

Helse Sør-Øst Forskningsgruppe Artrose

South-Eastern Norway Regional Health Authority Osteoarthritis research group (SEHA OA-research group)



The South-Eastern Norway Regional Health Authority Osteoarthritis research group (SEHA OA-research group) was established in 2006 and has been funded from the South-Eastern Norway Regional Health Authority, as a collaboration between Department of Orthopaedics, Oslo University Hospital, Ullevål, and Diakonhjemmet Hospital and characterized as “*a vibrant research environment in the Oslo region*” by the NIFU-step evaluation in 2008: “*This research group has received grants in 2006 and 2007. Despite the short time interval, the group has published 71 articles in international scientific journals with peer review. This must be described as more than satisfactory. A contributing factor to this has been the connection to international research networks and cooperation between Ullevål University Hospital, Diakonhjemmet Hospital, Martina Hansen Hospital, Rikshospitalet University Hospital and Akershus University Hospital. The research group has contributed to building a vibrant research environment in the Oslo region*”.

Main Aims 2011-2013

The overall goal is to further develop our established multidisciplinary SEHA OA-research group by conducting epidemiological studies, clinical trials, and translational research targeting the main priorities within OA research including the use of new MRI technology.

Main Aims

1. To establish a population based *prospective cohort* of individuals with musculoskeletal pain and OA in a municipality in Norway
2. Examine the effect of *interventions* on clinical, radiological and MRI changes in the hip, knee and hand OA
3. Conduct *translational research* by studying basic science within the area of cartilage and joint biomechanics during motion within our randomized clinical trials of patients with OA
4. To use *advanced MRI technology* to examine changes in cartilage after surgery and exercise therapy interventions
5. To study longitudinal associations between *imaging abnormalities and functional outcomes*

Main Aim 1 - Prospective cohort - Short background, Design and Methods

The Musculoskeletal Ullensaker Study – the MUST Study Part I and II

Part I: Survey – started winter 2010 and Part II: Clinical study – started spring 2010

The MUST Study started as the Ullensaker Survey Study in 1990 by professor Dag Bruusgaard and Olav Rutle at the Institute of General Practice and Community Medicine, University of Oslo with follow-up surveys in 1994 and 2004. Musculoskeletal pain has been the main focus, and the study has included Ullensaker Municipality inhabitants from seven birth cohorts (those born 1918-20, 1928-30, 1938-40, 1948-50, 1958-60, 1968-70 and 1978-80).

A new postal survey, representing both a follow-up of those who previously have participated in the Ullensaker Survey Study and new individuals (a total of 12 000 inhabitants) started during the winter 2010 within the SEHA OA research group (the MUST Study (Part I). Those individuals who self-report OA in the survey (Part I) will be invited to participate in the prospective OA-cohort study, The MUST Study Part II (started spring 2010)

Design. Prospective Cohort of those who participated in the survey from 1990 and Cross sectional population based study of the whole Ullensaker municipality

Methods. The survey will be sent out to the 12 000 inhabitants in Ullensaker municipality and estimated response is 60%. Estimated prevalence of OA is 12.8% and with a positive response rate of 80% of those who report OA gives us 922 individuals in total that will go through a clinical examination in Part II of the MUST study. The participants are asked for permission to connect the data with relevant national databases (registries): "Reseptregisteret", "Nasjonalt register for leddproteser", "Forløpsdata trygd", "Medisinsk fødselsregister", "Kreftregisteret", and "Dødsårsaksregisteret". (REK has approved)

The postal survey includes questions on pain and symptoms, general health and quality of life, use of health care services, functional ability, and physical activity/ exercise habits.

This clinical examination (Part II) will include assessment by rheumatologist, orthopaedic surgeon, physicians, and physical therapist and include standardized tests of self reported function (KOOS, HOOS, AUSCAN), functional ability as Moberg Pick Up Test, 6 min Walk Test, Chair Stand Test, One leg standing test, an indirect measurements of oxygen uptake (Åstrand test), muscular strength (quadriceps, hamstrings and handgrip strength) using isokinetic strength measurements, conventional radiograph (standardized weight-bearing x-rays using the Synaflexer frame), MRI (hip/knee/hand OA), DXR (of the spine and hip) and ultrasound for hand OA. Blood and urine samples will be collected, a digital photo of hands with OA will be taken, and a cardiovascular assessment will be performed (including measurement of vascular function in collaboration with cardiologist Anne Grethe Semb and PhD student Sella Provan). There has been established a biobank for blood and urine samples at the Diakonhjemmet Hospital and the biological material will be destructed when the project ends in 2035. The cross-sectional examinations are expected to provide data on frequencies of various abnormalities (clinical, functional, imaging) in different types of hand OA and in particular new knowledge on associations between MRI findings in hand OA and abnormalities on conventional radiographs, as well as associations between MRI pathologies and functional status. Further, the comprehensive assessment of markers of inflammation (ultrasound power Doppler, MRI synovitis and bone marrow edema as well as soluble

biomarkers) give opportunities for examinations of associations between these biomarkers and cardiovascular endpoints.

A planned post doc study based on the MUST Study Part II: Evaluation of knee function in individuals with knee osteoarthritis (post doc Britt Elin Øiestad)

Main Aim 2 - Intervention studies - Short background, Design and Methods

1. *The MUST Study - Part III: Joint action for better joints - A community based intervention for patients with osteoarthritis.*

Post doc student Nina Østerås, PT, PhD, has received 3 years full time funding from the Postgraduate Funding for physiotherapist in Norway (part III). The study aim is to assess effects of a community based intervention for patients with OA including Patient Education Programs and digital intervention to facilitate physical activity compared with ‘treatment as usual’.

Design. A multicentre randomized controlled trial. The methodology will follow CONSORT guidelines.

Methods. The OA patients will be recruited through the MUST Study. Interventions: Physiotherapists, and possibly other primary health care professionals, in Ullensaker municipality that are interested in conducting Patient OA Education Program will attend a two-day Training Program at Diakonhjemmet Hospital. Outcome measurements: WOMAC for knee/hip OA/ and AUSCAN for hand OA. a) pain, stiffness, fatigue, and function, b) health related quality of living, c) physical activity self-efficacy level and the frequency of physical activity, d) work-ability and sick leave, e) use of health care services and need for elective surgery, f) cost-effectiveness

2. *The Hip OA RCT – intervention study – short and long term follow-up*

- The effect of exercise therapy and patient education compared to patient education alone in individuals with hip OA – a prospective randomized clinical trial. (PhD student Linda Fernandes, PT, turned in her PhD July 2010)(2;3) completed
- The long term effect of exercise intervention for patients with hip OA – a prospective randomized controlled trial (PhD student Ida Svege, PT, financial support VIRUUS Oslo University Hospital, Ullevål) ongoing – funded through 2012

3. *Biomechanical characteristics of patients with hip osteoarthritis with mild to moderate pain: A prospective, randomized clinical trial (Postdoc student Ingrid Eitzen) (see also Aim 3; translational research) new*

4. *The Oslo CARE (Cartilage Active Rehabilitation Education) study (intervention study and translational research – see also Aim 3 and 4)*

- Changes in knee function after a new rehabilitation program (the CARE program) for patients with cartilage injury - a prospective cohort study ongoing

Methods. Forty-nine patients scheduled for cartilage repair surgery with a focal femoral condyle cartilage lesion assessed with knee arthroscopy were included. Outcome

measurements were Lysholm score, Cincinnati score, IKDC2000, all subscales of KOOS (pain, symptoms, ADL, Sport, QOL), isokinetic quadriceps and hamstring muscle strength tests (Biodex 6000), four single leg hop tests, and the Tegner activity scale. The three months active rehabilitation program included neuromuscular and strength exercises under the supervision of a physical therapist. Patients were tested prior to start (baseline) and re-tested after the end of the three months active rehabilitation program (post rehab test). At post rehab test all patients were offered cartilage repair surgery. After 3 months rehabilitation 67% had postponed surgery.

5. *The OMEX study (Osteoarthritis Meniscus EXercise study)*

- The effect of exercise therapy versus surgical treatment for patients with degenerative meniscus lesion (PhD student Silje Stensrud, PT, financial support from Southern Denmark University (professor Ewa Roos) ongoing

Main Aim 3 - Translational research - Short background, Design and Methods

Mesenchymal stem cells to regenerate cartilage - A randomized controlled trial including the Oslo CARE Study (a sub-study).

Postdoc Åsbjørn Årøen is funded from the Norwegian Research Council and the project leader is professor Lars Engebretsen with active collaboration with basic scientists professor Brinchman and professor Reinholdt at Oslo University, Rikshospitalet, and the University of Minnesota with professor Robert LaPrade.

A sub-study is The Oslo CARE study – a rehabilitation study of individuals with cartilage lesions prior to cartilage repair Project group: Asbjørn Årøen and PhD student Jan Harald Røtterud, professor May Arna Risberg, physical therapist Turid Høysveen, professor Lars Engebretsen.

Aims the Oslo CARE study

- Examine the knee articular cartilage morphology and GAG content at baseline (pre exercise therapy) and investigate differences between injured and uninjured knee
- Examine changes in the knee articular cartilage morphology and GAG content from baseline to post exercise therapy program in injured and uninjured knee (n = 25)
- Examine association between changes in symptoms, function and MRI findings in patients with articular cartilage injury who have gone through exercise therapy.
- Investigate the knee articular cartilage using MRI including dGEMRIC and T2 mapping prior to surgery and at 1 year follow-up (n = 25)

Design. Stem cell study is a basic science study, and the effect of two surgical interventions is a randomized clinical trial. The Oslo CARE study is the rehabilitation trial of this study which is a prospective cohort study including MRI and dGEMRIC

Methods. For the “Stem Cells in a Clinical Trial to Repair Injured Articular Cartilage” study. For the substudy The Oslo CARE study: Forty-nine patients eligible for cartilage repair are included and followed through a systematic rehabilitation program. MRI and dGEMRIC has been undertaken at baseline and follow-up will be carried out in 2010 and 2011. See aim 2 for *Methods* and aim 4 for *Methods* regarding the dGEMRIC method.

Joint Biomechanics

Joint loading and motion have shown to be of significance for the development and progression of OA(1).

The study “*Biomechanical characteristics of patients with hip osteoarthritis with mild to moderate pain: A prospective, randomized clinical trial*” – post doc project Ingrid Eitzen –

is a translational research project including both a clinical trial and a biomechanical study. The knowledge within joint loading, motions, and muscle activation patterns within patients with hip OA is sparse, and to our knowledge nobody has studied joint biomechanics between two different intervention programs for patients with hip OA. Our research group has already carried out a randomized clinical trial on the effect of exercise and patient education in patients with hip OA (Linda Fernandes’ dissertation – finished July 2010)(2;3). Included in this RCT we also have biomechanical data on gait analysis, sit-stand analyses and balance. None of these data has been analysed or published and Ingrid Eitzen, defended her PhD Aug 25th 2010) will include biomechanical analyses within this RCT.

Methods biomechanics. Kinematic data will be collected using Proreflex MCU240 (Qualisys Medical AB, Sweden) motion analysis system with eight cameras at a sampling frequency of 240 Hz and synchronized with three force plates sampling at a rate of 960Hz (AMTI Model LG6) at the Norwegian School of Sport Sciences. Reflective passive anatomical markers defining the joint centers will be placed over the medial and lateral malleolus, medial and lateral femoral condyle, bilaterally over the greater trochanter, and bilaterally on the top iliac crest. Both feet will be defined by two markers attached to the heel of the shoe and one marker at the 5th metatarsal head. All kinematic and kinetic data will be post-processed using custom-made software (Labview). Kinematic and kinetic data will be calculated using Visual 3D software (C- motion Inc, Crabbs Branch Way Rockville MD). The Visual 3D will calculate the six degrees of freedom of a link rigid segment (i.e. rigid-body analysis) in an inertial reference system and use that information to compute joint kinematics and kinetics. Kinematic variables include hip, knee, and ankle angle, in the sagittal and frontal planes.

Main Aim 4 - Advanced MRI technology - Methods

The ACL children study (MRI) and the Oslo CARE study (MRI and dGEMRIC)

Methods. The dGEMRIC (delayed Gadolinium enhanced MRI of cartilage) technique is a contrast-enhanced MRI technique that is potentially clinically useful for imaging the biochemical changes in cartilage of patients with early arthritis. Previous studies have demonstrated the ability of the dGEMRIC technique to detect early osteoarthritis in patients by measuring the relative glycosaminoglycan (GAG) concentration in cartilage. The primary aims of these studies are to detect changes in cartilage in patients with early signs of osteoarthritis using the dGEMRIC technique and a 3 Tesla scanner (Oslo University Hospital, Ullevål). The aim is to develop new knowledge on the morphology of cartilage and the GAG content in knees with cartilage injuries. Furthermore, the aim is to study changes in morphology and GAG content using exercise therapy as intervention. Only a few preliminary

studies have examined changes in GAG content in patients with cartilage injuries using exercise therapy as intervention(10). This MRI technique is new more knowledge on changes in morphology and GAG content is needed before huge clinical randomized controlled trials can be initiated. Therefore, a prospective pre-post design is used for the Cartilage-Rehab study, in addition to the studies where we now will include MRI in the long term follow-up studies of randomized controlled trials of different surgical techniques (ACI, MFX). These MRI studies will be and are currently performed in collaboration with Charles Mamisch from Department of Orthopaedic Surgery, University Bern, Switzerland and Orthopaedic Surgery, Children´s Hospital, Harvard Medical School, Boston.

We have an ongoing prospective cartilage-rehabilitation study (the Oslo CARE study) with already included all 49 patients with cartilage lesions >2 cm eligible for surgical treatment. All these patients go through a 3 months exercise therapy program to examine changes in symptoms and knee function (VAS for pain, the KOOS score, single leg hop tests, isokinetic muscle strength tests) from pre- to post training. Already 11 of these subjects have also included MRI using the dGEMRIC technique. The last 14 subjects in this study will also include MRI with dGEMRIC. Furthermore, 40 children (under 13 years of age) who have ruptured their ACL are included in an MRI study of their meniscus and cartilage lesions

MRI analysis: Tallal Charles Mamisch, MD, PhD, Department of Orthopaedic Surgery, University Bern, Switzerland and Orthopaedic Surgery, Children´s Hospital, Harvard Medical School, Boston will perform all the MRI analysis and dGEMRIC analysis.

Main Aim 5 - Imaging and function - Short background, Design and Methods

A hand OA cohort was established at Department of Rheumatology Diakonhjemmet Hospital in 2001. 209 patients underwent comprehensive clinical assessments (ref Ann Rheum Dis) but also baseline radiographs (these examinations are the basis of the PhD work of Barbara Slatkowsky-Christensen (submitted UiO June 2010)). Follow-up examinations were performed 2006-7 and included clinical, radiographic and functional assessments (similar to baseline) but also comprehensive ultrasonography (US) and MRI examinations. Data are being analysed and were presented by PhD fellow Ida Kristin Haugen and medical student Alexander Mathiessen at the EULAR congress 2010. An MRI atlas and US atlas are being developed under supervision of Professor Desiree van der Heijde, Hilde Berner Hammer and Tore K Kvien. Further, the external validity of the new imaging modalities will be explored by association studies to conventional radiographs and functional assessments. Ida Kristin Haugen is also working on imaging and functional data from the Framingham Community cohort (n = 1028) and from the Framingham Offspring cohort in collaboration with professor David Felson and data from the Osteoarthritis initiative in collaborations with professor Felix Eckstein. The main objectives of these studies are to explore the association between the degree of osteophytes, synovitis and PD activity in finger joints of hand OA patients and compare with the similar findings on other imaging modalities (conventional radiographs and MRI) as well as clinical symptoms and signs (pain and functional assessments). Alexander

Mathiessen plans to perform a PhD study on US assessments of OA patients with Hilde Berner Hammer as the main supervisor when he has completed medical school.

Research environment – SEHA OA-research group with national and international collaborators

The SEHA OA research group is a well established multidisciplinary collaboration between clinical researchers, basic science researchers and clinicians (rheumatologists, orthopedic surgeons, physical therapists, nurses). The SEHA OA research group is a multidisciplinary research group between Department of Orthopaedics, Oslo University Hospital, Ullevål and Diakonhjemmet Hospital in close collaboration with national and international collaborators
Department of Orthopaedics, Oslo University Hospital, Ullevål

The research unit at the Department of Orthopedics (Forskning og kompetansesenter for Ortopedisk avdeling:) is a very well established research environment with professor Lars Engebretsen as chairman.

The following research groups are established within the Department of Orthopaedics, Ullevål (http://ullevaal.no/modules/module_123/proxy.asp?iInfoId=23411&iCategoryId=510&iDisplayType=2)

- Cartilage Research group: Chair Professor Lars Engebretsen and postdoc student and orthopaedic surgeon Asbjørn Årøen
- Osteoarthritis Research group – the SEHA OA research group: Chair professor May Arna Risberg and with an executive group consisting of professor Lars Engebretsen, professor Lars Nordsetten and professor Tore Kvien
- Norwegian Research Center for Active Rehabilitation (NAR): Chair professor May Arna Risberg. NAR was established at the Orthopedic center in 2003 with the aim of combining the research and clinical expertise, facilities and resources from three institutions to improve knowledge within active rehabilitation of individuals with musculoskeletal disorders. NAR has proven a high quality research program also due to the international collaboration with University of Delaware (professor Lynn Snyder-Mackler) and the grants achieved from the National Institutes of Health, USA in 2006 (Grant # 2 RO1 HD 037985-06). Currently NAR has 9 physical therapy PhD students. www.aktiv-rehab.no.
- *OSTRC*. Oslo Sport traumatology Research Center (OSTRC) in collaboration with Norwegian School of Sports Sciences, Oslo Sports Trauma Research Centre: www.ostrc.no
- *CIRRO*. Centre for radiostereometric- and bone remodelling analysis Oslo University Hospital. CIRRO was established in 2004 as a centre for radiostereometric analysis (RSA).

In 2009 we had a total of 25 full-time research positions, and 2.5 full-time positions as research coordinators. We have extensive collaboration with both national and international institutions. For the year 2009, we had 280 publications, and published 55 articles in international scientific journals together with our collaborators.

Diakonhjemmet Hospital – EULAR Center of Excellence

Department of Rheumatology has responsibility for rheumatic joint diseases in Oslo and regional functions in Helse Sør-Øst. Patients with OA represent the largest increasing population of patients referred to the hospital. The National Research centre for Rehabilitation in Rheumatology (NRRK) (established 1999) is funded by the Norwegian Regional Health Authorities and is part of the Department of Rheumatology at Diakonhjemmet Hospital. NNRK is a multidisciplinary research group organised as a unit within the Department of Rheumatology. The Department has an increasing research activity with 8 PhD during 2008-2010 and 103 PubMed listed publications in international journals 2009-2010 compared to 66 2007-8 and 50 2005-6. *The Department of Rheumatology, Diakonhjemmet Hospital is EULAR center of Excellence 2008-2013 which mean that the Department is one out of 18 leading rheumatological research groups in Europe.*

Over the last five years, a strong organisation has been built up and the group now includes researchers (at the PhD level) from the main health professions (physiotherapy, occupational therapy, medicine, psychology and nursing) in addition to health economy and a part time statistician. The department has a strong focus on international networking – 50% of the publications of the group leader during the last years have co-authorship of non-Norwegian researchers. NRRK has active research collaboration with several European hospitals and research centres during the ETIC collaboration (www.star-etic.se), CARE (www.rheumacare.org) and European League Against Rheumatism (www.eular.org). See also <http://www.nrrk.no>

National and International collaborators part of the SEHA OA research group

National collaborators

- Oslo University Hospital, Rikshospitalet - basic scientist professor Finn Reinholt and Jan E. Brinchmann. Professor Jan E Brinkmann will serve as co-worker on the project “Mesenchymal stem cells to regenerate cartilage” and will actively contribute to data collection and analysis, as well as in the publication process.
- Universitet I Oslo – Bård Natvig. Bård Natvig is project leader for the MUST study, Part I and II
- Akershus University Hospital- phd student and orthopaedic surgeon Jan Harald Røttterud. Jan Harald Røttterud is a phd student as well as an orthopedic surgeon on an ongoing cartilage research project within the OA-research group with Asbjørn Årøen as the main supervisor; including also the ongoing Oslo CARE Study.
- Lovsienberg Hospital- phd student and orthopaedic surgeon Kirsten Ljungren
- Martina Hansen hospital - phd student and orthopaedic surgeon Stig Heir
- Norwegian School Sport Sciences, Department of Sport Science: Professor Roald Bahr with the collaboration on the hip and knee OA studies using motion analysis lab at the institution.
- Professor Dag Bruusgård, Universitetet i Oslo, Board Member SEHA OA-research group)
- Kommuneoverlege Ullensaker commune: Unni- Berit Skjervheim Board Member SEHA OA-research group

International collaborators

- University of Delaware - Professor Lynn Snyder-Mackler. Lynn Snyder-Mackler is professor at the University of Delaware and an active formal collaborator through ongoing research projects both within biomechanics/motion analysis and clinical trials with funding from National Institutes of Health (NIH) – a new postdoc study is planned with a international scholarship for a 6 months visit to the University of Delaware (postdoc project for Ingrid Eitzen)
- University of Minnesota - Professor Robert LaPrade. Professor and orthopaedic surgeon Robert LaPrade is working with the cartilage group in the Oslo Sports Trauma Research Center, and is an independent investigator of our randomized, controlled cartilage study
- University of Southern Denmark - Professor Ewa Roos. Professor Ewa Roos is the principal investigator of the project “The effect of meniscectomy vs exercise - a randomized clinical trial - the OMEX study”. Silje Stensrud is the PhD student on this project that takes place at the Department of Orthopaedics, Oslo University Hospital. Professor May Arna Risberg and Professor Lars Engebretsen are co-supervisors.
- University of Bern, Switzerland and Orthopaedic Surgery, Children´s Hospital, Harvard Medical School, Boston - Charles Mamisch. Charles Mamisch is responsible for all data analysis in the MRI studies: the children ACL MRI study and the MRI and dGEMRIC study of the Oslo CARE study (cartilage study). Both of these studies are ongoing.
- Collaboration with the Osteoarthritis Initiative (OAI)- Felix Eckstein, Paracelsus University, Salzburg, Austria - OAI is a large-multicenter cohort study examining risk factors for knee OA. In this study we studied the relationship between radiographic hand OA features and knee cartilage thickness at baseline and 1-year cartilage loss in a subsample of 765 subjects. Ida Haugen scored the x rays for presence of hand OA features, analyzed the data and drafted the manuscript. We found that radiographic hand OA was significantly associated with decreased knee cartilage thickness. These results may suggest a systemic susceptibility for OA. However, we were not able to show any association between hand OA and risk of knee cartilage loss after 1 year.
- University of Boston, Medical School. Professor David Felson. Professor David Felson will be a collaborator in our OA-research group, both as a significant reviewer for our annual seminars/meetings and as a co-worker for the postdoc project (Britt Elin Oiestad) within knee OA
- Professor Desiree van der Heijde, University of Leiden. Desiree van der Heijde is co-supervisor of phd student Ida Krisn Haugen and is supporting the work on developing MRI and ultrasonography scoring systems in hand osteoarthritis. Desiree van der Heide was responsible for the development and validation of the most widely used radiographic scoring system in rheumatoid arthritis (van der Heijde Sharp score).
- Dr. Jessica Bijsterbosch, University of Leiden. Jessica Bijsterbosch is one of our international collaborators within our OA research and in particular with the ongoing research together with phd student Ida Haugen and her co-supervisor Desiree van der Heijde.
- Professor Margreet Kloppenburg, University of Leiden. Margreet Kloppenburg is one of our international collaborators within our OA research and in particular with the ongoing research together with phd student Ida Haugen and her co-supervisor Desiree van der Heijde.