RESEARCH

– scientific strategy 2015 and publications 2014

at the

DEPARTMENT
OF ORTHOPEDICS

LUND UNIVERSITY
SKÅNE UNIVERSITY HOSPITAL
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The Department of Orthopedics at Skåne University Hospital

The Department of Orthopedics at Skane University Hospital consists of three units: Lund, Malmö and an elective procedures site in Trelleborg. The unit in Malmö was founded in 1911 and the one in Lund in 1914. These were the first two orthopedic departments in Sweden.

In Lund and Malmö, a complete orthopedic elective and emergency service is present, including spine, tumour and pediatric units. In Trelleborg, elective orthopedic procedures with special focus on hip and knee arthroplasties, shoulder surgery, foot- and ankle surgery and sports medicine are performed.

The Department of Orthopedics has access to 152 beds, 16 operating rooms, complete technology, 85 orthopedic surgeons (incl. 25 residents) and 500 other staff. Annually we perform about 11 000 surgeries, 53 500 outpatient visits, 32 000 A/E visits, 34 500 other visits (nurse, physiotherapy). The total turnover is about SEK 655 M (EUR 73 M).

The Department has achieved a world reputation from its many years of research as well as continuous clinical experience, supported by being a World Health Organisation Collaborating Centre for Evidence-Based Health Care in Musculoskeletal Disorders since 2007 and one of only sixteen members worldwide of the prestigious International Society of Orthopaedic Centres (ISOC).

Our physicians and other staff work in an integrated and cooperative group practice that strives to provide the highest quality and most cost-effective care for 130 000 patients annually.

For nearly a century, the Department of Orthopedics in both Lund and Malmö has been involved in advances to alleviate suffering from musculoskeletal disorders. Problems identified in the clinic are taken to the laboratory bench for study, and the results are then translated back into clinical practice.

Lund University is Sweden’s strongest comprehensive research university; in recent years it has been awarded more research funding than any other Swedish full-scale higher education institution. In an independent review “RQ-08” of the quality of all research at Lund University, the Department of Orthopedics in Lund was ranked as outstanding, and in Malmö as excellent.
Currently, 250 investigators, including 5 professors (3 full professorships), 4 visiting professors, 25 associate professors and 52 PhD students employed by the Department of Orthopedics or closely linked to it, with nearly SEK 40 million in annual funding, are doing research and performing clinical trials in virtually every aspect of musculoskeletal pathology. Each year, about 5 doctoral dissertations are defended and over 150 peer-reviewed scientific papers are published.

The Department of Orthopedics started RC Syd, a national register centre in charge of 25 national quality registers (today RC Syd has developed into Epidemiology and Register Centre South, ERC Syd, Lund, Sweden). ERC Syd also now includes former EpiCentrum which is a regional centre of excellence for studies in musculoskeletal research including epidemiology. The Department of Orthopedics is still responsible for five national orthopedic quality registers.

LUMSI (Lund University Musculoskeletal Institute) was formed in 2010 by the Department of Orthopedics thanks to financial support from Region Skåne. This group includes orthopedics, rheumatology, hand surgery, pain, rehab and preclinical activities. The aim is to collaborate across borders within Research & Education. The group is led by the Department of Orthopedics.

In 2013, Arthroplastywatch was started by the Department of Orthopedics. It is a unique meeting place for information on joint implants. Data are collected around the clock through our specially developed search routines. The data are examined in several steps of medical and statistical expertise.

Arthroplastywatch has been developed as an information project during 2011-2012 with the purpose of collecting data on arthroplasty safety issues from a wide range of information sources on the Internet and disseminating this in one single, publicly accessible channel.

The Department of Orthopedics is represented in a variety of specialist associations in Swedish Orthopedics, in several cases, as chair, and is represented in the Swedish Orthopaedic Society Board. The editor of Acta Orthopaedica is a consultant at the Department of Orthopedics.

The current president of ISPO, the International Society of Prosthetics and Orthotics is affiliated with the Department of Orthopedics as a register holder of the Swedish national amputee register. ISPO aims to improve the quality of life for persons who may benefit from prosthetic, orthotic, mobility and assistive devices.
Research as well as education of future doctors and other students within healthcare professions is a significant part of the activities. We are especially pleased to have an education unit, and our own training laboratory, which together with the Practicum Clinical Skills Centre at the hospital, can provide practical treatment.

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CLINICAL SCIENCES LUND AND MALMÖ

The major part of the health care consumption in musculoskeletal disorders is caused by fractures, joint diseases (osteoarthritis and rheumatoid arthritis), back problems, injuries and tumors. In the most recent WHO report on health presented in 2012, musculoskeletal conditions were identified as the second leading cause of disability globally. This is reflected in the research activities within the Academic Department in Lund and Malmö.

Research on joint disease and its consequences spans from basic genetic and biochemical investigations to applied projects which monitor in national quality registers the treatment of patients with osteoarthritis to outcome of arthroplasty and includes the following:

- Development of methods for diagnosis and monitoring of early-stage osteoarthritis through MRI, patient administered outcome scores, radiography, arthroscopy, and analysis of cartilage biomarkers as well as investigation of disease mechanisms;
- Epidemiology and risk factors for osteoarthritis following joint injuries;
- Improvement of diagnostic and reconstructive techniques after knee ligament injury;
- Improve and develop techniques for joint replacement in the rheumatoid joint;
- Identification underlying causes for joint implant loosening in hip and knee and investigate patterns of knee joint implant failure.

Research on osteoporosis and fragility fractures ranges from genetic and biochemical investigations to applied clinical studies in large population-based cohorts as well as nationwide registers monitoring the development and outcome of fragility fractures, and include the following studies:

- The genetic background of fragility fractures;
- The pathophysiology of reduced bone strength and interventions to evaluate if bone strength can be improved;
- Epidemiology and risk factors for osteoporosis and fragility fractures through cohorts and registers;
- Improvement of diagnostic procedures and prophylactic interventions for fragility fractures, leading the international best practice evaluation of secondary prevention (www.iofbonehealth.org/capture-fracture);
- Development of techniques for treatments of fragility fractures, fracture healing, and rehabilitation;
- Estimates on the burden of fracture in economic terms as well as health care utilization.
Biomaterial, bone and matrix biology research includes studies on bone induction and its stimulation by human recombinant growth factors and new synthetic bone substitutes and peptides for fracture repair. It also includes studies on tendon and cartilage repair.

Research on lumbar back pain and sciatica aims to optimize patient information, surgical methods, postoperative treatment and utilization of hospital resources.

Research on different methods of treatment for gangrene of the lower extremity caused by diabetes is evaluated with regard to quality of life, cost, etc.

Research on orthopedic oncology evaluates diagnostic procedures, surgical techniques and prognostic classification of soft tissue tumors. Surgical treatment of skeletal metastases is studied concerning technique and outcome.

Research in hand surgery includes evaluation and treatment of ligament injuries in distal radius fractures in young patients.

Research in pediatric orthopedics targets early identification, monitoring and treatment of congenital disorders of the hip, gait and function analysis in children with cerebral palsy and pathophysiology in Perthes’ disease.

The research is closely dependent on collaboration with the clinical department of Orthopedics, with most investigators holding positions as orthopedic surgeons or associated specialties. Furthermore, the infrastructure includes modern laboratory space and imaging facilities at the Clinical and Biomedical Research Centers in Malmö and Lund and Skåne University Hospital. Currently, about 30 graduate students mostly physicians are working on their Ph.D. theses within the Department.

Our research has been successful in obtaining regional, national and international grants with also young researchers receiving positions from the Swedish Research Council. A major 4-year EU grant of 2 million Euro on implementation research has been completed through Professor Anthony Woolf, at present Visiting Professor at our department, with our department as one of the major partners in the consortium. Website: www.eumusc.net.

LOAD (Lund University network for OsteoArthritis research and Development) was established in November 2010 with the aim to gain new knowledge of the relationship between factors related to OA by applying a unique combination of methodologies available within the network. The network consists of senior researchers in orthopedics, radiology, medical radiation physics, physical therapy, biochemistry, epidemiology and biomechanics that have collaborative projects and joint research grants. Scheduled meetings occur on a monthly basis as well as a yearly conference.
These research projects thus involve the whole staff at the Department of Orthopedics in Lund and Malmö. For a complete listing of participants in each project, please contact the primary investigator.

For further information you may also visit our websites at:
www.med.lu.se/klinvetlund/ortopedi
www.med.lu.se/klinvetmalmo/osteoporsforskning

This report was edited by:

Professor           Professor
Leif Dahlberg       Kristina Åkesson
Lund                Malmö
Sponsors

Awards, Prizes and Dissertations 2014

AWARDS AND PRIZES

David Buchebner, PhD student at the Clinical and Molecular Osteoporosis Research Unit, studies the relationship between vitamin D and bone health. At the Swedish Endocrinology Society meeting Endodiabetes 2014, his study was awarded best scientific poster.


Hans Wingstrand was elected honorary member at The Departments of Orthopedic at Skåne University Hospital, 2014.

Jesper Fritz received Best Paper Award, at The Swedish Orthopaedic Society (SOF), Helsingborg 2014

Jesper Fritz received Presidential Poster Award I, Am Soc of Bone and Min Research, Houston, USA 2014

Marcus Cöster Presidential Poster Award II, Am Soc of Bone and Min Research, Houston, USA 2014

Professor Lars Lidgren, Professor Hans Wingstrand and Otto Robertsson MD, PhD were elected honorary members of the Lithuanian Orthopedic Society at its annual meeting in Kaunas, 2014. For many years they have worked with Lithuanian colleagues and contributed to the development of orthopedic surgery, research and quality improvement in Lithuania.

The Tissues in Motion (TIM) program at Lund University has awarded Marcus Cöster, PhD student, and Maria Herlin, post doc, each a research grant for younger researchers. Both belong to the Clinical and Molecular Osteoporosis Research Unit.
Ola Belfrage: Allograft bone in hip revision: the effect of locally applied pharmacological treatment. Lund University, Faculty of Medicine, Doctoral Dissertation Series 2014:45

Per Bosemark: Enhancing bone healing through concurrent anabolic- and anti-catabolic pharmacological treatment. Lund University, Faculty of Medicine Doctoral Dissertation Series 2014:104

Fredrik Detter: The Influence of Physical Activity on Musculoskeletal Characteristics and Fracture Risk at Growth. A Population-Based Prospective Controlled Exercise Intervention Study at Growth. Lund University, Faculty of Medicine Doctoral Dissertation Series 2014:100


Jan Juréus: Osteonecrosis. Prognosis and Prevention of the Consequences of Osteonecrosis. In Lund University, Faculty of Medicine Doctoral Dissertation Series 2014:106

Mats Molt: On New Implants - The results of five prospective, randomized RSA trials with aspects on phased introduction and continuous migration. In Lund University, Faculty of Medicine Doctoral Dissertation Series 2014:137.


Per Swärd: Knee injuries and their consequences – the impact of impact. Lund University, Faculty of Medicine Doctoral Dissertation Series 2014:60
Joint Arthroplasty in the Hip and Knee – fixation, function and survival

GUNNAR FLIVIK

Group members: Abdulemir Ali, Ola Belfrage, Uldis Kesteris, Sverrir Kiernan, Martin Sundberg, Erik Weber

Background: Total joint arthroplasty, both in the hip and knee, is a successful procedure with generally good results. Developments have been fast and indications for surgery have gradually widened, with younger patients being considered for surgery as results have been improving. However, late aseptic loosening as well as wear remains a problem, and sometimes early loosening occurs without an obvious reason. The consequence of component loosening and the ensuing bone loss is often a major challenge in revision surgery.

Projects: In a range of ongoing investigations we are studying different factors involved in the fixation and function of the prosthesis components. We are evaluating surgically relevant factors such as different operative techniques, pain treatment regimes, bone preparation models, types of bone cement and different prosthesis designs, both cemented and uncemented. We are also exploring the importance of anatomic restoration and how to optimize the biomechanical conditions. Another area of ongoing study is the role for bisphosphonates in joint arthroplasty.

In many of these studies we use RSA (RadioStereometric Analysis) which is a radiographical method by which the 3D-micromotion of the implant in its bone bed can be followed with a very high degree of accuracy. This is the most exact method there is when it comes to measuring migration and wear patterns of prosthesis components. In the studies we have also access to evaluation with gait analysis, peroperative navigation tools and 3D-templating. Our groups of patients are also being followed up with strictly clinical and conventionally radiological examination methods as well as a comprehensive package of questionnaires, covering both general health and disease specific questions.

Furthermore, we carry out complementary biomechanical in vitro laboratory studies. Concurrently with the continuous data we contribute to both the National Hip and Knee Registers we are also following up our own hospital’s material of patients with primary as well as revision hip and knee prostheses.

Aim: Our aim is to evaluate and improve factors of importance for optimal implant function and survival, and not least patient satisfaction and pain relief.

Significance: With success for our studies we can contribute to even better joint function and life quality for patients with hip and/or knee prostheses. We can also decrease the need for re-operations, which are often complex, costly and for the patient trying surgery.

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Tailored treatment of hip fracture – minimising complications and optimising functional outcome

CECILIA ROGMARK

Group members: Ammar Al-Jobory, Susanne Hansson, Olof Leonardsson, Sebastian Rönnquist

Background: A hip fracture is a potential treat to an old individual’s life and independency. The injury is common, and costly to society. In spite of numerous studies leading to improvements within particular issues, the clinical pathway is suboptimal, with unsatisfactory patient reported outcome regarding pain, function and quality of life.

Project and preliminary results: Our scientific achievements so far have e.g. lead to a new national treatment rationale for femoral neck fractures; internal fixation with a failure rate of nearly 50% has changed to hip arthroplasty, after which only 5% suffers failure. This project is a continuum, aiming at develop suitable treatment of hip fracture in different patient groups via clinical trials, and observational studies based on the Swedish Hip Arthroplasty Register.

• Which is the true incidence of complications after hip fracture related arthroplasty?
• Are register data reliable regarding surgical outcome?
• Which are the risk factors for complication after arthroplasty?
• Which type of hip arthroplasty leads to best results?
• Are patients satisfied with modern hip fracture treatment, or if no so, what can be improved?

Aim: To give recommendations regarding best treatment and rehabilitation of hip fracture for individuals of different ages and with different functional demands. Long term outcome in terms of surgical, functional and patient reported outcome are considered.

Significance: The current project will further analyse implant alternatives and scrutinize the entire clinical pathway, with the ambition to secure a lasting improvement in patient reported outcome. Currently many patients fail to recover after a hip fracture, and the reason may be insufficient implementation of scientific results, unclear responsibility for rehabilitation issues – and defeatism amongst care givers and patients.

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Soft tissue biomechanics in hip disease and following hip surgery

HANS WINGSTRAND

Group members: Martin Clauss, Thomas Ilchmann, Aurimas Sirka, Justinas Stucinskas, Sarunas Tarasevicius

Background: This project focuses on hip joint soft tissues. Sonography, intracapsular pressure measurements, MR and CT techniques were used in this clinical project to diagnose and follow synovitis in various hip disorders and following surgery.

Projects and results: In one project the soft tissue biomechanics of the hip joint capsule in and its influence on clinical symptoms, radiological findings and subsequent loosening in hip joint arthroplasties are studied.

We use ultrasonography (US) as a method of examination of THA hips for signs of synovial edema/free fluid in the joint. Pain in OA hips might be of capsular/synovial origin due to its rich sensory innervation. We investigate the intracapsular pressure and the elasticity of the hip joint capsule in OA and correlated these parameters to pain and to the radiographic stage of OA. Joint dislocation remains one of the most disturbing complications after THA. We investigate the soft tissue reaction in relation to soft tissue repair, component wear in relation to aseptic loosening of the prosthetic components.

In a pediatric project concerning Legg-Calve-Perthes Disease, Transient synovitis and Septic arthritis of the child’s hip scintimetric, sonographic and MR studies indicated that increased intracapsular pressure, caused by synovitis with effusion is a factor in the disturbed blood supply to the epiphysis. Synovitis causes cartilage oedema and ensuing cartilage hypertrophy with a risk of joint deformation, incongruency and poor containment.

Serial MRI and plain radiography was used to follow the development of the femoral head. In cases of incongruency a proximal femoral varus, derotation and extension osteotomy reduced cartilage incongruency and an improved sphericity of the femoral head.

Aim: To study the significance of hip joint soft tissue pathophysiology and biomechanics in various hip disorders and following hip surgery.

Significance: Soft tissue reactions in various hip disorders and after hip surgery has so far attracted little interest but have significant biomechanical, clinical and prognostical effects.

Six theses have to date been defended as results of these projects focused on the soft tissues around the hip, now continued in cooperation with Dept of Orthopedics, Kaunas Medical University, Lithuania, and Dept of Orthopedics, hip section, Liestal, Switzerland.

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Lumbar pain and sciatica – diagnostics, RSA, treatment and long-term outcome

BJÖRN STRÖMQVIST

Group members: Paul Axelsson, Bo Jönsson, Gauti Sigmundsson, Fredrik Strömqvist

**Background:** Both on an international and national level, surgical treatment of lumbar spine disorders is performed to an increasing extent. Improved diagnostic modalities contribute to this but also a high number of new implants with variable scientific documentation. Main aim of surgical treatment is pain relief/pain reduction and to functional improvement. To demonstrate the utility of new treatments, prospective long-term follow-up using multiple result parameters is required.

**Project and preliminary results:** Prospective long-term follow-up has been performed since the 1980s and subsequently been converted into a national register, Swespine, which today is used by 90% of departments in Sweden. Using this, all treatments can be documented regarding outcome. The Swespine register is unique in the world containing almost 100,000 operations performed on the spine evaluated by patient-based data on a prospective basis. Register data have also been utilized for implementing value based spine surgery.

RSA has been utilized for demonstrating high-precision mobility patterns in various lumbar conditions as well as under normal conditions and in healing processes. An algorithm for testing new implants has been developed. Also DCRA has been added to the armamentarium. The possibility to regain mobility in the thoracolumbar junction after removal of implants inserted for treating unstable fractures has been demonstrated and has clinical implications.

Biochemical studies of cartilage markers in disc herniation in collaboration with the department of cell and molecular biology, has demonstrated the possibility to monitor events in the disc in blood tests and further studies are ongoing.

Minimally invasive treatment of lumbar spine disorders has been evaluated in prospective studies, examples are ultrasound treatment for disc herniation, percutaneous treatment of disc herniation and interspinous spacer for spinal stenosis. Also bone inductive substances in conjunction with fusion have been studied in prospective randomized studies.

Evaluation by functional and ADL parameters is studied in multidisciplinary projects on disc herniation surgery.

Significant gender related differences in preoperative quality of life and function before disc herniation surgery have been identified with higher pain levels, inferior function and lower quality of life in females, and the causes are being analysed. The limited number of patients requiring fusion in conjunction with spinal stenosis surgery has been described based on register data. Further, predictors of successful and
unsuccessful surgical treatment of lumbar spinal stenosis have been identified and form important information to patients when discussion on surgical treatment is performed.

The outcome of surgical treatment of lumbar disc herniation in patients aged <20 years has been explored and shows similar preoperative pain and disability as in adults but the outcome after surgery is better regarding both aspects. Even in this group, girls have more preoperative affliction than boys but improve to the same extent postoperatively and patient satisfaction is similar for both genders.

Aim: The overall aim is to improve patient information before surgery and patient selection for surgery, pinpointing well functioning surgical techniques and deleting non-efficient treatment modalities. A treatment algorithm is gradually being developed.

Significance: The treatment program has significantly improved treatment for patients with lumbar spine problems, an important contribution on a humanitarian basis for the individual and on an economical basis for the society. Prognostic factors for outcome of lumbar spine surgery have been and are continuously established, facilitating shared decision-making between patient and physician when surgical treatment is contemplated.

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Biomaterials and Biomechanics Unit

LIZ TANNER

Group members: Gunnar Flivik, Hanna Isaksson, Magnus Tägil

Since May 1997, the biomechanics and biomaterials laboratory has provided an interface for researchers with engineering and medical backgrounds, bridging the biomechanical/biomaterial research with more biologically oriented animal models and clinical research.

The facilities within the unit are:
1) a mechanical testing laboratory with biaxial (tension/compression and torsion) mechanical test machine
2) a RSA laboratory (RadioStereometric Analysis), a technique that with a very high degree of accuracy can measure the stability of artificial joints implanted into the body, furthermore we measure in 6 degrees of freedom with some different precision values for each type of measurement
3) a biomaterials production facility for ceramic bone substitute materials
4) animal model facilities for bone and bone substitutes in in vivo studies
5) a complete set of hard tissue preparation equipment: Exakt saw, diamond saw and grinding machine provide hard tissue histology investigation for a combination of mineralized bone, metal and biomaterial study
6) this laboratory is a part of a centre for Biomechanics at Lund University

The general aim of the biomechanics laboratory is to use the techniques of engineering, biomaterials and biomechanical sciences together with biological and animal models to improve the repair and regeneration of tissues in the skeletal system. A clear link to clinical use and clinical trials is prioritised.

Our mechanical machine is used for mechanical testing of new materials or bone tissue. The RSA laboratory assesses the behavior of joint implants in the body. A large number of RSA-studies are ongoing evaluating factors such as cementing technique, bone preparation, prosthesis design and fixation methods, both cemented and uncemented.

We are investigating injectable bone substitute materials, that have a similar composition to bone, and which can integrate with normal tissue. We are studying how these materials can stimulate repair of tissue, through optimizing the chemical composition or the mechanical properties of the materials. We are also studying the effects of antibiotics in the material on its biomechanical and biological properties.

This work is being done in collaboration with the Biomechanics Group in the Department of Biomedical Engineering of LTH

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Experimental orthopedics

MAGNUS TÄGIL

Group members: Ola Belfrage, Per Bosemark, Hanna Isaksson, Jan Jureus, Neashan Mathavan, Mea Pelkonen, Christina Perdikouri

Aims: The primary goal of this project is to solve the unsolved problems of a fracture that does not unite, in spite of repeated surgical attempts. A non-uniting bone defect is devastating for the patient and today these patients tragically face amputation of the limb as the ultimate desperate solution.

Project: In our project we try combinations/mixtures of cells, bone substitutes, bone grafts and bone active drugs. We will combine mesenchymal cells with bone-inducers and antibiotics incorporated in biomimetic scaffolds. The cells, proteins, and drugs provide bioactivity, while the scaffolds provide structural support (osteoconductivity) for the cells and act as matrices for the induced new compound tissue growing in. The scaffolds, made of injectable polysaccharides/polymers or 3D printed polymers/ceramics, can be designed to serve as a bioactive reservoir allowing for a controlled release of drugs, proteins, antibiotics and local nutrients. The end result will be a “smart” bone substitute, with the bone induced in vivo, in the patient, using the technique of tissue engineering, and with all ingredients already incorporated.

We will develop new ways of producing bone inductive proteins by harvesting proteins from the culture medium of growing bone cells. This will provide us with much cheaper but still effective proteins that will allow us to treat fractures, in sites known to be problematic, primarily with bone inducing proteins and not as today first when everything has failed, thereby decreasing the incidence of non-unions.

We will develop a muscle cell model, to explore our hypothesis why fractures/bone defects do not heal in sites lacking muscle coverage. It will allow us to study solutions, using cultured muscle satellite cells as well as bone substitute doped with the cultured cells and the harvested proteins.

We will develop animal models to test combinations of the harvested proteins and bone-forming muscle cells in the most extreme challenging situation of bone healing, i.e. non-united fractures, large bone defects and infections. Finally, the developed smart bone substitute will provide an injectable product, 1) loaded with the bone-inducing proteins above, 2) anti-bone-resorbing drugs like bisphosphonates, 3) cell nutrients such as sugars, or 4) antibiotics as local infection control, capable of solving many of the problems in bone healing and a putative commercial product to move into the next phase of clinical trials.

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Foot & Ankle: Clinical, radiographic and patient-reported outcome of surgical treatment

ÅKE CARLSSON

Group members: Jack Besjakov, Maria Cöster, Ylva Ericsson, Ilka Kamrad, Magnus Karlsson, Håkan Magnusson, Björn Rosengren.

Background: The Swedish Ankle Register (www.swedankle.se) contains data on all ankles replaced by a prosthesis since 1993, including secondary procedures and complications, and since 2008 also information on primary ankle fusions. The register serves as a basis for clinical development and research.

Projects: Project 1) Validation of the foot-specific SEFAS score (Self-reported Foot & Ankle Score). The score has been validated for ankle arthrodesis, ankle replacement and disorders of the mid and forefoot. The results are published in Acta Orthopaedica 2012 and 2013. Further analyses of this questionnaire are now being undertaken.

Project 2) Clinical and radiographic evaluation of the Mobility ankle prosthesis. More than 100 cases performed in Malmö are followed clinically, by radiographs and by validated questionnaires.

Project 3) The prevalence of primary ankle osteoarthritis. Radiographic evaluation of ankle osteoarthritis by different projections.

Project 4) Balance, walking velocity, oxygen consumption and muscle strength. Patients undergoing ankle fusion or replacement due to osteoarthritis are examined before and two years after surgery together with controls.

Project 5) Patient-reported outcome and satisfaction following primary ankle replacement and fusion by generic and region-specific questionnaires.

Project 6) Self-evaluated outcome and satisfaction after second procedures following primary ankle replacement and fusion.

Aim: To evaluate the clinical, radiographic and patient-reported outcomes after ankle fusion and replacement. The intention is to elucidate the treatment method of preference in relation age, sex and diagnosis. We also intend to clarify the prevalence of idiopathic osteoarthritis.

Significance: The literature contains only scarce information on the functional results after ankle replacement and comparisons with results after ankle fusion are non-existing. By our studies orthopaedic surgeons and health care authorities will be guided in decision making regarding surgical treatment of osteoarthritis and other disorders of the ankle.

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This 63 year old man had his left ankle replaced by a Mobility prosthesis due to osteoarthritis. (Picture to the right)

There was no history of a previous trauma. Now, three years later, he is scheduled for replacement of his contralateral ankle. (Picture to the left)
Minor amputations in diabetic patients and factors related to outcome

HEDVIG ÖRNEHOLM

Group members: Jan Apelqvist, Magnus Eneroth, Jan Larsson

**Background:** Around 4% of the Swedish population has diabetes. A considerable proportion of these patients will at some point in their life have foot-related problems, the most severe being ulceration, infection and gangrene.

Almost half of all non-traumatic amputations in the industrialized world are performed on diabetic patients. In most studies the major (above the ankle) amputation rate only is reported. The principal aim of minor (below the ankle) amputations in these patients is to avoid major amputation in order to facilitate ambulation. Although minor amputations are performed in large numbers on diabetic patients, in most countries the incidence is unknown and little is known about the outcome.

**Project:** We analyze factors leading to amputation and those that influence the outcome of such surgery. Can the outcome be predicted by using specific parameters? Which factors play a greater part in outcome after surgery? Trying to find the answers to these questions will hopefully lead to better treatment options for these patients.

Taking the patients’ aspect into account is also important. A large proportion of these patients are elderly and have to rely on family or social services in their everyday living. How amputation affects their quality of life is also subject to our studies.

**Aim:** The goal is to reduce the number of major and minor amputations in these patients.

**Significance:** Reducing amputation rate is important not only for the patient but also for society in general as an amputation is associated with higher costs than if you can avoid an amputation.

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Prosthetic joint infection, PJI

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Group members: Anna Holmberg, Annette W-Dahl

Background: Since 1975 the Swedish Knee Arthroplasty Register (SKAR) has registered information on knee arthroplasties performed in Sweden. This large nationwide database provides unique possibilities to study a low-frequent complication like deep infection and recently the results of a study on open debridement an exchange of tibial insert were published. The incidence of PJI after a primary knee arthroplasty has been estimated to be around 1.5% but there are indications of increasing infection rate and today infection is the most common reason for early revision after a primary knee arthroplasty. During the years 2009 to 2013 all orthopedic departments performing primary hip and knee arthroplasties in Sweden participated in the PRISS (prosthetic related infections should be stopped) project which aim was to reduce the rate of PJI by half. To enhance evaluation of the project a study was conducted on the rate of hip PJI during the years before the project was started.

Project: 1. Open debridement and exchange of the tibial insert, followed by antibiotic treatment, has become increasingly common as a treatment for early or haematogenous prosthetic joint infection. We have found 75% success rate with respect to healing of infection with retained prosthesis. The next step in the evaluation of the method is to study how the patient reported outcome is affected. Before the primary operation patients operated in the region of Skåne have answered the EQ-5D questionnaire on health related quality of life, the KOOS questionnaire about knee function, and evaluated pain on a visual analogue scale. The questionnaires were repeated at one year after operation.

2. Data from the SKAR will be matched with data from the Swedish prescribed drug register in order to identify all patients treated for infection after primary knee arthroplasty. Two time periods will be studied, before and after the PRISS project.

Aim: 1. Reveal how PJI treated with open debridement and exchange of tibial insert affects patient reported outcomes.

2. Reveal the rate of infection after primary knee arthroplasty in Sweden and evaluate the effect of the PRISS project.

Significance: Deep infection is a devastating complication that can have severe consequences for the patients and brings high costs to the health care system. The studies will increase our knowledge on incidence, treatment and prophylactic measures. Further, it will contribute to the development of research methods based on compiling data from different sources.

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Background: Musculoskeletal conditions are the leading causes of chronic pain and reduced quality of life in an ageing European population. The burden on society due to these conditions will rapidly increase making it an urgent matter. However, there is lack of knowledge of natural history, future disease prognoses and monitoring of treatments on population level, critical for health care planning. Osteoarthritis, a chronic degenerative joint disease causing pain and reduced joint function is one of the most common causes of musculoskeletal disability in developed countries.

Projects: We determine the specific roles of meniscus lesions, position and degradation in early osteoarthritis pathogenesis are as well developing an innovative bone biomarker to predict incidence and progression of the disease in collaboration with biomechanical engineers. We will accomplish our goals by novel analysis of large datasets including state-of-the-art repeat knee MRIs and radiographs.

Further, in our population-based epidemiologic and health economic studies of musculoskeletal disease, we focus on chronic musculoskeletal conditions and injuries in general. We use physician-coded steadily growing in- and outpatient health care data in southern Sweden currently encompassing about 20 million person-years. Personal identifiers are used to set up linkages, not attainable in any other way, with, e.g., data on sick-leave, diagnoses, surgical procedures, prescribed drugs and socio-economic variables.

Aim: To gain novel insights on musculoskeletal diseases and injuries with focus on osteoarthritis aetiology, occurrence, natural history, treatments, prediction, disease monitoring, and burden of disease to allow for better care, decision making, resource prioritizing, and methods of prevention.

Significance: Considering meniscal damage is present in about every third knee in middle-aged and older adults, and is the most potent risk factor for knee OA so far identified, understanding of its natural course is highly needed. In clinical practice early identification of patients at high risk is vital for early information and potential intervention.

With our current translational approach pushing the frontiers in our fields of research, we will provide much needed new knowledge and information to researchers and clinicians specializing in musculoskeletal conditions, and the patients. Public health professionals, politicians, and policy makers are just a few examples of other professionals who will benefit from the information the team will provide.
The research group is a cross-disciplinary unit, and includes me as PI and epidemiologist, three statisticians, a postdoc health economist, a postdoc political scientist and expert in insurance medicine, two orthopaedic surgeons, a couple of physicians under specialty training in orthopaedics, data managers/SAS analysts, a biomedical analyst, a secretary, a grant manager, a research administrator/economist. I am currently mentoring five PhD students as main advisor, a postdoc radiologist, as well as serve as co-mentor additional PhD students in the field.

We collaborate with Lund University postdoc researchers in several disciplines to facilitate register research. The group is active in the Lund University Strategic Research Area “Epidemiology for Health (EpiHealth)”, the Lund University osteoarthritis network LOAD, and the by the Faculty of Medicine officially supported creative research environment for young investigators in osteoarthritis, ReLOAD. We work in close collaboration with Patrik Önnerfjord, PhD at Lund University and his massspectrometry lab.

We have a comprehensive international network of active collaborators in the fields of biomechanics, clinical epidemiology, MRI analysis methodology, orthopaedics, radiology and rheumatology in Australia, Denmark, Finland, Germany, Norway, United Kingdom and USA. The group is supported by the Swedish Research Council, ALF, Crafoord Foundation, Österlund Foundation, Kock Foundations, The Swedish Rheumatism Association, and the Medical Faculty Lund University.

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Health services use and work disability in patients with musculoskeletal disorders

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Background: Every third visit to a GP as well as one third of the disease burden in sick leave practice comes from musculoskeletal disorders (MSKD:s) which cause a high degree of functional impairment, work disability and decreased quality of life for people of all ages.

Project: We keep a focus on structured and continuous follow-up, evaluation and benchmarking. With this program it is possible to achieve new ways for collaboration with research groups and decision makers within Sweden, Europe and other parts of the world including European programs.

We use registers from the Swedish National Insurance Agency (Försäkringkassan), the local health authorities of Region Skåne and national registers on occupation, income, education. We also include data from National Disease Registers (Nationella kvalitetsregister) and plan to include data from the municipality level.

Aim: Aims of the program

- To study the impact on Functioning, Activity and Participation due to musculoskeletal disorders on a group level for different inflammatory MSKD diagnoses
- To estimate of the impact of MSKD:s and other chronic conditions on the health care system and the national social insurance system
- To study the Burden of Disease and Cost of Illness due to musculoskeletal disorders on a group level for different inflammatory MSKD diagnoses
- To evaluate the effect of a national rehabilitation program in Sweden on work participation and health related quality of life in patients with back pain
- To evaluate in register based follow-up studies, the effects of structured interventions and work place interventions in patients with back and neck pain on work participation and health related quality of life in the Work-Up study
- To compare end bench mark tools for evaluating MSKD outcomes in primary care in collaboration with Keele University, UK
- To study the development and implementation of guidelines for the treatment, rehabilitation and sick leave procedures for patients with inflammatory MSKD:s

Significance: The program has a focus on the consequences for the individual and the society in patients with inflammatory MSKD.

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The Swedish Knee Arthroplasty Register (SKAR)

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Group members: Kaj Knutson, Lars Lidgren, Otto Robertsson, Anna Stefánsdóttir, Martin Sundberg, Annette W-Dahl.

Background: Since 1975 the Swedish Knee Arthroplasty Register (SKAR) has prospectively followed patients operated on with knee arthroplasty and thus celebrates its 40 year anniversary this year. The register was started in the seventies at a time when new implants designs were being invented and there was an explosive expansion in the number of implants available. The Swedish orthopedic surgeons realized that in this environment it would be impossible for an individual surgeon to base his choice of optimal operative treatment on his own experience, thus a national project was started.

Project: Initially, the register only gathered a minimal set of data for each primary operation containing information on identity, age, disease, treating hospital, what implant was inserted and the method of fixation. As an additional measure of outcome, self-administered questionnaires have been sent to subsets of patients. In 2009 the register added a number of questions to its form concerning previous surgeries, surgical methods used (tourniquet, drainage, CAS, MIS), prophylaxis (infection, thrombosis) as well as timing and in 2013 registration of tibia osteotomies was started. The registry has in the past succeeded in giving early warning about inferior techniques and implants as well as stimulating hospitals and surgeons to improve their routines. Since 2009, all six hospitals in the Region of Skåne have delivered data on patient reported outcome measures both pre- and postoperatively and additional 10 hospitals in the rest of the country have since then started reporting PROMs.

Aim: The original aim of the project was to detect which implants were suitable respectively unsuitable for use in patients with different types of knee destructions. Later on the register started evaluating patient satisfaction and different health measures in order to better understand the results of knee arthroplasty from the patient perspective. Further, by the new variables concerning surgical techniques and drug prophylaxis we hope to be able improve knowledge on the efficacy of the treatment.

Significance: During 2014 13 000 primary arthroplasties and 900 revisions were reported in Sweden. 57% of the primary surgeries and 52% of the revisions were performed in women. Further increase in the demand for knee arthroplasty is expected if only because of changes in the age-profile of the population in the coming years.

The cost for revisions is substantially higher than that for primary operations, especially in infected cases. The number of revisions is affected by many factors such as unsuccessful methods or implants, where the revision rate will be higher than the average. Therefore, it is of the highest importance that the use of such methods, implants and techniques can be limited to reduce the extra cost and suffering. Sweden has comparatively low rate of revisions after knee arthroplasty which may be contributed to the long history of registration and feedback to surgeons on what implants and methods are successful.
Epidemiology of Fractures

BJÖRN ROSENGREN

Group members: Daniel Jerrhag, Anton Karlsson

Background: With the anticipated changes in population size and age-structure even small changes in risk of disease can significantly alter resource demands for society. The lifetime risk of fragility fracture at age 50 years in Sweden is as high as 50% in women and 25% in men and more than 3% of the Swedish national health care costs are the result of osteoporosis related diseases.

The lack of current data on occurrence of overall and type-specific fracture disease makes predictions on the future number of fractures uncertain.

Project and preliminary results: Our earlier work infers that hip fracture incidence has levelled off in Sweden and has since the mid-1990s been replaced by a decreasing incidence. In women this appears to be the result of cohort+period effects, with a lower incidence in those born recently than those born earlier.

As no changes in prevalence of osteoporosis have been apparent in our studies, the changes in fracture incidence seem associated to other factors, probably linked to changes in society during the lifespan (from 1885 to 2011) of the examined individuals.

Aim:

- Improve projections of fracture burden, by defining changes in regional and nationwide fracture epidemiology during the recent 30 years including effects of age+cohort+period and medication, migration, and urbanization.
- Produce algorithms to identify individuals at high risk of fracture to better target preventive strategies.
- Define time trends in fracture severity (classification) and treatment protocol for common fracture types.
- Make cost and resource descriptions and cost benefit-analyses for both pharmacological regimes and other interventions for different fracture types.

Significance: This project will enable more accurate prediction of the future fracture burden, imperative for society and politicians to know when planning the future resources for fracture care.

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Determining mechanisms in osteoarthritis to enable proper diagnosis, treatment and prevention

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Group members: Shahrzad Hosseininia, Therese Jönsson, Henrik Owman, Ulf Sigurdsson, Jon Tjörnstrand, Ylva Ericsson, Paul Neuman, Carl Johan Tiderius

Background: Osteoarthritis (OA) is a chronic degenerative joint disease, causing pain and functional impairment, which results in reduced physical and daily activities as well as decreased quality of life. It is the 11th highest global contributor to years lived with disability. The risk for developing OA is related to the individual’s cartilage quality and to risk factors such as meniscectomy, obesity, muscle weakness, major injuries and, in the hips, developmental joint anomalies.

All joints can be affected but OA is most commonly seen in the knees, hips, fingers and spine. The hallmark of OA is cartilage loss, which together with joint pain defines the disease. It is a complex disease that often causes great suffering due to pain, reduced mobility and reduced quality of life.

Project: We combine state-of-the-art magnetic resonance imaging technology (dGEMRIC) with molecular composition analysis to examine cartilage structure and quality. Using this approach we can identify metabolic events that will result in cartilage structural changes as well as relate the MRI signal to molecular content.

In vitro, we use dGEMRIC on excised cartilage samples which are also analysed for molecular composition. In vivo, we follow patient cohorts at increased risk of developing OA longitudinally, from emergence of risk factors to radiographically diagnosed OA.

The combination of advanced imaging methods and molecular indicators, applied in parallel to experimental models and patient cohorts, provides novel understanding and new means to detect the process leading to disease. Moreover, we study effects of early intervention i.e. physiotherapy to improve treatment of OA patients.

Aim: The aim of our research is to get the whole picture of OA; from comprehension at molecular and structural levels, to understanding which external factors that influence progression of the disease. By determining disease mechanisms at early stages of OA, methods for proper diagnosis, treatment and, not the least, prevention of the disease can be developed.

Significance: Besides causing pain and hampered physical mobility for the affected patient OA has effects in a larger context due to huge socioeconomic expenses associated with the disease. Both from a patient and a socio-economical perspective it is thus of utter importance to develop better diagnostic methods, treatment interventions and prevention programs.

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From joint injury to osteoarthritis – molecular markers and structural changes

ANDRÉ STRUGLICS

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Background and significance: Osteoarthritis (OA) is a common musculoskeletal disease causing destruction of joint tissues leading to pain and disability. Little is known about disease onset and the mechanisms, and no disease modifying drug or reparative surgical intervention are available. OA affects elderly people, but middle-aged people with symptomatic OA are increasing. This increase is due to the strong linkage between joint injury and OA.

Project and preliminary results: We use animal models, and body fluids from cross sectional and longitudinal patient cohorts for immunochemical assays of cytokines and joint tissue molecular markers, use MRI for analysis of joint structures, and monitor patient-reported outcomes.

Preliminary data:
- Explant cultures of mechanically injured bovine cartilage shows increased release of MMP generated FGFV-aggrecan fragments. Combined mechanical injury of the cartilage and co-incubation with the synovium increases both aggrecanase generated ARGS- and MMP generated FGFV-aggrecan fragments. These results indicate differences in the process of activating aggrecanases and MMPs.
- Synovial fluid TNF-α concentration is elevated directly after ACL injury and remains elevated over 5 years compared to knee healthy controls. Knee injuries with an osteochondral fracture have higher synovial fluid TNF-α concentrations compared to knees without fractures. This suggests that knee injuries associated with an osteochondral fracture cause joint inflammation which may contribute to the development of OA.

Aim: Investigate the biological response following joint injury and the processes leading to OA. Relate molecular markers to imaging and clinical outcomes in the early phases of knee injury and OA. Validate aggrecan protein fragments as biomarkers of OA disease burden and prediction.

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Joint preserving surgery for knee osteoarthritis

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**Background:** High tibial osteotomy (HTO) is a joint preserving surgical alternative in the treatment of knee osteoarthritis (OA). From being the standard treatment for knee OA in the late 1960’s, HTO has decreased substantially and represented less than 2% of the primary knee reconstruction surgery in Sweden in 2013.

HTO is mostly performed in younger and/or physically active patients and was the most commonly used surgical alternative before 2000. However since 2000, these patients are predominantly treated with total knee arthroplasty. For HTO, there is a lack of information regarding its use and outcome as well as patient selection as compared to knee arthroplasty surgery for which there is a national registration.

**Project and preliminary results:** In a population based study of HTO in Sweden between 1998 and 2007 the majority of patients showed to be younger than 55 years of age and most of them men. The risk of revision for HTO to be converted to a knee arthroplasty was 30% at 10 year. The risk of revision increased by increasing age and was significant higher in women than men.

In 2013 national registration of knee osteotomy’s were started using the same methods that already are used for knee arthroplasty surgery in Sweden. During the first two years just over 400 osteotomies are registered.

**Aim:** To gain knowledge of knee osteotomy, the reasons for surgery, surgical methods and techniques used, complications and the patient perspective on outcome.

**Significance:** The information will allow for comparison of the joint preserving knee osteotomy and the knee arthroplasty surgery and may origin in new treatment recommendations.

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Risk Factors for Osteoporosis, Falls and Fractures with Special Reference to Physical Activity

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Group members: Jack Besjakov, Caroline Karlson, Magnus Dencker, Björn Rosengren
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Background: The accrual of bone mineral at growth and the age related bone loss influence who will develop osteoporosis and fractures. But also skeletal architecture influence bone strength and muscle function determine who will fall. Thus, it is imperative to determine regulation and suitable interventions that could improve each trait and identify risk individuals for fractures.

Project and preliminary results: Secular changes of fractures are followed in regional and national registers. Bone and muscle trait evaluations are done in several population-based cohorts of children, adolescents, adults and elderly now followed for 10-40 years by bone scanning, neuromuscular tests, anthropometry, fall frequency and fracture registration.

Data has shown that hip fracture incidence has decreased while proximal humeral fractures have increased. Fracture incidence in children has increased. As well as total number of fractures in old ages. This has necessitated recalculations for prediction of future fracture burden. Daily physical training at growth enhances bone mass, bone size, reduces overweight and improves school performance. The benefits remain remains in adulthood. Daily physical activity should therefore be implemented in school. Clinical functional tests could identify fallers and should therefore be used in the health care.

Aim: 1) study regulation and how to modify bone mass, skeletal architecture, muscle function and adiposity during growth and ageing; 2) evaluate risk factors and prognostic factors for osteoporosis, fall and fractures; 3) evaluate if benefits achieved by interventions remains in a long term perspective; 4) follow fracture epidemiology to improve projections for the future.

Significance: Our studies increase the understanding of the pathophysiology of osteoporosis, improve our ability to target risk individuals, improve the prediction of fracture in the future and identify beneficial intervention strategies.

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Dissecting the genetic component of osteoporosis and fracture

FIONA MCGUIGAN

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Background: Osteoporosis is a complex multifactorial disease regulated by genetic and environmental factors. The influence of genetic factors is significant affecting all aspects of the osteoporotic phenotype, not just bone density. However, osteoporosis is a polygenic condition and each gene confers a relatively small effect. Although our genetic makeup is unchanging, genes do not act uniformly throughout life, but respond to changes in internal (e.g. systemic hormones) or external triggers (e.g. mechanical stimulus) and environmental factors (e.g. smoking, diet). Osteoporosis risk may also be affected by epigenetic modifications which affect gene expression without altering the DNA-sequence.

Projects: As a senior researcher in Professor Åkesson’s group, I lead several projects analyzing candidate genes for osteoporosis risk, with particular interest in gene-environment interactions and interplay between bone and other systems. One such example revolves around a gene identified in a knockout mouse model, which affects both metabolism and bone in mice lacking the gene for an accessory protein involved in an important signaling pathway. The aim is to study the association between this gene and bone and body composition in young and elderly women to identify age-related regulatory effects. In another project, the association between the Pirin gene and bone density is being investigated in relation to dietary phytoestrogen exposure and heavy metals. This is complemented by studies of expression levels and protein localization in bone cell lines.

Aim: To explore the effects of genetic variation and gene-environment interactions on bone and body composition parameters.

Significance: In terms of health and economic benefits, discovery of genes and understanding gene-environment interactions and epigenetic modifications affecting bone density and fracture could lead to earlier diagnosis of osteoporosis. Exploring factors influencing bone activity at the cellular level also introduces the possibility of identifying novel targets for pharmacological treatment.

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Frailty, falls and fractures in the elderly, especially hip fractures

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**Background:** Patients with hip fractures constitute one of the most resource consuming groups in health care. They consume one fourth of all bed days in orthopedic departments in Sweden. We have pioneered a treatment program with fracture repair (osteosynthesis), immediate direct weight bearing, and continued walking rehabilitation in the patient’s own home.

During the last decades the risk of hip fracture has doubled in persons above 80 years of age and the total number of elderly in the population is increasing. We must therefore continue the improvement in the overall care, operation techniques and rehabilitation of the hip fracture patients, as well as in the prevention.

**Project:** The research project contains epidemiological, prognostic, preventive and technical as well as rehabilitation and economical aspects of the hip fracture treatment. The project further contains optimized patient care including rapid handling to operation, prevention of infection and pressure ulcers, pain management and improved nutrition.

It includes the nationwide quality register RIKSHÖFT (www.rikshoft.se). In a European Commision project called Standardized Audit of Hip Fractures in Europe (SAHFE), the Swedish national registration has spread internationally widely also outside Europe.

Techniques used are: epidemiology, balance testing, patient inquires, skeletal scintimetry, bone densitometry, histology, MRI, CT, x-ray, ultrasound, pressure measurement.

The project parts are listed below:

- Fracture epidemiology, background factors, screening and prevention of sarcopenia, osteoporosis and falls.
- Comparison of osteoporosis treatments
- Comparison of operation methods
- Investigation of femoral head blood circulation and vitality after femoral neck fracture, osteonecrosis
- Acute fast track treatment from hip fracture to operation and rapid rehabilitation
- Nutrition, pain relief and prevention of pressure ulcers and cognitive impairment in hip fracture patients
- Bone transplantation, bone substitutes and healing improvement
- Nationwide registration of quality in treatment of all Swedish patients with hip fractures and international comparisons
Aim: To optimize the health of the hip fracture patients and help them to regain the same functional level as before the fracture, if possible improve further.

Significance: The optimal treatment of this large and increasing group of elderly patients has great importance both for the individual and the society with its limited resources for health care.

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Regulation of skeletal integrity: Genetic variation, risk factors and fracture

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Background: Osteoporosis is a major public health concern, causing over 70,000 fragility fractures each year in Sweden, inflicting enormous costs on health care system and suffering on the patient. The current difficulty to offer patients an optimal treatment calls for further research on underlying mechanisms to find better intervention options.

The pathogenesis of fragility fractures is complex, including environment, biomechanics, hormones, cellular regulatory mechanisms and genetics, the latter accounting for <80% of skeletal variance. We integrate basic and clinical research to evaluate in parallel the different aspects of this multifaceted interaction.

Project: Our overall objective is to identify and evaluate internal and external risk factors for osteoporosis and fracture, as well as opportunities to influence these factors and ultimately contribute to better bone health and reduced risk of fragility fractures.

We currently focus on delineating interactions between bone and skeletal muscle, adipose tissue, glucose metabolism, and inflammation. Of particular interest is our recent finding on the role of inflammatory genes and bone loss in elderly women, suggesting that low grade inflammation is involved in osteoporosis development with advancing age. In addition, we performed a genome-wide association study in our cohort of 75-year-old women, the results will provide further insight into etiological pathways for fracture susceptibility.

Aim: Our general aims are to: 1) Define external and internal risk factors for bone strength and fracture from young adults to the very elderly; 2) Identify genetic determinants influencing bone mass, bone loss and fracture at different ages; 3) Investigate underlying mechanisms influencing bone cell activity in humans and in animal models; 4) Evaluate and target clinical interventions based on evidence from research studies.

Significance: By combining clinical, genetic and molecular studies, we contribute to a better understanding of the underlying mechanisms of osteoporosis and fragility fractures, which in the longer term can be used to achieve a personalized treatment for patients. Our results are implemented in the clinic, where they contribute to improved prediction and monitoring of fragility fracture risk.

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Wrist fracture: A register study with an analysis of causes and suggestions for intervention

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Group members: Antonio Abramo, Anna Kajsa Harding, Philippe Kopylov, Marcus Landgren, Ante Mrkonjic

Background: The distal radius fracture (DRF) comprises about one-sixth of all fractures in the emergency room. In Skåne, the incidence is 26 per 10,000 annually increasing with age and with female predominance 4:1. In the majority of cases, the patients will have some form of residual symptoms lasting up to one year after the injury. In approximately 10%, the patient has not returned to work one year after the fracture7 and at present we do not know why. In the proposed project, we will continue our previous work, using an own DRF-register, running since 2001, to find hypotheses explaining inferior outcome. In the fracture register, we have identified all fractures in adults in Lund and prospectively recorded the subjective outcome after three and twelve months using DASH, a validated patient-administered outcome score. We have correlated the subjective outcome to demographic and radiographic data.

Population: We have identified 450 patients between 2003-2012 with an inferior outcome (DASH >35) after one year out of 4000 prospective patients in total. These patients have been sent a new enquiry 1-10 years later and approximately 50% still have a DASH score >35 implying that the fracture is not so benign as we have expected.

In patients in the working age 18-65 an additional survey was distributed in the first weeks after the injury to map socioeconomic data as well as an estimation of previous pain history and attitudes towards pain. These patients will be summoned for a visit to the hospital including a clinical examination as well as a radiogram.

With the use of our register data we aim to identify key factors that predict an inferior end result after a DRF: The incidence of a previous pain history already at the time of fracture will be investigated and correlated to short (3 months) and long (one year and beyond) term subjective outcome; the incidence of ulnar instability due to ligament injuries between the radius and ulna will be investigated and correlated to short (3 months) and long (one year and beyond) term subjective outcome; the incidence of surgical failures (osteoarthritis) will be investigated and correlated to short (3 months) and long (one year and beyond) term subjective outcome; the incidence of rehabilitation failures (reflex dystrophia) will be investigated and correlated to the long term subjective outcome; the degree of osteoporosis, comorbidity and mortality will be correlated to the Yellow flags question as well as the 3 and 12 month subjective outcome to be able to identify patients not getting well for other reasons than wrist fracture; the length of sick-leave will be correlated to the Yellow flags question as well as the 3 and 12 month subjective outcome to see if long sick leave can be predicted.

Intervention: We will use the data from the various substudies to design intervention protocols to lower or at best irradiate a bad result after a distal radius fracture.

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Prevention of hip dislocation and musculoskeletal deformities in children with cerebral palsy

GUNNAR HÄGGLUND

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Background: CPUP, a cerebral palsy register and a health care programme for children with CP, was established in Southern Sweden in 1994 as a joint project between the pediatric orthopedics and the child rehabilitation units. The background was that we saw that a number of children with CP had developed hip dislocation and severe contractures.

Project: The basis of CPUP is to identify all children with CP and offer them participation in the programme. CPUP includes a standardized follow-up of each child in terms of an assessment form. The children are assessed 1-2 times a year. The form includes information on the child’s gross and fine motor function, range of joint motion, use of orthoses and treatment. The programme also includes a standardised radiographic follow-up of the children’s hips and spine. All reports are administered via Internet.

In 2005, a 10-year follow up showed that hip dislocation is preventable and also that there was a decrease in the number of children that developed severe contractures, windswept deformity and scoliosis.

In 2005, CPUP received funding as a National Quality Register. Since 2007 all counties in Sweden have joined CPUP. CPUP became a National Quality Register in Norway in 2009, and in Denmark in 2013. It is also used on Island, Scotland and New South Wales. Since 2011 adults with CP are included in CPUP. This total population followed prospectively is used for several research projects.

Aim: The aims are to: 1) prevent hip dislocation and severe contractures; 2) gain knowledge about CP; 3) improve the co-operation between the various professionals with respect to people with CP.

Significance: This is a unique total population of people with CP followed prospectively in a standardised way. It has been used in three PhD-theses, it is used in five PhD-projects and more than 30 scientific papers based on the material has been published.

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Radiostereometric analysis of skeletal growth in children

HENRIK LAUGE-PEDERSEN

Group members: Gunnar Hägglund  
Doktorand: Catherine Sharan

Background: RSA (Radiostereometric analysis) as developed by Göran Selvik 1974 has been used extensively for orthopedic and radiographic research. The radiostereometric technique can be used to determine the three-dimensional dynamics of one skeletal structure relative another and therefore we found it suitable for investigating physeal growth.

RSA permits accurate determination of longitudinal growth and rotational movements over short periods of time. This makes it possible to detect an incomplete physeodesis at a very early stage, and, if necessary, do a repeat operation before an angular deformity or inaccurate correction of LLD is of any clinical importance.

Project and preliminary results: After establishing the accuracy of the method on the first 10 children and following another 50 children closely with this technique, we now perform RSA on all physiodesis as a routine follow-up postoperatively and at 12 and 15 weeks postoperatively.

Leg Length Discrepancy: Children with LLD are treated with percutaneous physeodesis and followed with RSA. The time perspective from physiodesis to physeal arrest is evaluated in relation to age and gender. A prospective study using eight plates instead of percutaneous physeodesis is carried out with the potential possibility of this method to be reversible and making correction of LLD a very accurate procedure.

Extreme tall stature: Girls with predicted height >187cm (+3sd) and boys >200cm were earlier on occasionally treated with hormones by the paediatricians to reduce height at skeletal maturity. In corporation with the paediatricians we now treat some of these children with knee physeodesis and follow them with RSA.

Fractures: Physeal fractures can result in partial or complete arrest of the physis leading to asymmetrical growth or growth arrest.

Aim: To develop new methods for reversible treatment of LLD. To evaluate knee physeodesis as treatment for extreme tall stature. To improve RSA as a clinical tool for monitoring Physiodesis and fractures in relation to physes.

Significance: To accomplish reversible physeodesis in patients with LLD would largely improve final results. Physeodesis is probably a much safer and more reliable method for treating extreme tall stature. Introducing RSA as a tool for follow up after physeodesis has made this procedure much safer.

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Molecular imaging of the hip – exploring the path from DDH to OA

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Background: In Malmö, screening for developmental dysplasia of the hip (DDH) has been in use since 1956. There is a general assumption that DDH in infancy is related to hip dysplasia in adulthood, but the link is far from understood.

Hip dysplasia, characterized by a steep acetabulum with undercoverage of the femoral head, is a major cause of osteoarthritis (OA). In order to detect early signs of OA, sensitive diagnostic tools are needed. Delayed Gadolinium-Enhanced MRI of Cartilage (dGEMRIC) is a non-invasive technique to study joint cartilage integrity, in particular the cartilage glycosaminoglycan (GAG) content. The method has been developed by our group since the late 1990’s.

In dGEMRIC, the negatively charged contrast medium (Gd-DTPA²⁻) is given intravenously and distributes in the cartilage in an inverse relationship to the amount of negatively charged GAGs, which are lost early in OA. Because Gd-DTPA²⁻ shortens the longitudinal relaxation time (T1), T1 in the presence of Gd-DTPA²⁻ (usually referred to as the dGEMRIC index) correlates to the cartilage GAG content.

Figure 1: Hips with neonatal dislocation had a higher mean acetabular index than control hips in spite of early treatment.
**Project and preliminary results:** In a first radiographic evaluation of 246 children at age 1 year, the acetabular index (a measure of hip dysplasia) was significantly higher in neonatally dislocated hips than in stable hips (see figure). This indicates that a dislocatable hip does not normalize within one year, despite adequate diagnosis and treatment. Future studies will include examination of adult patients who were dysplastic at the 1-year radiographic control to evaluate any persisting radiographic abnormalities and early degenerative cartilage changes. The follow-up will include dGEMRIC, radiographic measures and clinical scores.

**Aim:** The purpose of this project is a longitudinal follow-up of patients who were diagnosed with hip dislocation neonatally. Since early treatment has lowered the rate of late presenting DDH by factor 10, the patients diagnosed early probably constitute the majority of DDH patients. There is one Norwegian study indicating that even such patients have a more than doubled risk of later total hip replacement. However, they are a much less studied group than the more serious (but less common) late diagnosed DDH patients.

**Significance:** OA is the most common joint disease with an economical burden for society that is second only to cardiovascular diseases. Hip dysplasia is a major cause of early hip OA. DDH is generally associated with hip dysplasia but very little is known about the longitudinal relationship. Our research group has a unique possibility to address this issue due to the DDH register since 1956, including radiographs, and a new sensitive method to detect early cartilage changes, dGEMRIC.

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Rheumatoid surgery

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**Background:** Despite improvements in the medical treatment of rheumatoid disorders, that have reduced the need for rheumatoid surgery, there are still many rheumatoid specific orthopedic problems to be addressed. The new biological antirheumatic drugs modulate the immune system, but it is still unclear if their use affects the incidence of infection in conjunction with orthopedic surgery.

**Project:** a) Since 2006 patients receiving biological antirheumatic drugs have not paused their medication when undergoing orthopedic surgery at the rheumatoid unit of the department of orthopedics at Skåne University hospital. The incidence of deep infection after primary hip and knee arthroplasty among rheumatoid patients has been studied and the results are being prepared for publication. b) For the rheumatoid patient maintained movement of an arthritic ankle joint can be provided by an ankle prosthesis. The survival rate of ankle prosthesis is however still disappointing and an obvious need for improvements. A multi-center pilot study on a new ankle prosthesis is ongoing. c) Due to bone loss it is challenging to convert a joint with ankle prosthesis to an arthrodesis. Techniques to achieve bony fusion are being developed and evaluated.

**Aim:** a) To provide information on the safety of performing surgery with ongoing treatment with biological antirheumatic drugs. b) To contribute to the development of a better ankle prosthesis. c) To improve and evaluate the methods used to convert an ankle prosthesis to a fusion.

**Significance:** Better understanding of the effect of anti-rheumatic medication in conjunction with surgery will increase patient safety. Improvements in surgical methods will give better results and decreased need for reoperations.

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Knee injury & Osteoarthritis – outcomes, Risk factors and treatment options

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Background: OA is the most common reason for musculoskeletal disability in the western world and accounts for a large proportion of the global disease burden. Little is known about the pathogenesis and there is currently no disease modifying treatment available. Knee injuries often occur in sports. The most severe knee injury is the anterior cruciate ligament (ACL) tear, resulting in instability and decreased activity level in the short term and increasing the risk knee osteoarthritis (OA) in the longer term. Meniscus tear is another example of knee injury where an increased risk of subsequent OA have been determined but for other types of knee trauma diagnoses (such as patellar dislocations and contusions), a corresponding increased risk is still to be determined.

Projects: We focus our research on longitudinal cohorts of patients with knee injury:

1) The KANON-trial, a randomized controlled trial comparing the effect of surgical and non-surgical treatment strategies after ACL injury in young active adults. After two and five years, we could not identify differences in clinical outcome or the frequency of radiographic OA (5 years). We continue to follow this cohort over 10 and 15 years.

2) The Acute Knee injury Project (AKP), a prospective cohort study of 1145 patients with acute knee injury. All patients received treatment in the normal clinical setting and a 10 year follow up is planned.

3) The EDEMA-cohort, a cohort of approximately 100 individuals with acute haemarthrosis where synovial fluid was aspirated within 25 days of injury and where MRI was performed within a week of aspiration.

4) The MOHAK-trial, an ongoing trial including patients with acute knee injury. Haemarthrosis is aspirated at the time of clinical assessment; serum samples and patient reported outcomes are collected at the same time. MRI is routinely performed within one week of injury.

Aim: The general aim of our research is to identify injury related factors with possible relation to the long term outcome after injury. We cover the traumatic response of injury from a biology- (serum and synovial fluid samples), structural- (imaging) and patient perspective (patient reported outcomes) to identify early markers of OA and to identify targets of therapy to reduce the risk of OA development.

Significance: Osteoarthritis is not primarily a lethal disease, but it causes severe pain, disability, and reduced quality of life for several hundred millions of people worldwide. With the increased number of aging people, a cure for this disease is urgently needed.

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Knee function and development of knee osteoarthritis in ACL injured patients

PAUL NEUMAN

Background: Anterior cruciate ligament (ACL) injuries are common among young athletes involved in sports with knee pivoting and cutting movements. ACL injuries are functionally disabling with knee joint instability predisposing the knee to subsequent injuries and in the long-term to the early onset of osteoarthritis (OA).

Risk factors for subsequent knee OA are clearly multifactorial. It has been estimated that OA develops in approximately 0-90% of patients with ACL tears 10-20 years after the injury and so far there are no studies that prove that ACL reconstruction can minimize the future development of knee OA. According to the literature meniscal injuries and meniscectomies are well documented risk factors for the development of knee OA after ACL injury. ACL reconstruction, cartilage lesions together with bone marrow lesions, obesity, knee joint laxity, loss of knee motion, decreased muscle strength and inferior neuromuscular function need further documentation.

Project and preliminary results: We evaluate ACL injured patients activity level, subjective knee function with self-administered questionnaires like the Knee Osteoarthritis Outcome Score (KOOS), knee function evaluated with manual examination, knee radiography, contrast-enhanced MRI (dGEMRIC) and biomarkers from synovial fluid and serum after the acute injury and at follow-up during 20 years.

We show that ACL injured patients treated with early neuromuscular knee rehabilitation and activity modification without primary ACL reconstruction have a much lower prevalence of radiographic knee OA 16 years after injury than presented in the literature before. We also show that a concomitant meniscus injury treated with partial meniscectomy is the strongest risk factor for development of radiographic knee OA.

ACL injured patients, ACL reconstructed or not, have an inferior knee cartilage quality compared with controls according to indirect measurement of cartilage content of glycosaminoglycan (GAG) by dGEMRIC, both 3 weeks and 2 years after the injury.

The general decrease in cartilage quality in ACL-injured patients compared with references provide evidence for structural matrix GAG changes that seem more pronounced if a concomitant meniscal injury is present. The fact that post-traumatic OA commonly develops in ACL-injured patients, in particularly those with meniscectomy, suggests that decreased GAG content discerned by dGEMRIC may be an early biomarker for OA.

Aim: To study ACL injured cohorts in an ongoing effort to characterize patients with a good or an inferior outcome, and to find risk factors for development of knee OA.

Significance: Our results have direct clinical implications in counseling the ACL injured patient about different treatment options.

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Sarcoma Research

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Background: Soft tissue sarcoma is a heterogenous group of tumours with some 50 histopathologic types. Two thirds of the tumours are highly malignant and one third of the patients die because of metastatic disease. Novel prognostic tools, treatment-predictive markers and development of targeted therapies are needed for improved survival.

The management of soft tissue sarcoma patients in southern Sweden is since long centralized to the Sarcoma Group in Lund. A large data base on tumour characteristics, treatment and outcome and a tissue bank comprising close to 1000 patients have been created.

Project and preliminary results: We have recently 1) Validated the prognostic importance of invasive growth pattern, which is now included in the high-risk criteria in the Scandinavian Sarcoma Group prognostic SING system. 2) Described the changing clinical presentation of angiosarcoma after breast cancer treatment, reported results indicating that surgical excision of all irradiated skin and extrathoracic soft tissue may improve prognosis in secondary angiosarcoma and identified differences in gene expression patterns between primary and secondary angiosarcomas. 3) Demonstrated that simple guidelines combined with an open access tumour clinic are efficient for referral and centralisation of soft tissue sarcomas. 4) Achieved data showing that among small (≤ 5 cm) soft tissue sarcomas, which in general have a good prognosis, tumours with high risk of metastasis can be identified by the presence of tumour necrosis and vascular invasion.

Aim: We apply a translational approach to study genetic and molecular profiles, validate gene/protein expression patterns in large clinical materials, link novel markers to prognosis, and apply the findings for refined diagnostics and prognostics in soft tissue sarcomas.

The projects are carried out in collaboration between the Departments of Orthopedics¹, Oncology², Pathology³ and Clinical Genetics⁴. International collaborations include groups in Scandinavia within the Scandinavian Sarcoma Group and The Netherlands.

Significance: Soft tissue sarcomas are rare tumours where the majority are of high malignancy grade. There are many different histotypes with different genetic aberrations and clinical behaviour. Adjuvant, and sometimes neoadjuvant, treatment (chemotherapy and radiotherapy) is considered when the tumour is regarded as a "high-risk tumour". However, the effect of chemotherapy is uncertain and different histotypes are more or less prone to respond to such treatment. Better and more precise diagnostics and prognostics is needed in order to improve survival and outcome for patients with soft tissue sarcomas.

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Scientific papers 2014

DEPARTMENT OF ORTHOPEDICS, LUND UNIVERSITY

This list includes original papers, review papers and book chapters (but not abstracts) authored by members of the staff and printed in 2014.


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