

Symptoms, Functional Aspects and Health Related Quality of Life in Patients with Hand Osteoarthritis

Thesis by
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In memory of my beloved father Dr. med Franz Slatkowsky

Alles, was uns imponieren soll, muß Charakter haben.

Johan Wolfgang von Goethe

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Abbreviations

ACR	American College of Rheumatology
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AIMS2	Arthritis Impact Measurement Scales 2
AS	Ankylosing spondylitis
ASU	Avocado soybean unsaponifiables
AUSCAN	Australian Canadian HOA Index
BEJC	Bony enlargement joint count
CHFS	Cochin Hand Functional disability Scale
CMC	Carpo-metacarpal joint
COX 2	Cyclooxygenase 2
DAS	Disease activity score
DIP	Distal inter-phalangeal joints
DMOAD	Disease modifying osteoarthritis drug
DMARD	Disease modifying antirheumatic drug
EULAR	European League Against Rheumatism
FIHOA	Functional index for hand osteoarthritis
FM	Fibromyalgia
GARP	Genetics, Arthrosis and Progression
GOGO	Genetics of Generalized Osteoarthritis
HAQ	Health Assessment Questionnaire
HOA	Hand osteoarthritis
HRQoL	Health Related Quality of Life
HOOS	Hip dysfunction and Osteoarthritis Outcome Score
ISH	Index of Severity for osteoarthritis of the Hip
ISK	Index of Severity for osteoarthritis of the Knee
KOOS	Knee injury and Osteoarthritis Outcome Score
LMJC	Limited motion joint count
MCP	Meta carpal joints
MHAQ	Modified Health Assessment Questionnaire

MHQ	Michigan Hand Outcomes Questionnaire
MMP	Matrix Metalloproteases
NSAID	Non-steroidal anti-inflammatory drug
OA	Osteoarthritis
OAKHQOL	Osteoarthritis Knee and Hip Quality of Life Questionnaire
OARSI	Osteoarthritis Research Society International
OMERACT	Outcome Measures in Rheumatoid Arthritis Clinical Trials
ORAR	Oslo Rheumatoid Arthritis Register
PIP	Proximal inter-phalangeal joints
PROs	Patient reported outcomes
QALY	Quality of life adjusted years
RA	Rheumatoid arthritis
RAI	Ritchie articular index
SACRAH	Score for assessment and quantification of chronic rheumatic affections of the hands
SJC	Swollen joint count
SLE	Systemic lupus erythematosus
SYSADOA	Symptomatic slow-acting drugs for OA
TJC	Tender joint count
TNF alpha	Tumor necrosis factor alpha
VAS	Visual analogue scale
WOMAC	Western Ontario McMaster Universities Osteoarthritis Index

List of papers

- I. Slatkowsky-Christensen B, Kvien TK, Bellamy N. Performance of the Norwegian version of AUSCAN - a disease-specific measure of hand osteoarthritis. *Osteoarthritis Cartilage* 2005;13(7):561-7.
- II. Slatkowsky-Christensen B, Mowinckel P, Loge JH, Kvien TK. Health-related quality of life in women with symptomatic hand osteoarthritis: a comparison with rheumatoid arthritis patients, healthy controls, and normative data. *Arthritis Rheum* 2007;57(8):1404-9.
- III. Slatkowsky-Christensen B, Mowinckel P, Kvien TK. Health status and perception of pain: A comparative study between female patients with hand osteoarthritis and rheumatoid arthritis. *Scand J Rheumatol* 2009;38(5):342-348.
- IV. Slatkowsky-Christensen B, Haugen IK, Loge JH, Kvien TK. Distribution of joint involvement in women with hand osteoarthritis and associations between joint counts and patient-reported outcome measures. *Ann Rheum Dis* 2009;69(1):198-201.

1. Introduction and background

1.1 Diseases

Musculoskeletal diseases (MSD) are increasingly recognised as a major and important group of afflictions. Rheumatic diseases, representing a substantial part among them, embrace a wide range of conditions, which are characterised by a distinct heterogeneity. Osteoarthritis (OA) is the most common rheumatic joint condition and is generally regarded as a degenerative disease (1). However, an inflammatory component plays an additional role in OA (2-5). Rheumatoid arthritis (RA) is a systemic, highly inflammatory and more severe disease with a lower prevalence, normally with symmetrical joint involvement (6). Both diseases may involve hands and feet and can be subject to differential diagnosis.

1.1.1 Osteoarthritis

This research project was started because the department, as part of a long-term strategy, wanted to focus more on OA. The research agenda in the nineties had main focus on RA, reactive arthritis and secondary osteoporosis and it was considered important to enhance the focus on other joint diseases and in particular OA. HOA was then a reasonable choice because quite a few of these patients had been referred to and examined at the department of rheumatology.

Main signs and symptoms of OA are typically pain, stiffness and reduced physical function, which can influence the patients' lives considerably. Patients with OA have barely been a priority for healthcare systems for a long period of time, but fortunately interest in OA has recently improved. Serious efforts have been made to enhance the understanding of the condition in terms of patho-physiological mechanisms including cartilage degradation and inflammation and the complex process affecting many different joint areas in the body (5;7-10). Furthermore, work to find new pharmaceutical treatment strategies, especially disease modification, has been intensified, but so far no suitable disease-modifying agents are on the market (2;9;11-17).

OA is oftentimes described as a booming epidemic (4) and it is a fact that both prevalence and incidence numbers are expanding along with the elderly populations. The overall self-reported prevalence of OA in a Norwegian population study (age 20-80 years) was 12.8% (14.7% in women, 10.5% in men) (18). Prevalence studies from either Scandinavia and

other European countries and the United States (19-24) indicate both similar and diverging figures. The prevalence of knee and hip OA in Norway was 7.1% and 5.5%, respectively (18). Other population studies on radiographically assessed hip / knee OA both from Scandinavia and northern Europe have shown higher numbers (20;21;25).

Incidence figures for Norway can be calculated from a Norwegian population survey (26) and the 10-year incidence for HOA is 5.6%, for hip OA 5.8% and for knee OA 7.3% (26). Respective figures from a Swedish study over a 5 year period are 13.6% (HOA) and 4.5% (knee OA) (19;20). A study from the United States from the mid-nineties found an annual incidence of 1% for radiographic knee OA in women over the age of 70, HOA and hip OA were somewhat lower (27). Both prevalence and incidence numbers show huge discrepancies across studies due to heterogeneous populations and inconsistencies in the criteria.

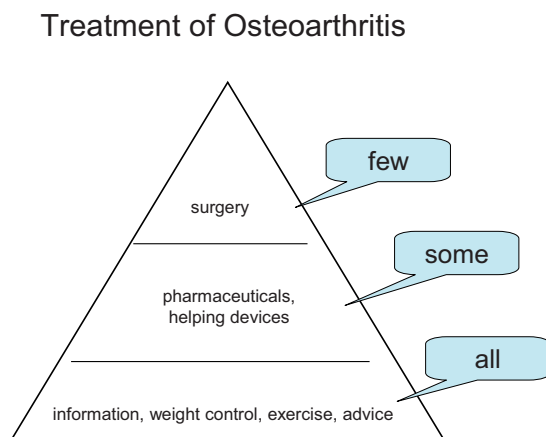
Geographical variations also have an influence on the occurrence of OA. Furthermore, diverse risk factors do have an impact on incidence and prevalence. The most prominent factors for development of OA are age, female gender, genetic factors, excessive physical activity in either work or leisure time, overweight and other lifestyle factors (19). It is established that age is the strongest risk factor for OA. The high incidence of OA in postmenopausal women implies that hormonal factors can account for a distinct influence on this high occurrence (28). Genetic factors are relevant as well (29-31). There is increasing evidence that physically straining activities can be a risk factor, especially for knee OA (32;33). Important life style factors (i.e. overweight) together with expanding populations of the elderly can contribute to explain the rising prevalence of OA (4;34-36).

OA can be detected in any joint in the body, but the most frequent sites are the hips, knees and hands. Classification criteria, diagnosis and management recommendations for all three forms of OA have been published (37-46).

The strongest focus on OA is most frequently on the weight bearing joints (hip and knee) since it affects a majority of patients and is a prime origin for pain, disability and impaired health related quality of life (HRQoL) among the elderly (47). Moreover, most studies concerning treatment options for OA have been conducted in patients with knee or hip OA.

HOA can be regarded as an isolated, localized form of OA but is usually seen as part of a generalized disease (48-52).

Figure 1



Therapeutic management options for OA today are multidisciplinary and complex (Figure). The initial and fundamental approach to treatment is information and education of patients and to encourage patients to perform appropriate exercises. Physiotherapy, occupational therapy including distribution of helping/technical devices (53-60) and support from nutritional therapists are also essential parts of the management program (61;62).

Symptom modifying drugs such as traditional "painkillers" are in the first line of the pharmacological treatment of the disease. Paracetamol is still the first option in most existing management guidelines or recommendations (22;40;41;45;46;63). The second alternative, if response to paracetamol is insufficient, are non-steroidal anti-inflammatory drugs (NSAIDs) both for oral and topical use (64;65) and the newer generation of cyclooxygenase 2 (COX 2) selective inhibitors. These selective COX 2 inhibitors were developed with the intention to minimise gastrointestinal side effects, which can be associated with the intake of traditional NSAIDs, especially in older rheumatic patients. Selective COX 2 inhibitors have been shown to increase cardiovascular risk, but subsequent studies have also supported that non-selective NSAIDs also increase this risk (66-68). If pain relief is not achieved by paracetamol and NSAIDs / COX 2 inhibitors, opioids might be indicated (69-71).

In recent years symptomatic slow-acting drugs for OA (SYSADOA) like glucosaminoglycans (sulphate and hydrochloride) and chondroitin sulphate and combined glucosamine/chondroitin supplements have experienced a renaissance after being used in veterinary medicine for ages (72-74). They have been included in existing treatment recommendations (22;40;41;45;63). At the same time, the evidence is much debated and inconclusive (75-83). Further, also other nutritional supplements and compounds such as ASU= avocado soybean unsaponifiables (84) and diacerein, a natural interleukin inhibitor (17;85-87) have also been seen as therapeutic opportunities and have been addressed in several treatment recommendations (22;40;41;45;63). Nevertheless, recent recommendations do not include these any more, due to shrinking evidence, notably because of negative findings in a big, independent, placebo controlled, randomised trial (75;88;89).

In active inflammatory conditions with joint effusion and/or synovitis, intra-articular steroid injections can be indicated (90-92). Hyaluronic acids, also administered intra-articularly, (93-99) have also shown modest effect in knee OA.

Efforts to find new pharmaceutical treatment strategies have been intensified and the research agenda has focused on new potential treatment options targeting inflammation in and around the joint and possible disease-modifying OA drugs (DMOADs), unfortunately with no convincing results so far. Potential candidates for disease-modification are as of now inhibitors of pro-inflammatory cytokines like interleukins (17;100-105), tumor necrosis factor alpha (TNF) (106;107) and metalloproteases (MMPs) (5;17;108-110).

In patients with advanced joint disease orthopaedic surgery and mostly joint replacement therapy with prostheses is widely used (22;40;41;45;63).

1.1.2 Osteoarthritis of the hand

HOA is a heterogeneous and common condition which characteristically affects the distal (DIP) and proximal inter-phalangeal joints (PIP) and the carpo-metacarpal joint of the thumb (CMC).

For the most part HOA affects multiple PIP and DIP joints, but some patients present with isolated CMC joint involvement. The subset of erosive HOA is characterized by

considerable, clinical inflammation and significant and specific radiographic findings (erosions) (111;112).

Main symptoms of HOA are, as in all types of OA, pain, stiffness and impaired physical function, which can have a substantial influence on patients' quality of life (113-117). Typically, HOA patients are afflicted with pain and stiffness in the hands resulting in problems with fine motor tasks (writing, buttoning, turn movements etc.) and activity limitations (57;118). Moreover, HOA patients experience loss of grip-strength and often involuntarily drop objects out of their hands (48;49;114;119-124). Classification criteria for HOA were developed a long time ago (38) and in recent years new recommendations for the diagnosis and management of HOA have also been developed (16;45;46;49). HOA is also a key manifestation for a more generalized disease and a part of the proposed classification criteria for generalized OA (50;52). Presence of HOA may also be a predictor for knee and hip OA (125).

Unfortunately, few accepted and validated HOA disease specific outcome measures exist compared to RA (126-129). Therapeutic approaches in HOA comprehend patient information and exercise, occupational therapy, orthoses and helping devices (57). Pharmaceutical options are mostly the same as for other types of OA, but fewer controlled studies have been performed (16;49;53;130). A recent trial showed effect on HOA of a combination of low dose prednisolone and dipyridamole (131). Surgical alternatives are essentially directed towards the CMC joint (5;45;132).

Table 1: **Comparison disease characteristics OA and RA**

Differences	OA	RA
Pathogenesis	mostly cartilage / moderate inflammation	massive inflammation
Joint findings	Osteophytes / nodes / moderate soft tissue swelling	considerable soft tissue swelling
Distribution of joint involvement (hands)	PIP / DIP / CMC	MCP / PIP / wrist
Radiographic findings	Osteophytes / joint space narrowing	Erosions
Extraarticular disease		only RA
Laboratory findings	microCRP	Elevated ESR + CRP positive rheumatoid factor + anti-CCP
Synovial fluid	low leucocyte count	high leucocyte count

1.1.3 Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic, inflammatory and symmetrical joint disease. Hands, knees and feet are the most frequently affected joint areas, and the wrists, MCP and PIP joints are the typically involved joints of the hands (Table 1). RA can develop into a severe systemic condition with extra-articular involvement of various internal organs. Fortunately, joint deformities and severe, systemic manifestations are less common nowadays (133;134) since new treatment modalities have provided a better and more satisfying management of the disease (135-139). The prevalence of RA is approximately 0.5-1% and the incidence is 25-50 per 100 000 (6;140-142). RA is 2-3 times more prevalent in women than men (142;143). RA can be a differential diagnosis to HOA.

A variety of outcome measures to monitor this condition exists within three main dimensions: Inflammatory activity, joint damage, HRQoL (144-152).

Suppression of inflammation is the main objective in the treatment of RA (137), which may lead to prevention of radiographic progression, suppression of symptoms as pain and stiffness and amelioration of function. Suppression of inflammation can be achieved with anti-inflammatory drugs (symptom modifying) and corticosteroids (symptom and disease modifying) (136;137;153;154). The most commonly used disease modifying antirheumatic drugs (DMARDs) in the 1980s were gold salts. Methotrexate became the most widely used DMARD in the 1990s (155;156), either as monotherapy or in combination with sulphasalazine and hydroxychloroquine. Leflunomide became available in the last part of the 1990s.

Considerable progress in the development of new treatment strategies has brought along a new era of therapy for RA patients in the last decade (157). The new biological agents (e.g. TNF and interleukin inhibitors) (135-137) have revolutionised the management of RA and ameliorated the patient's disease activity and quality of life. Importantly, access to the new drugs has been followed by an increasing focus on improved treatment strategies concentrating on early diagnosis, early use of methotrexate and tight control according to a treatment target and then switching of therapy, if the target is not achieved (158-162).

1.2 Assessment of health status

Assessment of health status is important for the evaluation of the course of rheumatic diseases. Measurement of disease activity in RA (163;164) and HOA is advised (165) and is used to predict the disease course and outcome and most importantly, the effect of treatment. Several instruments are available to measure the burden of disease and a variety of patient reported outcomes (PROs) and appropriate function tests are also accessible. In RA, joint counts, assessment of structural damage and PROs are used to assess the course of the disease (163). In HOA, only few specific instruments for measurement of health status are available (116;126;128;165) and consensus on how to assess the condition has not been achieved. Nevertheless, recommendations for a core set of signs and symptoms in the assessment of OA including pain, function, patient global and imaging have been developed (166). Instruments to address these dimensions in OA are available, and are most comprehensively validated for weight bearing joints (167-170).

1.2.1 Pain

Pain is the cardinal symptom in various rheumatic diseases, among them HOA (5;45;46;57;116;117;122;124;165;168), and is the signature problem for patients with RA (171;172). Pain is also part of the three main domains in the recommended OMERACT core set for assessment of OA (166) and recommended as an evaluation domain in the OARSI set of responder criteria for OA (173). The symptom of pain can be assessed by diverse outcome measures, both generic and arthritis specific. The 100 mm visual analogue scales (VAS) or 11-point numeric rate scales (range 0-10) are most widely used.

1.2.2 Physical function

Physical function is impaired as a result of the patho-physiological, inflammatory and degenerative processes in RA and HOA, resulting in structural changes. These structural abnormalities together with pain and stiffness cause disability. Impaired physical function has a considerable effect on RA and HOA patients' every day life (46;116;117;119;121;122;124;165;174;175). Disability is one of the three domains in the OMERACT OA core set (166) and function is a recommended evaluation domain in the OARSI set of responder criteria for OA (173). Hand function can also be assessed by grip strength and other functional performance tests (176;177).

1.2.3 Stiffness

Stiffness is a typical symptom associated with most rheumatic conditions such as both RA and HOA. It affects function and has its peak in the morning or after longer periods of immobilisation. Morning stiffness is commonly assessed in RA, but was not included in the ACR or OMERACT core sets (178-180). However, stiffness is one of the dimensions in the widely used PROs in OA (116;117;126;127;165;167;181;182) and has been included as a key proposition in the newly published EULAR recommendations for the diagnosis of HOA (46).

1.2.4 Health Related Quality of Life

HRQoL is an eclectic umbrella term and sums up the impact of a disease on various dimensions of health in the patient's life. Pain and physical function are essential constituents of HRQoL, but in addition HRQoL can be influenced by mental health, sleep disturbance, fatigue, social interaction, vitality and several other domains. HRQoL can be assessed by several established PROs (183). Appropriate validated and frequently used

outcome measures can be generic or condition specific, multidimensional or monodimensional. The SF-36 is the most widely used generic, multidimensional outcome measure (152). Multidimensional arthritis specific instruments are the Arthritis Impact Measurement Scales 2 (AIMS2) (149). HOA specific instruments include the Australian Canadian HOA index (AUSCAN) and the score for assessment and quantification of chronic rheumatic affections of the hands (SACRAH) (116;117;181). The Michigan Hand Outcomes Questionnaire (MHQ) (184) is a generic, multidimensional outcome measure for the hands. Specific PROs for functional assessment of the hands are the algofunctional index for OA of the hand (128), the Cochin Hand Functional disability Scale (CHFS) (185) and the functional index for HOA (FIHOA) (129). For the rating of OA of the lower limbs several multidimensional, specific questionnaires are available such as the Western Ontario McMaster Universities OA Index (WOMAC) (167), the Hip dysfunction and Osteoarthritis Outcome Score (HOOS) (169), the Knee injury and Osteoarthritis Outcome Score (KOOS) (170), the Indexes of Severity for osteoarthritis of the Hip (ISH) and Knee (ISK) (186) and the osteoarthritis Knee and Hip Quality Of Life (OAKHQOL) questionnaire (187). The Health Assessment Questionnaire (HAQ) (151) and the modified HAQ (MHAQ) (150) are commonly used in RA but also in other arthritides.

Self-efficacy is defined as individual's estimation of their capability to plan and perform courses of action. The Self-efficacy scales assess coping abilities in RA patients (188).

1.2.5 Joint counts

Joint counts are central in the rating of disease activity in RA (147;189), but are not yet established as such in HOA. Joint assessment in HOA usually comprises evaluation of pain on palpation, soft tissue swelling / synovitis and bony enlargement (as an expression for osteophytes).

1.2.6 Fibromyalgia-like symptoms

Fibromyalgia (FM) symptoms are prevalent in rheumatic diseases. (190;191). At the same time, the diagnosis of FM is in itself challenging (192;193) since symptoms can overlap with other related diseases (194). Also, the American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia have limitations and are not recommended for use in the clinical setting (192;195). Yunus et al. recommended to assess FM-related symptoms like muscle pain, headache, concentration problems, numbness and abdominal

pain, since these symptoms are essential clinical manifestations (196). A recent review by Prodiger et al. evaluate 16 frequently employed instruments to assess FM symptoms (197). Thus, so far no gold standard for the diagnosis and treatment of FM exists (193), even though EULAR recommendations for the management of FM have been published (198).

2. General aim and specific research questions

2.1 General aim

The general aim of this thesis was to assess the burden of disease in patients with HOA through a comprehensive clinical examination including completion of patient-reported questionnaires.

2.2 Specific research questions

- How does the Norwegian translation of the AUSCAN perform in the Oslo HOA cohort? (paper I)
- How does the AUSCAN perform compared to other arthritis specific (WOMAC, AIMS2, HAQ, MHAQ, self-efficacy scales) and generic (SF-36, several VAS) outcome measures as well as a performance based test (grip strength)? (paper I)
- Are levels of pain, physical function and quality of life different between HOA patients, RA patients and healthy controls? (paper II)
- How is the level of HRQoL in the two rheumatic diseases (HOA, RA) in comparison with healthy controls and population norms? (paper II)
- Are pain levels, physical function and HRQoL different between patients with HOA and RA? (paper III)
- Do HOA patients experience FM-like symptoms and how are their levels compared to RA patients? (paper III)
- How is the association between joint involvement and levels of pain, physical function and other dimensions of health? (paper IV)

3. Materials and methods

3.1 Patients and controls

3.1.1 The Oslo Hand Osteoarthritis Cohort

The Oslo HOA cohort was initiated in the year 2000 with the primary intention to provide an opportunity to evaluate the burden of disease (assessment of pain, physical function, stiffness, mental health and HRQoL in general) in HOA. Secondly, a cohort of HOA would potentially provide opportunities for studying the prediction of long term outcome.

Patients between 50 and 70 years of age (mean age 61.6 years) with HOA were eligible to be enrolled in the HOA cohort, if they did not have any other rheumatic diseases. Potential study participants were selected by using diagnostic codes in the hospital data system. After a thorough review of patient records from the rheumatology outpatient department of the preceding two years, we identified 275 eligible patients with clinical HOA. Two hundred and nine (76%) individuals consented to participate in the data collection. All patients reported OA pain during the last month before screening. The 19 male participants of the cohort were not included in the analyses in articles II, III and IV.

A total of 159 (83%) of the 190 female patients used for the analyses fulfilled the American College of Rheumatology (ACR) clinical classification criteria for HOA (38), whereas 31 (16%) had clinical HOA without formally fulfilling these classification criteria.

Radiographic OA abnormalities (Kellgren/Lawrence grade 2 or higher) in at least one of the finger joints were found in 176 (93%) patients (199). Seventeen (9%) and 112 (59%) participants also fulfilled the clinical and radiographic ACR classification criteria for hip OA (39) and knee OA (37), respectively.

3.1.2 The Oslo Rheumatoid Arthritis Register (ORAR)

The ORAR was established in 1994. Mail surveys were performed in 1994, 1996 and 2001. Further, a clinical examination with a comprehensive data collection was performed in 1996-97 in individuals less than 70 years, and the respondents were re-examined 2 years later. These examinations had a particular focus on osteoporosis, but also on inflammatory activity and HRQoL.

Data from 194 women with RA, age between 50 and 70 years, (mean age 61.1 years) from the ORAR were incorporated as a comparison group in the analyses. The data from the 1998 / 1999 assessment were used for the comparative analyses (200). Only routinely examined patients from the outpatient department from the previous 2 years and patients without any clinical evidence of HOA were eligible for inclusion in this comparison group.

3.1.3 Healthy controls

The healthy control group comprised 144 female, healthy individuals (mean age 60.8 years), who had been randomly selected from the population register in Oslo and had undergone the same procedures and examinations as the RA cohort in the 1998-99 data collection (200;201). From the original 249 controls included in the RA study on vertebral deformities (201;201) we included individuals between 50 and 70 years of age according to the inclusion criteria for the study, but excluded individuals with clinical signs of OA or who reported OA as a concomitant disease.

3.1.4 Population norms

The population data were gained from a random computer draw of the National Population Register among all Norwegian inhabitants between 50-70 years of age with the same digit in their social security number. Data from 384 female individuals (mean age 59.2 years) were used for this analysis (202;203).

3.2 Data collection/logistics

Two hundred and seventy-four individuals with HOA between 50 and 70 years of age, who had been examined at the outpatient rheumatology department within the previous 2 years were enrolled in the HOA cohort and contacted by mail. The patients who consented to participate received a booklet of questionnaires by mail and returned the completed booklet when they subsequently attended the clinical examination and other assessments according to the research protocol.

The clinical examination was performed by one experienced clinician (BSC). All patients were interviewed by a study nurse, who also collected demographic information and completed the performance based grip strength test (204). All patients had radiographic examination of their hands (conventional radiographs) and provided a blood sample (ESR, used for the ACR classification criteria for the hip). The patients also had a DXA scan (205).

Data from women with RA and individuals representing the general population between ages 50 and 70 years were already available and were used for the comparative analyses (200).

Table 2: PROs and function test in patient groups and controls

		OA	RA	Control
Specific measures				
OA specific	AUSCAN	X		
	WOMAC	X		
Arthritis specific	AIMS2	X	X	
	HAQ	X	X	
	MHAQ	X	X	
	Self- efficacy scales	X	X	
Generic measures	SF 36	X	X	X
	SF-6D	X	X	X
	VAS	X	X	X
	(pain, fatigue, global and fibromyalgia like symptoms)			(pain and fatigue)
Performance based measure	Grip strength	X	X	

Table 3: **Data reported in the individual papers**

	Paper I	Paper II	Paper III	Paper IV
Demographics				
Age	X	X	X	X
Gender	X	females	females	females
Disease duration	X	X	X	
Education		X		
Co-morbidity		X		
Outcome measures				
SF-36	X	X	X	X
SF-6D		X		
AIMS2	X		X	X
HAQ			X	X
MHAQ	X		X	
AUSCAN	X			X
WOMAC	X			
VAS pain	X	X	X	X
VAS fatigue		X	X	
VAS global			X	
VAS (fibromyalgia like symptoms)			X	
Self efficacy scales			X	
Grip strength		X	X	X
Joint counts				X
Radiology				
Hand x-rays	X	X		

3.3 Patient-reported outcome measures

3.3.1 OA-specific measures

AUSCAN

The Australian Canadian HOA Index is a disease-specific health status measure developed for HOA, which addresses pain (5 items), stiffness (1 item) and difficulties with daily activities (9 items) during the last 48 hours (127). We used the Likert scale version, which gives the patient a choice of five response options (none, mild, moderate, severe, extreme (0-4)) within each of the 15 items. The pain dimension measures the amount of hand pain at rest, when gripping, lifting, turning or squeezing objects. The stiffness dimension asks for stiffness after wakening. The physical dimension is capturing difficulties with the following tasks: turning taps and a round doorknob or handle, doing buttons, fastening jewellery, opening a new jar, carrying a full pot with one hand, peeling vegetables/fruits, picking up large, heavy objects and wringing out washcloths.

Subscale scores were calculated by simple summation of the assigned values scored on component items and we presented normalised data with a score range of 0-10. The translation procedures followed standardised, international guidelines (206). Professor Nicholas Bellamy gave permission to use the AUSCAN free of charge for this non-commercial research project.

WOMAC

Western Ontario McMaster Universities Osteoarthritis Index is a widely used, self-administered, specific outcome measure for hip and knee OA. It is a multidimensional self-administered measure which captures pain, stiffness and physical functional disability (167). The questionnaire contains 5 questions on pain, two on stiffness and 17 different questions on physical function. Scores are calculated in the same manner as the AUSCAN scores. The WOMAC was as the AUSCAN employed by courtesy of professor Bellamy.

3.3.2 Arthritis specific measures

AIMS2

The Arthritis Impact Measurement Scales 2 (AIMS2) is a multidimensional instrument which was initially developed for RA, but can also be used in other rheumatic arthritides such as OA. It captures several relevant domains of health and has been widely used by our research group, especially in the data collection for the ORAR. The questionnaire has 12

scales (one of them with a focus on hand and finger function). The scales can be merged into five main components: physical, mental, social, pain, and work. Each scale is graded from 0 to 10 (10 representing the poorest health) (149).

HAQ

The Health Assessment Questionnaire measures self-reported physical function in RA and is also applied in other rheumatic diseases (151). It consists of 20 questions on eight categories of relevant physical functions: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and common daily activities. The highest score for any question in each of the eight categories is selected to represent that respective category. The scores in each category range from 0 (without any difficulty) to 3 (unable to do) and the score is upgraded to the level of 2, if the patient reports use of helping devices and /or receives assistance within the same category. The mean score of the eight categories is calculated (range 0-3, 3 = worst) and presented as the HAQ score.

MHAQ

The Modified Health Assessment Questionnaire is a modified version of the original HAQ. Each of the eight items represents one of the eight categories of the HAQ. A mean MHAQ score is computed from all eight items, with a range from 1 to 4, with 4 representing the worst level of functioning (150).

Self-efficacy

The Self-efficacy Scales measures the perceived ability to influence rheumatic pain (five items), physical function (nine items), and symptoms (six items). The scale ranges from 10 (very uncertain) to 100 (very certain) (188).

3.3.3 Generic measures

SF-36

The Short Form-36 is the most commonly utilized generic, multidimensional health status questionnaire, measuring 8 dimensions of health: physical function (10 items), role limitations due to physical health problems (4 items), bodily pain (2 items), general health (5 items), vitality / energy (4 items), role limitations due to emotional problems (3 items), and mental health (5 items). SF-36 scores range from 0 to 100, with low scores indicating poor health (152).

SF-6D

The Short Form-6D is a preference-based utility instrument based on data from the SF-36, which are converted to a utility score. The score is based on 6 dimensions of health (physical functioning, role limitations, social functioning, pain, mental health, and vitality), each with 4–6 levels. The score range is from 0.29 to 1.0, with 1.0 reflecting perfect health (207;208).

Visual analogue scales (VAS)

Visual analogue scales (0 -100 mm) were used for joint pain, fatigue and patient global assessment (general OA disease activity) in this thesis, with no and intolerable pain / fatigue / disease activity as the anchoring points. The exact Norwegian expression we used for the VAS global was: Spørsmål om sykdomsaktivitet ” Vi ber deg vennligst vurdere aktiviteten i artrosesykdommen i løpet av den siste uken. Når du tar alle symptomer med i betraktning, hvordan synes du tilstanden er? ” The respective English translation is as follows: Question about disease activity “ We ask you kindly to assess the osteoarthritis disease activity during the past week. Taking all symptoms into account, how is your condition? ”

Perceived intensity of FM-like symptoms was also explored by VAS. The following symptoms were examined: abdominal pain, headache, numbness in fingers, muscle pain / muscular tenderness, and concentration problems, with anchors being no symptoms / intolerable symptoms.

3.4 Physical examination and other assessments

3.4.1 Joint counts and clinical examination

All joint assessments were performed by the same clinician (BSC). The CMC, MCP, PIP and DIP joints were examined for 4 categories of abnormalities and corresponding joint counts were computed: tenderness / pain on motion (tender joint count (TJC)), soft tissue swelling (swollen joint count (SJC)), bony enlargement (hard tissue swelling, including Heberden and Bouchard nodes) (bony enlargement joint count (BEJC)) and limited motion, defined to be less than “normal“ range of motion (limited motion joint count (LMJC)). Absence or presence of abnormal findings in individual joints was scored as 0 and 1, respectively.

For each of the 4 categories of clinical abnormalities, we computed several different combinations of joint counts: DIP joints (range 0-8), PIP joints (range 0-10) including the

first interphalangeal joint (IP-1), CMC joints (range 0-2), DIP+PIP joints (range 0-18) and DIP + PIP + CMC joints (range 0-20).

3.4.2 Performance based measure

Grip strength

Grip strength (kg) was assessed in all patients (HOA, RA) and healthy controls with the Jamar hand dynamometer (Jamar, Clifton, NJ). The best performance of 2 attempts was recorded (204;209).

3.4.3 X- rays

Traditional x-rays of the hands in AP view were taken from all patients. The x-rays were graded according to the Kellgren and Lawrence scale (199), which is the most widely used scoring system for radiographic assessment of OA and was developed as early as 1957. The K&L score is used in both epidemiological and clinical studies due to a long tradition and high feasibility. It is a global score assessing the DIP, PIP, IP, MCP and CMC-1 joints on a 0-4 scale based on the presence and size of osteophytes, joint space narrowing, sclerosis, cysts and altered shape of bony ends: 0 = no OA, 1 = doubtful OA, 2 = definite minimal OA, 3 = moderate OA, 4 = severe OA. Epidemiological studies often use K&L grade ≥ 2 as an osteoarthritis definition.

3.4.4 Demographic variables

Demographic variables were obtained from the questionnaires and the patient interviews. The patients provided some information by filling out the questionnaires beforehand and gave additional information during the interview with the study nurse, who recorded duration of education, time from onset of disease (disease duration), concomitant medication and co-morbidities.

3.4.5 Blood samples

A blood sample was drawn from all patients. The ESR was used for the assessment of the ACR criteria for the hips (37).

3.5 Statistics

The statistical analyses were performed by Statistical Package for Social Sciences (SPSS, SPSS Inc, Chicago, Illinois) (version 10.1- paper I, version 12.0 - paper II, version 14.0 –

paper III and paper IV) and Statistical Analysis Software (SAS, Institute, Cary, NC) version 9.1.3 (paper III). P-values equal to or below 0.05 were regarded as significant. Statistical advice and help with statistical analyses with the SAS was given by one of the co-authors (PM).

3.5.1 Descriptive statistics

For descriptive statistics mean was used as index of location and SD as index of dispersion for continuous variables, whereas number of cases (N) and percentages were used for categorical variables. Cronbach alfa was used to explore the internal consistency (paper I).

3.5.2 Bivariate analyses

Two sample t-test was used for comparisons of two groups (paper I and IV), whereas one-way Analysis of Variance (ANOVA) was used for multiple group comparisons (paper II and III). Correlations were reported with Pearson correlation coefficient (paper I and IV).

Two sample t-test in paper I was applied to examine the discriminatory abilities of health status measures (AUSCAN, WOMAC, AIMS2, SF-36 and MHAQ) across different subgroups of patients (HOA patients in two different age groups, fulfilling / not fulfilling the ACR classification criteria, presence/absence of radiographic abnormalities and female / male gender). In order to compare the level of discriminatory abilities, differences were standardised (difference divided by the standard deviation of the difference).

In paper IV two-sample t-test was used to compare health status between patients with and without joint involvement in specific joints areas.

One way analysis of Variance (ANOVA) was used in papers II and III to assess the difference between groups. This test is equivalent to the independent sample's t-test.

In case of more than two groups we used Tukey's post hoc test for pairwise group comparisons.

S scores in paper II were calculated for the purpose of detecting the disparity in HRQoL between patient groups versus a control group and the general population and were calculated by subtracting the mean scores of each of the 8 SF-36 scales for the patient groups and the control group from the mean values of population norm values. These differences were divided by the standard deviation of the general population values for each score. This approach was also chosen in a previous paper from our research group on ankylosing spondylitis (202).

3.5.3 Multivariate analyses

Analysis of Covariance (ANCOVA) was employed for group comparisons of continuous variables in papers II and III with adjustment for, age, number of co-morbidities and years of education. Tukey's Post Hoc test for pairwise group comparisons was subsequently applied in paper II. Simes' procedure was applied for correction of multiple comparisons. This procedure was chosen over the more known, but conservative and low-powered Bonferroni correction.

3.6 Legal and ethical aspects

The study was conducted according to the ethical principles of the Declaration of Helsinki. All participating patients had given written informed consent before entering the study. The study was approved by the regional ethical committee, and the storage of data was approved by the Data Inspectorate.

4. Summaries of results

4.1 *Paper I*

Performance of the Norwegian version of AUSCAN - a disease-specific measure of hand osteoarthritis

The paper focused on the examination of the performance of the Norwegian version of the AUSCAN Index as a disease-specific health status measure in patients with HOA. As a first step we translated the English version of this questionnaire to Norwegian according to standardised guidelines. One hundred and ninety-nine patients with clinical HOA from the Oslo HOA cohort had undergone a comprehensive clinical examination including grip strength and completed several self-reported health status questionnaires. The AUSCAN HOA index captures three different dimensions of hand OA: pain (5 items), stiffness (1 item), and difficulties with daily activities (9 items). Our pre-study hypothesis was to identify AUSCAN as a specific hand measure with strong correlations to hand measures and lower correlations to other general measures of musculoskeletal health. The applied statistical methods were Pearson correlation coefficients, two sample t-test in order to demonstrate the discriminatory abilities of health status measures across different subgroups of patients and calculation of standardised differences (difference divided by SD of the difference) to compare the level of discriminatory abilities. The internal consistency of the AUSCAN regarding pain and function was excellent. The AUSCAN pain and physical scores correlated substantially to each other and moderately to the stiffness scale. The AUSCAN physical scale correlated moderately to substantially to other measures within the same dimension, the highest correlation being seen with the AIMS2 hand and finger function scale ($r = 0.73$). The standardised differences between patients with and without radiographic abnormalities were numerically larger for the AUSCAN pain and physical scales than for other measures. In conclusion, the Norwegian version of the AUSCAN appeared to have an acceptable clinimetric performance and is a suitable tool for assessment of HOA.

4.2 Paper II

Health-related quality of life in women with symptomatic Hand osteoarthritis: a comparison with rheumatoid arthritis patients, healthy controls, and normative data

Data on the burden of disease in HOA are limited, and the main objective of this study was to highlight HRQoL in patients with HOA by comparison with RA patients, healthy controls, and normative data from the general population,. The comparison groups comprised 190 HOA and 194 RA patients, 144 healthy women and 384 population norms, all females within the same age range of 50-70 years. Health status was assessed by the following patient reported outcome measures: the SF-36, SF-6D, MHAQ, pain and fatigue VAS. Grip strength was also measured. Scores were compared by ANOVA and the by ANCOVA, adjusting for age, number of co-morbidities and years of education. Further, the disparity between patients and population subjects was measured by calculation of S scores for the SF-36.

HOA and RA patients demonstrated worse scores on all assessed dimensions of health compared with healthy controls. RA patients had the most impaired general health (SF-36), poorest physical function (MHAQ, SF-36 physical, grip strength), and the worst level of fatigue compared with HOA patients. HOA patients showed worse mental health (SF-36). Mean utility scores (SF-6D) in HOA and RA were 0.64 and 0.63, respectively, with a mean difference compared with healthy controls of 0.13 in HOA and 0.14 in RA patients. A clear difference between individuals with a rheumatic diagnosis (HOA, RA) and population subjects was shown through the S scores, which demonstrated a clear gap between patients and controls. The S scores between healthy controls and the general population were 0, implying that the control group was representative for the general population. This paper demonstrates that HOA patients have a similar overall burden of disease compared to female RA patients and experience a considerable impact on HRQoL in comparison with healthy controls.

4.3 Paper III

Health status and perception of pain: a comparative study between female patients with hand osteoarthritis and rheumatoid arthritis

The aim of this study was to emphasise the burden of disease, evaluated by measures of pain and HRQoL between two groups of rheumatic diseases: female patients with HOA and RA. One hundred and ninety female HOA patients were compared to 194 female RA patients of the same age. We assessed HRQoL with the same instruments as in paper II and in addition the following questionnaires: AIMS2, HAQ and self-efficacy scales. We further compared levels of fibromyalgia (FM) - like symptoms (headache, muscle pain, numbness, and concentration problems). We used multivariate ANCOVA to adjust for age, number of comorbidities and years of education. Sime's procedure was used to adjust for multiple testing. Our findings pointed out that RA patients present a marked impairment of physical function compared to HOA patients. Pain, on the other hand, was numerically worse in two out of the three pain measures (SF-36 and VAS pain) and statistically worse in the AIMS2 in HOA. At the same time, the HOA group also had worse scores for FM-like symptoms. In conclusion, physical health was reported to be worse in RA, pain intensity on the other hand, was worse in HOA.

4.4 Paper IV

Distribution of joint involvement in women with hand osteoarthritis and associations between joint counts and patient-reported outcome measures

In this paper we explored the association between clinically assessed finger joint involvement (joint counts) and patient outcome measures in HOA. The study population consisted of 190 female patients from the Oslo HOA cohort. All participants had completed a comprehensive clinical examination with evaluation of tenderness / pain, soft tissue swelling, bony enlargement and limited motion in the DIP, PIP, MCP and CMC joints. Furthermore, grip strength had been measured and the patients had completed several patient reported outcome questionnaires (AUSCAN, AIMS2, HAQ, SF-36, VAS pain). Statistical methods were independent samples t-test and Pearson correlation coefficients. DIP joints were predominantly affected in HOA. Joint tenderness / pain was a major indicator of impairment of health status and presence of tenderness / pain in any PIP or DIP finger joint was associated with worse health status. Also the three remaining joint assessments were in general linked to poorer health status, but associations were mainly not statistically significant. Correlations between tender and swollen joint counts in most finger joint areas and scores of hand specific outcome measures (AUSCAN, AIMS2 hand + finger), VAS pain and grip strength were weak to moderate. As expected, associations between joint counts and scores of general pain, physical function and other dimensions of health (AIMS2 and SF 36) were low. In summary, our findings indicated that tenderness / pain joint counts (CMC, PIP and DIP) in HOA correlate moderately to worse scores for key dimensions of health.

5. General discussion

The primary purpose of this thesis was to bring the burden of disease for patients with HOA into focus and to describe and highlight main symptoms such as pain, stiffness, limited function and other relevant aspects of HOA. In the following, the strength and weaknesses of the applied methods will be discussed followed by a discussion of the main results.

5.1 Methodological aspects

5.1.1 HOA patients

The Oslo HOA cohort was established in 2000 with the motivation to assess and outline the burden of disease in HOA. Most data from HOA cohorts are based on information from large, often community surveys (20;26;47;48;114;115;121;210-218) with substantial numbers of patients and often only self reported data. Few studies on HOA have attained patients from a clinic and or outpatient department as we have done (116;117;122;124;181;182). Since the threshold for receiving patients in our clinic is low, we were able to recruit patients for this study from our outpatient unit. This HOA cohort is therefore composed differently compared to for example the Norwegian population study from Ullensaker (18) or other population based studies. Hence, the Oslo HOA patients represent a preselected group with a more distinct disease and it is likely that the characteristics of the cohort are different from the general HOA population. This difference limits the external validity and caution should be applied in the interpretation of the results on a population level. Thus, population based study findings might represent the underlying general population to a greater extent than the hospital-based Oslo HOA cohort. However, in the Oslo HOA study we were able to conduct a very comprehensive data collection with a joint examination of the patients. A similar detailed assessment of the condition would be difficult to perform in a large population study.

Further, a significant part of the patients in the Oslo HOA cohort had a more generalised condition. As many as 60% of the cohort (female participants) had also clinical knee OA and 9 % hip OA, according the respective ACR classification criteria (37-39). Simultaneous

occurrence of OA in different joint areas has also been observed in other studies (50;51;212;219;220).

No gold standard for the diagnosis of HOA has been developed so far, but the newly published EULAR recommendations for the diagnosis of HOA (46) suggest 10 clinically oriented key propositions, a result of scientific evidence and expert opinion, which should be taken into consideration for the diagnosis of HOA (table 4). This publication recommends the consideration of a composite of several key features of HOA including risk factors, clinical manifestations, differential diagnosis, imaging and laboratory assessments for the achievement of the diagnosis of HOA. The main differences between the ACR classification criteria and the EULAR recommendations is that the first was generated for a research setting, whereas the EULAR recommendations emphasise a clinical diagnosis. The inclusion criteria for the Oslo HOA study were predominantly chosen on the grounds of typical clinical features of HOA, at a time when the EULAR recommendations were not yet developed. We therefore used the available ACR classification criteria in order to describe our cohort. This approach has also been used by others for hospital based studies on HOA (116;117;122;124;181;182).

One of the 10 propositions in the EULAR paper refers to subsets of HOA i.e. IP (inter-phalangeal) OA, thumb base OA or erosive OA, which seem to have different risk factors (221;222) and can lead to different outcomes (111;122;124;124;223). In retrospect, it might have been an advantage to distinguish between these three subsets in our study. To our knowledge, so far only few other publications refer to studies where patients were recruited similarly to our approach and with a comparable number of patients (116;117;124;181;182). In the studies from Austria patients were selected from an outpatient clinic in order to assess pain, function and stiffness in rheumatic hands by using the SACRAH (116;117;181;182). In a French study patients were recruited from two rheumatology and rehabilitation departments with the intention to explore disability and pain induced by IP and thumb base HOA (124). Both studies had similarities with the Oslo HOA cohort with regard to patient enrolment and achieved similar results regarding impaired function and pain in HOA.

The Genetics, Arthrosis and Progression (GARP) study from the Netherlands investigated the course of HOA over two years by using the self-reported outcome measure AUSCAN,

and by performing joint examination (lateral pressure on IP and CMC joints) and radiographs (224). The results showed worsening of pain and function and radiographic progression.

It is known that OA / HOA is more common in women than in men (18;27;216;225;226), but the female / male ratio in our study was higher than seen in most populations surveys on HOA but a few papers which are hospital based refer to comparable ratios (116;117;124;181;182;224). We were unable to find a good explanation for the high female / male ratio besides the fact that hospital referred patients may be preselected and that HOA might be more severe in females than in males. After consulting with our statistical collaborator, we decided not to include the men in the analyses for papers II-IV, since the number of men was too small. Moreover, the healthy control group, which was to our disposition comprised women only and we did not have access to similar data from an existing cohort of healthy men.

Another proposition from the EULAR paper focuses on the importance of the differential diagnosis. We excluded patients with signs and symptoms of other arthritides from inclusion in the cohort and also conducted assessment of laboratory tests and radiographs of the hands, which is advised in the EULAR recommendations.

Table 4: **10 key propositions EULAR recommendations for the diagnosis of HOA**

1	Risk factors: sex, age, menopause, family history, obesity, high BMD, forearm muscle strength, joint laxity, usage
2	Typical symptoms: pain, stiffness
3	Clinical hallmarks (Heberden+ Bouchard nodes, deformities)
4	Functional impairment
5	Polyarticular HOA/ increased risk development of OA at other sites
6	Subsets with different risk factors and outcomes
7	Erosive HOA
8	Wide differential diagnosis (PSA, RA)
9	Gold standard: plain radiographs (JSN, osteophytes,sclerosis)
10	Blood tests (not needed for diagnosis, but for differential diagnosis)

EULAR evidence-based recommendations for the diagnosis of hand osteoarthritis: report of a task force of ESCISIT (46).

5.1.2 RA patients

The rationale for the use of RA patients as a reference population and control group was that RA patients usually show substantial symptomatology connected to the hands and that RA is a differential diagnosis to HOA (46). Even more importantly, RA is generally appraised as a severe rheumatic disease by patients, health care providers, decision makers and regular people. Previous studies had shown that impairment of function in OA might attain the same disability level as in RA (116;117;124;185;227;228).

A strength of this comparison was that the RA patients were recruited from a well studied cohort in the ORAR register and that both the RA and HOA patients had been examined in the outpatient clinic during the 2 years preceding their assessment for this study. The assessment of the RA patients had been performed in the same department and the RA patients had answered many of the same outcome questionnaires and performed the same

performance based test (grip strength) as the HOA patients. The ORAR is presumed to be representative for the general RA population in Oslo and is 85% complete for the age group of 20-79 years (6;229). RA is generally considered a severe and disabling disease, in contrast to HOA, which is often regarded as a more benign “wear and tear” arthritis condition. Our hypothesis based on clinical experience was that patients with HOA might have a similar overall burden of disease as patients with RA.

5.1.3 Controls and population norms

Control groups are widely used to position research data and to demonstrate how patient groups might differ from the underlying population. Similar utilisation of controls has also been applied in earlier studies from our group across different rheumatic conditions such as systemic lupus erythematosus (SLE), ankylosing spondylitis (AS) and RA (200-202;230-232;232;233) and has also been used in another HOA study (116). Data from the control group used in this HOA study were originally collected in a study on vertebral deformities in female RA patients, i.e. the data from both RA patients and controls were from the same comparative study. Therefore, we assumed that these controls might constitute a suitable control population also for the HOA patients (200;201;232). The controls were defined as “healthy” since individuals with concomitant OA or clinical signs of OA were excluded. A particular strength was that we were able to use two different control groups as reference populations regarding the SF-36 data. One group comprised the individuals from the RA study (200;201) and in addition population norms for SF-36 were used for comparison. The population norms were gained from a random computer draw from the National Register of Norway (203). We had no access to the data on concomitant diseases in this sample. As a consequence this population group was not screened for rheumatic diseases for example OA, which can be regarded as a limitation. However, HRQoL measures were similar in the controls and population norms.

5.1.4 Outcome measures, instruments and clinical examination

When we started our HOA project, we had the idea to include similar dimensions of assessment which are widely used in outcome research in RA. Thus, we wanted to perform a comprehensive data collection including PRO's, a functional performance test, imaging and joint assessment. We further considered the recommendations of outcome measures from the OMERACT conference in 1996 (166). Moreover, in a later published opinion paper Kloppenburg et al. (165) underline that future research in HOA should explore

outcomes, including components of disease activity, function and damage, which supports our approach to assess HOA.

Measurement of HRQoL in HOA was the main objective in our study and included assessment of signal symptoms like pain/function and other relevant components of HRQoL through a variety of instruments / PROs. It is important to utilize measures mirroring key signs and symptoms of OA according to the OMERACT core set (166). Also other and newer publications like the EULAR recommendations for the diagnosis of HOA (46) and the paper from Kloppenburg et al (165) emphasise the importance of main symptoms in the assessment of HOA. Symptoms in HOA were measured by the disease specific AUSCAN (HOA) and WOMAC (knee and hip OA). The AUSCAN is a widely used self-reported HOA measure and has also been applied in the data collection in other HOA cohorts (113;123;182). Both AUSCAN and WOMAC measure pain, stiffness and function. Ideally, one could have included other specific measures like the SACRAH (116;117), the Cochin functional index (185;228) or the FIHOA (129). Unfortunately, the only other multidimensional specific questionnaire SACRAH was not published and available for us at the time of our data collection and we did not have access to specific functional outcome measures like the FIHOA at that time point. The MHQ is a non OA specific measure which also could have been included since it focuses on hand function and has been used for HOA in other studies (114). However, our patients were already presented with a comprehensive booklet of outcome measures and we did not want to appear too demanding.

Other arthritis specific questionnaires we used included AIMS2, HAQ and MHAQ, which made our data collection quite extensive. AIMS2 was included mainly because it comprises scales with a specific focus on upper extremity function whereas the scores of MHAQ/HAQ as well as the SF-36 physical functioning scale are more strongly influenced by lower extremity function. Further, we also had access to AIMS2 data in the comparative RA control group. The MHAQ should be scored in the same way as the original HAQ with a range from 0-3. Historically, in Norway the MHAQ has been scored on a scale from 1- 4 as originally suggested by Ted Pincus. His idea was to use the same qualifiers as were used in the Steinbrocker functional classification (234). However, we are now changing to a score from 0-3 which makes it consistent with the HAQ score. The widely used generic SF-36 is another important instrument commonly used to outline health status and allows comparison of HRQoL across different diseases and with healthy individuals. We further calculated the

utility measure SF-6D. Preferably, we might have appended other additional utility measures, for example, the EQ-5D or 15D (208;235). There exists no standardised utility measure so far and we chose to restrict the data collection to one accepted utility instrument with the intention to spare our patients the burden of too many questionnaires.

Psychological and sociological factors can affect outcome in chronic rheumatic disease (236). The arthritis self-efficacy scales reflect the patient's perceived capability to cope with their pain, physical function and symptoms of rheumatic diseases. Self-efficacy data were also available from the RA control cohort, which gave us the opportunity to also compare self-efficacy levels between HOA and RA.

The idea to include FM-like symptoms was based on the awareness that secondary fibromyalgia is frequent in RA and other rheumatic diseases (190;191) and these symptoms were assessed also in the ORAR data collection. To our knowledge these symptoms had not been examined in HOA before. A gold standard for the diagnosis of FM is not yet established (192), but Yunus et al. have suggested assessment of FM-like symptoms on VAS earlier (196).

The sole performance based test in our data collection was grip strength. We chose this approach since it is a well-established instrument and the control RA group had performed the same assessment. Ideally, one might have added other performance based tests such as the Moberg pickup test (176) or the Arthritis hand function test (177), but again we had to restrict the number of included instruments in the examinations due to feasibility reasons. Joint counts are part of the composite disease activity score (DAS) in RA (147;189). We employed joint counts in our assessment of HOA and contemplated that joint assessments could be part of a future composite score in HOA, as suggested in a recent publication (237). The EULAR recommendations for the diagnosis of HOA focus on the importance of typical symptoms such as pain and stiffness as well as functional impairment in the assessment of HOA (46). Another recent publication on the research agenda for HOA recommends measurement of pain, function, stiffness for HOA as well (165). We did not include the assessment of aesthetic damage in our data collection, since we were not aware of the importance of this issue for patients at the time of the data collection, nearly 10 years ago. Newer publications have emphasised that aesthetic damage is a concern for patients with rheumatic diseases (114;238). In retrospect, we should have included an accordant

instrument like the MHQ to give the patients the opportunity to express this important dimension.

Radiographic examination was performed, but assessment of radiographic joint abnormalities was not part of the current research questions and has not been performed until recently (239-242).

5.1.5 Statistical methods

We used parametric statistical methods such as t-test, ANOVA/ ANCOVA and Pearson correlation coefficients in the analyses for this thesis because the distributions of the residuals were close to normal. Comparisons between patient groups and healthy controls were performed on a group level using independent samples t-tests. Initially, we used matched paired analyses, which we thought were the most appropriate tests for case/control studies. After consultation with our statistician, though, we altered our approach to group-wise comparisons, because our design was only matched on age and gender and in this case it is more appropriate to do the analyses on a two-sample group level with adjustments for relevant confounding factors.

We performed one-way ANOVA in parts of the analyses, even though we had two groups only. However, for a two-group comparison, the ANOVA F-test is equivalent to the more known independent sample t-test.

We used a radar chart, also referred to as spider diagram, which recently has been highlighted as an effective way of presenting data on general health (i.e. SF-36 data) (243).

5.2 Main results

5.2.1 Clinimetric properties of the Norwegian AUSCAN

The AUSCAN is a widely used multidimensional HOA specific patient-reported outcome measure and was at the time of our data collection the only accessible specific questionnaire for HOA. Bellamy et al. have shown that the instrument is reliable, valid and responsive in the original English version (127) and the AUSCAN has been described as a robust outcome measure for HOA in a review article (244). The Canadian GOGO study and a community based survey from England supported that the AUSCAN has good construct validity and is

reliable (242;245;246). Moreover, the GOGO study demonstrated that the AUSCAN can measure change over time (247). The AUSCAN has been translated into numerous languages, as well, and performs suitably after translation and cultural adaptation. Few of these studies have been published, but are referred to in the AUSCAN manual.

Our study on the clinimetric performance of the AUSCAN included numerous other instruments for comparison. The Norwegian version of the AUSCAN showed good internal consistency within the scales as also previously demonstrated for the original version and other translations. We found substantial correlations between the AUSCAN pain and physical dimension of a magnitude which was consistent with the association between other pain and physical dimensions in the current study and pain and physical scales in RA (248). As expected, AUSCAN pain correlated moderately (with values between 0.48-0.64) to other pain measures, and correlations were weaker to other dimensions. A strength was that we were able to study correlations to three different measures (VAS, AIMS2 and bodily pain in SF-36). The strongest association was observed with AIMS2 pain, the weakest was as expected to SF-36 which captures a wider and more general pain construct than AUSCAN pain.

Correlation of AUSCAN physical could be studied for numerous physical measures and scales. The strongest correlation was with AIMS2 hand and finger which supports that both these instruments measure the same construct. Correlations to HAQ and SF-36 physical were as expected weaker since these instruments have a rather strong focus on lower extremity function.

An important feature is to which extent an instrument is able to discriminate between subgroups of patients, based on demographic and disease characteristics. In our study patients reported worse health with increasing age. Females, in general, reported worse health than men. Further, the AUSCAN discriminated more than other instruments between patients fulfilling and not fulfilling the ACR classification criteria for HOA and having versus not having radiographic OA findings. These observations support that the AUSCAN is more specific for HOA features than the other included instruments.

In summary, the AUSCAN integrates core measures of HOA like pain, function and stiffness and our results support its performance as a HOA specific multidimensional

outcome measure also in the Norwegian translation with satisfactory levels of validity and discrimination between relevant subgroups of patients (126;127).

We have at a later time point also used the Norwegian translation of the AUSCAN in an intervention study with CrX-102 versus placebo in patients with HOA (131). This dataset was also used to further explore responsiveness of the AUSCAN (237). The results also supported that AUSCAN is responsive to changes in health status in HOA. Thus, AUSCAN is appropriate for use in clinical trials.

5.2.2 Comparison of HRQoL between patients and controls

Gabriel et al. showed in an elegant study that the disease specific indirect and nonmedical costs for OA are considerable and approach those for RA compared to controls (249). Since OA has a very high occurrence the disease has a substantial impact on society from a health-economic point of view.

The research group at Diakonhjemmet hospital has earlier compared HRQoL in patients with other rheumatic conditions (SLE, AS and RA) to controls (202;233). Dagfinrud et al. demonstrated that AS inflicts all main dimensions of health (202) and Uhlig et al. showed that RA imposes a considerable burden of disease across all age groups in both women and men (233). The burden of disease in rheumatic conditions can be assessed by a variety of questionnaires as has been outlined in previous chapters of this thesis.

When we sought to illustrate HRQoL in HOA in comparison to healthy controls the SF-36 along with VAS scales seemed to be the appropriate choice of instruments. Patients with HOA and RA had statistically worse crude scores for all dimensions of health (SF-36) in comparison to healthy controls in our study. The adjusted average difference in utility (SF-6D) between healthy controls and patients with HOA and RA was 0.13 and 0.14 which suggests that HRQoL is decreased by 13 quality adjusted life years (QALYs) in 100 HOA patients compared to healthy controls. The overall differences between healthy individuals and patients, either with HOA or RA, were of a similar magnitude. We chose to illustrate the distinct disparity between the two rheumatic diseases and the controls by showing the crude SF-36 values in a spider diagram and by S scores. This graphic presentation gives a visual illustration of the gap between healthy and diseased individuals. The spider diagrams can also be used to illustrate longitudinal changes (243). It was expected to find a difference

between the diseased and the healthy groups of individuals. Even so, it was somehow surprising to acknowledge how much alike the two rheumatic diseases presented themselves in all 8 SF-36 dimensions. We are not aware of other studies comparing RA and HOA in the field of HRQoL as clearly. Controls and norms were similar, which supports the validity of the results of the chosen control population.

5.2.3 HRQoL in patients with HOA compared to RA

RA is considered to be a severe and disabling disease leading to impaired function and HRQoL. In clinical practice we had observed that patients with HOA also suffered from considerable disability and reduced HRQoL and our study hypothesis was that HOA might have a similar effect on some dimensions of HRQoL as RA.

We actually showed that the global measures of HRQoL (SF-6D) were similar in patients with HOA and RA. However some differences were observed within other dimensions of HRQoL.

Functional impairment in HOA has been studied by several research groups and in different populations (57;116;122-124;128;223;250-252). Leeb et al showed that severity of function loss may be comparable in RA and OA (116). However, when a subgroup of patients being treated with NSAIDs in both groups were compared, RA patients showed significantly worse function (116). Jones et al. demonstrated a link between pain and function loss (123) and Bagis et al. found that structural changes on radiographs were connected to impaired function in HOA in postmenopausal women (122). On the other hand, Patrick et al. reported an optimistic functional development for nodal HOA compared to erosive disease (223).

However, none of these studies compared HRQoL in HOA with another joint disease in a similar, comprehensive manner involving as many questionnaires.

Our study indicated that HOA and RA had similar impact on HRQoL, even if the primary objective was to focus on the comparisons with controls (Paper II). The comprehensive collection of data with also arthritis specific measures that were relevant both for HOA and RA opened the opportunity to do direct comparisons between HOA and RA (Paper III).

Importantly, we found that patients with RA have worse physical function in several different scores (SF-36 physical, M-HAQ, HAQ, AIMS2) and more impaired grip strength for RA than patients with HOA.

Pain is a prominent symptom in rheumatic diseases among them HOA (49) and its assessment is recommended (165). Yet, pain on usage can not be a specific clinical marker for HOA since its sensitivity is low (165). In our study pain was significantly worse in HOA patients in one out of three measures and numerically higher in the remaining two pain outcomes. Interestingly, in the study from Leeb et al. the SACRAH pain score was not significantly different between HOA and RA but numerically higher for HOA, which to some extent underlines our findings. In the subgroup of patients on NSAID treatment in the same Austrian study, the HOA patients showed less pain compared to RA. In retrospect, it might have been an advantage to perform subgroup analyses in our patients according to concomitant medication.

Furthermore, both HOA and RA patients in our study showed elevated levels of FM-like symptoms, but the HOA patients scored numerically and partly statistically higher on 4 out of 5 relevant VAS indicating possible differences in pain perception between HOA and RA. Clauw et al. debate that pain in rheumatic diseases might not only originate from the joint but also from outside the joint (253). We are not aware of previous studies exploring widespread pain symptoms in HOA.

Another remarkable finding in our comparison was that mental health more impaired in HOA than in RA. Also this result should be further investigated and needs replication in other studies.

The fact that HOA patients, even if they are not representative for the underlying general population, report so much pain is remarkable. The lack of effective pharmaceutical treatment options or access to pharmaceutical treatment might also play a role (116;117). Self-efficacy pain was almost identical between HOA and RA. Our longitudinal data may hopefully provide a chance to highlight the association between self-efficacy and HRQoL in HOA.

Further, our findings may lead to a change in the appreciation of HOA as a severe disease and to increased awareness towards HOA in the medical community.

5.2.4 Association between joint counts and PROs

Assessment of joint involvement has not been part of the core measures in HOA. However, both joint swelling, tenderness and limited motion should have the potential to be responsive measures in the assessment of the condition, whereas bony enlargement, reflecting osteophytes, is probably not responsive. We wanted to explore both the joint distribution and the association to outcome measures in paper IV.

Research on distribution of joint affection in HOA has revealed that DIP joints are most frequently involved, followed by CMC I, PIP and MCP joints (117;122;210;216;250;254). It is further acknowledged that HOA is symmetrical (48;216;217;255) and that it clusters by row and ray (46;216;217).

Joint involvement in the Oslo HOA cohort showed more frequently joint involvement in the right hand suggesting an association to the dominant hand. Involvement of DIP joints was most frequent, which is consistent with previous findings (210;216;250;254;256;257). However, most of these previous studies have reported results from population based surveys and with joint assessment by radiographic methods or patient self-reported joint symptoms, and only a few studies have gained their data from smaller often hospital based studies (116;117;122;124). The consistency in findings regarding joint involvement across different methodology supports the confidence in the findings by clinical joint assessment. Joint counts have been infrequently applied in HOA research, so far. There is solely one other study by Spacek et.al. which employed joint counts in the assessment of HOA using the Ritchie articular index (RAI), which was developed for RA initially (124). This study recruited patients in a similar manner as applied in our study and further used a functional index the CHFS and VAS pain in the assessments, but focused on the distinction between nodal and thumb base HOA. Spacek et al. report that pain was associated with disability (124). Bagis et al. assessed tenderness by palpation, but did not execute a full joint examination (122). They found impaired grip and pinch strength in patients with DIP affection and even more so in patients with DIP and PIP involvement. Also, tenderness / pain lead to worse hand function.

Our study showed that joint tenderness/pain in the CMC, PIP and / or DIP joints was associated with worse health status across all measures reflecting pain, stiffness and physical function of the hand (AUSCAN, AIMS2 hand and finger function and VAS pain). Moreover, joint tenderness/pain was associated with worse function (AIMS2, SF-36 and HAQ and grip strength). The other three categories of abnormal joint findings were also correlated with worse pain and function, but not on a statistically significant level. The association between joint counts and outcome measures supports the external validity of joint counts as a potential outcome measure.

We have later also examined the responsiveness of different combinations of joint counts as well as composite scores (237). The results indicated that joint counts and composite scores have the potential to be responsive to improvement during anti-inflammatory treatment in HOA. Additional research is required to try to identify valid and responsive measures taking joint assessments as well as patients reported measures into account.

6. Conclusions

6.1 Answers to research questions

- The background and main objective of this thesis was to examine the burden of disease in the Oslo HOA cohort. We have been able to show that the AUSCAN performs well in the Norwegian translation and is valid and reliable.
- Further the thesis showed that HOA and RA patients had worse health and a substantial burden of disease compared to controls and population norms.
- RA patients experienced a higher level of disability and functional impairment than HOA patients. The HOA patients reported higher levels of pain and FM-like symptoms than the RA group.
- DIP joints were most frequently affected in the Oslo HOA cohort and the joint assessment for pain was correlated to impaired health to a greater degree than the other joint assessments.
- In summary, the burden of disease is considerable in HOA despite being generally perceived as a mild rheumatic disease.

6.2 Clinical implications

We have in this study demonstrated that HOA is a disease which leads to considerable pain, disability and impaired HRQoL. Importantly, we have also shown that the overall decrease in HRQoL is close to the level of patients with RA. Hopefully, these findings may contribute to a raised awareness for HOA as a disease that requires increased attention from society, patients, researchers and clinicians. Unfortunately effective treatment modalities are still limited. Effective disease modifying therapies will hopefully be available in the future. Assessment of therapies requires availability of reliable, valid and responsive outcome measures. Parts of this thesis have hopefully contributed to progress in the identification of such measures.

This thesis is based on cross sectional data. However, the plan has always been to conduct a follow up examination of these patients, since long-term data are more valuable for the prediction of the course of the disease and outcomes. The follow up examination has been

performed in 2008 / 2009 with stronger focus on imaging modalities than in the cross-sectional data. The initial cross-sectional research was the basis for the longitudinal follow up of patients with HOA in our clinic and has contributed to an increased research interest for HOA. The research focus also stimulated the initiation of the OA clinic in 2003 which has provided a novel, dedicated and multidisciplinary management opportunity for patients with OA in the clinical setting (258).

7. Errata

Article III

Page 344, HAQ and MHAQ – the explanation, the arthritis impact measurement scale 2 - is incorrect, the correct definition is health assessment questionnaire and modified health assessment questionnaire.

Article IV

Page 3, discussion, paragraph 4, DIP and DIP joints is incorrect – the correct terms are DIP and PIP joints.

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9. Papers I – IV

