25TH ANNIVERSARY

## Oslo Diabetes Research Centre







UiO **: University of Oslo** 

## ANNUAL REPORT 2014 Oslo Diabetes Research Centre



Print and layout: GRØSET™

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## STEERING COMMITTEE FOR OSLO DIABETES RESEARCH CENTRE

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KÅRE BIRKELAND Professor, MD, PhD (Vice Chairman)

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**JENS PETTER BERG** Professor, MD, PhD

**TORILD SKRIVARHAUG** Associate Professor, MD, PhD

**BETH TYRDAL / NINA MAAGAARD HOLM** Research secretary



## BOARD FOR AKER AND ULLEVÅL DIABETES RESEARCH FUND

#### **KNUT DAHL-JØRGENSEN**

Professor, MD, PhD (Chairman)

#### **KRISTIAN F. HANSSEN** Professor, MD, PhD

ERIK SCHULTZ MBA

**PER M. THORSBY** MD, PhD, Consultant

## DIABETES IN A LIFE-COURSE PERSPECTIVE

Today it is estimated that 382 million people in the world have diabetes and the number is expected to increase to 592 million in the next 20 years. In Norway, 12.000 people get diabetes every year, approximately 200.000 are diagnosed with the disease and probably around 170.000 do have it, but still do not know. Diabetes is a serious disease. In Norway three out of four have at least one complication, one of five get serious eye complications, 500 suffer from amputations and 100 need kidney transplantations every year. The risk of life threatening myocardial infarction and stroke is 2-4 fold increased compared to those without diabetes. Research to prevent these devastating complications is extremely important both for the individual and society.

Oslo Diabetes Research Center has a strong clinical basis and is the only center in Norway covering the whole life-span of diabetes, from the fetus, through childhood and adolescence to early and late adult life. This life-course approach to diabetes attempts to capture the complex influence of factors operating at different points in life integrating both early-life and adult lifestyle models into a wider framework through an extensive collaboration between our ten established research group and their internal and external collaborators. In the life-course perspective to diabetes we aim to assess how the effect of factors operating at different stages of life, from in utero to late adulthood, might accumulate and interact to determine development of diabetes and its complications later in life. Our ultimate aim is to contribute substantially to prevent diabetes - and in the meantime - its complications.

#### A 25 year history

Aker University Hospital was the leading hospital in diabetes research in Norway and the researchers wanted to improve its organization and funding. At the initiative of Knut Dahl-Jørgensen, Kristian Hanssen and Øystein Aagenæs, the Board of Aker Diabetes Research Centre was constituted December 29th 1989. In addition to the three founders Stein Vaaler and Medical Director Ragnar Andersen were members of the board. Knut Dahl-Jørgensen had addressed different possible funding sources. By New Year the center received a generous anonymous gift and the Aker Diabetes Research Foundation was established with Kristian Hanssen (Chairman), Øystein Aagenæs, Nils Norman and Erik Schultz at the Board. The capital was invested optimally and more gifts were received the next years. The Foundation should support the network of Pediatric Department, Department of Internal Medicine and the Hormone Laboratory. The official opening ceremony took place March 23rd 1990 with the Minister of Health, The Oslo Health Governor, representatives of WHO, the Norwegian Diabetes Association, The Norwegian Research Council, the University of Oslo and Directors of Aker Hospital. Beth Tyrdal was employed as administrative secretary and an office was established close to the pediatric outpatient clinic. Knut Dahl-Jørgensen was elected the first Chairman, acting the first ten years. In 1998 the Pediatric Department was moved to Ullevål University Hospital. The research center was renamed Aker and Ullevål Diabetes Research Center and Kristian Hanssen became Chairman until 2012. At the time of the large fusion of hospitals in Oslo in 2009, the center was renamed Oslo Diabetes Research Center. Knut Dahl-Jørgensen was again appointed Chairman. In spite of re-organizations and moving clinical departments, the researchers kept together and improved in quality and quantity. As we got a major funding support from the South-East Health Region, we got more partners from the Institute of Basic Medicine and Institute of Health and Society and from the National Hospital. Then all diabetes researchers in Oslo networked in one research center.

#### Progress in research from the first years

During the first years we performed clinical studies of intensified insulin treatment introducing insulin pumps and insulin pens to Norway. The Oslo Study was among the first to show that near-normoglycemia could retard the progression of early microvascular complications. The patients were followed for a long time and after 18 years we could demonstrate the relationship between hyperglycemia and degree of coronary atherosclerosis. Our results were confirmed by the DCCT/EDIC study several years later. Norway was among the first countries to generally introduce intensified treatment, and is even today a country that uses insulin pumps most frequently. We can now register that the frequency of late complications is decreasing. This is due to the early focus on epidemiological research. Now the center is fronting the epidemiologic research in Norway. Our clinical studies showed a high degree of coronary atherosclerosis in rather young type 1 diabetic patients, and that the patients had none or few symptoms.

That led to a large prospective study of early degree of atherosclerosis in children and adolescents with type 1 diabetes and healthy control peers. In a large cross sectional study of type 1 diabetic patients who have had diabetes for more than 40 years (DiaLong), new imaging studies are made. In all these studies we search for the cause and effects of high blood sugar in the development of complications. We had early focus on protein glycation as one possible mechanism, and many new assays of "Advanced Glycation Endproducts" were run at the Hormone laboratory and in international collaboration. The aim has always been to prevent late diabetic complications.

The area of epidemiologic research is strong in this center. The incidence of childhood diabetes has been followed prospectively for forty years, detecting a mean increase of approx. 3% per year. Norway has one of the highest incidences, the cause being unknown. A national quality register was established, following all children with newly diagnosed diabetes in the country. Epidemiological research may develop new hypotheses searching for possible environmental causes of type 1 diabetes. All children with diagnosed diabetes in the country take part in this and blood samples from each child are collected annually in a large research biobank, which will be a valuable resource for future research and international collaboration. Each year the clinics get a quality report, benchmarking between hospitals, and they meet annually to "learn from the best".

Genetic factors are important for the development of both type 1 and type 2 diabetes. One group is working especially to explore such factors for type 1 diabetes and other autoimmune diseases. They try to define new risk genes and study the function of these genes. They also study gene and environment interactions.

The cause of type 1 diabetes is not known, but viruses has been a hot candidate. We recently detected a low grade persistent enterovirus infection in the insulin producing islets of Langerhans in pancreas of newly diagnosed patients. These pancreatic tissue samples are now studied in fifteen different recognized international laboratories to get new knowledge of which mechanisms that destroy the insulin production. We work with Finnish collaborators to develop a vaccine. We also plan a clinical trial to study whether anti-vital treatment can maintain insulin production.

New insulin producing cells can be given by islet cell transplantation or by whole pancreas graft transplantation. This treatment steadily improves the results. The isolation and purification of donor cells and the treatment itself is optimized and improved by our team in tight international collaboration.

Diabetes in pregnancy and gestational diabetes increases the risk to mother and child. New, advanced in-vivo studies of the human placenta function and its blood perfusion and metabolite and gas exchange are ongoing. The early detection of gestational diabetes is outmost important. Some immigration groups in Norway have a notably high incidence. This has been explored for several years by our dedicated research group, showing the importance of socio-economic factors and lifestyle. Large prospective studies (STORK and STORK-Groruddalen) are ongoing, and will reveal new knowledge of the gestation and birth, as well as the long term consequences for the child.

Our center started in 1990 a research program focusing on type 2 diabetes. Stein Vaaler was instrumental to establishing a clinical research facility within the Hormone Laboratory. He recruited Reidun Sletmo as study nurse and Kåre I. Birkeland as research fellow. This laboratory has developed into a modern laboratory for metabolic studies and randomized clinical studies and is still a core facility for research in metabolism and type 2 diabetes within our center. The research in type 2 diabetes has focused on mechanistic studies of insulin resistance and secretion, clinical intervention studies and epidemiological research.

#### Increased scientific production and impact

The scientific production has increased in line with the increase in people involved. In the first years we were less than ten people, and now we are about 120.



We established six Research Groups in 2003, increasing to ten in 2014.



We had no post.doc. positions, now we have 14. We examined one Ph.D. student every second year the first ten years, now we have 7-8 a year.

The impact of our publications are steadily increasing. Last year seven of our papers were cited in the new Scientific Statement of Cardiovascular Disease in Diabetes of the American Heart Association and The American Diabetes Association.

#### **Funding activities**

In the beginning the Aker and Ullevål Diabetes Research Fund was the main contributor. This fund is still a very important contributor to cover administration and running costs, and making strategic investments. The center has the potential to attract more resources. Last year Lars Christian Steene got a large grant from the Norwegian Research Foundation. For the first time we were funded from the Novo Nordisk Foundation. We have been funded as an important research center of The South-East Health Region and we steadily attract funding for Ph.D. and postdoctoral fellowships. We are also an important international partner of the EU Seventh Framework for the study of viruses in the etiology of diabetes. We are also partners in a new Consortium INNODIA for IMI2-EU funding. In addition we get funding from the Faculty of Medicine, Health and Rehabilitation Extra Foundation and the Norwegian **Diabetes** Association.

#### 2014 - a successful year

The center is steadily improving its' international reputation. The Swedish Childhood Diabetes Fundation awarded its Nordic Johnny Ludvigsson-Prize 2014 to Knut Dahl-Jørgensen for excellent research in childhood and adolescent diabetes. The prestigious prize was handed by the Princess Victoria of Sweden.

In this year's annual report you may notice many publications in the highest ranked diabetes related scientific journals. The main achievement was the detection of a low grade persistent enterovirus infection in the insulin producing islets of Langerhans in the pancreas of patients with newly diagnosed type 1 diabetes. The results were published in Diabetes (Krogvold L et al) and the news spread rapidly worldwide by internet.

The last annual two-day "Solstua Seminar" was arranged in March and forty participants and invited speakers gathered for exchange of knowledge. One topic was vascular anatomy and function, even in the fetus, and cardiovascular disease in diabetes. In addition ten selected young fellows presented their work. This seminar is crucial for networking and collaboration within our center.

Beth Tyrdal, our dear administrative secretary, retired after 25 years of excellent duty. She was a fabulous "glue" in our center, taking care of everything and everybody. Now Nina Maagaard Holm has taken a new position as senior administrative coordinator, and she is heartly welcome. She has already updated our web-site *www.oslodiabetes.no* and we are strengthening our administration.



We need to expand and we hope now to proceed in the organizational development of the center. The fusion of our hospitals has in many ways been contradictive to our center. However a process has started within the Faculty of Medicine and the Oslo University Hospital to improve the infrastructure of the center. This will be an important step forward for diabetes research.

Knut Dahl-Jørgensen CHAIRMAN

LEADER	WORK PLACE	RESEARCH AREA	E-MAIL
Knut Dahl-Jørgensen (Chairman)	Pediatric Department, Oslo University Hospital	Diabetes in children and adolescents, etiology of type 1 diabetes, complications	knut.dahl-jorgensen@medisin. uio.no
Kåre I. Birkeland (Vice Chairman)	Department of Endocri- nology, Oslo University Hospital	Prevention and treatment of type 2 diabetes	k.i.birkeland@medisin.uio.no
Kristian F. Hanssen / Tore Julsrud Berg	Department of Endocri- nology, Oslo University Hospital	Diabetic late complications	k.f.hanssen@medisin.uio.no t.j.berg@medisin.uio.no
Geir Joner	Pediatric Department, Oslo University Hospital	Epidemiology and etiology of type 1 diabetes, complica- tions, mortality	geir.joner@medisin.uio.no
Anne Karen Jenum	Department of General Practice, University of Oslo	Diabetes and primary health issues in primary care	a.k.jenum@medisin.uio.no
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Trond Jenssen	Department of Nephrol- ogy, Oslo University Hospital	Diabetic nephropathy	trond.jenssen@rikshospitalet.no
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Jens Petter Berg	Department of Biochem- istry, Oslo University Hospital	Metabolomics of hyperglycemia	j.p.berg@medisin.uio.no
Torild Skrivarhaug	Pediatric Department, Oslo University Hospital	The Norwegian Childhood Diabetes Revgistry	torild.skrivarhaug@medisin.uio.no



## Research Group:CHILDHOOD DIABETESGroup Leader:Knut Dahl-Jørgensen

#### **Research focus**

The group has four main research areas. The first is the etiology and prevention of type 1 diabetes and autoimmune diseases, especially focusing the role of viruses and the interaction with the immune system in pancreatic and thyroid tissue samples. The last years we have succeeded in detecting a low grade persistent enterovirus infection in the insulin producing pancreatic islets of patients with newly diagnosed type 1 diabetes, and also in the thyroid of patients with newly diagnosed Graves' Disease. This indicates that viruses are important for the development of autoimmune diseases.

The second area is diabetes late complications. We have long term clinical studies on microvascular complications and the influence of glycemic control and advanced glycation. Recently the risk of early atherosclerosis in type 1 diabetes has been the focus in several of our studies, with measurement of vessel wall thickness (IVUS, IMT, MRI) and vessel elasticity, and biochemical markers, as well as clinical data and risk factors. In our large, nationwide clinical studies, now as part of the Childhood Diabetes Registry, we focus on important issues as intensified insulin treatment and pumps, diabetic nephropathy, diet, physical activity, quality of life and psychosocial problems and eating disturbances.

#### Projects

## Etiology and prevention of type 1 diabetes and autoimmune diseases:

- 1. Diabetes Virus Detection Project
- 2. Genetic studies of the importance of copy-number polymorphism in the development of type 1 diabetes.
- 3. Viruses, genetics and autoimmunity in thyroiditis. A biopsy study.

#### **Diabetes late complications:**

- 4. Atherosclerosis in Childhood Diabetes
- 5. Long term vascular changes in type 1 diabetes –

Clinical aspects and biological markers – 30 years follow-up of the Oslo Study

- 6. Advanced glycation of proteins and vascular complications in childhood diabetes
- 7. Diabetic nephropathy: Hypertension and microalbuminuria in Norwegian children with type 1 diabetes

#### **Clinical diabetes:**

- 8. Collaboration with the Norwegian Childhood Diabetes Registry. A nationwide prospective population-based study for research and quality improvement by means of benchmarking.
- 9. Dietary intake, meal pattern and physical activity in children and adolescents with type 1 diabetes
- 10. Diabetes in body and mind. The theory of the specific psychological processes in type 1 diabetes.
- 11. Children and adolescents with diabetes present state and future possibilities - A population-based study of factors affecting competences and treatment results in children and adolescents with Type 1 diabetes.
- 12. Eating disturbances in childhood diabetes.
- Childhood diabetes and celiac disease a population based study

#### Obesity and type 2 diabetes:

14. Pathways contributing to childhood weight development and overweight in Norway. Sub-study of The Mother and Child National Cohort.

#### Achievements 2014

Detection of a low grade persistent enterovirus infection in the insulin producing islets of Langerhans at diagnosis of type 1 diabetes.

#### Ambitions 2015-2016

Start a randomized controlled trial of antiviral treatment in newly diagnosed type 1 diabetes patients aiming to maintain and restore endogenous insulin production.



KNUT DAHL-JØRGENSEN

### **GROUP MEMBERS**

**KNUT DAHL-JØRGENSEN** Professor, MD, PhD

LARS KROGVOLD MD, Pediatrician, PhD student

MARTIN HEIER MD, Pediatrician, PhD student

LINE WISTING Master Degree Psychology, PhD student

**HANNA DIS MARGEIRSDOTTIR** MD, PhD, Pediatrician, post doc

**JAKOB LARSEN** MD, PhD, Pediatrician, post doc

**DAG HELGE FRØISLAND** MD, PhD, Pediatrician, post doc

**SARA HAMMERSTAD** MD, PhD, Endocrinologist, post doc

**UNNI METTE KØPP** MD, PhD, Pediatrician, post doc

**SIV JANNE KUMMERNES** R.N. Diabetes specialist nurse

INGVILD ELLINGSRUD

MARIE D. TONGA

HANS JACOB BANGSTAD Professor, MD, PhD

**JON HAUG** Dr.Philos, clinical psychologist

**KARI ANNE SVEEN** MD, physician (together with Kristian Hanssens Group)





KÅRE I. BIRKELAND

## Research Group:TYPE 2 DIABETES AND METABOLISMGroup Leader:Kåre I. Birkeland

#### Research focus

Our focus is on clinical epidemiological studies, observational studies and randomized clinical trials in subjects with obesity, prediabetes, gestational diabetes, metabolic syndrome and type 2 diabetes. We design and conduct our own studies, but also participate in international multi-center studies, both researcher initiated and studies sponsored by pharmaceutical companies, (phase II-IVstudies). Several of our researchers are also engaged in mechanistic studies and translational research in collaboration with different laboratories.

Our long-term goal is to contribute to prevention and better treatment of diseases related to overweight and physical inactivity, primarily type 2 diabetes and its complications. To achieve this, we search for etiological factors in disease development through hypothesis-generating epidemiological and observational studies and seek to test the hypotheses in mechanistic and randomized, controlled clinical trials. We aim to publish our results in internationally well recognized scientific journals and in relevant national and international meetings. We also engage ourselves in popular scientific publishing to increase knowledge about ours and others' research to the public. We collaborate closely and partly overlap with Anne Karen Jenum's group on the STORK-Groruddalen studies.

Our special focus for the coming years is epigenetics, gestational glucose metabolism and pregnancy outcomes. This project aims to characterize the influence of T2DM risk alleles and allele expression in pregnancy, combining two reasonably large cohorts of pregnant women (STORK, STORK Groruddalen; the second representing a multiethnic population). The multiethnic cohort will enable us to describe variant alleles and compare common SNP effects in different ethnic groups relative to established screening endpoints and glucose curve patterns. The influence of GDM and folate levels on methylation patterns will be analyzed in mid and late gestation. Additionally, glucose data will be analyzed using all available time points to extract additional information based on functional data analysis (FDA), which has shown to be superior in providing physiological interpretable and important temporal information, and can differentiate between women that did and did not develop GDM during pregnancy. The epigenetic modelling studies, showing activation or quiescence of the variant alleles by methylation, histone modifications etc. will be performed in close collaboration with Professor L. Groop, Lund University Diabetes Centre. As a continuation project, analysis of gene expression in placental tissue in our cohorts could allow determination and comparison of alleles with a putative relation to fetal glucose supply and neonatal fat mass, relative to the maternal metabolic changes in pregnancy. The combination of risk alleles and FDA will give novel insights in glucose responses during OGTT in healthy pregnant women, and increase knowledge of how variant genes and their expression during gestation influence pregnancy outcomes, and could guide later preventive interventions.

#### Projects

- 1. A genetic/epigenetic sub-project under the STORK and STORK-Groruddalen studies
- 2. The 4B study: The effect of bariatric surgery on bone marrow fat and glucose metabolism in subjects with type 2 diabetes and morbid obesity.
- The DIVINE-study a randomized, placebo-controlled intervention with high-dose vitamin D in type 2 diabetes.
- 4. The MyoGlu-study A controlled, intervention study of high-intensive exercise training in subjects with abnormal glucose tolerance and controls
- 5. The HypoAlert-study An observational study with hypo- and euglycaemic glucose clamp investigations of subjects with type 1 diabetes and hypoglycemia unawareness.
- 6. The ABCD (Asker and Baerum Cardiovascular Diabetes) Study
- The ORIGINALE study. An international, multi-center, follow-up, observational study of 12 000 participants in the ORIGIN study, ended in 2014
- 8. Several multi-center phase II, III and IV clinical trials in collaboration with the pharmaceutical industry.

#### Ambitions 2015-2016

- To recruit and obtain financial support for at least 1 new PhD or Post.doc each year
- To analyze and publish genetic and epigenetic results from the STORK-cohorts in collaboration with Lund Diabetes Research Center

#### **GROUP MEMBERS**

KÅRE I. BIRKELAND Profesoor, MD, PhD

**ANNE-MARIE AAS** Associate Professor, PhD

KIRSTI BJERKAN MSc, PhD student

**CECILIE WIUM** MD, PhD, consultant

CHRISTINE SOMMER PhD student

CHRISTIN W. WAAGE PhD student

ANNE-PERNILLE OFSTAD MD, PhD student

#### SEDEGHEH GHARAGZLIAN PhD

HILDE RISSTAD MD, PhD student

**SUSANNA E. HANVOLD** MSc, PhD student

**TORGRIM MIKAL LANGLEITE** MSc, PhD student

INGVILD HØGESTØL MD, PhD student

**ÅSE HALSNE** research nurse

ELINE BIRKELAND MSc, PhD student

**GØRIL VINJE** research nurse

**ANNE KAREN JENUM** Professor, MD, PhD

LINE SLETNER MD, PhD, post doc

HANNE LØVDAL GULSETH MD, PhD 15

## **Research Group:** DIABETIC LATE COMPLICATIONS **Group Leaders:** Tore Julsrud Berg and Kristian F. Hanssen

#### **Research focus**

Epidemiology and mechanisms of late complications. The mechanism by which hyperglycaemia is so deleterious to large and small blood vessels is basically unknown. A leading hypothesis is that glycation (the chemical reaction between glucose or intracellular metabolites of glucose and proteins) and subsequent rearrangements (Advanced Glycation Endproducts AGE's) is a main culprit. We have developed unique assays for different AGE's (CML, hydroimidazolone and Glucosepane) in blood. We have previously shown that serum AGE is associated with, and predicts coronary heart disease in type 2 diabetes. Furthermore, that serum AGE is associated with micro-vascular complications.

#### Projects

- 1. 30 years prospective study of late complications in type 1 diabetes (The Oslo Study)
- Prospective study: We have studied the progression of vascular changes, especially coronary vascular changes as measured by intravascular ultrasound (IVUS) and coronary angiography in the prospective Oslo Study and identified predictive parameters for this progression, especially AGE parameters.
- Specific aims: Serum and skin AGE, oxidative and inflammatory markers in relationship to status of vascular complications
- 2. Advanced glycation end products and vascular complications in childhood diabetes (together with Dahl-Jørgensen's group). Prospective study of early markers of atherosclerosis in a large group of adolescents with type 1 diabetes and controls. Study of the relationship to glycation.

3. Coronary and glomerular morphology in kidney transplants. Long term study in two contrasting groups. PI: Trond G. Jenssen together with Svein Kolset, Institute of Nutrition

Study the effect of long-term normoglycaemia vs. hyperglycemia on changes in the coronary arteries and the renal function and structure in type 1 diabetes patients. Two groups of patients with type 1 diabetes are studied, one group transplanted with a single kidney (HbA1c 8-8.5%), the other who received combined kidney-pancreas grafts and has obtained perfect normoglyacemia over the same period of time (HbA1c 4.5-5.5%). Advanced Glycation Endproducts (AGE, CM-L, hydroimidazolone) by immunohistochemistry in the glomerulus and in serum samples to test the hypothesis that glycation markers can predict the development and progression of late complication specifically early diabetic nephropathy and coronary heart disease.

- 4. DIALONG: A study of long term survivors with more than 40 years of type 1 diabetes. A large clinical and biochemical study especially on macro-vascular disease and skin and joint complications. Collaborators within the Oslo University Hospital and in Sweden, Denmark and the US.
- 5. Prospective study of pre-eclampsia in pregnant type 1 diabetes. In collaboration with research groups in Australia and US.

#### Ambitions and Achievements

One of the leading groups combining Clinical and Molecular Medicine data to understand late complications (Translational Medicine).

## GROUP MEMBERS

**TORE JULSRUD BERG** MD, PhD, Associate Professor

KRISTIAN F. HANSSEN MD, PhD Senior Professor of Medicine (Endocrinology)

**KARI ANNE SVEEN** MD, PhD

**BENTE K.KILHOVD** Consultant dr.med.

DAG FOSMARK Consultant, PhD (Department of Ophtalmology)

PETER TORJESEN PhD

MARTIN HEIER PhD student (together with Dahl-Jørgensens group)

LARS KROGVOLD PhD student (together with Dahl-Jørgensens group)

**MILIAM PEPAJ** PhD

**KRISTINE B. HOLTE** PhD student



TORE J. BERG



**KRISTIAN F. HANSSEN** 

## Research Group:

CHILDHOOD DIABETES AND DIABETES EPIDEMIOLOGY

### **Group Leader:**

Geir Joner

#### **Research focus**

Diabetes epidemiology, causes of type 1 diabetes and prevention, diabetes complications and mortality. Special emphasis on risk factors for type 1 diabetes using epidemiological approaches, including studies of infectious, dietary and other environmental factors, and potential gene-environment interactions. Research to prevent complications and premature death by studying of risk factors is also central to the group's work. The long-time goal is to reduce the incidence of type 1 diabetes in children and reduce the impact of complications of diabetes in children that already have the disease. The most important source for research is the Norwegian Childhood Diabetes Registry with biobank with > 90% of new cases of diabetes below 15 years included, the MOBA-study with biobank and other registers.

#### Projects

- The PAGE study (Prediction of Autoimmune diabetes and celiac disease in childhood by Genes and perinatal Environment): Studies of risk factors for type 1 diabetes and for celiac disease in The Norwegian Mother and Child Cohort (MOBA) linked to the Norwegian childhood diabetes registry.
- 2. Biomarkers for intrauterine environment and risk of childhood diabetes. Sera from 30 000 pregnant women linked to diabetes registry to identify women whose children later developed type 1 diabetes selected for biomarker studies, dietary and infectious.
- 3. Case-control study: Environmental factors and type 1 diabetes (gene environment interactions, major established genetic factors).
- 4. Mortality in a nationwide, population-based cohort of childhood-onset type 1 diabetes in Norway.

- 5. Classification of diabetes in children. Study of phenotypic presentation compared with genotypes, autoantibodies, c-peptid and family background.
- 6. A population based epidemiological study of diabetes complications in Norway 1973-2012. Clinical and register-based follow-up of several cohorts of subjects with t1d from childhood for complications and risk factors (project in preparation).

#### Achievements 2014

The PAGE-study started! This unique study on early risk factors with large potential has been planned for a long time. Lars Chr. Stene (Principal Investigator) received a large grant from the Norwegian Research Council (in 2013) making it possible to launch the study.

#### Three dissertations in the group:

Ingvild M. Sørensen, Magnhild P. Kolsgaard and Ingvild Eidem.

#### Ambitions 2015-2016

To present the first exciting results from the PAGEstudy on inflammation markers, vit D and metabolomics.

To publish Norwegian long-time mortality data.

To establish with sufficient funding two PhD-prosjects and recruit candidates.

**Project 1:** A population based epidemiological study of diabetes complications in Norway 1973-2014. Clinical and register-based follow-up of several cohorts of subjects with type 1 diabetes from childhood for complications and risk factors.

**Project 2:** A study of the interaction between genotypes and the immune system (immune markers) in the development of type 1 diabetes in children.



## GROUP MEMBERS

**GEIR JONER** Professor, MD, PhD

**LARS CHRISTIAN STENE** PhD, senior researcher

**TORILD SKRIVARHAUG** MD, PhD, Director, Norwegian Childhood Diabetes Registry **GERMAN TAPIA** PhD, researcher/postdoc

**VIBEKE GAGNUM** MD, PhD student

**INGVILD MENES SØRENSEN** MD, PhD

NICOLAI LUND-BLIX cand. scient, PhD student



**GEIR JONER** 

## **Research Group:** DIABETES AND RELATED HEALTH ISSUES IN PRIMARY CARE

**Group Leader:** 

Anne Karen Jenum

http://www.med.uio.no/helsam/forskning/ prosjekter/stork-groruddalen/. This project has so far developed 11 PhD projects, covering gestational diabetes and related maternal health issues, as well as neonatal body composition and fetal and childhood growth. Three PhD students using data from this cohort have finished their dissertations, and one has become a post-doc researcher in my group. Four PhD projects for general practitioners are funded by the Norwegian Medical Association, and one more has got a starting grant. Further, two more PhD students will use our data for at least one paper.

- 2. Cardiovascular disease, diabetes and ethnicity, and the quality of diabetes care in a multiethnic general practice population in Oslo. After finishing one thesis on this subject in 2013, we are now part of a multiregional Norwegian research group that has planned a much larger study in primary care and in collaborating hospitals (ROSA 4). The study will take place in five counties: Oslo and Akershus, Rogaland, Hordaland and Nordland. The study is approved by the Regional Ethics committee; data collection is funded and starts in January 2015. My group will lead the data collection in Oslo and Akershus, and have developed research protocols related to ethnicity and gender - and collaboration between primary care and hospitals. The former PhD student in this field has now got a postdoc grant to work with these issues.
- The Norwegian study in Renewing Health: Stim-3. ulating self-management in patients with type 2 diabetes mellitus through tele-care with the Few Touch application and health counseling - a randomized controlled trial, is a EU-funded project with the Norwegian study developed by Faculty of Health Sciences, Oslo and Akershus University College of Applied Sciences.

#### **Research focus**

We apply a life course approach in our research into the causation, care and prevention of type 2 diabetes and cardiovascular complications, especially when studying social and ethnic differences in health. The group members have a diverse professional background, facilitating synergies and convergence in research. Our group has two main areas of research, both originating from observations in primary care of the epidemic of diabetes, its different faces and the need to develop culturally sensitive interventions due to the demographic transition in Norway to a multiethnic country:

- 1. The Diabetes Care group working with the epidemic of type 2 diabetes, its complication and the quality of diabetes care in a multiethnic society and strategies for prevention
- 2. The Mother and Child Health group – working with the developmental origin of health and disease, not least type 2 diabetes and gestational diabetes, in a Norwegian mother, father and child multiethnic cohort and together with international collaborators.

We have performed and are involved in cross-sectional studies, cohort studies, qualitative studies, one RCT using new technology, and are involved in developing culturally sensitive interventions in primary care. Through 2014 we have included new members and collaborative partners and increased the number of subprojects.

#### Projects

1. The STORK-Groruddalen cohort study of 823 pregnant women from multiethnic women and investigates the effect of ethnicity and a range of environmental determinants on the prevalence and development of gestational diabetes (GDM), intrauterine growth and development and neonatal birth weight and anthropometric measures,



ANNE KAREN JENUM

- 4. The need for drug information about diabetes among Pakistani females in Norway. A qualitative study about the need for drug information about diabetes among Pakistani and other non-western women in Norway, originating from School of Pharmacy, Faculty of Mathematics and Natural Sciences.
- 5. Innovative Prevention Strategies for type 2 Diabetes in South Asians Living in Europe (InPreSD-SA) - a coordinated effort to target the excessive risk for T2D in South Asian populations in Europe. This multinational collaboration was initiated by Prof K Stronks, The Netherlands, AMC, Amsterdam and has collaborative partners in Edinburgh, Glasgow and Norway (Jenum and B Kumar). The aim of this project is to build on the findings of recent trials in order to accelerate knowledge production and the process of implementation of research findings by bringing together European experts. The focus will be dietary behaviour. We plan to conduct indepth analyses of the findings from relevant interventions studies with particular focus on the behavioural strategies employed (WP 4 - to be delivered by Norwegian partners). Our analysis will include consideration of the role of the environment in supporting healthy behaviour. Furthermore, we will critically evaluate dietary goals employed in current behavioural interventions. The findings will specify HOW to support South Asian people in the uptake and maintenance of a healthy diet and WHAT to focus on. This is an EU-funded three year project on the topic - Innovation to prevent and manage chronic diseases.

#### Achievements 2014

The PhD students have published 5 papers and the group leader is a co-author on two more papers in 2014, two more papers are accepted, three more papers submitted and two Master theses have been accepted.

We have achieved funding for two new PhD students, one starting grant, two new postdoc's and AK Jenum is a collaborating partner on two large international applications submitted in 2014.

#### Ambitions 2015-2016

Beside the planned progress of the PhD and postdoc projects based on the STORK Groruddalen study, AK Jenum has the responsibility for WP 4 in the EU funded InPreSD-SA study together with B Kumar, which will start soon. Further, my group, in collaboration with other national partners, is about to start data collection for a new large, multiregional Norwegian study on diabetes, with great potential for future research (ROSA 4). Together with other Nordic and Baltic collaborators, we are currently working on an application to the NordForsk. Through these and other collaborations with our partners in India, Qatar, UK, The Netherlands, Finland and other Nordic countries, our international network will be substantially strengthened in 2015-2016, facilitating more high quality research related to diabetes and ethnicity, applying a life course perspective.

### GROUP MEMBERS

**ANNE KAREN JENUM**, Professor, MD, PhD, MPH

LINE SLETNER, MD, PhD postdoc

PER LAGERLØV, pediatrician, ass. prof, PhD

ANH THI TRAN, MD, PhD, postdoc

BJØRN GJELSVIK, MD, PhD

TARJA KINNUNEN, PhD, Tampere, Finland

TORE JULSRUD BERG, ass. prof, MD, PhD

IDUNN BREKKE, PhD

BERNADETTE KUMAR, Head of NAKMI, PhD

**CHRISTINE SOMMER**, PhD student

NILAM SHAKEEL, PhD student

**ÅSE RUTH EGGEMOEN**, PhD student

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MARTHE-LISE NÆSS-ANDRESEN, PhD student

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KÅRE RØNN-RICHARDSEN, PhD student

WALAA METWALLY ALI ABDALAAH ABUELMAGD PhD student

**ANAM SHAKIL** (Master 2014)

**ANNEMETTE RISGAARD** (Master 2014)

## **Research Group:** DIABETES AND PREGNANCY **Group Leaders:** Tore Henriksen and Jens Bollerslev

#### **Research focus**

The nutritional and environmental conditions under which an individual develops from the one cell stage at conception to birth is now known to have major impact on the future health of the newborn child. Inadequate nutrition in this very early (fetal) period of life increases the risk of cardiovascular diseases, diabetes, overweight and certain cancers.

The research group "The maternal-fetal unit: Metabolic, nutritional, neuroendocrine and vascular interactions" investigates how fetal developmental conditions are formed by studying how maternal nutritional, metabolic and pathogenic factors interact with the placenta. Our research group has recently established a new sampling method that enables us to perform such investigations in a novel way.

The association between the developmental condition of the fetus and future health of the newborn is conceptualized in the term DOHaD (Developmental Origins of Health and Disease or "The Barker hypothesis"). As pointed out in recent international surveys the most effective way of preventing major cardiovascular diseases, diabetes and some forms of cancer is to optimize the developmental environment of the fetus and of early childhood. A variety of factors may influence the condition under which a fetus develops, including maternal obesity and other malnutritional states, infections, preeclampsia with placental dysfunction and exposure to toxic compounds. Worldwide maternal obesity has now become a main risk factor for pregnancy complications and fetal development. In Norway around 20% of young women (mothers to be) are now obese (BMI >30 kg/m2), and obesity has surpassed smoking as a risk factor in pregnancy.

The reason that obesity has adverse effects on pregnancy is primarily not high BMI per ce, but the profound changes in metabolism, endocrinology and inflammation that accompany adiposity. The result is obesity-induced metabolic dysfunction that has large impact on the environment in which the fetus develops. Many of the factors that may cause adverse fetal environments are preventable. However, in order to establish effective preventive measures it is fundamental to understand how a fetus may become exposed to inadequate nutrition and other adverse developmental conditions.

## Projects

#### **1.STORK-Rikshospitalet** The STORK cohort focuses of

The STORK cohort focuses on nutritional, metabolic, neuroendocrine and vascular aspects of the maternal-fetal interaction during development and growth of the fetus.

Two new projects have recently been started bases on the STORK cohort.

1. Healthy and unhealthy overweight in pregnancy: A longitudinal study of metabolic status and body mass index (BMI) in relation to pregnancy complications.

The STORK cohort enables us to analyze subgroups of obese pregnant women with respect to the relation between metabolic profiles and pregnancy outcome. This project is highly relevant in terms of selecting obese women for special pregnancy follow up.

2. Does hypercholesterolemia in pregnancy influence short- and longterm risk for cardiovascular disease in offspring by modulating markers of disease? The atherosclerotic process is driven by increased cholesterol levels in combination with an enhanced inflammatory response. Hypercholesterolemia is primarily lifestyle induced or it may be caused by a genetic disposition such as familial hypercholesterolemia (FH). Women with FH have been shown to experience very high levels of plasma lipids, in particular LDL cholesterol and they develop a prothrombotic and proinflammatory phenotype during pregnancy compared to non-hypercholesterolemic women. The significance of elevated cholesterol levels and prothrombotic "in utero" environment in relation to markers of risk in offspring has not been thoroughly investigated. The Barker hypothesis suggests that the risk of cardiovascular disease in adult life may be determined by an adverse environment before birth. This project aims to generate new knowledge about the effect of hypercholesterolemia during pregnancy and to elucidate if this is associated with increased levels of markers of risk in their offspring.



TORE HENRIKSEN

JENS BOLLERSLEV

#### 2. The STORK placenta-study

Transfer of nutrients from mother to fetus

The nutritional and environmental conditions under which an individual develops from conception to birth is now known to have major impact on the future health of the newborn child. In particular, inadequate nutrition in this very early (fetal) period of life may increase the risk of cardiovascular diseases, diabetes, overweight and certain cancers. Other environmental factors, including toxic compounds, may have long term consequences for the developing individual also in absence of structural malformation. Therefore, developmental origins of diseases have become a major conceptual framework and early life intervention is emerging as a primary objective in prevention of diseases. In fetal life placenta, which is situated between the mother and the fetus, is the organ that governs the environmental conditions of the developing fetus. Virtually all substances have to pass this "check-point" before reaching the fetus. The fundamental role of placenta in fetal development is therefore now increasingly acknowledged. Accordingly, our research group has recently developed a new method to study how maternal nutritional, metabolic and pathogenic factors interact with the placenta (The 4 vessel sampling method). The method is novel in a global perspective, and enables us to study the placenta in vivo by analyzing blood and tissue samples from arterial and venous vessels both on the maternal and fetal side.

#### Preeclampsia

Factors originating in placenta are a sine qua non in development of pregnancy induced hypertension (preeclampsia). "The 4 vessel sampling method" offers also a unique opportunity to study that placenta derived factors that induce hypertension during pregnancy. Many of these factors act on the maternal vascular endothelial cells and we have found that in women with preeclampsia, there is increased release of the antiangiogenic factor sFlt from placenta, whereas the proangiogenic factor PIGF shows decreased release.

#### 3. The Norwegian Fit for Delivery (NFFD)

Overweight and obesity have become increasingly

prevalent in Norway over the last two decades, also among women of childbearing years. It is now estimated that approximately 20% of all Norwegians are overweight. According to the North Trøndelag population study, the incidence of BMI>30 among women aged 25-30 has increased from 4% during the 1980's to 12% during the 1990's.

This is a clinical randomized clinical trial that examines whether a combination of dietary counselling and supervised exercise groups affects pregnancy outcomes, including gestational weight gain (GWG), birth weight, proportion of macrosomic newborns, and use of operative deliveries.

#### 4.SOFUS

SOFUS cohort study studies psychological stress among parents to be who have become to know that their unborn child has an developmental anomaly. The endpoints which are compared to a control group, and include psychometric and endocrine variables in the moteher and circulatory parameters in the fetus.

#### 5.Stork-3

The fetal liver is central in the energy use and metabolism of nutrients during fetal development. This project studies how blood flow in the umbilical vein (coming form placenta) is (re-)distributed between the liver and heart (ducus venosus) at different stages in the fetal development.

#### Achievments 2014

To have etasblished a, on global basis, unique and large cohort of placental blood samples from mother-fetus pairs. To have received funding for two post docs. Establishment of a close cooperation with Professor Thomas Jansson and his renowned Placenta Research Center in San Antonio, USA (from 2015 in Denver).

#### Ambitions 2015-2016

To describe for the first time in a sufficiently large cohort, mass transport of nutrients (glucose, amino acids and lipids) from mother to the fetus in vivo in the human.

**Research Group:** DIABETES AND PREGNANCY **Group Leaders:** Tore Henriksen and Jens Bollerslev

### GROUP MEMBERS AND CLOSE ASSOCIATES

TORE HENRIKSEN, Professor, MD, PhD

GUTTORM HAUGEN, Professor, MD, PhD

JENS BOLLERSLEV, Professor, MD, PhD

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TROND MICHELSEN, MD, PhD

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 $\textbf{KRISTIN GODANG,}\ MSc$ 

**THOR UELAND**, Post doc

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MARIE CECILIE PAASCHE ROLAND, MD, PhD

ANNE KAASEN, PhD, midwife

KATHRINE F FRØSLIE PhD, Dep. Of Biostatistics

GUN LISBETH OPHEIM, MD, PhD student

**ANE MOE HOLME**, MD, PhD student

MAIA BLOMHOFF, MD, PhD student

HILDEGUNN HORNE, MD, PhD student

JACOB JUEL CHRISTENSEN PhD-student, Dept. Of Nutrition





## **Research Group:** DIABETIC NEPHROPATY AND TRANSPLANTATION

Group Leader:

Trond Jenssen

TROND JENSSEN

#### **Research focus**

Molecular and morphological changes in the diabetic kidney. Cardiovascular risk factors and diabetes after organ transplantation. Pancreas and islet cell transplantation.

#### Projects

- 1. Posttransplant diabetes mellitus (PTDM). Occurrence, Pathogenesis, Risk factors, Follow-up and Treatment.
- 2. Studies on the role of glucagons in PTDM.
- 3. Studies on endothelial function and dysfunction in posttransplant diabetes, and after normalization of glycemia with pancreas transplantation.
- 4. Pancreas transplantation.
- Long-term development of diabetic and non-diabetic complications.
- Surgical and medical prerequisites for successful outcome of graft function.
- 5. Islet cell transplantation clinical outcome.
- 6. Metabolic risk factors for kidney graft and patient survival in renal transplant patients.
- Molecular changes in transplanted kidneys with emphasis on morphometry, basement membrane and proteoglycans.
- 8. Extracellular matrix changes due to hyperglycemia and inflammations in human endothelial cells.

At present 6 PhD candidates are directly involved in the projects. Parts of our work (Cardiovascular risk of PTDM, diagnostic instruments for PTDM, and longterm outcome for kidney and heart following pancreas transplantation) were in 2014 disclosed as oral presentations at the annual meeting of the American Transplantation Congress in San Francisco and at the annual meeting of the European Association for the Study of Diabetes in Vienna.

#### Achievements 2014

Ongoing research grants upheld. Group leader received an honorable award from the Norwegian Diabetes Association.

#### Ambitions 2015-2016

At least three of the candidates will finish their PhD thesis with scheduled defence within 1<sup>st</sup> quarter of 2016. Additional aim: Funding and recruitment of another 3-4 candidates for PhD thesis. New projects will focus on translational research, from bedside questions to the molecule. Especially we will focus on functional and molecular processes in the diabetic kidney before and after normoglycemia obtained by pancreas transplantation. Further studies will be undertaken on extracellular matrix changes in human endothelial cells due to high glucose levels and inflammation.

### GROUP MEMBERS

TROND JENSSEN, Professor, MD, PhD SVEIN O KOLSET, Professor TRINE M REINE, PhD, post doc JØRN PETTER LINDAHL, MD ANDERS HARTMANN, Professor, MD, PhD KARSTEN MIDTVEDT, MD, PhD IVAR EIDE, MD, PhD student FINN REINHOLT, Professor, MD, PhD OLE ØYEN, MD, PhD RUNE HORNELAND, MD, PhD student MARIT ELIZABETH VON DÜRING, PhD student ANNICKE STRANDA, PhD THEA ANINE STRØM HALDEN, PhD student ASTRI J MEEN, PhD student

## Research Group:

IMMUNOGENETICS OF AUTOIMMUNE DISEASES

### **Group Leaders:**

Benedicte A. Lie and Dag Undlien

#### Research focus

Our main research focus is to identify and characterize genetic factors that predispose to type 1 diabetes and other autoimmune diseases. We also explore the functional relevance of risk variants primarily through their influence of gene expression. The interaction between genetic and environmental risk factors, as well as their clinical relevance on disease subphenotypes and disease progression is also addressed.

#### Projects

- 1. Correlation between genetic risk variants for type 1 diabetes and other autoimmune diseases and their gene expression in the immunologically important thymus.
- 2. Characterization of the transcriptome of various immune cells in thymus.
- 3. Exploring and characterizing the HLA complex, the most important genetic contributor to type 1 diabetes and other autoimmune diseases.
- 4. Exploring genetic, epigenetic and environmental risk factors, and their interactions, in rheumatoid arthritis, an autoimmune disease sharing many risk factors with type 1 diabetes

#### Achievements 2014

- Characterized differences and similarities between HLA risk profile to type 1 diabetes and celiac diseases for individuals with both diagnosis.
- Identified autoimmune risk variants for autoimmune diseases that influence gene expression levels in thymus and pinpointed putative functional causal variants
- Mapped the primary HLA risk variants for different autoimmune diseases.
- Revealed that the HLA profiles of mixed connective tissue disease differ distinctly from the profiles of clinically related connective tissue diseases.
- Uncovered environmental risk factors for autoimmune disease.

#### Ambitions 2015-2016

- Characterize the transcriptome of various thymic immune cells, including antigen-presenting cells and different T cell subsets.
- Identify the tissue specific antigens and its alternative splice variants that are expressed in thymic epithelial cells with regard to positive and negative selection of T cells.
- Quantitatively measure the expression of different HLA alleles, including type 1 diabetes susceptibility and protective variants, in thymus.
- Explore methylation signatures of different immune cells and the influence of methotrexate treatment on the methylation patterns.

#### **GROUP MEMBERS**

BENEDICTE A. LIE, Professor, PhD

DAG UNDLIEN, Professor, MD, PhD

MARTE K. VIKEN, post doc

HANNA HELGELAND, post doc

FATEMEH KAVEH, post doc

INGVILD GABRIELSEN, PhD student

KARI GUDERUD, PhD student

LINE SUNDE, PhD student

MARTHE VESTBY, Master student

HAFSAH HUSSAIN, Master student

SIRI FLÅM, Medical Laboratory Scientist

**HELLE AKSELSEN**, Medical Laboratory Scientist







## **Research Group:** BIOMARKERS IN ENDOCRINOLOGY AND METABOLISM

### **Group Leader:**

Jens P. Berg



One of the research aims in our group is to increase our understanding of the mechanisms leading to and the metabolic consequences of increased blood glucose by studies of small molecule metabolite profiles (metabolomics). Recently initiated projects at the Hormone Laboratory study the mechanisms leading to  $\beta$ -cell dysfunction and aim to identify adequate biomarkers to assess changes in  $\beta$ -cell health and function. In addition we focus on the use, quality control, and interpretation of measures of glycemic control such as HbA1c and glycated albumin.

#### Projects

- 1. Prediction of early metabolite biomarkers in serum of autoimmune diabetes.
- 2. Biomarkers of pancreatic  $\beta$ -cell mass.
- 3. Studies of metabolic profiles in gestational diabetes.

#### Achievements 2014

Daniel Sachse's PhD based on urine metabolomic analyses of urine from the STORK-Groruddalen project studies of gestational diabetes. Proteomic analysis of vitamin D induced changes of the secretome from insulin secreting cells in culture.

#### Ambitions 2015-2016

Start of Mette E. Bornstedt's PhD project of proteomic analysis of insulin secreting cells.

Establish and perform studies of clinical samples to evaluate the performance of additional markers of glucose homeostasis such as glycated albumin, fructosamine and 1,5-anhydroglucitol.



### GROUP MEMBERS

JENS PETTER BERG Professor, MD, PhD

**PER M. THORSBY** MD, PhD, medical head of Hormone Laboratory

**DANIEL SACHSE** PhD student

**MILAIM PEPAJ** PhD

METTE E. BORNSTEDT MD

**BENEDICTE JØRGENRUD** PhD student

**MAY K BREDAHL** PhD

NINA GJERLAUGSEN MSc

**KARI JULIEN** B.Sc.

## THE NORWEGIAN CHILDHOOD DIABETES REGISTRY (NCDR)

### **Registry Leader:**

Torild Skrivarhaug

#### **Research focus**

The main research focus in this population-based, nation-wide childhood-onset diabetes registry are the following: Epidemiology in childhood-onset diabetes, focusing on incidence, prevalence, classification of childhood-onset diabetes in Norway, ethnicity and long-term complications and mortality. Quality in childhood diabetes care – a nationwide prospective population-based study for research and quality improvement by means of benchmarking. Clinical childhood diabetes, especially focusing on quality of life, diabetes treatment, co-morbidity, eating disorders and the transition from paediatric to adult diabetes care.

#### Projects

- 1. Mortality in childhood-onset type 1 diabetes (T1D).
- 2. Co-morbidity in children and adolescents with T1D. Assessing competencies and coping factors affecting functional and dysfunctional behaviour in children and adolescents with T1D.
- 3. Assessing metabolic control in the transition between pediatric and adult diabetes care, a collaboration between NCDR and the Norwegian adult diabetes registry.
- 4. How do young people with T1DM experience transition from pediatric to adult health care?
- 5. Classification of childhood-onset diabetes in Norway. To assess the epidemiology of different forms of diabetes and to classify incident cases on the basis of family history, clinical data, C-peptide, autoantibodies and HLA-genotypes.

- 6. The signification of analyzing Zn-antibodies at the diagnosis of T1D in children.
- 7. A national, population based study of the double diagnosis of celiac disease and T1D.
- 8. The incidence of severe hypoglycaemia in children with T1D in Norway and in the Nordic countries.
- 9. The PAGE study (Prediction of Autoimmune diabetes and celiac disease in childhood by Genes and perinatal Environment).
- 10. Childhood diabetes and ethnicity in Norway.

#### Achievements 2014

Three of the ongoing studies started in 2014: Sever hypoglycemia in children with T1D in Norway and in the Nordic countries, and the PAGE-study. NCDR received grant to include Disabkids in NC-DR's annual survey. Vibeke Gagnum received the ISPAD 2014 award "Best Oral presentation for Clinical Science".

#### Ambitions 2015-2016

To complete the first part of the mortality study; all-cause mortality and causes of death. To implement a national survey of life quality in children with diabetes using Disabkids, a validated PROM (Patient Reported Outcome Measure). To develop a validated PREM (Patient Reported Experience Measure) for NCDR in 2015, and to implement a national PREM survey in 2016. To publish data on incidens of severe hypoglycemia in children with T1D in Norway and the Nordic countries.

### GROUP MEMBERS

**TORILD SKRIVARHAUG** Associate Professor, MD, PhD

**GEIR JONER** Professor, MD, PhD

**KNUT DAHL-JØRGENSEN** Professor, MD, PhD

**LARS CHRISTIAN STENE** Senior researcher, Norwegian Institute for Public Health

**VIBEKE GAGNUM** MD, PhD student

**SIV JANNE KUMMERNES** R.N., diabetes nurse, masterstudent

ANN KRISTIN DRIVVOLL MSc

**DAG HELGE FRØISLAND** MD, PhD

LINE WISTING PhD student

HILDEGUNN STYVE BORKAMO MD

**PER THORSBY** MD, PhD

**HILDE BJØRNDALEN** MD, MHA

MARIA TONGA MD

DANIEL KWEKU DZIDZONU



TORILD SKRIVARHAUG

## THESIS 2014

**INGVILD EIDEM.** Pregnancy outcomes in women with type 1 diabetes in Norway, University of Oslo 2014.

#### MAGNHILD L. POLLESTAD KOLSGAARD.

Cardiometabolic risk factors and obesity treatment in children and adolescents. The Oslo Adiposity Intervention Study, University of Oslo 2014.

**MARTHE MÆHLEN.** Genetic predictors of RA susceptibility and severity, University of Oslo 2014.

MARIA CECILIE PAASCHE ROLAND. Fetal

growth: The role of maternal factors and placenta, University of Oslo 2014.

**DANIEL SACHSE.** The metabolic profile at the crossroads of pregnancy and infancy, University of Oslo 2014.

**LINE SLETNER.** Neonatal body composition. A life course approach to ethnic and socioeconomic differences in health, University of Oslo 2014.

**KARI ANNE SVEEN.** Long-term vascular and neurological complications in type 1 diabetes-clinical aspects and biological markers, University of Oslo 2014.

**INGVILD MENES SØRENSEN.** Biomarkers for intrauterine environment and risk of childhood type 1 diabetes, University of Oslo 2014.

**CECILIE WIUM.** Clinical and Pathophysiological Aspects of Type 2 Diabetes in South Asian Immigrants to Norway, University of Oslo 2014.

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#### International publications:

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#### **Other publications:**

Birkeland KI. How is the quality of the diabetes care?. Tidsskr Nor Laegeforen 2014; 134:133

Dahl SR, Thorsby PM. How to measure vitamin D status?. Tidsskr Nor Laegeforen 2014; 134:729-731

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Methi T, Thorsby PM. Why doesn't everyone develop type 2 diabetes? Tidsskr Nor Laegeforen 2014; 134:2284-2287

Pettersen KS, Jenum AK. Lav «health literacy» hos pasienter: betydning for sykepleierens helsekommunikasjon? Sykepleien Forskning 3.2014;272-280.

Stene LC, Joner G, Størdal K. Prediction of autoimmune diabetes and celiac disease in childhood by genes and perinatal environment: Design and initial aims of the PAGE study. Norsk Epidemiologi 2014; 24 (1-2): 111-119.

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#### Accepted papers:

Heier M, Margeirsdottir HD, Torjesen PA, Seljeflot I, Stensæth KH, Gaarder M, Brunborg C, Hanssen KF and Dahl-Jørgensen K. The AGE methylglyoxal-derived hydroimidazolone-1 and early signs of atherosclerosis in childhood diabetes. Accepted for publication in Diabetes and Vascular Disease Research 2015. Jan 23 [E-pub ahead of print] Krogvold L, Skog O, Sundström G, Edwin B, Buanes, T, Hanssen, K, Ludvigsson, J, Grabherr M, Korsgren O, Dahl-Jørgensen K. Function of isolated pancreatic islets from patients at onset of type 1 diabetes; Insulin secretion can be restored after some days in a non-diabetogenic environment in vitro. Results from the DiViD study. Diabetes 2015, Feb. 12. [Epub ahead of print]

Landrø NI, Jonassen R, Clark L, Haug KB, Aker M, Bø R, Berg JP, Neumeister A, Stiles TC. Serotonin transporter polymorphisms predict response inhibition in healthy volunteers. Neurosci Lett. 2015 Jan 1;584:109-12. Epub 2014 Oct 17.

Reppe S, Noer A, Grimholt RM, Halldórsson BV, Medina-Gomez C, Gautvik VT, Olstad OK, Berg JP, Datta H, Estrada K, Hofman A, Uitterlinden AG, Rivadeneira F, Lyle R, Collas P, Gautvik KM. Methylation of bone SOST, its mRNA, and serum sclerostin levels correlate strongly with fracture risk in postmenopausal women. J Bone Miner Res. 2014 Aug 22. [Epub ahead of print]

Risstad H, MD, Søvik TT, Engström M, Aasheim ET, Fagerland MW, Fagevik Olsén M, Kristinsson JA, le Roux CW, Bøhmer T, Birkeland KI, Mala T, Olbers T. Five Year Outcomes after Laparoscopic Gastric Bypass and Laparoscopic Duodenal Switch in Patients with Body Mass Index of 50 to 60 kg/m2 – A Randomized Clinical Trial. Accepted for publication.

Shakeel N, Eberhard-Gran M, Slinning K, Sletner L, Martinsen EW, Holme I, Sørum R, Jenum AK. Antenatal depression, prevalence and associated factors in a multiethnic population (in press, BMC Pregnancy and Childbirth)

Waage CW, Falk RS, Sommer C, Mørkrid K, Richardsen KR, Bærug A, Shakeel N, Birkeland KI, Jenum AK. Ethnic differences in postpartum weight retention: results from a multi-ethnic population-based cohort study (in press, BJOG).

#### Other publications/ Book chapters:

Krogvold L, Dahl-Jørgensen K. Diabeteshåndboken, ISBN: P9788205399167, Vaaler og Møinichen (red.). Kap. 5; Arv, miljø og mekanismer ved utvikling av type 1 diabetes.

#### INTERNATIONAL INVITED LECTURES / ORAL PRESENTATIONS / POSTER PRESENTATIONS:

#### **Invited lectures:**

Berg JP. The role of HbA1c in the diagnosis of diabetes mellitus: Pro. EuroLabFocus, Liverpool, UK, 9th Oct 2014.

Dahl-Jørgensen K. Cardiovascular disease outcomes in childhood onset diabetes. ISPAD Annual Meeting, Toronto, September 2014.

Dahl-Jørgensen K. What causes type 1 diabetes? Enterovirus – Results from the DiViD study. Barndiabetesfonden 25th Anniversary Conference, Linköping, October 2014.

Jenum, AK. The "Romsås in Motion" Study. A theory-based community intervention reducing inactivity in a low income multiethnic district in Oslo, Norway. First National conference on Physical activity and public health in Qatar. February 2014.

Krogvold L. The DiViD Study - Pancreatic Biopsies. nPOD annual meeting, Atlantic Beach, Jacksonville, USA. February 2014.

Stene LC. Overview of clinical studies: What have they taught us around the role of diet in susceptibility to islet autoimmunity and T1D? Maternal diet and prenatal environment. Invited presentation at the Juvenile Diabetes Research Foundation (JDRF) sponsored workshop: Role of Infant Diet in Susceptibility/Resistance to Type 1 Diabetes, Vienna Austria, September 15, 2014.

Stene LC. Type 1 diabetes epidemiology. Invited presentation on the 6th National Diabetes Symposium, 6th National Diabetes Symposium, Type 1 Diabetes in Childhood and Adolescence, November 8th, Jericho and November 9th, Gaza City, Palestine, 2014.

#### **Oral presentations:**

Eide IA, Strøm Halden TA, Åsberg A, Størset E, Hartmann A, Jenssen TG. Validity of glycated haemoglobin for diagnosing new onset diabetes after renal transplantation. World Transplant Congress, San Fransisco 2014.

Eide IA, Halden TAS, Hartmann A, Dahle DO, Åsberg A, Reisæter A, Jenssen T. Limitations of HbA1c for the diagnosis of PTDM. Eide IA, Åsberg A, Dahle DO, Jenssen T, Hartmann A. Scandinavian Transplant Congress, Copenhagen 2014.

Eide IA, Dahle DO, Åsberg A, Jenssen T, Holdås H, von Düring ME, Pihlstrøm H, Hartmann A. Arterial stiffness is associated with increased mortality in renal transplant recipients. Scandinavian Transplant Congress, Copenhagen 2014.

Eide IA, Jenssen T, Hartmann A, Reisæter A, Svensson M. The relationship between marine n-3 polyunsaturated fatty acid levels and blood lipids. Scandinavian Transplant Congress, Copenhagen 2014. Gagnum V, Stene LC, Sandvik L, Fagerland MW, Joner G, Skrivarhaug T. Mortality in a nationwide, population-based cohort of childhood-onset type 1 diabetes in Norway. Pediatric Diabetes Vol 15, Issue Suppl, 38. 40th ISPAD Annual Meeting Toronto Sept. 2014.

Hammerstad SS. Diabetes and Hepatitis C, a Twoway association. Seminar Diabetes 2014, Mount Sinai Hospital- NY. New York, USA, September 2014.

Hodnekvam ., Iversen HH, Hansen TWRH, Skrivarhaug T. How do young people with type 1 diabetes experience transitin from pediatric to adult health care? Pediatric Diabetes 2014, Vol 15(Suppl 19): 36. 40th Annual Meeting of the International Society for Pediatric and Adolescent Diabetes (ISPAD), Toronto, Canada Sept., 2014.

Krogvold L, Buanes T, Edwin B, Jahnsen F, Hanssen KF, Dahl-Jørgensen K. High Prevalence of Insulitis in Adult Patients at the Diagnosis of Human Type 1 Diabetes (T1D). Diabetes. 2014; 63(suppl 1): 175-OR. ADA 74th Scientific Sessions, San Francisco, June 2014.

Krogvold L, Edwin B, Buanes T, Frisk G, Anagandula M, Skog O, Korsgren O, Richardson SJ, Leete P, Morgan NG, Oikarinen S, Oikarinen M, Laiho JE, Hyöty, Ludvigsson J, Hanssen KF, Dahl-Jørgensen K. Low-grade enterovirus infection in the pancreatic islets of Langerhans in newly diagnosed type 1 diabetic patients. Pediatric Diabetes (2014) 15 (Suppl. 19), 29. ISPAD Annual Meeting, Toronto, September 2014.

Lindahl, JP, Reinholt F, Eide IA, Hartmann A, Øyen O, Jenssen T. In type 1 diabetic patients pancreas transplanted simultaneously with kidney preserves long-term kidney graft ultrastructure better than kidney transplantation alone. EASD Vienna 2014.

Jenssen T, Lindahl JP, Hartmann A, Endresen K, Günther A. Coronary artery disease in type 1 diabetic patients long-term after simultaneous pancreas and kidney transplantation compared with kidney transplantation alone. EASD Vienna 2014. Reine TM, Kolset, S.O. Serglycin in human endothelial cells. Nordic Proteoglycan meeting, Lund, 2014.

Von Düring ME, Jenssen TG, Bollerslev J, Godang K, Eide IA, Åsberg A, Hartmann A. Can visceral fat predict hyperglycemia after kidney transplantation? World Transplant Congress, San Fransisco 2014.

Von Düring ME, Jenssen TG, Bollerslev J, Godang K, Eide IA, Åsberg A, Hartmann A. Visceral fat and hyperglycemia predicts arterial stiffness in kidney

transplant recipients. World Transplant Congress, San Fransisco 2014.

Wisting L, Frøisland DH, Skrivarhaug T, Dahl-Jørgensen K, & Rø Ø. Disturbed Eating Behavior and Insulin Omission in Adolescents with Type 1 Diabetes. Nordic Eating Disorders Society, Stockholm, September 2014.

#### **Poster presentations:**

Birkeland KI, Lis Y, Lee S, Norheim F, Pourteymor S, Storaas T, Davanger S, Jensen J, Drevon CA, Holen T. Changes in muscle lipid stores after exercise training in subjects with prediabetes and healthy controls. EASD Vienna Austria 15-19 September 2014.

Dörje C, Mjøen G, Strøm EH, Øyen O, Jenssen T, Midtvedt K, Resæter AV. Protocol biopsy findings at 1 year in ABO incompatible renal allografts. Scandinavian Transplant Congress, Copenhagen 2014.

Eide IA, Åsberg A, TG Jenssen, Dahle DO, Hartmann A. Current smoking is associated with reduced renal graft survival. World Transplant Congress, San Fransisco 2014.

Eide IA, Åsberg A, Jenssen TG, Holdaas H, Dahle DO, von Düring ME, Hartmann A. Arterial stiffness is associated with increased mortality in renal transplant recipients. World Transplant Congress 2014, San Fransisco.

Eide IA, Jenssen T, Hartmann A, Reisæter A, Svensson M. The relationship between marine n-3 polyunsaturated fatty acid levels and artierial stiffness. Scandinavian Transplant Congress, Copenhagen 2014.

Gulseth HL, Wium C, Eriksen EF, Birkeland KI. The Effect of High-Dose Vitamin D Supplementation on Bone Mineral Density and Bone Turnover Markers in Subjects with Type 2 Diabetes and Hypovitaminosis D – a Randomized Controlled Trial ASBMR Houston, US 12.-15. September 2014.

Gulseth HL, Forsén L, Hoff M, Forsmo S, Langhammer A, Schei B, Midthjell K, Meyer HE. The Risk of Hip Fracture Is Increased in Subjects with Late-Onset Autoimmune Diabetes (LADA): Results from the HUNT Study ASBMR Houston, US 12.-15. September 2014.

Heier M, Margeirsdottir HD, Brunborg C, Hanssen KF, Dahl-Jørgensen K, Seljeflot I. Inflammation in childhood type 1 diabetes; influence of glycemic control. Poster at European Atherosclerosis Society, Madrid 2014. Skrivarhaug T, Drivvoll AK, Kummernes SJ, Dahl-Jørgensen K, Joner G. More children with severe diabetes ketoacidosis at onset of type 1 diabetes are vitamin D deficient - a population based, nationwide study from Norway. Pediatric Diabetes Vol 15, Issue Suppl, 38, 40th ISPAD Annual Meeting Toronto Sept. 2014.

Sommer C, Sletner L, Jenum AK, Mørkrid K, Birkeland KI. Impact of Maternal Metabolic Health on Offspring Birth Weight Abstract, poster presentation. American Diabetes Association 74th scientific sessions, June 12-17 2014, San Francisco, California, U.S.A.

Sommer C, Sletner L, Mørkrid K, Jenum AK, Birkeland KI. Maternal glucose and lipids are associated with offspring's birth weight independently of maternal BMI and weight gain – The STORK Groruddalen study. Abstract. Scandinavian Society for the Study of Diabetes 49th annual meeting, Uppsala, Sweden, May 9-11 2014.

Sveen KA, Dahl-Jørgensen K, Magyar WA, Tuzcu EM, Brekke M, Hanssen KF. Silent, advanced coronary artery disease in type 1 diabetes of forty years duration is prevalent and associated with glycaemic control, Abstract 1216 Poster session 108, EASD Conference, Vienna, September 2014.

Torbjørnsen, Astrid; Jenum, Anne Karen; Årsand, Eirik; Småstuen, Milada C; Lindberg, Inger; Tuula, Karhuula; Ribu, Lis. Long-term findings from three Scandinavian RCT studies in the European telemedicine Project RENEWING HEALTH: Self-management telehealth interventions with health counseling. 21th Annual Conference of the International Society for Quality of Life Research; Berlin , Germany, October 15-18 2014.

Von Düring E, Jenssen TG, Bollerslev J, Godang K, Eide IA, Åsberg A, Hartmann A. Can visceral fat predict hyperglycemia after kidney transplantation? Scandinavian Transplant Congress, København 2014. Von Düring E, Jenssen TG, Bollerslev J, Godang K, Eide IA, Åsberg A, Hartmann A. Arterial stiffenss and visceral fat after kidney transplantation. Scandinavian Transplant Congress, Copenhagen 2014.

Von Düring ME, Jenssen TG, Bollerslev J, Godang K, Åsberg A, Hartmann A. Differences in lipid profile and visceral fat but not in arterial stiffness in DM1- and DM2-patients after kidney transplantation. European Renal Assocation-EDTA Congress, Amsterdam 2014.

Waage CW, Falk RS, Sommer C, Mørkrid K, Richardsen KR, Bærug A, Shakeel N, Birkeland KI, Jenum AK. Immigrant women from South Asia, Middle East and Africa at increased risk of postpartum weight retention and of obesity and type 2 diabetes later in life: a multi-ethnic population based cohort study in Oslo, Norway, Abstract, poster presentation. European Association of the Study of Diabetes. September 15-19 2014. Vienna Austria.

#### NATIONAL INVITED LECTURES / ORAL PRESENTATIONS /POSTER PRESENTATIONS:

#### **Invited lectures:**

Haug J. Diabetisk slitenhet. Diabetesforum. Hedemark. Jan. 2014.

Haug J. Diabetes og psykisk helse. Diabetesforum. Vestfold, Telemark og Buskerud. Nov. 2014.

Jenum AK. MoRo-prosjektet - Mosjon på Romsås. Saturday seminar, September 13. 2014, The 200 year anniversary for The Medical Faculty, University of Oslo.

Köpp UM. Obesity – from mother to child? Obesity across nations, life span and levels of

of health care. Prevention, treatment and research.10 Year Anniversary Symposium for the Morbid Obesity Center, Vestfold Hospital Trust, Tønsberg, November 14-15 2014.

Næss-Andresen ML, Berg JP, Jenum AK. Iron deficiency and anemia during pregnancy in a multiethnic population. Oral presentation Primærmedisinsk uke okt. 2014. Abstract published in Utposten 2014.

Skrivarhaug T. The incidence of type 2 diabetes in children and adolescents in Norway. National diabetes meeting, Novo Nordisk, 13.01.2014.

Skrivarhaug T. The use of metformin in combination with insulin in type 1 diabetes. The use of GLP-1analog;does it has a function in the treatment of diabetes type 1 and type 2 in children younger than 18 years? National diabetes meeting, Novo Nordisk, 13.01.2014.

Skrivarhaug T. Diabetes team in the pediatric departments in Norway: Status? What is missing? Medisinsk fagråd, The Norwegian Diabetes Association, 03.03.2014.

Skrivarhaug T. What do we know? Why don't we reach the treatment goals? National diabetes meeting, Sanofi 03.04.2014.





Skrivarhaug T. Has the incidence in childhood onset type 1 diabetes stopped rising. The Diabetes Research Conference, The Norwegian Diabetes Association, 7.11.2014.

Skrivarhaug T: Is the incidence of type 1 diabetes in children and adolescents leveling off? The National Research Conference, The Norwegian Diabetes Association, Oslo Nov 6-7, 2014.

Stene LC. Research on risk factors for type 1 diabetes i The Nowegian Mother and Child Cohort.: The PAGE-project. Inviteted lecture Annual Meeting, The Norwegian Childhood Diabetes Study Group. Hotel Clarion Gardermoen, June 3rd, 2014.

Tran AT. Hjerte- og karsykdommer, diabetes og etnisitet. Kvaliteten av diabetesbehandling i en multi-etnisk populasjon i Oslo. Forskningsdagen, Primærmedisinsk uke (PMU). Oslo, 23.okt.

Torbjørnsen A, Jenum AK, Årsand E, Småstuen MC, Lindberg I, Karhula T, Ribu L. Quality of life and acceptability of self-management telehealth interventions in three Scandinavian RCT studies in the RE-NEWING HEALTH study. The Diabetes Association Research Conference, Gardermoen, November 2014.

Wisting L, Frøisland DH, Bang L, Natvig H, Skrivarhaug T, Dahl-Jørgensen K, Lask B, and Rø Ø. Comorbid Type 1 Diabetes and Eating Disorders - an investigation of assessment, prevalence, psychological correlates and metabolic control. Stipendiatkonferansen, Gardermoen, November 2014.

#### Oral presentation:

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