesis</td>
</tr>
<tr>
<td></td>
<td>Silicone prosthesis for the first MTP</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Surgery on ligaments and tendons</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Resection of nodulus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Surgery on ligaments and tendons</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Forefoot resection arthroplasty (Tillmann)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other minor surgery</td>
<td></td>
</tr>
</tbody>
</table>

1.2.3  Non-pharmacological, non-surgical treatment
Over the last decades, rehabilitation, (including patient education, physiotherapy and exercise) is increasingly reported to have an important impact on patients’ ability to manage disability and to improve physical functioning and self-management (87-89). Because of fear for aggravation of disease activity and symptoms, people with inflammatory arthropathies have earlier been advised to limit the amount of physical activity and to protect their joints when exercising physically. However, current evidence supports that people with joint diseases should be encouraged to exercise in order to maintain or improve physical and mental health and reduce the risk of co-morbidities (87-91). Thus, rehabilitation programs based on updated knowledge have the potential of enhancing the beneficial effects of surgical interventions for patients with inflammatory joint diseases (73;87;91).

1.3 Measures of disease status

Measures of disease status in inflammatory arthropathies can be categorised into three main dimensions (figure 1):

- markers of inflammation measured by laboratory tests
- alteration in structural damage illustrated by abnormalities on x-rays
- functional consequences of the disease measured by patient-reported outcome measures (PROMs)

Laboratory markers of disease activity or x-rays were not included in this project. However, several studies report that disease activity and radiographic damage are strongly related both to physical functioning and pain (34;48;92-95). In chronic diseases quantifiable and standardized information concerning health status, pain and function are of special importance since such information is critical in the documentation of patient outcomes and results of care.
Such information can be collected easily and effectively from questionnaires completed by the patient (96).

‘Patient-reported outcome measure’ (PROM) is a short-hand term referring to the array of questionnaires, interview schedules and other related methods of assessing health, illness and benefits of health care interventions from the patient’s perspective. PROM, addressing constructs such as health-related quality of life, subjective health status and functional status, are increasingly used as primary or secondary end-points in clinical trials (97). In PROMs, attention is given to patients’ preferences and wishes, thus providing a feasible and appropriate method for addressing the concerns of patients both in the context of clinical trials and in clinical care (97). The PROMs used in this project are thoroughly described in section 3 (Material and Methods) and discussed further in the section 5 (Discussion).

2. General aim and specific research questions

2.1 General aim

The general aim of this thesis was to explore longitudinal outcomes and other relevant aspects related to elective orthopaedic surgical procedures in patients with inflammatory arthropathies, with a special focus on potential differences in upper and lower extremities.

2.2 Specific research questions

1. What is the overall magnitude of change in lower and upper limb physical function over a 10-year period in patients with RA?

2. Are there differences in disease characteristics in patients referred for hand surgery compared to those referred for foot surgery?
3. Clinical outcomes after orthopaedic surgical procedures in patients with inflammatory:

- how are the longitudinal changes in pain, physical function and health related quality of life?
- how are the longitudinal changes in clinical outcomes for replacement surgery compared to non-replacement surgery?
- how are the longitudinal changes in clinical outcomes for surgical procedures in the upper limbs compared to the lower limbs?

4. Cost-outcome descriptions of elective orthopaedic surgical procedures in patients with inflammatory arthropathies:

- how are the over all costs per QALY gained of surgical interventions?
- how are the costs per QALY gained after replacement surgery compared to the gain of non-replacement surgical interventions?

3. Material and methods

3.1 Study designs

Papers I, III and IV have longitudinal observational study design, whereas Paper II is based on a cross sectional study design.

3.2 Data sources

Paper I is based on data from patients included in the Oslo Rheumatoid Arthritis Register (ORAR) supplemented with data collected from the patients’ hospital records. Outcome measures reported from the ORAR are measures of physical function and general health (MHAQ, AIMS2 and SF-36).
Papers II, III and IV include patients’ with confirmed inflammatory arthropathies consecutively admitted and assessed for surgical procedures 2005-2006. The patients responded to a booklet of questionnaires including AIMS2, HAQ, SF-36, EQ-5D and visual analogue scales (VAS) addressing patient global, fatigue, general pain and pain in actual joint (Table 6). Demographic data and information on medication were confirmed in the hospital records. In addition, Paper IV also includes data from the hospital’s cost per patient accounting system (KOSPA) database (section 3.4.4).

Table 6 Data sources and variables used in Paper I-IV

<table>
<thead>
<tr>
<th>PAPER</th>
<th>Data source</th>
<th>Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paper I</td>
<td>Data from the ORAR Hospital records</td>
<td>Demographic and disease related variables, MHAQ, AIMS2, SF-36, RA-related surgical procedures</td>
</tr>
<tr>
<td>Paper II</td>
<td>Cross-sectional data from patients undergoing surgical procedures Data from the patients hospital records</td>
<td>AIMS2, HAQ, SF36 Demographic and disease related variables including sex, gender, disease duration and medication</td>
</tr>
<tr>
<td>Paper III</td>
<td>Longitudinal data from patients undergoing surgical procedures Hospital records</td>
<td>Demographic variables, AIMS2, HAQ, SF-36, EQ-5D and visual analogue scales (VAS) addressing patient global, fatigue, general pain and pain in actual joint.</td>
</tr>
<tr>
<td>Paper IV</td>
<td>Longitudinal data for patients undergoing surgical procedures KOSPA database Hospital records</td>
<td>Demographic variables, SF-36, EQ-5D Costs related to the hospital stay</td>
</tr>
</tbody>
</table>

3.3 Study populations

Patients from the ORAR (see description below) are included in Paper I. Paper II to IV are based on patients’ with confirmed inflammatory arthropathies who were admitted and assessed for surgical procedures at Diakonhjemmet Hospital 2005-2006.
3.3.1 The Oslo Rheumatoid Arthritis Register

The ORAR was established during the years 1991 to 1994 (27;98), with the purpose of providing epidemiological data that is representative of the entire population in the county of Oslo, with a population of approximately 550 000 inhabitants (98). The number of enrolled individuals in 1994 was 1,552 patients (27). The diagnosis of RA, a residential address in Oslo and the age at disease onset more than 16 years, are the inclusion criteria (41). The register is continuously updated and the completeness of the register is estimated to be 85% of the total population of patients with RA in the geographic area of Oslo (27).

3.3.2 Patients undergoing surgical procedures 2005-2006

Paper II to IV consists of patients’ with confirmed inflammatory arthropathies consecutively admitted and assessed for surgical procedures from February 2005 to May 2006. The database consists of 414 patients who underwent orthopaedic surgical treatment and responded to the surveys (replied both by mail and at hospitalisation) at baseline and at least one point of follow up. The distribution of diagnoses was as follows: RA (64.2%), JIA (3.9%), AS (5.1%), PsA (7.4%) and other arthritides (12.0%). Mean (SD) baseline age was 57.5 (13.1) years and 76.7 % were female.

In Paper II to IV, patients with osteoarthritis were not included. Patients who underwent revision surgery, surgery because of fractures or secondary infections were also excluded, and each patient was only included once, even if they underwent multiple interventions during the inclusion period. The patients responded to questionnaires preoperatively and 3, 6, 9 and 12 months after the surgical intervention.

3.4 Assessments

3.4.1 Demographic and disease related variables
Self-reported questionnaires and the hospital records were used to obtain information about demographic and disease related variables like gender, age, disease duration, medical treatment and surgical intervention.

3.4.2 Patient-reported measures

In this project, patient-reported outcomes were recorded by means of the following instruments:

- Four visual analogue scales addressing patient global assessment of disease, fatigue, general pain and pain in the specific joint undergoing surgical intervention
- Two standardised, disease specific instruments for measuring physical function: the HAQ (MHAQ) and the AIMS2
- The generic health status instruments Short Form-36 and EQ-5D

3.4.2.1 The Health Assessment Questionnaire and the Modified Health Assessment Questionnaire

The Modified Health Assessment Questionnaire (MHAQ) is an 8 item shortened version of the Health Assessment Questionnaire (HAQ) developed for patients with RA and osteoarthritis (92;99). HAQ and MHAQ focus on physical function. The HAQ includes questions assessing difficulty over the past week in 20 specific functions, grouped into 8 categories: dressing and grooming, arising, eating, walking, personal hygiene, reaching, gripping, and other activities. Modification of the HAQ (MHAQ) was done by including only one item within each of the 8 categories. The responses to “are you able to do…” were scored 0-3 in the HAQ (without any difficulty = 0, unable to do = 3) and 1-4 (without any difficulty
= 1, unable to do = 4) in the MHAQ. The MHAQ has been shown to provide essentially the same information as the longer original HAQ, but the scores are generally lower (100).

3.4.2.2 The Arthritis Impact Measurement Scales

The expanded version of the Arthritis Impact Measurement Scales (AIMS2) is a disease-specific measure of physical, social, and emotional well-being designed as a measure of outcome in arthritis, and has been translated into many languages including Norwegian (101-104). The first 57 items of AIMS2 are broken into 12 scales: mobility (five items), walking and bending (five items), hand and finger function (five), self-care tasks (four items), household tasks (four items), social activity (five items), support from family and friends (five items), arthritis pain (five items), work (four items), level of tension (five items) and mood (five items). The scales may be combined into a five-component model reflecting the physical dimension, affect, symptoms, social interaction and role. The score of each scale ranges from 0-10 (10 represents worst health). AIMS2 was scored according to the AIMS2 user’s guide issued by the Boston University Arthritis Centre.

3.4.2.3 The Short Form 36

The Short Form 36 (SF-36) is a generic health status measure, not specific to any age, disease, or treatment group, and has been used in a variety of conditions including RA, musculoskeletal disorders and patients who have undergone replacement surgery(105;106). The SF-36 assesses eight areas of health as follows: limitations in physical activities caused by the disease, limitations in the social functioning of patients as a result of physical and/or emotional problems, limitations in the usual role functioning (work or other daily activities) as a result of emotional problems, limitations in the usual role functioning as a result of physical health problems, bodily pain, general mental health (feelings of well-being,
depression etc.), vitality (energy and fatigue), general health perceptions. Scores in the range 0-100 are calculated for each of these different aspects of health, with low score indicating poor health status. The SF-36 has been compared to various disease specific instruments. In a study of RA patients, the physical functioning scale of the SF-36 did not seem to capture all aspects of physical health, but showed to be more sensitive than disease-specific measures for low levels of physical disability (106).

3.4.2.4 Visual analogue scales

Visual analogue scales (VAS) are also included in Paper III. VAS is used to record the patients’ health status. The 4 different VAS included are as follows: pain, fatigue, general pain and pain in the actual joint. The score was recorded on a 100 mm scale and patients were asked to mark the score that best represented their pain or fatigue the last week.

3.4.3 Utility scores

The term utility comes from the field of economics and refers to the total satisfaction from consuming a good or a service. In health science, utility is defined as a preference for a particular health status or outcome. Utilities can be transformed to quality adjusted life years (QALYs), which is a common “metric” for outcomes, used for cost-utility analyses. Utility scores quantify health related quality of life along a criterion that typically ranges from 0 (death) to 1 (full health). Utility scores can be negative, reflecting health states worse than death (107). Different methodological approaches are used by health economists to determine weightings for utility scores or QALY analyses, e.g. standard gamble (SG), time to trade-off (TTO), and rating scales (RS) (107-110). SG is a method of calculating utility values for health states in which participants are asked what percentage risk of death, if any, they would take in order to have the chance of a return to normal health (107). In the TTO method,
participants are asked if a treatment was available that could return them to good health, but would reduce the length of their life, how many of they remaining years would they be prepared to relinquish in return for normal health (107). In the RS method, the subjects are asked to locate their health state on a rating scale (e.g. 0-100) (110).

The utility scores (EQ-5D and SF-6D) are single index number instruments which have the advantage of showing the overall measure as a single number which might facilitate the understanding and comparison of the scores. EQ-5D and SF-6D are utility scores reported in quality adjusted life years (QALYs) (105;106;111;112). QALY is a measure used to elicit preferences for health states and is based on two factors: the length of life and the quality of those life years. QALYs are frequently used in political- and priority discussions regarding health care. Health care have two major objectives: to keep people alive and to improve their health related quality of life and effectiveness of health care can be assessed in terms of changes in QALYs. Different HRQoL instruments, both generic and diseases specific instruments may be reported as QALYs (113;114). The utility scores were in Paper III used for evaluation of the longitudinal impact of surgical interventions and in Paper IV to calculate the cost per QALY after surgical procedures.

3.4.3.1 SF-6D

The SF-6D is derived from the SF-36 and transformed to a utility score (scale 0-1, where 0 is equal to death and 1 is equal to perfect health). The eight dimensions of SF-36 are translated into 6 dimensions (physical function, role limitations, social function, pain, mental health and vitality) by means of an algorithm. The level of severity in each dimension is determined by responses of related items in SF-36 (115). The lowest achievable value with SF-6D for living patients is 0.29 (112). The SF-6D is based on SG as valuation technique.
3.4.3.2 EQ-5D

The EQ-5D is a standardised instrument for the use as a measure of health outcome, designed for self-completion (116). The EQ-5D has a 3-level, 5 dimensional systems, including the following five dimensions: mobility, self care, usual activities, pain/discomfort and anxiety/depression. The patients are asked to indicate no, moderate or severe problems with each of the five dimensions (111;112;116). The scoring of the EQ-5D instrument is translated into a utility weight where 0 represents death and 1 perfect health (111;112;116). Also negative values can be achieved in living patients, indicating that living persons can have a health status worse than death (maximum -0.59). The EQ-5D is based on TTO and visual analogue scales as valuation techniques.

3.4.4 Costs

The costs for the hospital stay were estimated by use of data from the KOSPA database (Paper IV). The KOSPA is an iterative calculation model, which allocates hospital costs to the different patient activities based on the electronic patient activity register (Distributed Information and Patient system in Hospitals (DIPS)) and a set of cost allocation criteria. The KOSPA model was developed by Analysesenteret AS, Oslo (www.asl.no) and adapted at Diakonhjemmet Sykehus AS, Oslo and a number of other hospitals in Norway. The KOSPA database system calculates the cost per patient during the hospital stay and may also calculate the costs per outpatient during day treatment in hospital. Some costs, such as use of imaging and operation resources (i.e. surgical materials and personnel time), are assigned directly to each patient. The ward costs, including nurses, physicians and physiotherapists time use, as well as pharmaceuticals and other utilities, are estimated as an average cost per day in the wards and are assigned to each patient according to their length of stay in the respective
wards. Overhead costs (excluding depreciation and cost of capital) are distributed according to a set of criteria (such as the number of employees, the number of beds in use etc.).

The costs calculated for each patient in this study were the costs the first year after surgery, which were defined as all hospital related costs including preoperative examinations, stay in the hospital and all postoperative follow-up visits.

3.4.5 Cost per QALY

The *cost per QALY* measure is calculated by the utility score and the relevant costs. Costs per QALY is a standardised measure and may therefore be used for comparison between studies. Yet, the costs included in the stipulations are the relevant costs for the actual intervention or service, thus, for comparison and interpretation of results, the costs included must be thoroughly defined (117). This issue is further addressed in the Discussion-part.

3.4.6 Economic model

A modification of an economic model described by Faulkner et al was adopted in Paper IV to calculate the cost-effectiveness of the surgical interventions (118). The economic model was created to estimate costs concerning total hip arthroplasty (THA). The model calculates expected costs for several years and includes costs concerning implant and surgical intervention, various hospital costs, patients’ age at time of surgical intervention. In addition, for this study, we included the outpatient costs the first year concerning the surgical intervention, the possibility of re-revisions and adjustments for differences in mortality rates in RA compared to the general population.

3.4.7 Surgical procedures
In Paper I, the hospital records were used for recording the number and category of RA-related surgical procedures for each patient. The surgical procedures were categorised in two main groups: surgical procedures involving upper or lower limbs. In Paper I, numbers of surgical procedures were used as a covariate in the statistical analyses.

In Paper II to IV all the patients included had undergone different surgical procedures and in Paper III and IV the different surgical procedures were also categorized into replacement and non-replacement procedures.

The primary large joint replacements are referred to as replacement surgery in this project, whereas the total replacements in the small joints (MCP, PIP and MTP joints) were categorized as other surgical procedures. This categorising was performed in order to establish more homogenous groups according to the postoperative follow-up and rehabilitation program.

3.5 Statistics

The statistical analyses in this thesis were performed using the statistical package for the social sciences for Window software, versions 14-15 (SPSS, Chicago, IL, USA) (Paper I-IV). Microsoft Office Excel 2003 was used for the probabilistic and subgroup analyses (Paper IV). P-values equal to or below 0.05 were considered to be statistically significant. A statistician was consulted about the statistical analyses.

Descriptive statistics were presented as numerical values or percentages, median (interquartile range) or mean (standard deviations (SD)) and 95% confidence intervals. Within group changes from baseline to follow-up examinations were analysed using paired t-test for
continuous variables and independent sample t-tests were used to compare longitudinal changes between groups.

Analyses of covariance (ANCOVA) were applied to compute the 10 year changes in physical function with adjustments for age, sex, disease duration, and number of surgical procedures in Paper I. Cross-tables and chi-square tests were used to compare differences in the medication and the distribution of the diagnosis between the groups of patients in Paper II.

Uncertainty in the model parameters (survival of the arthroplasty, costs and utility changes) was assessed by means of probabilistic analyses. Beta distributions were fitted to the estimated probabilities for survival of the arthroplasty, and gamma distributions were fitted for the estimates of in- and outpatient costs and utility changes. The parameter estimates were assessed by 25,000 simulations with the specified distributions. In the cost-outcome analyses, all mean costs and QALYs for the different types of surgery were estimated on the basis of Monte Carlo simulation (119). Monte Carlo simulation is a problem-solving technique used to approximate the probability of certain outcomes by running multiple trial runs, called simulations, using random variables.

A widely used strategy for dealing with missing longitudinal data is the last observational carried forward (LOCF) method. LOCF is a simple longitudinal imputation method, were the missing data point is given the same value as the last observed value (120). LOCF was used to replace missing values during follow-up in Paper II – IV.

The standardized response mean (SRM) reflects the magnitude of an improvement (or deterioration) and was computed as the change from baseline to the 2 months follow-up,
divided by the standard deviation of this change score. The magnitude of the SRMs were interpreted in terms of the thresholds introduced by Cohen for effect sizes: “trivial” (<0.20), “small” (>0.20<0.50), “moderate” (>0.50<0.80) or “large” (>0.80) (121). SRMs are comparable across the different instruments, independent of the instrument scales.

3.6 Legal and ethical aspects

All studies were conducted according to the principles of the Declaration of Helsinki. Patients gave written informed consent before participation. The studies were approved by the Regional Committee for Medical Research Ethics. The storage data was approved by the Data Inspectorate.

4. Summary of results

4.1 Paper I

*Patients with Rheumatoid Arthritis report greater physical functional deterioration in lower limbs compared to upper limb over 10 years.*

The purpose of this study was to examine to overall magnitude of change in self-reported physical function over a 10 year period in RA patients, and to compare 10 year changes between the lower and upper limbs concerning physical function.

A total of 414 patients collected from patients in the ORAR register with mean age 55 years were included in these analyses. The mean disease duration was 11.6 years at baseline. 56% of the patients underwent surgical intervention because of their RA during the 10 year follow-up period. The change in overall physical function was measured by the SF-36, the MHAQ and the AIMS2. Changes in physical function in upper and lower limb were measured by AIMS2 physical and MHAQ. The analyses were adjusted for age, sex, duration of disease, and number of surgical procedures in the lower and upper limbs.
The overall physical function deteriorated in RA patients over a 10 year period. The patients reported that lower limb function deteriorated more than upper limb function over a 10-year period, and the results were consistent after adjustment for number of surgical procedures. Our results indicated a greater deterioration in physical function in the lower than upper limb over a 10 year period in patients with established RA.

4.2 Paper II

Patients with inflammatory arthropathies undergo feet surgery later in the disease course than hand surgery

The main objective of this study was to compare disease duration, patient-reported health status measures and use of medication in patients with inflammatory arthropathies referred for hand or foot surgery.

During the study period, 116 patients with inflammatory arthropathies undergoing hand and foot surgery were included. A comprehensive booklet of disease related and generic questionnaires were filled in by the patients at baseline and data on disease duration, surgical treatment and medication were collected from the hospital records.

Baseline values for the patient-reported health status measures were mainly similar for the patients undergoing surgical procedures in the upper and lower limb. However, patients undergoing surgical procedures in the foot had significantly longer disease duration than patients undergoing surgical procedures in the hand (19 vs. 13 years, p= 0.04). Further, we found that patients undergoing foot surgery were more frequently on potent medication at the time of surgery compared to patients undergoing hand surgery (71 vs. 50 %, p=0.02). Our findings supported that foot affliction in inflammatory arthropathies may be underestimated.
4.3 Paper III

*Orthopaedic surgery in 255 patients with inflammatory arthropathies: longitudinal effects on pain, physical function and health related quality of life.*

In this paper our main objective was to examine the effectiveness of orthopaedic surgery, with regard to longitudinal changes in pain, physical function and HRQoL. We also wanted to explore the differences in effectiveness between replacement and non-replacement surgical interventions, and between surgical procedures in upper and lower limb.

255 patients with inflammatory arthropathies, mean age 57.5 years responded to mail surveys before surgery and 3, 6, 9, 12 months after surgery. SRMs were calculated to estimate the magnitude of improvement and facilitate comparison between the different measurements with various numerical scales.

Significant improvements were seen for most of the dimensions of health. Yet, the largest improvement was seen for the pain scores, and especially for pain in the actual joint. Similar improvement was seen after surgery in the upper and lower limbs, but patients undergoing replacement surgery experienced larger improvement than patients undergoing other surgical procedures.

Our results indicated that surgical procedures in patients with inflammatory arthropathies have major positive impact on pain in actual joint, but less improvement in other dimensions of health. Health benefits after replacement surgery were larger than health benefits after other surgical procedures.

4.4 Paper IV

*Cost-effective analyses of elective orthopaedic surgical procedures in patients with inflammatory arthropathies*
The main aim of this study was to examine the cost per QALY gained of surgical interventions in patients with inflammatory arthropathies and, secondly, we assessed the costs per QALY gained for replacement compared to non-replacement surgery.

In total 248 patients with inflammatory arthropathies undergoing orthopaedic surgical treatment were included. These patients responded to mail surveys at baseline and 3, 6, 9 and 12 months after surgical intervention. The comprehensive booklet of questionnaires also included the utility scores EQ-5D and SF-6D, and the health benefit from surgery was subsequently translated into QALYs.

The KOSPA system was used to derive the direct treatment costs for each patient the first year.

Significant improvements in utility scores were found at 12 months follow-up (0.10 with EQ-5D and 0.03 with SF-6D (p<0.05)). We found that the estimated 10-year cost per QALYs gained were €5,000 for hip replacement surgery (€18,600 using SF-6D) and €10,500 (SF-6D €48,500) for all replacement procedures. The five-year cost per QALY was €17,800 for non-replacement surgical procedures measured by EQ-5D (SF-6D: €67,500).

In conclusion, we found that elective orthopaedic surgery in patients with inflammatory arthropathies was cost-effective when measured with EQ-5D. Some procedures were also cost-effective when SF-6D was used in the economic evaluations. We confirmed, as shown in previous studies, that hip replacement surgery was the most cost-effective procedure, irrespective of analysis method.

5. Discussion

The general discussion of this thesis will focus on two main issues: First, the methodological aspects, in terms of design, data collection, outcome measures and statistical procedures are discussed, and secondly, the main results and their clinical implications.
5.1 Methodological aspects

5.1.1 Study samples

In epidemiological, observational studies, the participants are selected from a larger group of potential subjects, and the validity of the extrapolation of results depends on the representativeness of the sample included (122). The identification and inclusion of non-random samples impact the validity of the study, and a high level of representativity is needed for generalisation of the results to the entire underlying population.

Different types of selection bias may influence epidemiological studies, like for example left and right censorship (123). Left censorship in longitudinal studies refers to the potential bias introduced when the most severely affected patients are excluded from the recruitment, for example due to the effort of filling in the questionnaires or not being able to complete the intervention of interest. On the other hand, bias related to potential loss of follow-up is described as right censorship. The results of the current studies may to a certain degree be influenced of both left and right censorship, and this will be discussed below.

5.1.1.1 The Oslo Rheumatoid Arthritis Register

Paper I includes patients from the ORAR which is annually updated with new and deceased cases, and was estimated in 1994 to have a completeness of 85 % (27;124). The assumption is that results from ORAR are representative of the underlying population of RA patients in Oslo. A population survey in 1994 supported this hypothesis (27;125), which is important for the external validity of results from ORAR. More recent data collections may be influenced by factors that have interfered with the completeness of the register, for example new characteristics and organisation of the health care. There has been an alteration in the
functional assignment between the rheumatology centres in Oslo, the patients have recently got the opportunity of 'free choice' of hospital, and the number of patients treated in private practice in Oslo may have increased. However, the number of patients in ORAR has been quite stable since the establishment in 1994, with a numeric increase over the years, which approximately mirror the increased population in Oslo. The differences between the respondents and non-respondents have been estimated and indicated only minor differences in age, disease duration and percentage with positive rheumatoid factor (11).

5.1.1.2 Patients undergoing surgical procedures

Paper II, III and IV include patients with confirmed inflammatory arthropathies consecutively admitted and assessed for surgical procedures between February 2005 and May 2006 at Diakonhjemmet Hospital in Oslo. The database included 361 patients with inflammatory arthropathies who were asked to participate in this study at the time they were inducted for the surgical intervention. The patients who responded positively and completed the preoperative questionnaire were included in the database. Patients who fulfilled the planned surgical intervention were included in the current analyses (70%). The "non-participants" (30%) were excluded for three reasons:

- the planned surgical procedure was not performed for reasons due to the patients health
- the patient underwent a revision surgery
- the follow-up questionnaires were not completed

The response rate in this study was similar to other surveys based on ORAR (11;125). However, examples of left censorship bias may be represented, as some of the most severely diseased patients may have been excluded due to the reasons mentioned above.
Further, right censorship bias may also have occurred, as patients who underwent replacement surgeries were more likely to have missing values in their follow-up data than patients who underwent non-replacement surgery. Likewise, the oldest patients also had a slightly higher percentage of missing values than the younger patients, whereas missing values were independent of gender and diagnosis.

In Paper III and IV, the different surgical procedures were divided into main categories of surgical interventions, like replacement and non-replacement surgery. This approach gave the opportunity of estimating and analysing outcome after broader categories of surgical interventions. The term replacement surgery refers to the primary large joint arthroplasties whereas total replacements in the small joints (MCP, PIP and MTP joints) were categorized together with other surgical procedures for analytic purposes. This categorisation was performed in order to establish more homogenous patient groups, based on the differences in extent and content of the postoperative rehabilitation program in patients undergoing large joint versus small joint arthroplasties and non-replacement procedures.

5.1.1.3 The KOSPA database

The KOSPA database (described in section 3.4.5) is the hospital’s cost per patient accounting system which is an iterative calculation model. The hospital costs are allocated to the different parts of patients activities based on the electronic patients activity register and a set of cost allocation criteria. The costs included in the database are partly assigned each individual patient. Some of the costs are average costs and some are overhead costs distributed by an interactive calculation model and numerous data are taken into account in these calculations, e.g. registration in the hospital records according to diagnoses, interventions and length of stay in hospital. Such factors are registered in the hospital records by different health
professionals which may create some inaccuracy in the data recorded for each patient. However, the fact that many of these data are controlled by other professionals compensate for some of the uncertainties.

5.1.2 Study designs and data collection

The designs and methods applied in this thesis have limitations and strengths which will be discussed below. Paper I, III and IV are based on longitudinal study designs which involves data collection at more than one point of time and is appropriate for studying variables or phenomenon over time (126-128). Even if the randomised controlled trial (RCT) design is associated with the highest level of evidence, longitudinal observational studies can also provide important evidence of effectiveness because the patient population is closer to an unselected population and the follow-up is performed in a real life setting (129;130). The term effectiveness, as opposed to efficacy, refers to how well a treatment performs outside the context of an RCT. Few RCTs or comparative observational studies examining effects of surgical interventions for patients with rheumatic diseases are available (131). A strength of the observational longitudinal design applied in this project, was that the study population probably reflects the 'real-life' situation closer than populations in clinical trials with strict inclusion criteria. Thus, the results of such studies may have high external validity for clinical practice (126-128).

Paper II is based on a cross-sectional study design. Cross-sectional designs involve collection of data at one point in time, and are especially appropriate for describing the status of a phenomenon or examining associations between phenomena at a fixed point in time. The main advantage of cross-sectional designs is that large amounts of data may be collected with moderate resources (132).
5.1.3 Assessment

5.1.3.1 Patient-reported outcome measures

In chronic diseases, quantifiable and standardized information concerning health status, pain and function are of special importance since such information is critical in the documentation of patient outcomes and results of care. This information can be collected with high feasibility and effectively from questionnaires completed by the patient (96). Such PROMs are increasingly being recognised as important complements to information and knowledge obtained from clinical assessments (92-94).

Patient-reported data rely on the assumption that information given by the participants themselves is valid, reliable and responsive. This assumption has also been supported in recent studies (133;134). A study comparing patient-reported and physician-reported assessments concluded that improvements in signs and symptoms of active RA in RCTs appear to be best reflected by patient-reported measures. (133;135).

Conclusively, PROMs have shown to provide information similar to many clinical measures and are at least as responsive. Further, PROMs also appear to be a cost effective and attractive approach for quantitative assessment and monitoring of health status of the individual patient (92) and should be included when results are reported in RA clinical trials.(136).

Both generic and disease specific PROMs are used in this thesis. Generic health status instruments are designed to capture various aspects of health in any population irrespective of diseases or condition and may have the potential to highlight domains of disease consequences. Generic instruments can be used for comparisons between different patient groups and between patients and healthy controls. However, it may be questioned if the broad
scope of generic instruments adequately reflects health problems in populations with specific disorders, and the instruments may contain irrelevant items (137;138).

*Diseases-specific instruments* are useful for assessing and monitoring disease related factors in patients with specific diseases or disorders, and are likely to address issues that are relevant to the respondents, thereby also with the potential of being more sensitive to change than generic instruments. Because of the different qualities of the instruments, they may provide complementary information.

HRQoL represents the patient's evaluation of the impact of a health condition on daily life and has originated from two different approaches: health status and health value/preference/ utility assessment (139). In general, health status measures describe a person’s functioning in one or more domains (e.g. physical functioning or mental wellbeing), whereas utility measures assess the value or desirability of a state of health against an external metric. Utility measures are generic, direct or indirect measures that are summarized and expressed as a single number (140-142). Direct health utilities are usually ascertained via face-to face interviews, with computer assisted administration being the state of the art. Indirect health utilities use population assigned weight to calculate utility scores for particular health states from health scale instruments (143;144). The ease of administration of these indirect measures enables them to be used in national surveys, and they are commonly used as the source of quality of life weightings in economic evaluations. EQ-5D (111;116) and SF-6D (115) are examples of such indirect utility measures and single index number instruments.

The advantage of the single number utility score compared to a profile instrument is the perspective of an “overall outcome”, which may be more easily understood and interpreted than the more complex profile indexes. On the other hand, a weakness with the single number index compared to the profile index is that no detailed information is provided regarding
which specific domains contribute to change in scores during clinical course or after interventions.

A strength of this study is the comprehensive data collection, including utility scores, generic instruments and disease specific measures, thus capturing the same construct or domain by use of several different instruments (112). Consistent results across instruments support the robustness of the results. However, in Paper III, the large number of instruments may have represented a burden for the patients, since missing values occurred with a frequency of about one third at each point of follow-up. Further, a large number of tests may also increase the chance of finding statistically significant results just by chance (type I error). Statistical adjustments of numerous tests may be used to reduce this problem, as for example the Bonferroni correction (122). However, since Paper III was considered to be an explorative study, such adjustments were not applied.

In Paper IV, the two utility instruments EQ-5D and SF-6D were used to capture patients perceived health changes after surgical intervention. Due to the well known different profiles of these instruments with regard to floor and ceiling effects, the two instruments showed, as expected, different magnitude of improvement (112;141). Consequently, more favourable cost per QALYs were reported when the surgical intervention was evaluated by the EQ-5D than when evaluated by the SF-6D. EQ-5D and SF-6D are the most widely used utility measures and were therefore chosen for this study. Due to feasibility reasons, additional utility measures, e.g. 15-dimentional (15D) (145) and Health Utility Index (HUI) (146) were not included, since this would have increased the burden for the patients.

5.1.3.2 Cost analyses
Economists are interested in quantifying the effects of health care interventions for different diseases; as such indexes may facilitate comparison of cost and benefit for different interventions. The QALYs are frequently used for this purpose, and may act as an important factor in the decision and priorities between different health care procedures (109;113;114;147). Utilities are transformed to QALYs as the common “metric” for outcomes and necessary for a cost-utility analysis.

The utility scores are generic and thereby eligible for use in different studies and diseases. However, the costs included for services or interventions may differ between studies. E.g. some studies include only direct costs or the actual cost for a specific treatment and some studies also include indirect costs (e.g. economics concerning lost work ability). To make QALY analyses comparable, the costs included must be defined precisely, so that the results can be interpreted correctly (117). The cost analyses in Paper IV were based on several assumptions which are important for the interpretation of the results: The costs calculated for each patient were the costs for the first year after surgery, which were defined as all hospital related costs including preoperative examinations, stay in the hospital and all postoperative follow-up visits. We assumed that the costs in the second and subsequent years after surgery would not be influenced by the surgical intervention, and no medical or other costs were included beyond the first year. However, the consequence in terms of over- or underestimation of the cost-effectiveness ratio is difficult to assess.

Costs were measured in 2005 and 2006 Norwegian Kroner (NOK) and adjusted to 2008 level by means of the consumer price index. The exchange rate used was €1.00~NOK 8.92 (xe.com 2009.05.26).

We also adopted an economic model suggested by Faulkner et al (118). This model was in addition modified by three relevant factors:
• the outpatient costs of the surgical intervention;
• the possibility of re-revisions
• adjustments for the difference in mortality rates in RA compared to the general population.

The additional factors were taken into account to make the model more accurate and better adapted for the relevant patient group. We started by establishing a deterministic model based on the average costs and utilities in the different types of replacement and non-replacement surgery. Secondly, a probabilistic model was built, based on the same underlying data, but with the uncertainties of the parameters included. Additionally, the overall uncertainty of the model was assessed.

Another important assumption that was made before estimating the cost per QALYs was the duration of the effect after the surgical interventions. The Norwegian Arthroplasty register provides data on revision rates for the replacement surgery depending on type of surgery and varied from 0.5% to 2.8% pr. year, depending on the type of surgery (4). Earlier studies report that postoperative changes in outcome measures last for 10 years for replacement surgery (4;148-150). Based on this, we assumed a 5 and 10 years risk for revision of arthroplasties in our analyses (4).

We assumed no gain in HRQoL during the first year following revision surgery and the revision costs were estimated by use of the Norwegian Diagnoses Related Groups (DRG) cost weights. The cost of revisions for hip-, knee and ankle arthroplasties were about 20% higher than for primary surgery (data from the KOSPA register at Diakonhjemmet Hospital comparing costs for primary and revision replacement surgery). For arthroplasties in the upper extremities the cost weights were the same for primary and revision surgery (151).
Supported by the literature, a conservative estimation was made for the non-replacement surgical procedures, assuming that the postoperative changes in the outcome measures lasted for 5 years for non-replacement surgery (6;152). Based on the small sample size and the different procedures this may be a bias in Paper III and IV. The persistent effect after the non-replacement surgical interventions is hard to estimate. In Paper III and IV we focused on the non-replacement surgical procedures all together as one group and several different procedures were included in this group, and a 5 year effect of the procedures may therefore be low for some of the procedures, e.g. arthrodesis which is estimated to last longer. Studies with larger groups of patients are needed to differentiate between procedures and increase the accuracy of this estimate.

We modelled all cause mortality by assuming that patients with inflammatory rheumatic disease have an increased mortality. On the basis of published studies we assumed that the standardized mortality ratio (SMR) was 1.27 (153). Mortality rates for the Norwegian population were used to assess the survival rates for males and females separately (154) and adjusted for the increased SMR seen in RA (1.27) (153). This increased SMR was used for all patients in this study. However, different mortality rates after total replacement surgery have been reported (5;155). We used mortality data after surgical interventions which showed an mortality rate on 0.18% for hip- and 0.16% for knee arthroplasties (156).

The value of costs and money will change over time. Therefore costs and QALYs were discounted by 4% as recommended for assessing the net present value (NPV) in Norway (157).
A definition of the acceptable costs per gained QALY is needed for interpretation of the results. The Norwegian Directorate of Health has indicated that a gained QALY is valued to be equivalent to approximately €56,040 (NOK 500,000) and this limit for acceptable costs per QALY was used in Paper IV (158).

5.1.4 Data analyses

The data in all papers were considered as approximately normally distributed and parametric statistical methods were used in all analyses.

One of the main methodological problems in longitudinal studies is attrition, the situation that not all subjects have data on all time-points. Patients may miss one or more measurements during follow-up or miss the final examination. We do not consider the missing values to have a major impact on the results, since the LOCF method was used as a conservative method to handle missing values. Imputation of missing data may lead to an underestimation of the overall time effect, and possibly influence the results in the direction of underestimation of the benefits. This phenomenon is stronger when the percentage of missing data is higher (159).

The responsiveness of quality of life measures has received considerable attention in the literature. A two time-point (pre-post) study design is usually adopted to evaluate this property when a gold standard is not available. Among many indices, Cohen's effect size and the standardized response mean (SRM) are usually computed. To interpret the results, researchers commonly use the same criterion for both indices, even though they are different by definition (160;161). We also chose to apply the widely accepted criteria for strength of effects suggested by Cohen (121).
In Paper I and III SRMs were computed for all measures. The SRM makes it possible to compare the magnitude of change between the different instrument scales, independent of scaling properties (121).

5.2 Results

5.2.1 Physical function and surgical treatment of the upper and lower limb

RA is a chronic and potentially progressive disease (162). According to the results in Paper I, the overall physical function seemed to deteriorate over time, and this finding is supported also by other studies (29;35;163-165). RA may affect several joints and it is well established that the physical disability increases over time due to both inflammation and joint destruction (34;48;166). However, data on the progression of the disease in different joint areas are very limited. Such data are of interest for evaluation of the relative need for surgical procedures in the lower and upper limb, and for the understanding the disease course.

In Paper I, deterioration in physical function over a ten years period was consistent across several scales and instruments (SF-36 physical function, AIMS2 physical, mobility, walking and bending, hands and fingers, household and MHAQ). A strength of the study was the consistent results across several different outcome measures within the same dimension. However, the HAQ / MHAQ, AIMS2 and SF-36 are not designed for comparison across instruments, only for comparison for different patient groups or within the patient. Thus, as described by Cohen, SRMs can be used for comparisons of different instruments with different scales and were presented in Paper I and III (121).
We adjusted for sex, age, disease duration and relevant surgical interventions performed during the 10 year follow up. Several variables may influence the patients’ physical function, and perhaps we might have included more items, as for example co-morbidities (167).

The disease duration was 11.6 years at baseline. Although adjustment for disease duration was performed in the analyses, all patients had established disease at baseline which is a limiting factor for the interpretation of the results. We do not know if the differences seen between lower and upper limb in established diseases also are similar earlier in the disease course (168).

The magnitude of deterioration was generally larger for activities related to lower than upper limb function. Possible explanations for this may be related to different stress on the joints due to weight bearing and that a possibly more active inflammation process leads to more joint destruction in the lower compared to the upper limb. However, radiographic data were not available to examine this hypothesis. We did not adjust for any pharmacological treatment since the main treatment is systemic with apparently similar effect on upper and lower limb. However, local pharmacological treatment might influence the result, but this information was not available. There are also reasons to believe that the joints that are treated with pharmacological injections are more likely to be localized in the lower limbs. Surgical interventions may also possibly influence the disease course differently for the upper and lower limb regarding pain and functional outcomes.

In Paper I, differences in disease course for upper and lower limbs were found, despite similar number of surgical interventions. However, we found that the disease duration at the time of surgery was significantly longer for patients referred for foot surgery compared to those
referred for hand surgery, and patients referred for foot surgery were also on more potent medication (Paper II). Previous studies have indicated that the foot is involved at the disease onset to at least the same degree as the hand (169). Studies by Anderson (1996) and Da Silva et al. (2003) claim that surgical intervention can be regarded as an outcome measure in the treatment of patients with inflammatory arthropathies (79;170). Large joint replacement is almost exclusively performed in cases of severe joint damage. According to these previous studies, surgery later in the disease course could indirectly pretend a milder disease in the feet compared to the hands. In contrast to this suggestion, we found that patients undergoing surgical interventions in the feet were on more potent medication at the time of surgery than patients undergoing hand procedures, thus indicating that patients with foot surgery were more severely affected by their disease (Paper II).

A possible explanation for the differences in the timing of the surgical treatment for hand and feet may be that impaired foot function affects patients to a lesser degree than impaired hand function. Other explanations may be that foot surgery has a lower priority than hand surgery, both from the surgeons’ and from the rheumatologists’ perspective. The current diagnostic criteria system for RA, The ACR 1987 revised criteria for the classification of RA (Table 1), seem to support this suggestion, since different focus on hand and foot involvement is apparent also in these criteria (41;171;172). Similar, the abbreviated joint counts with assessment of 28 joints included in the most widely used disease activity measure (DAS 28) is an illustrative example, as the joints of the foot are not included in this index (173).

Both Papers I and II focused on possible differences in disease course and timing of surgical treatment between the lower and upper limb in patients with inflammatory arthropathies. The findings indicated that the impact of foot affliction may be underestimated and that an enhanced focus is needed according to timing and planning of surgical interventions for
patients with multiple joint destructions. If surgery is postponed beyond a critical point, the post-operative benefits may be reduced and complication rate may be higher due to more extensive surgical procedures (5;174;175).

5.2.2 Patient-reported- and cost-effectiveness outcomes after surgical intervention

Significant improvement was seen for most of the health dimensions after surgical intervention in patients with inflammatory arthropathies, but the magnitude of improvement (as measured by SRMs) differed considerably. The largest improvement was observed for pain in the specific joint exposed to surgery, but improvement was seen also for general pain, physical function, mental health, vitality and social function (Paper III). Pain is reported to be the area of health where most patients would like to see improvement (7) and the level of pain is associated with most other self-reported health status measures (95;176). Britton et al showed that pain was the most informative outcome measure as predictor of revision and correlated well with the patients’ opinion (5;177). Patients referred for surgical interventions have expectations about improvement both concerning pain and physical function and our findings indicate that patients should be informed that the largest improvement can be expected in the area of pain. The expectations about the results of surgery might differ between the physician and patient, and patients expectations might differ according to their disease duration and adaptation to their condition (178-180).

For ethical and practical reasons we were unable to perform an RCT. Thus the efficacy of surgery could not be directly compared to a control group. However, in order to enhance the interpretation of the data, we took the opportunity to compare patients with replacement vs. non-replacement surgery and patients with procedures in the upper and lower limb.
Replacement surgery was performed in more than 25% of the patients (Paper III and IV), which is in accordance with previous studies (181;182). Compared to the patients who underwent non-replacement surgery, the replacement surgery group reported more pain and also worse health across several other dimensions of health preoperatively. Earlier studies have shown that preoperative factors with increased pain and reduced physical function predict the functional outcome after surgical intervention. These studies indicate that patients with severe preoperative status also gain less health compared to patients who have a better preoperative status (174;175;183). In contrast to this, we found that patients who underwent replacement surgery reported larger improvement in PROMs than the non-replacement group, even if the preoperative status was worse.

We found that the improvement course was similar in patients with replacement and non-replacement procedures and that the main improvement was observed during the first three months postoperatively (Paper III and IV), which is in accordance with previous studies reporting early improvement after replacement surgery (184;185). This may indicate beneficial results, since a study of Brander et al. indicate that improvement predicts subsequent improvement in 5 years after surgery (174).

Many patients will, during their disease course be in need of multiple surgical interventions. Thus, a comprehensive treatment plan should be established together with the patient, considering the general disease condition, order of surgical interventions for involved joints, medical treatment and patients’ preferences and priorities.

Pain relief and functional improvement are widely accepted treatment goals of surgical interventions, and patient-reported outcome measures are pivotal when evaluating results after
treatment (112). The combination of a disease-specific scoring system and a quality-of-life survey allow a more global assessment, and when evaluating surgical interventions it is necessary not only to analyse the benefit of the intervention, but also to ascertain the patients satisfaction (5;186).

Arthropathies entail considerable costs to patients in terms of pain and suffering and to society in terms of health care resources. The health care costs of RA are reported to be comparable to those of coronary artery disease (187;188). An additional challenge in the evaluation of specific surgical procedures in rheumatic diseases, is the progressive and fluctuating disease course (5), which complicates both the performance and interpretation of results of surgical interventions.

When evaluating surgical interventions in patients with inflammatory arthropathies also cost analyses are important (5). The real cost of any medical intervention is the health benefits by the best use of the resources, and the objective of economic evaluation is to scrutinize alternative use of health resources (189;190). Surgical interventions in patients with inflammatory arthropathies were found to be cost effective when measured with the utility score EQ-5D and mainly also when measured by SF-6D (Paper IV).

The replacement surgical treatment cost more than the non-replacement surgical procedures, but these procedures were more cost-effective than non-replacement surgery (Paper IV). The first-year costs were somewhat greater for patients who underwent replacement surgery than non-replacement procedures, but the gain in utility was larger, so the replacement surgery turned out to be most cost-effective. Total hip replacement (THA) seems to be the most cost effective procedure (The cost per gained QALY assessed by EQ-5D ranged from € 5,000 for
THA to €17,800 for non-replacement surgery) as also observed in earlier studies (148).

Previous studies indicate that total hip replacement surgery in patients with osteoarthritis and inflammatory arthropathies is more cost-effective than coronary artery bypass grafting and kidney transplantation (5;190). However, the cost outcomes reported in Paper IV were based on relative small sample sizes and this may limit the interpretation of the results.

The category non-replacement interventions in this study included many different types of surgical procedures. Uncertainty of the results due to the relative small sample sizes for the various non-replacement surgical procedures is a limitation and more research in larger study populations are needed to distinguish between cost outcomes for the different non-replacement surgical procedures. On the other hand, the positive effects of several of these procedures are expected to last longer than the 5 years used as a presumption in the calculation of costs in this study.

Although the costs from the surgical procedures, including the materials, were larger for replacement surgery than non-replacement surgery, time of stay in hospital was the single factor that most strongly inflated the total costs, independent of type of surgical procedure. Costs related to stay in hospital constituted nearly half of the total costs the first year. An implication of this finding is that the costs after surgical procedures have the potential to be decreased by reducing the length of stay in hospital. An earlier study has shown that reduction in the length of stay in hospital provide savings in the total costs without adversely affecting the overall outcome (25).

The cost-effectiveness analyses in Paper IV have some limitations. For example, the influence of medical costs and patients' ability to work were not considered. Cost-outcome descriptions
are important in modern medicine, as priorities have to be made between increasing numbers of costly therapeutic opportunities. Yet, it is important to be aware that QALYs are a simplified and theoretical way of describing health status, and changes in some health status dimensions might therefore not be captured by this approach.

A cost-effective use of resources implies that the treatment which gives the highest expected health gain per unit of cost should be prioritized (191). The use of expensive biological medical treatment in RA and related diseases has increased tremendously during the last years and has been shown to be effective, but not without side-effects (192-197). Systemic pharmacological treatment is considered the main and first-line treatment of rheumatic diseases. However, despite the fact that some recent studies have demonstrated a decline in orthopaedic surgery in patients with inflammatory arthropathies (9;13;170), and the fact that surgical interventions may have adverse effects (194), it is still important to consider surgery as a beneficial supplement or alternative treatment for patients with inflammatory arthropathies.

6. Conclusions

The overall physical function measured by the AIMS2 physical and the MHAQ deteriorated over a 10-year period in patients with established RA, and the lower limb function deteriorated significantly more than upper limb function.

Significant differences in disease characteristics were found for patients referred for hand and foot surgery. Patients undergoing surgical procedures in the foot had significantly longer disease duration and were more frequent on potent medication at the time of surgery compared to patients undergoing hand surgery.
We found that pain, physical function and health related quality of life improved significantly after surgical interventions in patients with inflammatory arthropathies, with the largest improvement in pain scores.

Patients referred for replacement surgery reported more pain, lower physical function and health related quality of life than patients referred for non-replacement surgical interventions preoperatively. However, improvements after surgery were larger for the replacement group compared to the non-replacement group. The results for upper and lower limb surgery were similar for all outcomes.

Elective orthopaedic surgery in patients with inflammatory arthropathies was cost-effective when measured with the EQ-5D, and some procedures were also cost-effective estimated with the SF-6D. Replacement surgery was more expensive procedures than non-replacement surgical interventions. Yet, replacement surgery was more cost effective, since then gains in QALYs were larger after replacement than after non-replacement surgery. Hip replacement surgery was most cost-effective, irrespective of analysis method.

7. Clinical implications

This thesis provides relevant data concerning the progress of physical function in patients with inflammatory arthropathies. Despite a more severe disease progression in the lower compared to the upper limb, the lower limb seem to be treated later in the disease course. This observation might indicate that the disease severity in the lower limb is underestimated and that treatment procedures are initiated later than for the upper limb.
A treatment plan based on clinical decisions and patients’ priorities is important to ensure adequate treatment at the right time for joints involved. Later treatment than necessary might indicate reduced treatment options for the patients.

This thesis also provides important data concerning patient-reported outcomes after surgical interventions. The data are relevant for the results to be expected from surgical procedures, and, according to this, patients' should be informed that largest improvement can be expected in pain scores.

Further, the cost benefit after surgical interventions is of importance for patient, physician, and society. Importantly we showed that the most expensive type of interventions (replacement surgery) also was the most cost-effective, and that surgical interventions, and especially replacement surgery, represent an important cost-effective treatment alternative for patients with painful, destructed joints.

8. Reference List

Reference List


(100) Uhlig T, Haavardsholm EA, Kvien TK. Comparison of the Health Assessment Questionnaire (HAQ) and the modified HAQ (MHAQ) in patients with rheumatoid arthritis. Rheumatology (Oxford) 2006 Apr;45(4):454-8.


(143) Tsevat J. What do utilities measure? Med Care 2000 Sep;38(9 Suppl):II160-II164.


(191) NOU 18 Prioriteringer på ny (Ranking on priorities again). Statens forvaltningstjeneste (Royal commission); 1997.


Orthopaedic surgery in 255 patients with inflammatory arthropathies: longitudinal effects on pain, physical function and health-related quality of life


*Ann Rheum Dis* 2009 68: 1596-1601 originally published online October 24, 2008
doi: 10.1136/ard.2008.096362

Updated information and services can be found at:
http://ard.bmj.com/content/68/10/1596.full.html

These include:

**Supplemental Material**
http://ard.bmj.com/content/suppl/2009/10/02/ard.2008.096362.DC1.html

**References**
This article cites 33 articles, 8 of which can be accessed free at:
http://ard.bmj.com/content/68/10/1596.full.html#ref-list-1

**Email alerting service**
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Topic collections**
Articles on similar topics can be found in the following collections

- **Pain (neurology)** (30099 articles)
- **Degenerative joint disease** (9417 articles)
- **Musculoskeletal syndromes** (16821 articles)

**Notes**

To order reprints of this article go to:
http://ard.bmj.com/cgi/reprintform

To subscribe to *Annals of the Rheumatic Diseases* go to:
http://ard.bmj.com/subscriptions
Orthopaedic surgery in 255 patients with inflammatory arthropathies: longitudinal effects on pain, physical function and health-related quality of life

H Osnes-Ringen,1,2 T K Kvien,1,2 J E Henriksen,1 P Mowinckel,1 H Dagfinrud1,2

ABSTRACT

Objective: To examine the effectiveness of orthopaedic surgery in patients with inflammatory arthropathies with regard to longitudinal changes in pain, physical function and health-related quality of life and explore differences in effectiveness between replacement versus non-replacement surgery and surgery in the upper versus the lower limb.

Methods: 255 patients (mean age 57.5 years (SD 13.1), 76.7% female) with inflammatory arthropathies underwent orthopaedic surgical treatment and responded to mail surveys at baseline and during follow-up (3, 6, 9 and 12 months). The booklet of questionnaires included the arthritis impact measurement scales 2 (AIMS2), health assessment questionnaire (HAQ), short form 36 (SF-36), EQ-5D and visual analogue scales (VAS) addressing patient global, fatigue, general pain and pain in the actual joint. Standardised response means (SRM) were calculated to estimate the magnitude of improvement.

Results: Significant improvement was seen for most of the dimensions of health, the largest improvement for pain in the actual joint (SRM 1.17) at one year follow-up. SRM for AIMS-2 physical, SF-36 physical and HAQ were 0.1, 0.48 and 0.05, respectively. The overall numeric improvement (SRM) in utility was 0.10 (0.37) with EQ-5D and 0.03 (0.27) with SF-6D. Improvement overall was similar after surgery in the upper versus the lower limb, but was larger in patients undergoing replacement surgery than in patients undergoing other surgical procedures (SRM 1.54 vs 1.08 for pain in the actual joint).

Conclusions: Surgical procedures have a major positive impact on pain in the actual joint, but improvement is less in other dimensions of health. Health benefits were larger after replacement surgery than after other surgical procedures.

Joint destruction is one of the most serious consequences of inflammatory arthropathies. The overall treatment goal for these patients with established disease is to reduce pain, minimise loss of function and preserve health-related quality of life (HRQoL). Signs and symptoms of inflammatory arthropathies have been proved to be reduced with drug treatment, but still many patients need surgical intervention,1,2 even if the level of health status in patients with rheumatoid arthritis (RA) has improved over the past years.3

Orthopaedic surgery may be expected to provide pain relief and preserve and even improve function in patients with inflammatory arthropathies. Patient-oriented evaluations of pain, function and HRQoL are of importance when evaluating whether treatment goals have been achieved by surgical interventions.4 Patient-reported outcome (PRO) measures provide opportunities to address dimensions of health that are of relevance to the patient and are shown to be as reliable and responsive as physician measures and congruent with measures of inflammation.5,6

Randomised controlled trials (RCT) or comparative observational studies examining the effects of surgical interventions for patients with rheumatic diseases are lacking.7 However, even if RCT are associated with the highest level of evidence, longitudinal observational studies can also provide important evidence on effectiveness because the patient population is unselected and the follow-up is performed in a real-life setting.8,9 The objective of this study was to examine the effectiveness of orthopaedic surgery in patients with inflammatory arthropathies with regard to longitudinal changes in pain, physical function and HRQoL. We especially focused on comparisons between replacement and non-replacement surgery and between surgery performed in the upper and lower limbs.

MATERIALS AND METHODS

Patients

This study included 255 patients with inflammatory arthropathies and inclusion occurred during the period February 2005 to May 2006 at Diakonhjemmet Hospital, Oslo, Norway. The 255 patients underwent orthopaedic surgical treatment and responded to the mail surveys at baseline and at least one point of follow-up. Patients with the diagnosis of osteoarthritis were not included and we also excluded patients who underwent revision surgery, surgery because of fractures or secondary infections. Each patient was only included once (first intervention during the inclusion period).

The distribution of diagnoses was as follows: RA (64.2%), juvenile RA (3.9%), anklyosing spondylitis (5.1%), psoriatic arthritis (7.4%) and other arthritides (12.0%). The mean baseline age was 57.5 years (SD 13.1) and 76.7% were women. Patients with RA underwent more replacement surgery than patients with other arthritides (30.4 vs 17.8%). The distribution of surgical procedures in the upper and lower limb was similar in RA and the other arthritides.

Age and gender were similar in the groups of patients who underwent surgery in the upper and lower limb. The patients who underwent...
replacement surgery were older (61.4 vs 56.0 years, p = 0.006) than patients who underwent other surgical interventions, but the sex ratio was similar. All patients were seen by a physiotherapist as part of the routine and, if needed, they were offered physiotherapy after the surgical procedure.

### Data collection

The PRO were recorded at hospital admission and then by mail surveys 3, 6, 9 and 12 months after the surgical procedure. The booklet of questionnaires included both generic and disease-specific health status measures (arthritis impact measurement scales 2 (AIMS2), the health assessment questionnaire (HAQ), the short form 36 (SF-36), the utility instrument EQ-5D and four visual analogue scales (VAS), which addressed patient global assessment of disease, fatigue, general pain and pain in the specific joint undergoing surgery.

### Instruments

AIMS2 is a multidimensional disease-specific measure that has been translated into many languages including Norwegian.10 11 The first 57 items of AIMS2 are broken into 12 scales: mobility (five items); walking and bending (five items); hand and finger function (five items); arm function (five items); self-care tasks (four items); household tasks (four items); social activity (five items); support from family and friends (five items); arthritis pain (five items); work (four items); level of tension (five items) and mood (five items). The scales may be combined into a five-component model reflecting the physical dimension, affect, symptoms, social interaction and role. The score of each scale ranged from 0 to 10 (10 represents worst health). AIMS2 was scored according to the AIMS2 users’ guide issued by the Boston University Arthritis Centre.

The HAQ is a disease-specific measure for RA and asks questions about the patient’s ability to perform activities of daily living.12 The HAQ includes questions assessing difficulty over the past week in 20 specific functions, grouped into eight categories: dressing and grooming; arising; eating; walking; personal hygiene; reaching; gripping and other activities. The responses to “are you able to do…” were scored 0–3 (without any difficulty = 0, unable to do = 3). The total HAQ score is the mean of the scores for the eight categories. Scores were adjusted for the use of assistive devices.

The SF-36 is a generic health status measure and has been used in a variety of conditions including RA, musculoskeletal disorders and patients who have undergone replacement surgery.13–15 The SF-36 is a generic health status measure and has been used in a variety of conditions including RA, musculoskeletal disorders and patients who have undergone replacement surgery.13–15 The SF-36 is a generic health status measure and has been used in a variety of conditions including RA, musculoskeletal disorders and patients who have undergone replacement surgery.13–15 The first 57 items of AIMS2 are broken into 12 scales: mobility (five items); walking and bending (five items); hand and finger function (five items); arm function (five items); self-care tasks (four items); household tasks (four items); social activity (five items); support from family and friends (five items); arthritis pain (five items); work (four items); level of tension (five items) and mood (five items). The scales may be combined into a five-component model reflecting the physical dimension, affect, symptoms, social interaction and role. The score of each scale ranged from 0 to 10 (10 represents worst health). AIMS2 was scored according to the AIMS2 users’ guide issued by the Boston University Arthritis Centre.

The HAQ is a disease-specific measure for RA and asks questions about the patient’s ability to perform activities of daily living.12 The HAQ includes questions assessing difficulty over the past week in 20 specific functions, grouped into eight categories: dressing and grooming; arising; eating; walking; personal hygiene; reaching; gripping and other activities. The responses to “are you able to do…” were scored 0–3 (without any difficulty = 0, unable to do = 3). The total HAQ score is the mean of the scores for the eight categories. Scores were adjusted for the use of assistive devices.

The SF-36 is a generic health status measure and has been used in a variety of conditions including RA, musculoskeletal disorders and patients who have undergone replacement surgery.13–15 The SF-36 is a generic health status measure and has been used in a variety of conditions including RA, musculoskeletal disorders and patients who have undergone replacement surgery.13–15 The SF-36 is a generic health status measure and has been used in a variety of conditions including RA, musculoskeletal disorders and patients who have undergone replacement surgery.13–15 The SF-36 is a generic health status measure and has been used in a variety of conditions including RA, musculoskeletal disorders and patients who have undergone replacement surgery.13–15 The SF-36 is a generic health status measure and has been used in a variety of conditions including RA, musculoskeletal disorders and patients who have undergone replacement surgery.13–15

### Statistical analyses

Changes within patient groups during follow-up from baseline to 12 months were examined by paired sample t test. The standardised response mean (SRM) reflects the magnitude of an improvement (or deterioration) and was computed as the change from baseline to the 12-month follow-up divided by the standard deviation of the change score. The magnitude of the SRM was interpreted in terms of the thresholds introduced by Cohen16 for effect sizes: “trivial” (SRM <0.20), “small” (SRM >0.20–0.50), “moderate” (SRM >0.50–0.80) or “large” (SRM >0.80).

The SRM is comparable across the different instruments, independent of the instrument scales. An independent sample t test was used to compare longitudinal changes between groups (replacement vs non-replacement surgery and surgery in upper vs lower limb). The last observation carried forward (LOCF) was used to replace missing values during follow-up. p Values equal to or below 0.05 were considered to be statistically significant. Correction for the number of tests was not performed as this was an explorative study. SPSS 14.0 and SPSS 15.0 were used in the analyses.

### RESULTS

Surgical procedures in upper versus lower limbs were performed in 42.4% and 57.6% of the 255 patients. Replacement surgery was performed in 25.6% of the patients and 75.0% of these procedures were performed in the lower limbs. Significant improvement was seen for most of the dimensions of health (fig 1), but the magnitude of improvement differed considerably. Not surprisingly, the largest improvement was observed for pain reported from the specific joint exposed to surgery (SRM 1.17), but other pain measures also improved (SRM pain VAS 0.43, AIMS2 pain 0.52, SF-36 bodily pain 0.47; fig 1).

The improvement for physical functioning differed between instruments. The SRM for SF-36 physical was 0.48, but only 0.05 for HAQ and 0.10 for AIMS2 physical. Other dimensions of health also improved, but with small effect sizes, eg, fatigue VAS (0.23) and the SF-36 mental (0.22), vitality (0.24) and social function (0.16) (fig 1).

The pattern of improvement was similar overall after surgical procedures in the lower and upper limb, but changes were, as expected, different for measures that specifically addressed functional aspects in the lower (eg, SF-36 physical, AIMS2 mobility, AIMS2 walking and bending) versus the upper (eg, AIMS2 arms) limbs (table 1).
A larger improvement across all dimensions of health was observed after replacement surgery compared with non-replacement surgery (table 2).

The overall improvement (change) in utility was 0.10 (SRM 0.37) with EQ-5D and 0.03 (SRM 0.27) with SF-6D. Figure 2 illustrates that this improvement was generally captured within 6 months. The other HRQoL instruments showed the same pattern of response as SF-6D and EQ-5D. A large improvement was observed after 3 months and stabilised thereafter.

The gained HRQoL expressed in utilities was larger after replacement surgery than after non-replacement surgery (table 2).

**DISCUSSION**

Pain is the area of health in which most patients with RA would like to see an improvement. The current study demonstrates that a major improvement is observed in patient-reported pain after orthopaedic surgical procedures in patients with inflammatory arthropathies (fig 1). This finding was consistent for procedures in the lower and upper limb and for replacement and non-replacement surgery (tables 1 and 2).

Improvement in the measures of physical functioning was generally smaller than in measures of pain (fig 1). This observation supports the theory that pain in the actual joint

**Table 1** Mean baseline values for measures of pain, function and HRQoL, change and SRM from baseline to 12 months and the mean difference between the changes in patients with surgical procedures in the upper versus lower limbs

<table>
<thead>
<tr>
<th>Measure</th>
<th>Upper limb</th>
<th>Lower limb</th>
<th>Between-group difference</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HAQ (0–3)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.71</td>
<td>0.035</td>
<td>0.12</td>
<td>0.66</td>
</tr>
<tr>
<td><strong>SF-36 (0–100)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental health</td>
<td>75.45</td>
<td>2.68</td>
<td>0.20</td>
<td>72.20</td>
</tr>
<tr>
<td>Vitality</td>
<td>43.13</td>
<td>3.26**</td>
<td>0.13</td>
<td>42.65</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>33.66</td>
<td>7.96**</td>
<td>0.45</td>
<td>35.22</td>
</tr>
<tr>
<td>General health</td>
<td>48.04</td>
<td>0.41</td>
<td>0.03</td>
<td>46.06</td>
</tr>
<tr>
<td>Social function</td>
<td>68.98</td>
<td>1.56</td>
<td>0.07</td>
<td>64.29</td>
</tr>
<tr>
<td>Physical function</td>
<td>49.75</td>
<td>2.89**</td>
<td>0.21</td>
<td>38.20</td>
</tr>
<tr>
<td><strong>VAS (0–100)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General pain</td>
<td>53.00</td>
<td>12.12***</td>
<td>0.47</td>
<td>47.84</td>
</tr>
<tr>
<td>Pain in operated joint</td>
<td>58.49</td>
<td>33.56***</td>
<td>1.12</td>
<td>60.50</td>
</tr>
<tr>
<td>Fatigue</td>
<td>46.61</td>
<td>7.05*</td>
<td>0.26</td>
<td>46.14</td>
</tr>
<tr>
<td>Patient global</td>
<td>54.31</td>
<td>11.06***</td>
<td>0.46</td>
<td>53.15</td>
</tr>
<tr>
<td><strong>AIMS2 (0–10)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mobility</td>
<td>1.60</td>
<td>0.22</td>
<td>0.14</td>
<td>2.01</td>
</tr>
<tr>
<td>Walking and bending</td>
<td>4.58</td>
<td>0.01</td>
<td>0.00</td>
<td>5.74</td>
</tr>
<tr>
<td>Hand and fingers</td>
<td>3.41</td>
<td>0.27</td>
<td>0.13</td>
<td>2.56</td>
</tr>
<tr>
<td>Arms</td>
<td>2.21</td>
<td>0.28</td>
<td>0.17</td>
<td>1.27</td>
</tr>
<tr>
<td>Household</td>
<td>1.63</td>
<td>0.24</td>
<td>0.15</td>
<td>1.59</td>
</tr>
<tr>
<td>Self-care</td>
<td>0.65</td>
<td>0.16</td>
<td>0.11</td>
<td>0.55</td>
</tr>
<tr>
<td>Pain</td>
<td>6.49</td>
<td>1.16***</td>
<td>0.55</td>
<td>5.90</td>
</tr>
<tr>
<td>Physical</td>
<td>2.36</td>
<td>0.01</td>
<td>0.01</td>
<td>2.30</td>
</tr>
<tr>
<td>SF-6D (0–1)</td>
<td>0.60</td>
<td>0.02</td>
<td>0.16</td>
<td>0.59</td>
</tr>
<tr>
<td>EQ-5D (0–1)</td>
<td>0.47</td>
<td>0.06*</td>
<td>0.23</td>
<td>0.45</td>
</tr>
</tbody>
</table>

* p<0.05; ** p<0.01; *** p<0.001. p Values for within-group changes were based on a paired sample t test, p values for between-groups differences were based on an independent sample t test.

AIMS2, arthritis impact measurement scales 2; HAQ, health assessment questionnaire; HRQoL, health-related quality of life; SF-36, short form 36; SRM, standardised response mean; VAS, visual analogue scale.
is probably the most important indicator of treatment benefit and this observation is of relevance when informing the patients preoperatively about their treatment expectations.

We also observed an improvement in other dimensions of health that are important to patients but not considered as directly related to benefit from surgery. For example, both fatigue and SF-36 vitality, as well as SF-36 mental and social functioning improved more than some of the scales reflecting physical functioning, even if the effect sizes were small or trivial (fig 1). It is known that the level of pain is strongly related to most other self-reported health status measures. The observed improvements in measures of fatigue, mental and social functioning may thus also reflect reductions in pain intensity. Furthermore, pain has a major impact on the patient’s global assessment of the disease and we assume that the improvement in global VAS is caused by an improvement in pain. This assumption is also supported by a strong correlation (r = 0.64, p<0.01) observed between changes in these two dimensions in the current study. The different magnitude of improvement with EQ-5D and SF-6D was as expected based on the different profiles of these instruments with regard to ceiling and floor effects.

A limitation of this study was the lack of other disease activity measures, including joint counts and acute phase reactants. However, inflammatory activity is strongly related both to physical functioning and pain, and the apparent differences in the magnitude of improvement between these dimensions do not support the belief that the inflammatory activity was considerably changed during follow-up. The rate of non-respondents was similar to the observed rates in mail surveys in the Oslo RA register. Patients who underwent replacement surgery had a few percentages more missing values than patients who underwent non-replacement surgery and the oldest patients also had a slightly higher percentage of missing values than younger patients. The missing values were independent of gender and diagnosis. We do not consider the missing values to have any major impact on the results because LOCF was used as a conservative method to handle missing values. A possible influence on the results was probably in the direction of an underestimation of the benefit.

Cost-effectiveness analyses are important in modern medicine as priorities have to be determined between an increasing number of costly therapeutic opportunities. The different magnitude of improvement with EQ-5D and SF-6D was as expected based on the different profiles of these instruments with regard to ceiling and floor effects. We have previously shown that lower limb function deteriorates more than upper limb function over a 10-year period in patients with RA. Therefore, we wanted to compare the outcomes of upper and lower extremity surgery. Many of the replacement surgical procedures in the lower limb are also performed in patients with osteoarthritis.

Replacement surgery was performed in 25.6% of patients, and this frequency is in accordance with previous studies. Compared with patients who underwent non-replacement surgery, the replacement surgery group reported worse health preoperatively, and a larger improvement was observed during follow-up, although both groups had a significant improvement in most scores (table 2). This preoperative difference in HRQoL between the patients who underwent replacement surgery versus non-replacement surgery may be a bias in the study.

Table 2  Mean baseline values for measures of pain, function and HRQoL, change and SRM from baseline to 12 months and the mean difference between the changes in patients with replacement surgery versus other procedures

<table>
<thead>
<tr>
<th></th>
<th>Replacement surgery</th>
<th>Non-replacement surgery</th>
<th>Between-group difference</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline Change SRM</td>
<td>Baseline Change SRM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAQ (0–3)</td>
<td>0.80 0.04 0.09</td>
<td>0.62 0.01 0.03</td>
<td>0.03 0.62</td>
<td></td>
</tr>
<tr>
<td>SF-36 (0–100)</td>
<td>Mental health</td>
<td>72.64 5.59** 0.45</td>
<td>73.25 1.78 0.13</td>
<td>3.74 0.08</td>
</tr>
<tr>
<td></td>
<td>Vitality</td>
<td>42.97 5.39* 0.30</td>
<td>43.00 3.90** 0.22</td>
<td>1.42 0.62</td>
</tr>
<tr>
<td></td>
<td>Bodily pain</td>
<td>30.69 14.68*** 0.70</td>
<td>35.20 7.53*** 0.42</td>
<td>6.46 0.03</td>
</tr>
<tr>
<td></td>
<td>General health</td>
<td>47.04 3.41* 0.26</td>
<td>46.82 1.87 0.12</td>
<td>0.98 0.68</td>
</tr>
<tr>
<td></td>
<td>Social function</td>
<td>61.33 5.39*** 0.36</td>
<td>67.90 2.02 0.09</td>
<td>7.11 0.06</td>
</tr>
<tr>
<td></td>
<td>Physical function</td>
<td>32.04 17.27*** 0.78</td>
<td>47.19 5.52*** 0.39</td>
<td>12.12 0.00</td>
</tr>
<tr>
<td>VAS (0–100)</td>
<td>General pain</td>
<td>53.94 19.42*** 0.76</td>
<td>49.19 7.70*** 0.32</td>
<td>11.09 0.01</td>
</tr>
<tr>
<td></td>
<td>Pain in operated joint</td>
<td>66.17 49.17*** 1.54</td>
<td>58.40 28.93*** 1.08</td>
<td>20.64 0.00</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>47.77 11.10** 0.41</td>
<td>46.47 4.77** 0.19</td>
<td>5.51 0.19</td>
</tr>
<tr>
<td></td>
<td>Disease activity</td>
<td>59.11 19.84*** 0.73</td>
<td>52.37 8.79*** 0.38</td>
<td>10.62 0.01</td>
</tr>
<tr>
<td>AIMS2 (0–10)</td>
<td>Mobility</td>
<td>2.05 0.11 0.06</td>
<td>1.75 0.02 0.02</td>
<td>0.19 0.42</td>
</tr>
<tr>
<td></td>
<td>Walking and bending</td>
<td>6.25 1.30** 0.45</td>
<td>4.95 0.20 0.10</td>
<td>1.10 0.00</td>
</tr>
<tr>
<td></td>
<td>Hands and fingers</td>
<td>2.63 0.08 0.06</td>
<td>2.85 0.22 0.12</td>
<td>0.08 0.77</td>
</tr>
<tr>
<td></td>
<td>Arms</td>
<td>2.06 0.32 0.24</td>
<td>1.57 0.03 0.02</td>
<td>0.34 0.16</td>
</tr>
<tr>
<td></td>
<td>Household</td>
<td>2.01 0.01 0.01</td>
<td>1.44 0.11 0.17</td>
<td>0.13 0.58</td>
</tr>
<tr>
<td></td>
<td>Self-care</td>
<td>0.87 0.01 0.01</td>
<td>0.54 0.03 0.04</td>
<td>0.03 0.89</td>
</tr>
<tr>
<td></td>
<td>Pain</td>
<td>5.91 1.45*** 0.66</td>
<td>6.27 0.97*** 0.47</td>
<td>0.43 0.21</td>
</tr>
<tr>
<td></td>
<td>Physical</td>
<td>2.68 0.25 0.23</td>
<td>2.18 0.04 0.05</td>
<td>0.21 0.15</td>
</tr>
<tr>
<td>SF6D (0–1)</td>
<td>0.57 0.06*** 0.54</td>
<td>0.60 0.02* 0.18</td>
<td>0.03 0.04</td>
<td></td>
</tr>
<tr>
<td>EQ5D (0–1)</td>
<td>0.39 0.22*** 0.76</td>
<td>0.48 0.06* 0.24</td>
<td>0.15 0.00</td>
<td></td>
</tr>
</tbody>
</table>

*p<0.05; **p<0.01; ***p<0.001. p Values for within-group changes were based on a paired sample t test, p values for between-group differences were based on an independent sample t test.

AIMS2, arthritis impact measurement scales 2; HAQ, health assessment questionnaire; HRQoL, health-related quality of life; SF-36, short form 36; SRM, standardised response mean; VAS, visual analogue scale.
Importantly, the mean change in EQ-5D utility was 0.22 in the replacement surgery group and only 0.06 in the non-replacement surgery group and only 0.06 in the non-replacement group. Replacement surgery is more expensive than other procedures, but also that disability and other HRQoL scores predicted subsequent prosthetic surgery in a cohort of early RA patients.33

Self-administered questionnaires were used for the assessment of all outcomes in the current study. PRO have been shown to provide information similar to many clinical measures and are at least as responsive.34 Furthermore, self-reported questionnaires appear to be a cost-effective and attractive approach for quantitative assessment and monitoring of health status of the individual patient.35 A strength of this study was the use of several instruments capturing the same construct or domain.35 Consistent results across instruments support the robustness of the results. An exception was the results achieved with the instruments measuring physical function, but the scale from SF-36 has a stronger focus on lower limbs than AIMS2 physical and HAQ. However, the large number of instruments represented a burden for the patients as missing values occurred with a frequency of approximately one third at each point of follow-up. Therefore, a conservative analytical approach (LOCF) was used to replace missing values.

Surgical interventions are complicated procedures that can have major and fatal consequences for the patient. The outcome not only depends on the operative technique, the proper selection of the type of surgery and postoperative rehabilitation, but also on the progression of the disease and the state of advancement of pathological changes in other joints. Further research is needed to evaluate the costs and consequences of surgical procedures that are offered to patients with inflammatory arthropathies. RCT are needed, but are difficult to perform.

The current observational study showed that surgical procedures had a major positive impact on pain, but the overall improvement on physical functioning was of similar magnitude as the improvement in psychosocial variables and fatigue. These observations support the belief that pain rather than function should be the major indication for surgical procedures and contributes to the understanding of how patients should be informed about their expectations of surgical procedures.

Competing interests: None.

Ethics approval: Ethics approval was obtained.

Patient consent: Obtained.

REFERENCES


