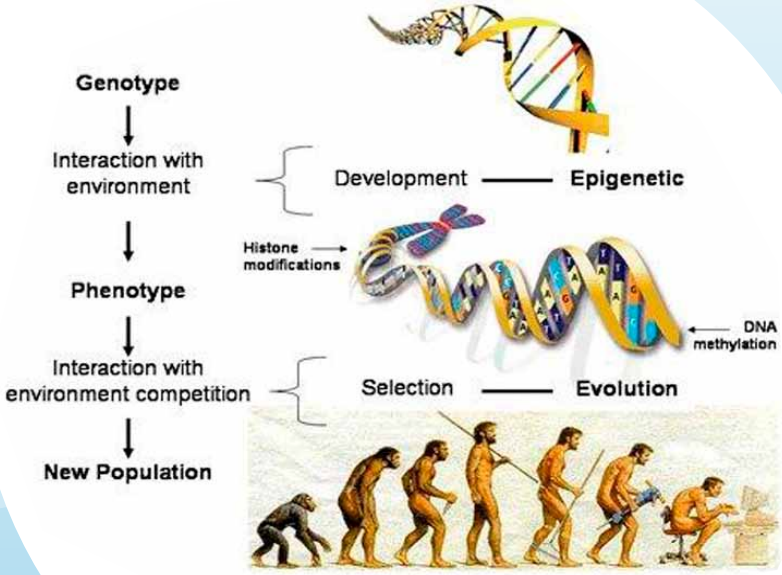
Oslo Diabetes Research Centre



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ANNUAL REPORT 2012

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Steering Committee for Oslo Diabetes Research Centre

- Kåre Birkeland, Professor dr.med.
- Knut Dahl-Jørgensen, Professor dr.med.
- Kristian F. Hanssen, Professor dr.med.
- Anne Karen Jenum, Professor dr.med.
- Geir Joner, Professor dr.med.
- Benedicte Lie, Professor dr.philos
- Dag Undlien, Professor dr.med.
- Trond G. Jenssen, Professor dr.med.
- Tore Henriksen, Professor dr.med.
- Jens Bollerslev, Professor dr.med.
- Jens Petter Berg, Professor dr.med.
- Beth Tyrdal, Research secretary

Board for Aker and Ullevål Diabetes Research Fund

- Knut Dahl-Jørgensen, Professor dr.med.
- Kristian F. Hanssen, Professor dr.med.
- Erik Schultz, MBA
- Per M. Thorsby, Consultant

Collaborating partners

Oslo University Hospital

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- Ragnheidur Bragadottir, Consultant dr.med., Ophthalmological Dep
- Magne Brekke, Consultant, Dep of Interventional Radiology
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- Helene Holm, Midwife/Diabetes nurse, Dep of Obstetrics and Gynecology
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- Ellen Jørum, Professor dr.med., Dep of Neurophysiology
- Kristin Ørstavik, PhD, Dep of Neurophysiology
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- Reidun Mosand, Diabetes nurse, Dep of Endocrinology
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- Ludvig Sollid, MD Professor, Institute of Immunology
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- Frode Lars Jahnsen, MD, PhD, Dep of Pathology
- Bjørn Edwin, MD, PhD, Dep of Surgery
- Trond Buanes, Professor, Dep of Surgery
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- Per Ole Iversen, Professor dr.med.
- Svein Olav Kolset, Professor dr.philos.
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Asker and Bærum Hospital
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- Wenche Nystad, PhD

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- Trond Markestad, Professor dr.med., Dep of Pediatrics

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- Marit Graue, PhD, Assoc. Professor

University of Northern Norway
- Svein Ivar Mellgren, Professor dr. med., Dep of Neurology

Sunnås sykehus
- Nils Hjeltnes, Consultant dr.med.

Others
- Jacob R. Larsen, MD, PhD, Medical Director

International Collaborators
- Prof Vincent Monnier, CWRU, Cleveland, Ohio, USA
- Prof Timothy Lyons, Oklahoma University, Oklahoma, USA
- Prof Alicia Jenkins, University of Melbourne, Australia
- Prof Johnny Ludvigsson, Linköping University, Sweden
- Prof Mikael Knip, Helsinki University, Finland
- Prof Heikki Hyöty, University of Tampere, Finland
- Prof John Todd, University of Cambridge, UK
- Flemming Poicot, Jim McGuire and Jørn Nerup, Steno Diabetes Centre, Copenhagen, Denmark
- Prof John Gerich, Rochester NY, USA
- Prof Michael Stumvoll, Tübingen, Germany
- Prof Ashimina Mitrakou, Athens, Greece
- Prof Timon van Haeften, Holland
- Prof Ole Schmitz, Aarhus, Denmark
- Prof Allan Flyvbjerg, Aarhus, Denmark
- Prof Steve Chadban, Sydney, Australia
- Prof Olle Korsgren, Uppsala, Sweden
- Prof Gun Frisk, University of Uppsala, Sweden
- Prof Bart Roep, Leiden University, Holland

Diabetes research is dynamic!

We are here focusing on some few areas in our research. For a more comprehensive survey, see the individual reports from the research groups. 2012 was a satisfactory year for the Research Centre. We had three PhD. dissertations in 2012:

Hanna D. Margeirsdottir: “Atherosclerosis and childhood diabetes”. It is well known that young people with type 1 diabetes have increased risk of cardio vascular disease. Hanna investigated a large cohort of young type 1 diabetes for markers of early atherosclerosis compared to a control group of more than a hundred children!
Main Mentor: Knut Dahl-Jørgensen.

Torgeir Søvik: “Surgical Treatment of severe Obesity with laparoscopic gastric bypass and duodenal switch”. Bariatric surgery is fast becoming a tool to “treat” type 2 diabetes. It is reassuring that the surgeons are investigating the different procedures in a scientific way. Main mentor: Tom Mala.

Tone G. Valderhaug: ”New Onset diabetes after Renal transplantation”. It is well known that diabetes might develop after kidney transplantation. This study details the factors behind this development. Main mentor: Trond G. Jenssen.

The etiology of type 1 diabetes is still unknown. But recent research from Dr. Krogvold and co-workers from our research centre have unravelled several new and exciting findings on the status of biopsies of beta cells in newly discovered type 1 diabetes. Vitamin D is still interesting and we are eagerly awaiting the results of the DIVINE study from the Research Centre: A randomized controlled study on high dose vitamin D in subjects with type 2 diabetes and low serum vitamin D.

Furthermore Ingvild Sørensen and co-workers from Department of Pediatrics, OUH and National Institute of Public Health have in a recent paper in Diabetes shown that the offspring of pregnant women with serum vitamin D in the lowest quartile had more than the double risk of developing type 1 diabetes compared with the offspring of those with levels above the upper quartile. In addition, we are now seeing a more formal collaboration between the diabetes group at the National Institute of Public Health and Oslo Diabetes Research Centre. This is very important for the future!

Gestational diabetes is still a hot topic both as an entity in itself and as a predictor of future permanent diabetes. Several papers have come out from the research centre regarding insulin secretion, insulin resistance, the influence of ethnicity on outcome for babies.
See pages 9 and 10.
The proposed new criteria for gestational diabetes, (IADPSG) were turned down by a recent consensus conference organized by National Institutes of Health in the US. This makes it easier to develop strategies that both are reasonable and does not place unreasonable burden on the pregnant woman.

I was invited to give a talk at the 90 years of insulin treatment symposium in Barcelona. The discovery of insulin is really a spectacular story. The drama of scientific minds, sheer luck and personal abilities (and disabilities) came together to create a milestone in Medicine and for millions of patients with diabetes. My task at that event was to present more than 30 years of the ongoing Oslo Study as this was one of the first studies to prove the pivotal role of hyperglycemia already in the late 1980s well before the DCCT study.

Meetings:
The yearly Solstua seminar had “epigenetics and genetics of diabetes” as main theme. Epigenetics is the new buzz word in medicine. When there is something we do not understand in medicine (and there is a lot of that stuff!) wise people will nod their heads and say “it is probably due to epigenetics” and we all nod together! We had Charlotte Ling from Lund University to cover both the epigenetics of insulin secretion and pregnancy. She did this task splendidly! This year the discussion between the participants was also especially live! The venue at the seaside in Son is marvellous and we welcomed spring there

In December, we had a symposium entitled “Trends in Diabetes Research”. We were able to attract world renowned researchers like Professor Monnier from Cleveland USA who talked about the biochemical mechanisms of late complications, especially Advanced Glycation Endproducts (AGE), Professor Boulton, president of the European Association for the Study of Diabetes, who talked about his favourite theme: “The Diabetic Foot”, Professor Hans-Henrik Parving, Copenhagen “Update on Nephropathy in type 1 and type 2 Diabetes” and Professor Christian Berne from Uppsala ”Diabetes treatment in Scandinavia: Past, present and future”.

After lunch we had speakers from Oslo Diabetes Research Centre covering pregnancy, epidemiology, and etiology of type 1 diabetes and registry of children and adolescents with type 1 diabetes. The symposium also marked my formal (but not real retirement) from clinical work.

Organizational development:
We have created a more formal steering group of the nine group leaders of research. It has been difficult to bring these extremely busy researchers together on a regular basis. We have now succeeded: Sushi in a nice restaurant after working hour is the answer! We are thus able to develop a more formal organization. We hope in the future to have a common localization for the different research group. The difficult localizing situation for Endocrinology both for clinical care and research within Oslo University and the Medical Faculty has been recognized by the Dean and the Research Director. We are having a constructive dialogue with them. Hopefully, a viable plan will emerge eventually.

At the end a personal comment:
This is my last editorial of the annual report. It has been a pleasure serving as chairman of this Research Centre. Knut Dahl-Jørgensen is the new chairman and I am happy to wish him every success with developing the Research Centre.

Major Funding:
Regional Health Authority (Helse Sør-Øst), Oslo University Hospital, Medical Faculty, University of Oslo, Aker and Ullevål Research Fund, Norwegian Research Council, Health and Rehabilitation, Norwegian Diabetes Association, EU grants.

Kristian F. Hanssen
Chairman Professor dr. med

Leader	Work place	Research Area	Email
Kristian F. Hanssen (Chairman)	Department of Endocrinology, Oslo University Hospital	Diabetic late complications	k.f.hanssen@medisin.uio.no
Knut Dahl-Jørgensen (Vice-Chairman)	Pediatric Department, Oslo University Hospital	Diabetes in children and adolescents Etiology of type 1 diabetes, complications	knut.dahl-jorgensen@medisin.uio.no
Geir Joner	Pediatric Department, Oslo University Hospital	Epidemiology and etiology of type 1 diabetes, complications, mortality	geir.joner@medisin.uio.no
Benedicte Lie/ Dag Undlien	Department of Medical Genetics, Oslo University Hospital	Genetics and epigenetics of type 1 diabetes	b.a.lie@medisin.uio.no d.e.undlien@medisin.uio.no
Kåre I. Birkeland	Department of Endocrinology, Oslo University Hospital	Prevention and treatment of type 2 diabetes	k.i.birkeland@medisin.uio.no
Anne Karen Jenum	Department of General Practice, UiO	Diabetes and primary health issues win primary care	a.k.jenum@medisin.uio.no
Tore Henriksen/ Jens Bollerslev	Department of Endocrinology and Obstetrics, Oslo University Hospital,	Diabetes and pregnancy	tore.henriksen@rikshospitalet.no jens.bollerslev@rikshospitalet.no
Trond Jenssen	Department of Nephrology, Oslo University Hospital	Diabetic nephropathy	trond.jenssen@rikshospitalet.no
Jens Petter Berg	Department of Biochemistry, Oslo University Hospital	Metabolomics of hyperglycemia	j.p.berg@medisin.uio.no

Group leader: Kristian F. Hanssen

Research Group: Diabetic late complications

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).**

a. ***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.

b. ***Cross-sectional study:***
Assess both macro and micro vascular status of the patients and associate with skin (measured in Dr. Monnier's lab Cleveland, USA) and serum AGE. A number of parameters have been followed prospectively over 25 years, and I have given valuable data for our cross-sectional study (together with many groups within OUS, especially Dr. Brekke, Department of cardio-vascular radiology and Dr. Fosmark, Department of Ophthalmology).

Specific aims:

- To study cardiac events; sub endpoints will be the vessel area stenosis, significant plaque (>0.5 mm) progression both on IVUS, and coronary artery stenosis on coronary angiography.
- Serum and skin AGE, oxidative and inflammatory markers in relationship to complication status.

There are few studies that have examined long term complications and intensive diabetes treatment with such a long duration of the disease, and it is a unique opportunity to study the relationship between complications and biochemical markers of complications.

2. ***Glycation in the arterial wall:***
We are studying glycation modification in the arterial wall in atherosclerosis with and without diabetes by western analysis, immunohistochemistry and LC MS/MS (mass spectrometry). We have already discovered some modifications in the wall that might be involved in the increased propensity to atherosclerosis in diabetes.

3. ***Advanced glycation of proteins and vascular complications in childhood diabetes*** (together with Dahl-Jørgensens group):
Prospective study of early markers of atherosclerosis in a large group of adolescents with type 1 diabetes and controls and its relationship to glycation.

4. ***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%).

- To investigate proteoglycans and glycosaminoglycans which are important components of the filter network of the basement membrane.

- To explore proteoglycans (syndecan-1) and macrophage transcription factors (Id-1) in blood samples as markers of early kidney changes.
- Advanced Glycation Endproducts (AGE, CML, 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).

5. ***DIALONG:***
   A study of long term survivors with more than 40 years of type 1 diabetes. A large clinical and biochemical study in the planning process. Collaborators within Oslo University Hospital and in Sweden, Denmark and US.

Group members:
- Kari Anne Sveen, PhD student
- Bente K. Kilhovd, Consultant dr.med.
- Tore J. Berg, Consultant dr.med.
- Dag Fosmark, Consultant PhD (Department of Ophthalmology)
- Peter Torjesen, PhD
- Martin Heier, PhD student (together with Dahl-Jørgensen´s group)
- Lars Krogvold, PhD student (together with Dahl-Jørgensen´s group)
- Milaim Pepaj, PhD

Group Leader: Knut Dahl-Jørgensen

Group name: Childhood Diabetes

Research focus:
The group has four main research areas. The first is the ethiology 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 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:
Ethiology 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 (se page 13). 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
13. 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

Group members:

PhD students:

1. Hanna Dis Margeirsdottir, MD, Pediatrician
2. Lars Krogvold, MD, Pediatrician
3. Kari Anne Sveen, MD, Physician (together with Kristian Hanssen´s Group)
4. Dag Helge Frøisland, MD, Pediatrician
5. Martin Heier, MD, Pediatrician
6. Sara Hammerstad, MD, Endocrinologist
7. Unni Mette Køpp, MD, Pediatrician
8. Line Wisting, Master Degree Psychology

Master students:

1. Siv Janne Kummernes, RN, Diabetes specialist nurse
2. Ingvild Ellingsrud, MD
3. Marie D. Tonga, MD

Senior Independent Investigators:

1. Hans Jacob Bangstad, MD, PhD, Professor
2. Jon Haug, Dr.Philos, Clinical psychologist
3. Torild Skrivarhaug, MD, PhD, Norwegian Childhood Diabetes Registry

Group leader: Geir Joner

Group name: Childhood diabetes and diabetes epidemiology

Research focus:

Main focus is on diabetes epidemiology and causes of type1 diabetes and prevention. Special emphasis on studies of nutritional factors and viral infections as risk factors and the role of gene-environmental interaction in the pathogenesis of type 1 diabetes. Research to prevent complications and premature death is also central to the group's work. The purpose of our research is to reduce the morbidity and complications of diabetes in children and adolescents, and it is achieved through the study of the causes and risk factors for complications and death. The most important tool for research is the Norwegian Childhood Diabetes Registry where > 90% of new cases of diabetes below 15 years has been registered since 1989 and the biobank established in 2001.

Projects:

1. **Prediction of Autoimmune diabetes and celiac disease in childhood by Genes and perinatal Environment (PAGE):**
   Data and biological samples from The mother and child-study (Norwegian Institute of Public Health) linked to the Norwegian Childhood Diabetes registry to study the effect of genetic and non-genetic risk factors for t1d and celiac disease.

2. **A population based epidemiological study of diabetes complications, mortality and cause of death in Norway 1956-2011:**
   Clinical and register-based follow-up of several cohorts of subjects with t1d from childhood for complications and death.

Maternal infections and nutritional status during pregnancy and risk of type 1 diabetes in children – a nested population-based case-control study. Data and biobank samples from 30000 pregnant women 1992-1994 linked to the Medical Birth Defect Registry of Norway and The Norwegian Childhood Diabetes Registry.

Group members:

- Group leader: Geir Joner, MD, PhD, senior consultant, Oslo University Hospital and Professor, Faculty of Medicine, University of Oslo
- Lars Chr. Stene, PhD, senior researcher
- Torild Skrivarhaug, MD, PhD, senior consultant and Director, Norwegian Childhood Diabetes Registry
- Vibeke Gagnum, MD, consultant and research fellow
- Magnhild P. Kolsgaard, cand.scient, research fellow
- Ingvild Menes Sørensen, MD, research fellow
- Ingvild Eidem, MD, research fellow
- Siv-Janne Kummernes, registered nurse and register coordinator
- Anne-Kristin Drivvoll, statistician

Group leaders: Benedicte Lie/ Dag E. Undlien

Group name: Immunogenetics and epigenetics of autoimmune diseases

Research focus:

Our main research focus is to identify and characterize genetic factors which 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. Differences and similarities between genetic predisposition to type 1 diabetes and celiac diseases addressed in individuals with both diagnosis.
3. Interaction between genetic and environmental risk factors in rheumatoid arthritis, an autoimmune disease sharing many risk factors with type 1 diabetes.
4. Exploring and characterizing the HLA complex, the most important genetic contributor to type 1 diabetes and other autoimmune diseases.
5. Study epigenetic variations and their relevance to type 1 diabetes and other autoimmune diseases.

Group members:

- Marte K. Viken, post doc
- Hanna Helgeland, post doc
- Marthe Mæhlen, PhD student
- Ingvild Gabrielsen, PhD student
- Yngvild Storlykken, Master student
- Maria Dehli Vigeland, Master student
- Siri Flåm, Medical Laboratory Scientist

Group leader: Kåre I. Birkeland

Group name: Type 2 diabetes and metabolism

Research focus:

Our main focus is on clinical epidemiological studies, observational studies and randomized clinical trials in subjects with obesity, prediabetes, metabolic syndrome and type 2 diabetes. We initiate and conduct our own studies, but participate also in international multi-center studies. These may be researcher initiated studies or clinical trials of new pharmacological agents for diabetes and related disorders (phase II-IV clinical studies) sponsored by pharmaceutical companies. 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.

Group members:

- Kåre I. Birkeland, MD, PhD, Professor II, group leader
- Anne Karen Jenum, MD, PhD, Professor at Institute for Health and Society, Department of General Practice, UiO and Professor II at University College of Oslo
- Anne-Marie Aas, PhD, Assistant Professor II, Department of Nutrition,
- Hanne Løvdal Gulseth, MD, PhD, post doc
- Erlend T. Aasheim, MD, PhD
- John Willy Haukeland, MD, PhD, consultant gastroenterologist
- Ingrid M Fange Gjelstad, PhD, post doc
- Per Medbøe Thorsby, MD, PhD
- Cecilie Wium, MD, PhD student
- Kirsti Bjerkan, PhD student
- Line Sletner, MD, PhD student

- Kjersti Mørkrid, M.Phil, PhD student
- Christine Sommer, PhD student
- Anne Pernille Ofstad, MD, PhD student
- Anh Trahn, MD, PhD student
- Torgrim Langleite, MSc, PhD student
- Susanna Hanvold, MSc, PhD student

Research nurses:
- Åse Halsne and Gøril Vinje
- Lise Marit Amlie, Bioengineer

Medical students:
Tuva Wyller, Sara K. Fidjeland, Hildegunn Grødal, Thea Drivnes, Nina Marie Aamodt, Hanna Jervell Heyerdahl

Group leader: Anne Karen Jenum

Group name: Diabetes and related health issues in primary care

Research focus:
Epidemiology, a life course approach to gestational diabetes and type 2 diabetes

Projects:
The main projects are

1. The STORK-Groruddalen cohort study of 823 pregnant women from multiethnic women 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.
   http://www.med.uio.no/helsam/forskning/prosjekter/stork-groruddalen/

2. Cardiovascular disease, diabetes and ethnicity, and the quality of diabetes care in a multiethnic general practice population in Oslo.

3. Renewing Health – Regions of Europe Working together for HEALTH – EU project including 9 of the most advanced Health regions of Europe.

Group members:
Group leader (from 2012):
Anne Karen Jenum, MD, PhD, Professor

Research fellows:
- Line Sletner
- Kjersti Mørkrid
- Christine Sommer
- Nilam Shakeel
- Åse-Ruth Eggemoen
- Christin Wiegels Waage
- Anh Thi Tran
- Astrid Torbjørnsen.

Master student:
- Anam Shakil (UiO)
- Annemette Estrup Risgaard (UMB)

Other members:
- Lis Riby PhD, Ass. Professor HIOA
- Martine Post (former master student)

Group leaders: Tore Henriksen/ Jens Bollerslev

Group name: Diabetes and Pregnancy

STORK, Rikshospitalet
STORK-Placenta, Rikshospitalet
There is accumulating evidence that the nutritional conditions under which the fetus develops (perinatal nutrition) may have long term effects on future health of the newborn, by modifying the risks of diabetes, adiposity and cardiovascular diseases.

STORK, Rikshospitalet, has for many years been the main project in the Thematic group ”Perinatal nutrition” at Faculty of Medicine, University of Oslo.

STORK-Placenta is a research project established in 2012 as an extension of the STORK project with the aim to understand more specifically the physiological and cellular mechanism behind the major findings of the STORK-project.

Both projects are included in the UiO/OUS

Research group “The maternal-fetal unit: Metabolic, nutritional, neuroendocrine and vascular interactions” (Leader:Tore Henriksen). STORK has from the beginning been a cooperative project between Department of Specialized Endocrinology, and Section of Obstetrics, Rikshospitalet, OUS.

The major findings in STORK are:
Statistically independent modifiable maternal determinants of birth weight are BMI, fasting plasma glucose and low pregestational level of physical activity. These determinants are all related to maternal nutritional and metabolic state.

Independent modifiable maternal determinants of percentage body fat at birth are BMI and fasting glucose.

These findings are in accordance with the results of large HAPO studies that were published in parallel with the STORK study.

The STORK study has in addition studied two other variables that the HAPO studies do not provide: Fetal growth (i.e. increase of fetal weight in last trimester of pregnancy) and the role of placenta in the association between maternal factors and birth weight/newborn body fat.

Independent modifiable maternal determinants of fetal growth are BMI and gestational weight gain, but not glucose.

When placenta (i.e. placental mass as a proxy of functional capacity) is introduced as a variable in any of the relations above major reductions of the effects were observed, indicating a central role of placenta in modifying the effects of maternal metabolic factors on fetal growth, weight and body composition at birth.

Closely linked to maternal BMI (adipose tissue) are inflammatory factors. The STORK study shows that besides maternal metabolic variables, inflammatory factors may independently affect birth weight, probably by modifying placental function. Given the impact of placenta maternal determinants of placental mass was studied. Several maternal metabolic factors were independent determinants of placenta mass, including BMI, gestational weight gain, total cholesterol and HDL-cholesterol. Maternal glucose was not an independent variable. Thus, maternal metabolic factors seem to affect fetal growth partly independent of placental mass (glucose), whereas others like lipids appear primarily to interfere with placenta growth.

In order to get better insight into the biological mechanisms the maternal-placental-fetal interaction a new method for studying placental function In vivo in the human was established in 2012 (STORK-Placenta). By this method, which has not previously been reported, we are able to obtain arterial and venous blood samples on both maternal and fetal side of placenta (Roland Paasche MC, Placenta, 2012; 33 (3), 224-6).

This method gives a unique opportunity to study transplacental transport of nutrients, like glucose and fatty acids, besides that release of hormones and other regulatory factors of metabolism may be determined on both maternal and fetal side of placenta.

In the same setting, biopsies of placenta villous tree (placental “membrane”), as well as omental and subcutaneous fat are obtained. Metabolic and inflammatory activity in adipose tissue may be related to placental functional parameters.

STORK-placenta is logistically very requiring because in needs to be performed in the operating theater during cesarean section. But still, 35 patients have already been included by February 2013 after starting in November 2012.

The project has been granted support (fellowship) from Helse Sørøst for 3 years.

Group members and associates of the research group ”The maternal-fetal unit: Metabolic, nutritional, neuroendocrine and vascular interactions”:

- Tore Henriksen, leder
- Jens Bollerslev
- Guttorm Haugen
- Thomas Åbyholm
- Svein Olav Kolset
- Elisabeth Qvigstad
- Bjørg Lorentzen
- Trond Michelsen
- Nanna Voldner
- Thor Ueland
- Kathrine Frey Frøslie
- Marie Cecilie Paasche Roland
- Camilla Friis
- Ane Moe Holme
- Kristin Godang

Group leader: Trond Jenssen

Group name: Diabetic Nephropathy

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

Projects:
1. New onset diabetes after transplantation (NODAT). Occurrence, Pathogenesis, Risk factors, Follow-up and Treatment. Ongoing non-sponsored intervention studies with DPP4-inhibitors. Studies on the role of glucagons in NODAT. Studies on endothelial function and dysfunction in post-transplant diabetes, and after normalization of glycemia with pancreas transplantation.
2. Pancreas transplantation. Long-term development of diabetic and non-diabetic complications.
3. Islet cell transplantation.
4. Metabolic risk factors for graft and patient survival in renal transplant patients.
5. Molecular changes in transplanted kidneys, with emphasis on diabetes, the basement membrane and proteoglycans.

At present 5 PhD candidates are directly involved in the projects. One of them is defending the thesis in 2013.

Parts of our work (follow-up of pancreas transplantation) were presented with oral presentations at the annual meetings of the American Society of Transplantation and also at the European Association for the Study of Diabetes in 2012.

Group members:
- Trond Jenssen, Professor OUS RH
- Jørn Petter Lindahl, MD, OUS RH
- Rune Horneland, MD, OUS RH
- Anders Hartmann, Professor OUS RH
- Ingrid Moss Kolseth, MD, OUS RH
- Karsten Midtvedt, MD PhD, OUS RH
- Svein O Kolset, Professor University of Oslo
- Ivar Eide, MD, OUS RH
- Trine Reine, PhD, University of Oslo
- Finn Reinholt, Professor OUS RH
- Annicke Stranda, PhD, University of Oslo
- Ole Øyen, MD PhD, OUS RH
- Thea Anine Strøm Halden, PhD student, University of Oslo

Group leader: Jens P. Berg

Group name: Biomarkers in endocrinology and metabolism

Research focus:
The research in our group aims to increase our understanding of the mechanisms leading to and the metabolic consequences of increased blood glucose by studies of small molecule metabolite profiles. Methods to detect and quantitate small molecular weight compounds (<1000 Da) in biological fluids by NMR spectroscopy and subsequent multivariate data analysis is fundamental in metabolomics. Application of these techniques have resulted in a paper describing changes in metabolite profiles in urine in pregnancy and post partum and identified increased excretion of citrate in urine from women with gestational diabetes.

In addition we focus on the use, quality control, and interpretation of measures of glycemic control such as HbA1c and glycated albumin.

Projects:
1. Studies of metabolic profiles in gestational diabetes; in collaboration with Dr. Anne Karen Jenum.
2. Head of working group for the evaluation of diagnostic use of HbA1c in Norway.

Groups members:
- Jens Petter Berg, MD, PhD, Professor
- Daniel Sachse, PhD student

Registry Leader: Torild Skrivarhaug

Name: The Norwegian Childhood Diabetes Registry (NCDR)

Research focus:
The main research focus in this population-based, nation-wide childhood-onset diabetes registry:

- 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:
Epidemiology

1. **Incidence and prevalence of childhood-onset type 1 diabetes in Norway.** This is the first time The Norwegian Prescription Database at the National Institute of Public Health and NCDR are linked with the purpose to give information about incidence of childhood onset type 1 diabetes and completeness of NCDR.
2. **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.
3. **Childhood diabetes and ethnicity in Norway.** To access the ethnic differences in T1DM in Norway and to compare the incidence of T1DM among child migrants in Norway with respect to their ethnic backgrounds or countries of origin in these regions.
4. **The signification of analyzing Zn-antibodies at the diagnosis of T1D in children.**
5. **Time trends in mortality in childhood-onset type 1 diabetes: A nationwide population based cohort study.** To evaluate absolute and relative mortality rates for childhood-onset T1D, the effects of sex and age at diagnosis, the cause of death. To examine short and long time trends in mortality. To assess socioeconomic status as a risk factor for mortality in T1D.

Clinical diabetes

6. **Co-morbidity in children and adolescents with type 1 diabetes.** This is a sub study of NCDR assessing competencies and coping; factors affecting functional and dysfunctional behaviour in children and adolescents with diabetes.
7. **A national, population based study of the double diagnosis of celiac disease and type 1 diabetes.** To assess the relationship between type 1 diabetes and celiac disease and to explore the extent of symptoms, treatment and quality of life.
8. **Ethnicity and diabetes in the Nordic countries.** This project is collaboration between the Nordic Childhood Diabetes Registries (Sweden, Denmark, Iceland and Norway). The aim is to assess if ethnicity is an independent factor influencing metabolic control in children and adolescents with type 1 diabetes residing in Nordic countries.
9. **Co-morbid diabetes and eating disorders – an exploration of prevalence, psychological correlates and diabetic control.** This project is a collaboration between NCDR and the Regional Eating Disorder Service (RASP) at Oslo University Hospital.
   1) To explore the cognitive and behavioural correlates of comorbid type 1 diabetes and eating disorders,
   2) To assess the prevalence and comorbid type 1 diabetes and eating disorders in Norway.
10. **Diabetic nephropathy.** Microalbuminuri and hypertension in Norwegian children with type 1 diabetes.
11. **Treatment in childhood type 1 diabetes.** To assess the extensiveness of treatment with insulin pump in children and adolescents in Norway and to find the predictors for successful insulin pump treatment.
12. **A global comparative study.** Implementations of guidelines in clinical practice – Benefits and challenges exemplified by international guidelines in Diabetes Mellitus in children.

Group members:

- Torild Skrivarhaug, Senior consultant dr.med., Director of the Norwegian Childhood Diabetes Registry
- Geir Joner, dr.med., Professor
- Knut Dahl-Jørgensen, Senior consultant dr.med., Professor
- Siv Janne Kummernes, RN, Diabetes nurse, Master student
- Ann Kristin Drivvoll, MSc
- Lars Christian Stene, Senior researcher, Norwegian Institute for Public Health
- Hans-Jakob Bangstad, Senior consultant, dr.med., Professor
- Per Thorsby MD, Senior consultant
- Dag Helge Frøisland, MD, PhD student
- Line Wisting, PhD student
- Vibeke Gagnum MD, Senior consultant

National collaboration:

- Hormone Laboratory, Oslo University Hospital, Aker Hospital
- Centre for Diabetes Genetics, Haukeland University Hospital
- Department of Medical Genetics, Oslo University Hospital and University of Oslo
- RASP (Regional Centre for Eating Disorders), Oslo University Hospital
- National Public Health institute, Oslo

International collaboration:

- EURODIAB
- The Nordic Childhood Diabetes Registry Study Group

Publications:

Basu A, Alaupovic P, Wu M, Jenkins AJ, Yu Y, Nankervis AJ, Hanssen KF, Scholz H, Henriksen T, Lorentzen B, Clausen T, Garg SK, Menard MK, Hammad SM, Scardo JA, Stanley JR, Dashti A, Aston CE, Lyons TJ. Plasma lipoproteins and preeclampsia in women with type 1 diabetes: A prospective study. *J Clin Endocrinol Metab* 2012 May; 97(5):1752-62.

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Some national and international presentations/ abstracts/posters:

Berg JP. Bruk av HbA1c ved diagnostisering av diabetes mellitus: Hva er nytt? Medarbeidermøte i NOKLUS. Oslo, 26. januar 2012.

Berg JP. HbA1c som diagnostisk kriterium. Årsmøtet i Norsk klinisk-kjemisk kvalitetssikring. Gardermoen, 16. februar 2012.

Berg JP. Glykerte proteiner i plasma og blodceller. Oslo Diabetes Forskningssenter. Oslo, 22. mars 2012.

Berg JP. Utfordringer med å tolke HbA1c analysert lokalt og sentralt. Nasjonalt møte for Barnediabetesregisteret. Gardermoen, 4. juni 2012.

Berg JP. HbA1c: Diagnostiske feilkilder. NOKLUS landskonferanse. Reykjavik, 14. september 2012.

Berg JP. HbA1c som diagnostisk verktøy. NOKLUS landskonferanse. Reykjavik, 14. september 2012.

Berg JP. Metabolske forandringer urin ved graviditet og svangerskapsdiabetes. Høstmøtet i Norsk Selskap for Medisinsk Biokjemi. Trondheim, 9. oktober 2012.

Berg JP. Hvordan skal vi sikre god diabetesdiagnostikk ved hjelp av HbA1c. Høstmøtet i Norsk Selskap for Medisinsk Biokjemi. Trondheim, 9. oktober 2012.

Berg JP. HbA1c til diagnostikk av diabetes – analysekrav, muligheter og begrensninger. Emnekurs i laboratoriemedisin. Primærmedisinsk uke. Oslo, 23. oktober 2012.

Berg JP. HbA1c ved diagnostikk av diabetes. Diabetesforskningskonferanse. Gardermoen, 16. november 2012.

Berg JP. Håndtering av prøver til glukosebestemmelse. Diabetesforskningskonferanse. Gardermoen, 16. november 2012.

Berg JP. HbA1c som diagnostisteringsverktøy. Roche Brukermøte i medisinsk biokjemi. Fornebu, 21. november 2012.

Berg JP. HbA1c – nytt diagnostisk verktøy. NOKLUS-kurs. Stavanger, 22. – 27. november 2012.

Berg JP. HbA1c som diagnostisk verktøy. Novo Nordisk Endokrinologimøte Vest. Bergen, 29. november 2012.

Berg JP. HbA1c som diagnostiseringsverktøy. Enklere diagnostikk. Hva betyr dette i praksis. Kveldsmøte.

Brekke I, Berg JE, Sletner L, Jenum AK. Sickness abscence in pregnancy among majority and ethnic minority workers in Norway. Abstract, Oral presentation by IB. På-tvers-konferansen 2012. Høgskolen i Oslo og Akershus, 16. januar 2012.

Dahl-Jørgensen K. Forebygging av aterosklerotisk hjertesykdom hos pasienter med type 1 diabetes. Bør vi begynne i ungdommen? Nasjonalt Diabetesmøte, Grand Hotell, Oslo. 6. september 2012.

Eggemoen ÅR. Utbredt vitamin D-mangel i enkelte etniske grupper – også blant gravide. Diabetesforskningskonferansen 15.-16. november 2012.

Frøisland DH, Graue M, Markestad T, Wenzel-Larsen T, Drivvoll AK, Skrivarhaug,T, Dahl-Jørgensen K. Health related quality of life among Norwegian children and adolescents with type 1 diabetes on intensive insulin treatment: a population based study. Oral presentation. Annual Meeting of the International Society for Pediatric and Adolescent Diabetes (ISPAD). Istanbul, October 2012. *Pediatric Diabetes* 2012, Vol 13, (Suppl 17), 37.

Frøisland DH. «Smart diabetes» - visuell læring med dagbok-apps på smarttelefon. Diabetesforskningskonferansen. Clarion Hotel Gardermoen, Oslo. 16. november 2012.

Frøisland DH, Arsand E, Skårderud F. Improving diabetes care for young people with type 1 diabetes through visual learning on mobile phones: mixed-methods study. *J Med Internet Res* 6 August 2012; 14(4):e111. doi: 10.2196/jmir.2155.

Haug J. Diabetes in body and mind: The problem of insulin omission. Invited lecture, Annual Meeting of the International Society for Pediatric and Adolescent Diabetes (ISPAD). Istanbul, October 2012.

Haug J. De spesifikke psykologiske utfordringene som er knyttet til type 1 diabetes.
Diabetesforskningskonferansen. Clarion Hotel Gardermoen, Oslo 16. november 2012.

Haug J. "Å snakke med barn og unge om vanskelige ting". Seminar Muskelsykdommer. Tromsø 17. februar 2012.

Haug J. "Psykologi og diabetes hos barn, ungdom og unge voksne". Stockholm DIP. 21. mars 2012.

Haug J. Psykologisk implikasjoner av diabetes og karbohydrat regning, Regionmøte Barnediabetes. Loka Brunn, Sverige, 2. mai 2012.

Haug J. "Diabetes in body and mind" Nordic Diabetes Meeting. Færøyene 8. juni 2012.

Haug J. "Diabetes i kropp og sinn". Hordaland Diabetesforum 10. oktober 2012.

Haug J. "Diabetes i kropp og sinn". Diabetesforbundets Landsmøte 20. oktober 2012.

Jenum AK. Helse og sykdom hos gravide i en multietnisk kontekst – årsaksforhold og forebyggingsstrategier. Abstract/Oral presentation by AKJ. På-tvers-konferansen 2012, Høgskolen i Oslo og Akershus, 16. januar 2012.

Krogvold L. Virus og type 1 diabetes – Studier av pancreas. Symposium «Trends in Diabetes Research». Rikshospitalet, Oslo, 6 December 2012.

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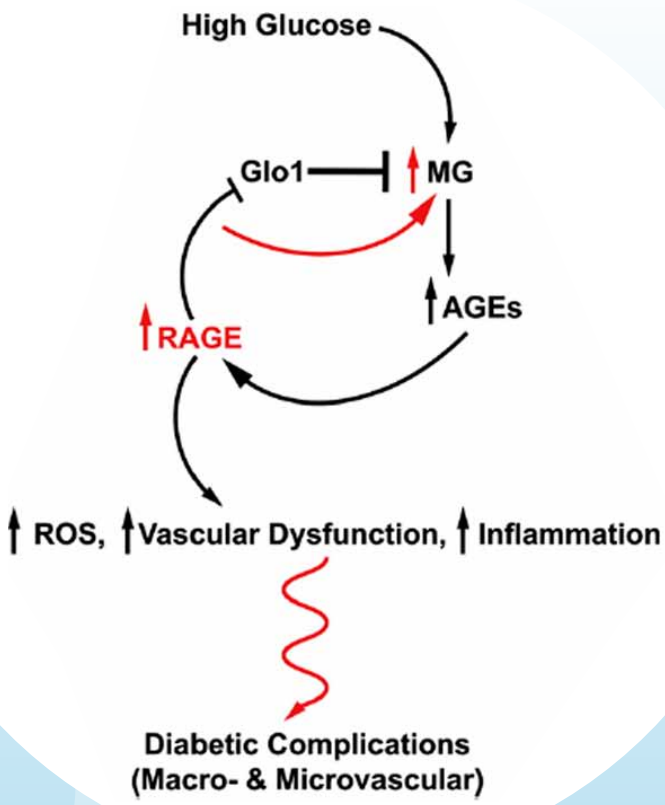

Fig. 1. RAGE – right in the middle of a vicious cycle of glycation and inflammation – potential links to diabetic complications. In hyperglycemia characteristic of types 1 and diabetes, a major result in excess production of methylglyoxal (MG). MG, though a series of subsequent reactions, may form the irreversible AGEs. When AGEs bind to their cell surface signaling receptor, a diverse set of consequences ensues – generation of oxidative stress, vascular dysfunction and inflammation – all of which synergize to trigger diabetic complications. The surprising finding that AGE levels were lower in hyperglycemic RAGE null mice led to the observation that RAGE downregulates Glo1, the chief enzyme responsible to detoxify MG. Hence, RAGE action contributes to AGE action, but, also to the perpetuatuion of AGE generation. We propose that a vicious cucle of AGE-RAGE stress is a key inciting factor in diabetes complications.