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Joint Destruction in Rheumatoid Arthritis:
Experimental, Clinical and Epidemiological Studies

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Cover illustrations:

Arthritic joint with inflammatory cellular infiltrates and cartilage damage in experimental arthritis (hematoxylin/eosin and Safranin O staining).

Plain radiograph in lateral view of an RA patient’s foot after hindfoot-arthrodesis.

Three-dimensional model of an RA patient during gait analysis.

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ABSTRACT

Background. Rheumatoid arthritis (RA) is a common autoimmune disease characterized by chronic polyarticular synovial inflammation. Erosive joint destruction represents a major unsolved complication of RA.

Objectives. The aim of this thesis was to obtain increased knowledge of joint destruction by using a multidisciplinary approach. Firstly, the pathophysiological background of joint destruction was investigated at a cellular level in experimental arthritis. Secondly, consequences of joint destruction on locomotor changes in RA patients and the effect of orthopaedic surgery on RA patients' mobility and locomotion were studied. Thirdly, epidemiological studies were performed to elucidate the overall use and application of orthopaedic surgery in Swedish RA patients.

Methodology and Results.
1) Collagen-induced arthritis (CIA) is a well-established animal model of arthritis with differential susceptibility in various rat strains. CIA in the arthritis-prone DA rat was used to study potent joint destructive cytokines (RANKL and IL-1β) in evolving arthritis, as assessed by immunohistochemistry. A concomitant expression of RANKL and IL-1β was detected at sites of bone erosion, supporting the hypothesis that they are central contributors to joint destruction. To elucidate potential phenotypical differences, the expression of IL-1β and TNF were documented in the DA rat compared with that of two arthritis-resistant rat strains. The DA rat expressed IL-1β in articular cartilage, while the arthritis-resistant rat strains did not. This might explain why erosive arthritides are so easily induced in the DA rat and supports the hypothesis that articular chondrocytes may themselves play a major role in cartilage destruction.

2) Gait parameters of a large RA cohort were compared with healthy controls assessed by three-dimensional gait analysis. In addition, gait patterns were documented before and after ankle/hindfoot arthrodesis, which is an effective intervention to reduce pain due to joint destruction in RA patients. Joint motion, moments and work in the lower limbs were significantly decreased in RA patients compared with controls. Intervention with ankle/hindfoot arthrodesis proved beneficial to functional ability with improvement of joint movement, moments and work in both the knee and hip.

3) Data from the Swedish inpatient registry were analyzed to assess the use and temporal trends of orthopaedic surgery due to RA joint destruction. Rates of hospitalisation for Swedish RA patients as well as the total number of RA-related surgical procedures of the lower limbs decreased during 1987-2001. In addition, the rates of upper limb surgical interventions decreased during 1998-2004. This suggests that new treatments may have improved long-term health outcomes and/or that changes in clinical practice have reduced the likelihood of admission for Swedish RA patients.

Conclusions. Increased knowledge of the cellular pathophysiology leading to joint destruction may contribute to the development of new targeted therapies. Better understanding of the clinical characteristics of RA patients and epidemiological trends is valuable in evaluating changes in therapies and interventions. A multidisciplinary approach is helpful and might contribute to improved strategies and influence the future care of RA patients.

This thesis is based on the following original papers and manuscripts, which will be referred to in the text by their Roman numerals:

Morphological characterization of receptor activator of NFκB ligand (RANKL) and IL-1β expression in rodent collagen-induced arthritis.

II. **Weiss RJ**, Erlandsson Harris H and Palmblad K.
Highly arthritis-susceptible DA rats express IL-1β in the articular cartilage.
Manuscript submitted.

Gait pattern in rheumatoid arthritis.
Manuscript submitted.

IV. **Weiss RJ**, Broström E, Stark A, Wick MC and Wretenberg P.
Ankle/hindfoot arthrodesis in rheumatoid arthritis improves kinematics and kinetics of the knee and hip: a prospective gait analysis study.


*Rheumatology (Oxford).* In press.
# TABLE OF CONTENTS

INTRODUCTION............................................................................................................ 1
General aim................................................................................................................... 1
Etiology of RA.............................................................................................................. 2
Pathophysiology of RA................................................................................................. 3
  The normal joint........................................................................................................ 3
  The inflamed joint..................................................................................................... 3
  Mechanisms of focal bone loss in RA....................................................................... 5
  Mechanisms of cartilage loss in RA.......................................................................... 7
Epidemiology of RA..................................................................................................... 7
Clinical manifestations and diagnosis of RA............................................................... 8
RA therapy .................................................................................................................. 11
  The medical management of RA has changed........................................................ 11
  Orthopaedic joint surgery........................................................................................ 12
  Gait analysis in RA patients....................................................................................... 13
  Experimental models of RA ....................................................................................... 15
  Collagen-Induced Arthritis...................................................................................... 15
SPECIFIC AIMS ............................................................................................................ 17
METHODOLOGICAL CONSIDERATIONS ............................................................... 18
  Experimental studies ................................................................................................. 18
  Clinical studies .......................................................................................................... 19
  Epidemiological studies ............................................................................................ 21
RESULTS AND DISCUSSION ..................................................................................... 22
  Experimental studies ................................................................................................. 22
  Clinical studies .......................................................................................................... 23
  Epidemiological studies ............................................................................................ 25
FUTURE PERSPECTIVES ........................................................................................... 26
CONCLUDING REMARKS ......................................................................................... 28
ACKNOWLEDGMENTS .............................................................................................. 30
REFERENCES ............................................................................................................... 33
# LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR</td>
<td>American College of Rheumatology</td>
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<tr>
<td>CIA</td>
<td>Collagen-induced arthritis</td>
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<td>DMARD</td>
<td>Disease-modifying antirheumatic drug</td>
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<td>HLA-DR4</td>
<td>Human lymphocyte antigen DR4</td>
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<td>ICD</td>
<td>International Classification of Diseases</td>
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<tr>
<td>IL-1β</td>
<td>Interleukin-1 beta</td>
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<tr>
<td>MMP</td>
<td>Metalloproteinase</td>
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<tr>
<td>MHC class II</td>
<td>Class II major histocompatibility complex</td>
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<td>NSAIDs</td>
<td>Non-steroidal anti-inflammatory drugs</td>
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<tr>
<td>OPG</td>
<td>Osteoprotegerin</td>
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<tr>
<td>RA</td>
<td>Rheumatoid arthritis</td>
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<tr>
<td>RANK</td>
<td>Receptor activator of nuclear factor-κB</td>
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<tr>
<td>RANKL</td>
<td>Receptor activator of nuclear factor-κB ligand</td>
</tr>
<tr>
<td>RF</td>
<td>Rheumatoid factor</td>
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<tr>
<td>SNHDR</td>
<td>The Swedish National Hospital Discharge Register</td>
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<tr>
<td>TNF</td>
<td>Tumor necrosis factor</td>
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INTRODUCTION

General aim

Rheumatoid arthritis (RA) is a chronic inflammatory disease that mainly targets the synovial tissue, cartilage and subchondral bone. It affects up to 1% of the general population and is characterized by symmetrical polyarticular inflammation, pain, progressive joint destruction, significant disability, decreased quality of life and premature death.

My personal goals with this thesis were to obtain increased knowledge of joint destruction. I chose a multidisciplinary approach, starting with preclinical laboratory experiments investigating the pathophysiological background of joint destruction at a cellular level in experimental arthritis. This was followed by clinical studies of consequences of joint destruction on locomotor changes in RA patients and the effect of orthopaedic surgery on RA patients’ mobility and locomotion. Finally, epidemiological studies were performed to elucidate the overall use and application of orthopaedic surgery in Swedish RA patients during the past decades.

This concept provided me with a suitable leifmotif for this present thesis and helped me to improve my knowledge to understand the basis of joint destruction in RA, essential for me as an orthopaedic surgeon who attends RA patients on a regular basis during clinical work and operations.

The general aims of this thesis were threefold (Figure 1):

1) In Papers I and II we studied cellular pathophysiology leading to joint destruction in an established joint destructive animal model which mimics RA.

2) In the clinical studies (Papers III and IV) we examined the consequences of joint destruction in RA patients on locomotor changes and the benefits of orthopaedic surgery on RA patients gait pattern.

3) In Papers V and VI we assessed the use and temporal trends of orthopaedic joint surgery due to RA joint destruction from an epidemiological viewpoint by analysing large cohorts of RA patients in a nationwide Swedish medical inpatient registry.
Etiology of RA

Although the exact initiating causes of RA are still unknown, numerous advancements in the understanding of the underlying disease mechanisms have been made. RA is considered to be a multifactorial disease, which may occur as a result from an interaction of both specific genetic predispositions and certain environmental factors. The clinical heterogeneity of RA is also determined by genetic and environmental factors that control the progression, degree and pattern of inflammation.

Family studies and studies in mono- and dizygotic twins support the concept that genetic factors are important for susceptibility to RA. While the RA concordance rate in monozygotic twins was up to 12-15%, dizygotic twins displayed a concordance rate of 4%, which equals a four-fold increased susceptibility of the latter to develop RA when compared with the normal population. Thus besides the clear indication that RA develops in genetically predisposed hosts, certain environmental exogenous stressors must also precipitate the disease.

The genetic system studied most thoroughly is the major histocompatibility complex (MHC) class II association, which has been considered to account for up to 30% of the genetic influence of the disease. One important function of MHC class II on antigen-presenting cells...
is to present antigens to T cells (or to their T cell-receptors), indicating that T cells play an important role in RA pathogenesis.

Although the picture of RA pathogenesis may be complicated and the search for unequivocal exogenous stressors has been unrewarding, the list of potential environmental factors has been narrowed-down to some classical risk factors. These include i.e. lifelong infectious load due to certain bacteria and viruses, the aging process responsible for an accelerated immunosenesence in RA patients, smoking as the most important lifestyle factor, hormonal imbalance during menopause, specific diets and a low socioeconomic position.

Pathophysiology of RA

The normal joint

Most joints in the adult body can be categorized as being synovial (also called diarthrodial) joints, which are freely movable joints. Examples of synovial joints are the shoulder, elbow, hip, knee and ankle, as well as the small joints of the hand and foot. In this type of joint the ends of the opposing bones are covered with articular (hyaline) cartilage that allows them to glide across each other with minimal possible friction. The components of the joints are enclosed in a dense fibrous joint capsule with an outer layer that consists of stabilizing ligaments which hold the bones together. The synovial membrane forms the inner layer and is characterized by macrophage- and fibroblast-like cells, secreting synovial fluid into the joint cavity to provide both nutrition and lubrication (Figure 2).

The inflamed joint

The articular manifestations of RA can be divided into two categories: (i) reversible signs and symptoms related to aseptic inflammatory synovitis and (ii) irreversible structural damage caused by synovitis. This concept is useful for disease staging, determining prognosis and medical or surgical treatment selection.

The synovial membrane normally contains a relatively thin intimal lining layer with only one or a few cell layers. After disease onset the normally hypocellular synovial membrane becomes hyperplastic, comprising a superficial lining layer of synovial fibroblasts and macrophages. The lining layer overlies an interstitial zone with marked cellular infiltrates
containing fibroblasts, macrophages, dendritic cells, mast cells, T cells and B cells (which differentiate locally into antibody-secreting plasma cells) \(^6\) (Figure 2).

The interaction between activated lymphocytes and monocytes, leading to production of pro-inflammatory cytokines, immunoglobulins and rheumatoid factors (RF) is central to this immunological reaction. It is not yet fully understood how many mediators are involved and how they combine, but interleukin-1 (IL-1) and tumor necrosis factor (TNF) are suspected to stimulate synoviocytes and osteoclasts, events that lead to the irreversible destruction of bone and cartilage \(^7\). These cytokines are also involved in the expression of cell-adhesion-molecules necessary for cell migration and inflammation on endothelial cells, which promote local accumulation of leukocytes. Synoviocytes are also known to produce matrix-metalloproteinases (MMPs), which are normally inhibited by the tissue inhibitors of metalloproteinases. In RA, the proportion of proteinases to their inhibitors is unbalanced.

The combined activity of these mediators appears to be the cause of synovial tissue inflammation, inflammatory constituents (e.g. pro-inflammatory cytokines) in the synovial fluid, synovial proliferation as well as cartilage and bone damage. Rheumatoid factor (RF) and other autoantibodies accumulate in the synovial tissue and fluid, where they maintain inflammation by activating complement in the adjacent bradytrophe cartilage and tissue. In addition to the cellular basis of synovial inflammation, newly formed blood vessels also infiltrate the synovial membrane. This neo-angiogenesis is known to be driven by the production of different growth factors which support synovial hyperplasia \(^8\). All these events lead to the development of a non-suppurative proliferating synovitis, also known as synovialitis pannus. The pannus extends over and sometimes through adjacent articular cartilage, leading to complete destruction of the cartilage, observed radiologically as joint space narrowing and bone erosion. Pannus growth can be compared with the progression of a benign tumor (tumor-like progression).
Mechanisms of focal bone loss in RA

Several studies have recently provided evidence that osteoclasts are the principal cell type for focal bone loss in RA. Most data are derived from experimental knock-out animal studies, in which osteoclast activity and differentiation are impaired by specific deletion of genes which are known to be important for osteoclast formation, or by targeting the cytokine receptor activator of nuclear factor-κB ligand (RANKL), also known as osteoprotegerin ligand (OPGL). RANKL, which is essential for differentiation and activation of osteoclasts, binds to its cognate receptor, the receptor activator of nuclear factor-κB (RANK), which is a member of the TNF family of receptors and expressed on osteoclast precursors, osteoclasts, dendritic cells and chondrocytes. RANKL is a membrane-bound ligand expressed in bone marrow stromal cells and is a potent stimulator of osteoclastogenesis. Mice with a disrupted RANKL gene exhibit severe osteopetrosis and defects in T- and B-
lymphocyte differentiation. In mice in which RANKL is blocked by an inhibitor called osteoprotegerin (OPG), focal bone erosions do not arise as they do not form osteoclasts, and/or as the osteoclast differentiation and activation is limited.

OPG is a naturally occurring protein also related to the TNF-superfamily and acts as an inhibitor of osteoclast formation. OPG-deficient mice exhibit decreased total bone density with a high incidence of fractures. The effect of OPG and RANKL (and its receptor RANK) on osteoclasts and the immune system is schematically depicted in Figure 3.

Osteoclastogenesis is influenced by both IL-1 and TNF, as both factors up-regulate RANKL expression in bone-lining and marrow stromal cells. TNF and RANKL act in synergy to enhance osteoclast differentiation, whereas IL-1 even delays osteoclast apoptosis. In addition, IL-1 and TNF induce apoptosis of osteoblasts, further contributing to bone loss in RA.

Figure 3. Schematic illustration of osteoclast formation. IL-1 and TNF induce RANKL expression on osteoblasts. RANKL binding to RANK expressed on haematopoietic progenitors activates a signal transduction cascade that leads to osteoclast differentiation. OPG produced by osteoblasts acts as a decoy receptor for RANKL and inhibits osteoclastogenesis and osteoclast activation by binding to RANKL. Adapted from Jones et al.
Mechanisms of cartilage loss in RA

Articular cartilage is formed by a non-mineralized surface layer and a deep mineralized layer adjacent to bone. However, only the resorption of the deep mineralized layer is osteoclast-mediated. Both the surface and the deep layer contain chondrocytes which regulate cartilage metabolism.

Cartilage degradation is regulated through different mechanisms. Chondrocytes switch from an anabolic matrix-synthesizing state to a catabolic state which is characterized by the formation of matrix-degrading enzymes (MMPs) that cleave cartilage components such as proteoglycan and collagen fibres. The chondrocytes themselves synthesize or respond to local cytokines released by the synovial membrane such as IL-1β and TNF. This has a synergistic effect in cartilage destruction, although the effect of IL-1β seems more potent than that of TNF. In addition, synovial fibroblasts, neutrophils and mast cells situated in the synovial membrane further release matrix-degrading enzymes, in turn contributing to cartilage degradation.

Unlike bone which is continuously remodelled throughout life, damaged cartilage has only a limited ability to repair its matrix. In contrast to bone remodelling in which non-resident cells of haematopoietic and mesenchymal origin are recruited to the bone surface, the cartilage remodelling process depends entirely on a single cell type, the chondrocyte.

Epidemiology of RA

RA has a worldwide distribution and affects all ethnic groups. The disease can occur at any age but its prevalence increases with age, the peak incidence being between the fourth and sixth decades. There are no reports of clustering in space or time that would unequivocally support an infectious cause. Furthermore, no environmental factors have been identified which would precipitate a disease onset with last certainty.

The majority of studies carried out in Northern Europe and Northern American areas estimated a prevalence of RA of approximately 0.5-1% and a mean annual incidence of 0.02-0.05%. However, while in Africa and among Caribbean blacks a slightly lower prevalence has been recorded, an increased prevalence has been reported for native American populations i.e. the Pima Indians (USA). In a more recent publication, the prevalence among the general adult Swedish population was determined to be 0.5%. The incidence of RA in women is higher than in men, with a varying sex-ratio of 2:1-3:1. Although
representative studies regarding this issue are sparse, these observations already suggest a possible influence of reproductive and hormonal-depending factors on the occurrence of RA. During the past decades a measurable decline in incidence has been observed in countries that were historically characterised in the literature by higher rates of RA incidence and prevalence. However, the limited number of representative and comparative studies in the current literature, and their sometimes great methodological differences, limit the generalizability of such observations, leaving us with some uncertainty about the epidemiology of RA in a worldwide context. Indeed, no major changes in RA prevalence and incidence have ever been reported for Scandinavia as a whole.

**Clinical manifestations and diagnosis of RA**

Clinical features of RA vary not only from one patient to another, but also in an individual patient during the disease course. In approximately two thirds of patients, prodromal symptoms, which may persist for weeks and defy diagnosis, are fatigue, generalized weakness and non-specific musculoskeletal symptoms prior to the appearance of clinically obvious synovitis.

RA is an insidious process that characteristically presents with symmetrical involvement of joints. First, appearance of symptoms is usually in the hands and feet and their adjacent structures, but onset may also occur in large joints such as the knee and hip. Persistent synovial arthroncus (joint swelling) with hyperthermia, morning stiffness, limitation of motion, feebleness and precocious juxtaarticular myoatrophy, accompanied by more-or-less severe pain, are cardinal symptoms. RA develops acutely in approximately one third of patients, i.e. some of the patients can even precisely state the day and location of the first symptoms, whereas others have more of an insidious disease onset. Diagnosis during the early weeks of the disease is essentially one of exclusion, although characteristic features such as symmetric sterile synovitis with typical serological findings strongly suggest RA.

Several different diagnostic autoantibodies with varying specificity have been described in serum from RA patients, but rheumatoid factor (RF) is at present the only autoantibody included in the American College of Rheumatology (ACR) classification criteria. About 85% of RA patients are seropositive for rheumatoid factor (RF). RF is predominately of the IgM subclass and specific for the Fc portion of autologous IgG. Patients with a high titer of RF develop a more severe and eroding arthritis than do RF-negative patients. Studies
indicate that RF titers tend to correlate with severe and unremitting disease, nodules and extra-articular lesions.

More recently, novel antibodies recognizing citrullinated proteins/peptides 34 and especially cyclic citrullinated peptides (Anti-CCP) 35 were demonstrated to combine reasonable sensitivity with high specificity for RA, and are increasingly used in the evaluation of possible RA patients. Furthermore, it has been shown that patients who are positive for anti-CCP antibodies at disease onset and their first clinical presentation have less favourable clinical and radiological disease prognoses, making the initial serological determination of a possible presence of anti-CCP antibodies a promising novel diagnostic tool for RA 36.

The erythrocyte sedimentation rate (ESR) is a measurement of the rate at which red blood cells settle and is related to several serum factors. ESR typically correlates with the degree of synovial inflammation, but this correlation varies greatly from patient to patient, and rarely does a patient with active inflammatory RA have a normal ESR. However, the ESR is generally a useful objective serological measure for following the course of inflammatory activity in an individual patient. C-reactive protein, an acute-phase reactant, can also be used to monitor the level of inflammation.

Small joint inflammation in the hands and feet are the hallmarks of early RA. Kerry et al. 37 reviewed 100 consecutive RA patients and observed that 32% of patients already had symptoms relating to the feet at initial presentation, and a further 47% developed foot symptoms later in the disease, corresponding to a total of 79% of patients with foot involvement. Clinical symptoms of the hindfoot and ankle in patients with RA usually increase with longer disease duration 38.

Manifestations in the knee joint are uncommon at the onset of RA, but eventually 90% of patients are affected later during disease 39. Consequently, the knee joint is affected twice as often as is the hip 39. Arthritis of the hip joint may occur at any time during the course of the disease and problems with the hip are reported in 20-40% of all RA patients 40. Involvement of the hand 41, the elbow 42 and the shoulder 43 in RA may result in serious impairment. Nonetheless, a good and pain-free mobility of those joints is decisive for the function of the upper limbs.

In patients with more severe disease extra-articular manifestations such as vasculitis, rheumatoid nodules, neurological, ocular and respiratory tract manifestations frequently
occur. Once established the clinical course of RA is unpredictable, with the majority of patients having a remitting course characterized by periods of reduction of symptoms.

The American Rheumatism Association 1987 revised criteria are the currently most accepted criteria for RA diagnosis and classification (Table 1). These criteria are easy to apply, are a valuable tool for physicians and provide a sensitivity of 90%. Biopsies and results of invasive procedures are not included.

**Table 1.** The 1987 revised criteria for the classification of rheumatoid arthritis, set by the American College of Rheumatology (ACR)\(^{32}\).

*Guidelines for classification:*

Four of seven criteria are required to classify a patient as having RA. Criteria 1-4 must be present for at least 6 weeks, criteria 2-5 must be observed by a physician.

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<td>1. <strong>Morning stiffness:</strong> Stiffness in and around the joint lasting 1 hour before maximal improvement.</td>
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<td>2. <strong>Arthritis of 3 or more joint areas:</strong> At least three joint areas, observed by a physician simultaneously, have soft tissue swelling or joint effusions, not just bony overgrowth. The 14 possible joint areas involved are right or left proximal interphalangeal, metacarpophalangeal, wrist, elbow, knee, ankle and metatarsophalangeal joints.</td>
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<td>3. <strong>Arthritis of hand joints:</strong> Arthritis of wrist, metacarpophalangeal joints or proximal interphalangeal joints.</td>
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<td>4. <strong>Symmetric arthritis:</strong> Simultaneous bilateral involvement of the same joint areas.</td>
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<td>5. <strong>Rheumatoid nodules:</strong> Subcutaneous nodules over bony prominences, extensor surfaces or juxtaarticular regions observed by a physician.</td>
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<td>6. <strong>Serum rheumatoid factor (RF):</strong> Demonstration of abnormal amounts of serum RF by any method for which the result has been positive in less than 5% of normal control subjects.</td>
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<td>7. <strong>Radiographic changes:</strong> Typical changes of RA on posterior-anterior hand and wrist radiographs must include erosions or unequivocal bony decalcification localized in, or most marked adjacent to the involved joints.</td>
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**RA therapy**

The major goals of therapy for RA are to relieve pain, swelling and fatigue. Furthermore, the improvement of joint function, the prevention of joint damage and disability and disease-related morbidity are of paramount importance. These goals are constant throughout the disease course, although the emphasis may shift to address specific patient needs. Treatment options in RA should be specifically adapted to the extent of inflammation, pain, deformity and dysfunction of the individual RA patient. If possible, RA patients are best served using a multidisciplinary approach through a ‘rheuma team’ comprising a rheumatologist, physiotherapist, occupational therapist, nurse, orthopaedic surgeon and hand surgeon. The individual RA patient’s requirement for treatment including medication, gait aids, orthoses, shoe modifications, rehabilitation and rheuma-surgery need to be identified. Patient education is also essential early in the disease course and on an ongoing basis. Educational topics include the nature of the disease and its prognosis, lifestyle and family counseling, enhancement of self-esteem, home modifications and medical disease treatment.

**The medical management of RA has changed**

During the late 1980s, the medical treatment strategies of RA patients has undergone a general change. It has been known for a long time that disease-modifying anti-rheumatic drugs (DMARDs) differ greatly in their mechanisms of action. Most of these actions are now well described for some agents, including e.g. Leflunomide, but are still less understood for others such as methotrexate, gold salts or hydroxychloroquine. DMARDs also vary greatly in their chemical structure, toxicity and indications for use. An effective DMARD is considered a drug that should prevent joint erosions and damage, control synovitis and constitutional features of the disease. The common practice of a selective use of DMARDS was changed to a consistent use of these drugs in almost all patients from the onset of joint inflammation. Several studies have shown that treatment with DMARDs early in the course of RA led to less joint inflammation, a decrease in joint damage and better health compared with the results following even short delays in treatment. Aggressive initial treatment of early RA with double or triple combinations of DMARDs significantly limits peripheral joint damage when compared with DMARD monotherapy.

Since TNF and IL-1 have been determined to be key cytokines in the pathogenesis of RA, specific targeted monoclonal antibodies have been developed that systemically inactivate and
block their biological functions. These substances are generally recognized under their description as ‘biologicaals’. The TNF-antagonists Infliximab, Etanercept, Adalimumab and the IL-1 receptor antagonist Anakinra, were the ‘first generation’ of biologicals to be approved for the treatment of RA. Although the three TNF inhibiting agents differ in their chemical structures, they are generally recognized to comprise a new class of biological agents. Based on their specific pharmacological target, they bind free soluble TNF and thus prevent its binding to the TNF receptor. This leads to reduction of inflammation and synovial swelling, and thus prevention of structural joint damage. In recent randomized clinical trials impressive functional and radiological improvements have been reported in patients with RA receiving TNF-antagonists as well as in patients receiving IL-1 receptor antagonists (IL-1Ra).

Nowadays, each RA patient should receive the most effective individually adapted combination treatment of DMARDs during the early course of the disease. If ineffective, treatment with biologicals can be introduced, preferably with concomitant methotrexate. Pain and stiffness is often treated with non-steroidal anti-inflammatory drugs (NSAIDs), which act as cyclooxygenase (COX) inhibitors, and have a potent anti-inflammatory, analgesic and antipyretic effect. Corticosteroids given orally, intra-articularly or intramuscularly reduce inflammation and have good effects on reduction of inflammation and slowing down radiological joint damage progression. They are generally not used continuously as a single treatment due to potential serious side-effects such as osteoporosis and increased fracture risk, but they may be used as a bolus treatment to suppress disease activity rapidly in cases of disease flare. Moreover, corticosteroids may be given in low doses in combination with DMARD treatment as a bridge therapy awaiting the effect of newly started DMARDs.

**Orthopaedic joint surgery**

Disease persistence marks the natural course of RA and remission is usually rare. The polyarticular joint involvement of patients with RA indicates the requirement of careful clinical and radiological follow-up. Abnormalities in RA patients’ radiographs include articular soft tissue swelling, juxtaarticular and diffuse osteoporosis, large bone erosions or pseudocysts, partial and complete dislocations, ankyloses and deformities of severely damaged joints. Erosions and, to a lesser extent, joint space narrowing are the most widely accepted and specific features that can be reliably assessed. RA may lead to joint pain and deformities often resulting in major deformities of the lower and upper limbs.
To some extent such problems can be treated through orthopaedic surgery. The goals of RA-surgery are to correct deformations, to replace destroyed joints, to reduce pain, to achieve best possible function and to avoid further deterioration of affected joints \(^{69}\). However, the chronic inflammatory process in RA joints may not be halted by orthopaedic surgery. James et al. \(^{70}\) demonstrated that 11% of patients underwent large- or small-joint surgery within 5 years of presentation of RA. The authors emphasized that the occurrence of severe joint failure in RA may already occur within a few years from disease onset \(^{70}\). In another population-based cohort of RA patients from Rochester, Minnesota, the cumulative incidence for all joint surgeries was 34% after 30 years of follow-up. The cumulative incidence of total joint replacement constituted 18% of all surgical interventions \(^{71}\). In a prospective study, Wolfe et al. reported that 34% of RA patients underwent some kind of surgical intervention during a 23 years period, 25% of these being total joint replacements \(^{72}\).

Joint surgery in RA is a marker of disease severity. Orthopaedic procedures such as synovectomies, reconstructive joint surgery, resection arthroplasties, joint arthrodeses and total joint replacements have substantially improved the overall function and the quality of life of RA patients \(^{68}\). Joint replacement surgery in RA not only has a direct effect on the joint being replaced, but also has a general overall beneficial effect on pain and disability irrespective of the presence of polyarticular disease \(^{73}\). Furthermore, this beneficial effect may be maintained for many years, even when the progressive nature of RA in other joints might be expected to undermine the advantages of surgery \(^{73}\).

Although the development of anti-rheumatic medications has rapidly progressed in recent years \(^{61,74}\), orthopaedic surgery still plays an important role as a treatment option in the disease course and the need for RA-surgery can be interpreted as a failure of conservative and medical care in RA.

**Gait analysis in RA patients**

Three-dimensional gait analysis is a method used to gain information about gait changes in patients with impairment and to quantitatively document disease progression. Normal gait is classified into stance and a swing phases. The stance phase of gait refers to the period when the same foot contacts the ground and the swing phase refers to when the foot is being advanced. The stance phase comprises approximately the first 60% of the gait cycle and is
Gait can be analyzed by using a biomechanical model based on the measured position of markers on a subject’s skin to infer the position of body segments. The most commonly used model for analysis of the lower limbs includes a distribution in seven rigid segments (pelvis, two thighs, two shanks and two feet) which are defined by markers attached to bony landmarks. Data concerning joint movements (kinematics), including angles, velocities and accelerations can thus be gathered.

An adequate description of a person’s gait pattern also includes kinetic data such as forces, moments and power. Force plates, one of the most important measurement devices for evaluating kinetic data, are needed to quantify forces generated during locomotion. Joint movements are caused by three different forces: external forces, which equal ground reaction forces, internal forces through muscular action and forces caused by the gravity of a body segment directed vertically to the ground from the segment’s center of mass. The moment of force acting at a joint is calculated by multiplying these forces with the perpendicular moment (lever) arm.

Joint power appears to be a good indicator for the ability to drive and control the movements of the lower limbs as it reflects the underlying neuromuscular control for mechanisms of human movement. Power combines both kinetic information (moment) and kinematic data (angular velocity) and is calculated as their product. Work, another important gait parameter, is calculated as the area under the power curve during an entire gait cycle. Thus positive work represents the sum of concentric muscular action and negative work the sum of eccentric muscular action at a joint.

RA has been clearly associated with locomotor impairment and there has therefore been an increasing use of gait analysis as an objective measure of function in this disease. The walking pattern is altered as a result of pain, stiffness and structural deformities in the weight-bearing joints of the lower limbs. Up to 90% of RA patients may develop problems in their feet during the disease course, apart from disease manifestations in the ankle and in the overlying leg joints such as the knee and hip. Of course the foot does not function in isolation, as it is at the end of a kinetic chain and the interface between ground and body. Its relation to more proximal joints must always be at the forefront of one’s thinking. Several gait studies in RA have revealed a decrease in gait velocity, stride length and single-limb-support. Functional limitations in gait may already be apparent in RA patients with less than two years
disease duration, which suggests an early adaptation to underlying local disease activity and impairment.

**Experimental models of RA**

Experimental animal models of arthritis provide the possibility to study pathogenesis, diagnosis and treatment of arthritis which in many aspects is comparable with RA in humans. Animal models may still differ from the human disease in some aspects. Nevertheless, they offer the possibility of investigating disease mechanisms and new potential treatments which otherwise could not be evaluated in humans due to reasonable ethical reasons.

**Collagen-Induced Arthritis**

Collagen-induced arthritis (CIA) represents one of the most established, widely used and most detailed characterized experimental animal model of arthritis. It was first described by Trentham et al. in 1977. There are genetically determined differences in susceptibility to arthritis among inbred animal strains. Major histocompatibility complex (MHC) alleles strongly influence the pathogenesis of arthritis in rats, but non-MHC genes also regulate susceptibility. In susceptible rat strains inflammatory arthritis is induced by the subcutaneous injection of native, homologous or heterologous type II collagen (the main collagen type in cartilage) emulsified in either complete (inactivated mycobacteria suspended in mineral oil) or incomplete Freund’s adjuvant (mineral oil) (Figure 4). CIA is caused by the induction of both cellular and humoral innate immune responses against type II collagen and is reported to be T cell-dependent.
CIA and human RA share several important clinical and histopathological features. Both forms of arthritis affect the peripheral joints, causing symmetrical arthritic lesions (\textit{Figure 5}). In addition, they are both mainly of a progressive rather than an intermittent nature and lead to chronic relapsing arthritis with the formation of synovial pannus with erosions in cartilage and subchondral bone. The most striking difference between CIA and human RA is the fact that CIA has no gender preference, unlike RA which is 3-fold more common in women\textsuperscript{87}.

\textbf{Figure 4.} Subcutaneous immunization of Dark Agouti (DA) rat with type II collagen emulsified with Freund’s incomplete adjuvant.

\textbf{Figure 5.} CIA in a Dark Agouti (DA) rat with a healthy hindpaw before the induction of experimental disease (\textit{left}) and maximal arthritis afterwards (\textit{right}).
SPECIFIC AIMS

Paper I
The aim of this study was to investigate the cellular mechanisms underlying joint destruction in evolving arthritis. As osteoclasts are key mediators of bone erosions we wanted to determine the expression of RANKL, essential for osteoclast development and activation, compared with the well-characterized and destruction-associated cytokine IL-1β during the course of CIA. Our immunohistochemical findings were related to the progressive destruction of cartilage and bone.

Paper II
Another approach to dissect differences in the varying susceptibility to arthritis in different rat strains, apart from genetical studies, is to elucidate phenotypical differences such as expression of molecules of pathogenetic importance. The aim of this study was to determine the expression of IL-1β and TNF, two pivotal mediators of arthritis, in three different rat strains, the highly arthritis-prone Dark Agouti (DA) rat and two arthritis-resistant rat strains, the Piebald-Viral-Glaxo 1AV1 (PVG.1AV1) rat (which is MHC-identical with the DA rat) and the Brown Norway (BN) rat.

Paper III
The objectives of Paper III were to examine and quantify the consequences of the combination of joint pain, inflammation and joint damage on locomotor changes in RA patients. We wanted to compare kinematic and kinetic gait parameters of a large RA cohort with healthy controls by using three-dimensional gait analysis.

Paper IV
The aim of this study was to evaluate the potential benefits of orthopaedic surgery due to joint destruction for RA patients’ gait pattern. We wanted to analyze the functional outcome and gait changes in the overlying leg joints such as the knee and hip of RA patients after ankle/hindfoot arthrodesis.
Paper V

In Paper V we wanted to investigate the temporal trends of orthopaedic surgery in RA patients based on a nationwide database analysis. This study aimed to analyze whether the use of lower limb surgery has changed in Swedish RA patients during the period 1987-2001.

Paper VI

The rationale of this study, which can be seen as an extension of Paper V, was to describe the overall use and temporal trends in orthopaedic upper limb surgery associated with RA on a nationwide basis in Sweden between 1998 and 2004.

METHODOLOGICAL CONSIDERATIONS

Detailed descriptions regarding methods used in this thesis are included in the individual Papers I-VI. Here only a brief summary of methodological principles and considerations are given.

Experimental studies

Experimental model

The experimental model of arthritis that was employed in Paper I was collagen-induced arthritis (CIA). Homologous type II CIA in the highly susceptible DA rat was chosen since this model mimics the human disease in many aspects and even fulfills the ACR criteria for diagnosis of RA. It is a stable and reproducible model which is well established in our lab. After subcutaneous immunization the incidence of arthritis is 100%, which is especially important when investigating disease-preceding timepoints.

Clinical evaluation of experimental arthritis can be performed in different ways. We used a scoring system based on erythema and swelling of joints. One practical limitation of the rat animal model used in this study is that as the rat is covered with fur, clinical evaluation is limited to only the fore- and hindpaws, which are furless. Other joints such as the knees, hips or even multiple vertebral joints of the tail may also be involved in the inflammatory process but can not be sufficiently clinically monitored.
However, compared to other scoring systems such as radiography and measurements of paw swelling using a plethysmometer, our system is easily conducted, has a high reliability and also correlates with the evaluation system for human RA patients.

**Cytokine assessment**

Intracellular immunohistochemical techniques were employed in this work to detect intracellular cytokine production. The limitations of intracellular cytokine staining methods include the uncertainty if the produced cytokine will indeed be transported extracellularly and if the detected cytokine represents a biologically active protein, as some cytokines first need proteolytic cleavage in order to become biologically active. Another shortcoming is the fact that this technique is only a semi-quantitative method, assessing the number of cytokine-producing cells. The total amount of the generated protein can not be assessed using this method.

However, these methods have already been demonstrated to correlate well with cytokine production at the mRNA level, verified by RT-PCR (reverse transcriptase polymerase chain reaction), and at the protein level assessed with ELISA (enzyme linked immunosorbent assay). Moreover, the immunostaining methods are applicable both on a single cell basis as well as on tissue samples.

Intracellular detection has a major advantage compared with techniques that only detect cytokines extracellularly, as intracellular cytokines may be of biological significance in the absence of their occurrence extracellularly. In addition, intracellular cytokine detection is independent of the interference with inhibitors and antagonists in the serum.

**Clinical studies**

Gait varies slightly between walks and subjects. To get consistent results, several gait trials are needed, which may pose a problem for RA patients with poor physical condition. Force plates are used to measure ground reaction forces during gait to calculate kinetic data. All subjects have to strike the force plates with only one foot. This may be difficult in elderly subjects with pathology or in subjects with limited stride length, as in this case the configuration of the force plate may not be ideal.
Inappropriate positioning of skin markers over bony anatomical landmarks may lead to changes in collecting data and measurement error. To limit shortcomings in Papers III and IV, a rigid protocol was required to ensure minimal measurement error and to increase measurement accuracy. Marker placement was always performed by the same trained person experienced in gait analysis studies using the same standardized protocol. For each RA patient and control subject, three complete walking trials were performed including kinematic, kinetic and time-distance parameters. A walking trial was only considered complete when a subject’s feet made clean contact with the force plate. The floor and the force plates were covered with the same film. Thus the force plates were not easily distinguishable to avoid biasing that subjects might contact the force plates in an unnatural way. Moreover, in order to avoid morning stiffness all gait analyses were performed in the afternoon.

There is some existing evidence in the literature that gait speed may affect gait parameters. When comparing normal gait with pathological gait characteristics, some investigators therefore recommend that gait analysis should be assessed using the same walking speed. Notwithstanding this possibility of bias, we chose to examine our study subjects at a self-selected walking speed but not to control the cycle time, as would e.g. be the case when probands are walking in time with a metronome. In general, patients with abnormal and/or pathological gait tend to walk slower than their healthy counterparts. The rationale for controlling the cycle time would provide a means of reducing the variability imposed by different gait speeds. However, diseased and healthy subjects are unlikely to walk naturally when trying to keep pace with a metronome. reported considerable differences in the gait of normal subjects between natural walking and constrained walking. This may be less of a problem if subjects are simply asked to walk slowly, but some study subjects might still find it more difficult or sometimes even impossible to walk in accordance with an ‘imposed cycle time’.

Despite the mentioned limitations of this technique, three-dimensional gait analysis is a powerful means of delivering objective measures and documentation of a patient’s status and performance. Analysis of a patient’s gait pattern may not only serve as a measure of treatment outcome but also as a useful tool in planning ongoing care.
Epidemiological studies

Due to its stable population, the public healthcare system and the comprehensive population registries, Sweden is an ideal country in which to perform epidemiological surveys. Patient registries provide valuable data to the field of medical research for both quality control and scientific research \(^{94,95}\).

Already as early as in the 1960s, the Swedish National Board of Health and Welfare started to prospectively collect data of individual patients who had been treated as inpatients at public hospitals. Data have been gathered in The Swedish National Hospital Discharge Register (SNHDR) on a nationwide basis since 1987 \(^{96}\). Data concerning date of admission and discharge, the main diagnosis and up to five contributory diagnoses, coded according to the *International Classification of Diseases (ICD)* are recorded \(^{97}\). Moreover, sex, age, surgical procedures, place of residence, hospital, administrative and other medical data are collected. All records are continuously gathered in the register and undergo periodical update data control. Continuous revisions ensure that compulsory variables are reported and that all codes for different variables and dates are valid. Obviously incorrect data are corrected in connection with the respective register quality controls. In the case of rheumatic diseases, such as RA, all secondary diagnoses are also gathered in the register. Consequently, diseases that more rarely result in hospital admissions are also represented if these patients have been admitted for other reasons \(^{94}\).

A major limitation of the SNHDR database is that it contains only a limited number of variables of observation. It does not provide any information on type, duration or dosage of medical treatment, no information about the onset of symptoms or date of diagnosis of chronic diseases \(^{95}\). Furthermore, data concerning disease activity scores, ACR criteria of diagnosis, laboratory parameters, quality of life scores, co-morbidities or adverse events can not be withdrawn from the SNHDR.

During the study period the clinical practice of admissions may have changed and differences in diagnostic routines between hospitals and physicians might have undergone unequivocal developments. In recent years, an economically driven shift has occurred in Swedish hospital care from inpatient to more outpatient settings, which are not included in this inpatient register.

Nonetheless, the potential for register studies involving data retrieved from everyday clinical practice based on the Swedish effort to register and monitor may not be underestimated. A
diversity of clinical issues, such as in our case RA, may be examined by registrations based on the individual personal identification number. Moreover, Swedish healthcare is public- and population-based. Use of patient data is not governed by private health insurance, but largely follows geographical referral patterns and is tax funded.

The SNHDR has all the advantages of a longitudinal register. It is an administrative database which is extensively used for medical research. General and specific validation surveys suggest that almost 90% of the registered diagnoses and surgical procedure codes are correct when compared with medical files. The nearly complete coverage on a nationwide basis of information on every discharge from inpatient care makes this register unique and most valuable for medical research.

RESULTS AND DISCUSSION

Experimental studies

Key Points:

Papers I+II

- Increase of RANKL and IL-1β expressing cells correlate with progression of synovial inflammation and clinical disease severity in CIA.

- A concomitant expression in areas of joint destruction indicates that RANKL and IL-1β are central contributors to joint destruction in CIA.

- IL-1β is expressed in articular cartilage of the arthritis-prone DA rat as opposed to in the arthritis-resistant PVG.1AV1 and BN rat strains. This may offer an explanation of why erosive arthritides are so easily induced in the DA rat and also supports the hypothesis that articular chondrocytes may themselves play a major role in cartilage destruction.

Cartilage and bone destruction of the articular joints occurs progressively in arthritis and ultimately leads to significant disability. Osteoclasts are the principal cell type responsible for bone resorption in RA. RANKL has been characterized as a key player in bone resorption in this inflammatory disease, being important for activation and survival of osteoclasts as well as for the differentiation from their precursor cells. Pro-inflammatory cytokines such as...
IL-1β and TNF are now commonly accepted as pivotal mediators in joint destruction in RA, providing validated targets for successful therapy.\textsuperscript{102,103}

In \textit{Paper I} we examined the spatial and temporal expression of the potent destructive cytokine RANKL compared with IL-1β in relation to the development of synovitis and subsequent destruction of cartilage and bone in an experimental model of RA. There was no RANKL-expression at the disease-preceding time point of CIA. However, a marked increase of both RANKL and IL-1β expressing cells significantly correlated with the progression of synovial inflammation and clinical disease severity. Significant expression of both cytokines was detected at sites of bone erosion, where a co-localization of osteoclast-like multinuclear cells was noted. Our data support the hypothesis that RANKL and IL-1β are central contributors to joint destruction in CIA. This study offers spatial and temporal conditions for the functional relationship through the concomitant expression of these cytokines accompanied by osteoclast-like cells near sites of bone erosion.

In \textit{Paper II} we demonstrated a distinct difference in articular cartilage, with chondrocytes expressing IL-1β but not TNF in the highly arthritis-prone DA rat as opposed to in the two arthritis-resistant BN or PVG.1AV1 rat strains (in which no cytokine expression was documented). The results were otherwise congruent among the rat strains. We observed TNF and IL-1β expressing cells within the synovial lining layer in all rat strains. Other tissues studied, such as auricular cartilage as well as muscle, lung, thyroid gland and kidney tissue, were devoid of cytokine expression. This study provides evidence that under normal conditions TNF and IL-1β may be expressed in rat articular tissue but not in other organs prone to autoimmune diseases (except for lymphoid tissue), indicating that the joints are particularly prone to cytokine production. This may offer one explanation why erosive arthritis is so easily induced in the DA rat and also supports the hypothesis that articular chondrocytes themselves may play a major role in cartilage matrix degradation.

\textbf{Clinical studies}

\textbf{Key points:}

\textit{Papers III and IV}

- Joint motion, moments and work in the lower limbs are significantly decreased in RA patients compared to in healthy controls.
Ankle/hindfoot arthrodesis in RA is an effective intervention to reduce pain and to improve functional ability.

Improvement of joint movement, moments and work in the knee and hip can be achieved by fusion surgery in the ankle/hindfoot of RA patients.

Chronic pain in combination with inflammation and joint destruction is one of the main causes of disability and loss of function in RA. The limited joint motion apparent in RA patients may be a way of reducing the moments across the joints and thereby the actual joint load, as moment arms of the ground reaction forces become smaller. A decrease of joint moments in the lower limbs limits the ability to produce forward propulsion during gait, but may also be considered as a strategy to reduce joint pain by reducing joint load. Other authors have previously shown that intra-articular corticosteroid injections in children with juvenile idiopathic arthritis decrease joint pain and consequently lead to improved range of motion and muscle generated joint moments in the lower limbs.\(^{104}\)

For work, the most evident difference between the RA patients and the controls was the reduced concentric work at the ankle. This may be explained as a consequence of the reduced internal plantarflexor moments during pre-swing due to pain and muscular weakness in the plantarflexor muscle group. The combined result of a decrease in ankle and hip work mirrors the marked reduction in forward driving concentric work produced by the plantar flexors and the hip extensors.

The findings of Paper III provide a database of kinematic and kinetic gait parameters of a large RA patient cohort compared with normal control subjects. Using this database as a reference for RA patients’ gait may help with the interpretation of clinical gait analysis data and may assist in the process of treatment decision-making in this patient group with complex walking problems.

Fusion surgery (Paper IV) is a well-established method for treatment of severe rheumatoid involvement causing pain, instability and/or severe deformity of the ankle/hindfoot.\(^{105,106}\) The improvement of our RA cohort after arthrodesis of the ankle/hindfoot concerning pain reduction and improvement of functional ability was expected, since arthrodesis represents a solid procedure with reproducible results.\(^{107,108}\)

We could demonstrate that our RA patients had a significant improvement in range of joint motion, moments and work in the overlying joints such as the knee and hip after one year of
follow-up. The RA cohort experienced normalisation of several gait parameters when compared with age- and sex-matched controls. This indicates that fusion surgery in the RA ankle/hindfoot leads to an overall better lower limb function including adjacent joints which did not undergo surgery.

**Epidemiological studies**

**Key points:**

**Papers V and VI**

- The number of surgical procedures of the lower limbs for RA inpatients decreased during 1987-2001.
- A stable occurrence of RA-related total joint arthroplasties (TJAs) of the elbow and shoulder was evident during 1998-2004.

This positive trend towards less RA-related orthopaedic joint surgery can be viewed as a combined result of improved diagnostic procedures, earlier therapeutic intervention, new and more effective therapeutic regimens and an improvement in rheumatological and orthopaedic practice. Comparison of patients who were treated in the early-1980s with those of the mid-1990s revealed less functional disability and reduced radiographic joint damage in the more recent cohorts \(^{109-112}\). Verstappen *et al.* \(^{113}\) reported that treatment with DMARDs immediately after diagnosis resulted in less joint surgery compared with a delayed start. Moreover, joint surgery occurred more frequently in RA patients who were not adequately responding to medical therapy \(^{113}\).

Analysis of data from the Swedish Knee Arthroplasty Register showed a large increase of knee arthroplasties due to osteoarthrosis were offered to an increasingly wider selection of patients during 1976-1997 \(^{114}\). While arthroplasties in knee-osteoarthritis constantly increased during 1976-1997, no such increase in the incidence of knee arthroplasties could be observed in patients with RA \(^{114}\). Similarly, in a study from Finland by Sokka *et al.* \(^{115}\), a 2-10 fold increase of TJA surgery between 1986-2003 was recorded in non-RA patients,
associated with an aging population, but no increase in patients with RA. The authors concluded that long-term outcomes of RA had improved, even prior to the availability of biological agents\textsuperscript{115}.

There is evidence from other parts of the world that the need for orthopaedic surgery in RA patients diagnosed after 1985\textsuperscript{71} and rates of hospitalisation for severe manifestations of RA are declining\textsuperscript{116}. Despite that several different factors may account for these changes, it was suggested that the long-term health outcomes of patients with RA have constantly improved since the early 1980s\textsuperscript{116}.

Kobelt et al.\textsuperscript{117} found a significant decrease in hospital care and surgery in a cohort of RA patients that commenced TNF-anatagonist therapy. The total number of orthopaedic procedures and major joint replacements were reduced by half during the treatment year. The authors suggested that the reduction in surgery was an effect of treatment change\textsuperscript{117}.

In conclusion, Papers V and VI demonstrate a decreasing trend in orthopaedic surgical interventions of the lower and upper limbs in Swedish RA patients, suggesting that new non-surgical anti-rheumatic treatments may have improved long-term health outcomes, and/or that changes in clinical practice have reduced the likelihood of clinical admission. These findings reflect trends in disease management and health outcomes of RA patients in Sweden.

**FUTURE PERSPECTIVES**

Despite novel medical treatments, the chronic inflammatory nature of RA leads to long-term joint damage, chronic pain, loss of function and disability in affected patients. Bone erosions are evident in over 90\% of patients 10 years after disease onset\textsuperscript{118}. Early diagnosis and treatment is essential in the management of RA, with the major goal of controlling symptoms of joint pain and inflammation, minimizing loss of function and reducing joint destruction and disability\textsuperscript{119}.

To date, biological agents such as anti-TNF and IL-1Ra have been shown to reduce the progress of joint damage and bone erosions in RA. However, up to 30-40\% of patients with established disease fail to respond to TNF antagonists and the majority of those that do respond do not achieve complete remission\textsuperscript{120}. Moreover, the long-term tolerability of these agents may also be of concern\textsuperscript{119,121}.
There is still a need for additional therapeutic progress with development of targeted therapies selectively inhibiting joint destruction. The destructive effects of IL-1 on cartilage and bone are well recognized. Because of promising effects in many animal models, IL-1Ra has been used with beneficial effects as a therapeutic agent (Anakinra) in human RA patients. However, this preparation has to be given subcutaneously in high doses on a daily basis to maintain blockade of IL-1 binding and signaling through its receptor. Local adverse injection reactions are common. Development of better strategies for neutralizing IL-1 might even further improve long-time prognosis in reducing joint destructive processes in RA patients which do not respond to anti-TNF therapy.

In addition, inhibition of RANKL through use of OPG or anti-RANKL antibodies which both block the function of RANKL, may be a new promising approach for the treatment of bone loss and bone erosions in RA. A fully humanized neutralizing antibody against RANKL, Denosumab, was recently developed. Preliminary results of studies using radiographs and magnetic resonance imaging (MRI) revealed that inhibition of RANKL by Denosumab may reduce bone erosions in patients with RA. Denosumab may be an attractive therapeutic tool for treatment of bone loss in RA patients and may also prevent and treat joint destruction. In addition to documenting and quantifying the efficacy of Denosumab therapy in large numbers of patients, it will also be essential to monitor and document its potential side-effects on the cardiovascular and immune systems.

Three-dimensional gait analysis includes the systematic evaluation of the dynamics of gait. It is a useful method to characterize and evaluate the walking pattern of patients with specific gait-related abnormalities. This technique has traditionally been a scientific tool whose primary use will continue in different fields of research. However, quantitative gait analysis has often been used for patients with neuromuscular conditions as part of the surgical decision-making process. There have been reports that preoperative gait analysis in children and adolescents with cerebral palsy had substantial effect on the orthopaedic decision-making process. Moreover, the impact of postoperative gait analysis on orthopaedic care should not be neglected.

The increasing urge to document and quantify the benefits of therapeutic interventions may have the consequence that gait analysis could also become a tool in routine clinical practice in other medical conditions. Computerized motion analysis can measure the initial deviation from normal as well as the improvements achieved through medical or surgical interventions. This technique offers a more accurate and objective assessment of gait parameters than...
conventional methods such as visual observation alone. The combination of a careful clinical assessment and gait analysis could be a powerful tool for the clinician not only in assessing treatment and outcome in patients, but also in planning ongoing care for these patients.

The most representative outcome measure of whether or not the course of RA is altered by a certain therapeutic intervention is the presence/absence or new occurrence of irreversible disability. Longitudinal observational studies in rheumatic diseases, which are an essential complement to randomized-controlled trials, should thus not only demonstrate that acute phase reactants and clinical indices decrease or increase over time, but also that disability and the use of orthopaedic joint surgery can be influenced by new medications.

Analyses of patient registries collecting long-term data from a wide range of RA patients are warranted. Datasets including a thorough and systematic follow-up of patient demographics, baseline disease characteristics, medication records, prior use of DMARDs, ACR core set of RA outcome, health assessment questionnaire (HAQ), disability index, physician assessment of disease activity, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), adverse events and employment status are excellent tools for improving the knowledge of rheumatic diseases. The Swedish rheumatology registries, including the Swedish RA registry and the biologics registries ARTIS (Antirheumatic Therapies in Sweden), SSATG (Southern Sweden Antirheumatic Therapy Group) and STURE (Stockholm Tumor Necrosis Factor-α Follow-up Registry) may be very helpful datasets for addressing numerous scientific questions, quality control and outcome of new therapeutic regimens in patients with rheumatic diseases. These datasets can serve as monitoring systems for the long-term surveillance required for the safe introduction of new treatments.

**CONCLUDING REMARKS**

My personal aim with this thesis was to obtain an overall picture of this destructive disease with the guiding theme of joint damage, which plays a central role in RA patients’ normal disease course. The problem of joint destruction in RA was therefore assessed using a relatively wide approach with studies encompassing experimental, clinical and epidemiological aspects of RA.

From a clinical orthopaedic surgeon’s point of view, experimental animal studies investigating the natural course and pathophysiological background of a disease could serve as a point of criticism since such disease stages do not usually occur in the clinical practice of
my surgical specialty. However, the multifactorial approach which I have included in my thesis work has changed my personal scientific interest in RA and in its background of joint destruction, which goes beyond the surgical facette. The three aspects of joint destruction in RA, linking basic laboratory work, clinical aspects and epidemiological investigations, became a natural leitmotif of my thesis. Acquiring more knowledge of the cellular pathophysiology leading to joint destruction may contribute to the development of new targeted therapies inhibiting joint destruction. Better comprehension of clinical characteristics of RA patients and epidemiological trends is valuable in evaluating changes in therapies and interventions. My belief is that a multidisciplinary approach is helpful and might contribute to improve strategies and influence the future care of RA patients.
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