Oslo Diabetes Research Centre

Annual Report 2022

Oslo universitetssykehus

UiO : University of Oslo

NIPH
Norwegian Institute of Public Health

Oslo Diabetes Research Centre

Oslo Diabetes Research Centre is committed to diabetes research that will improve the lives of all people living with diabetes and help prevent new cases of the disease. Our aim is to make a significant contribution to knowledge about the aetiology, pathogenesis, treatment and prevention of diabetes through basic and applied research, and to apply this knowledge to the benefit of the population. An important mission is also to promote the next generation of leading diabetes researchers.

We are a non-profit, medical scientific association, founded in 1990, which unite most of the diabetes research in the Oslo area. Our centre is closely affiliated with the University of Oslo, Oslo University Hospital and the Norwegian Institute of Public Health. We seek public and private funding to our research, and are generously supported by the Aker and Ullevål Diabetes Research Fund.

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STEERING COMMITTEE

OSLO DIABETES RESEARCH CENTRE

Jens Petter Berg

Tore Julsrud Berg

Kåre I. Birkeland

Hanna Dis Margeirsdottir

Ida Mynarek

Lars Christian Stene

Line Wisting

EDITORIAL

By entering 2022, we were happy to leave most of the restrictions imposed by the pandemic behind, and finally again do our patient-encounters in the clinical projects and meet for scientific and social gatherings like our regular Thursday-meetings and annual seminar.

Some highlights from the year include a large grant from the Juvenile Diabetes Research Foundation obtained by our senior researcher Line Wisting. Together with researchers at Stanford University, Joslin Diabetes Center, and Amsterdam University Medical Centers she will investigate the effect of a particular approach named “the Diabetes Body Project” to reduce eating disorder risk factors and symptoms, eating disorder onset, glycemic control, and diabetes psychological aspects among young females with type 1 diabetes.

An example of important international collaboration during the last year is the INNODIA project, that assembles a comprehensive, complementary consortium of leading clinicians overseeing type 1 diabetes registries and large clinical trial centers, aligned with basic science experts in beta-cell pathophysiology, immunology, biomarker discovery, bioinformatics, systems biology and trial design. Prof. em. Knut Dahl-Jørgensen is our representative and driving force in this collaboration, but he is accompanied by several other researchers from our center. Another example of international collaboration is our post.doc/senior researcher Gunn Helen Moen who has a position as visiting scientist in prof. David Evans’ group at the University of Queensland, Brisbane, Australia. Thirdly, prof. Tore Julsrud Berg was a Mary K. Iacocca Senior Visiting Research Fellow/Visiting Professor at the Joslin Diabetes Center, Harvard Medical School, Boston during the autumn semester, working with the Joslin Medalist Study in the group of Dr. George King.

During the year that passed, we are proud that Mette Bornstedt, Oddrun Kristiansen, Kristina B. Slåtsve and Therese Weider, all affiliated with our center, completed their PhD theses. Congratulations!

We hosted two very interesting seminars in 2022. Our annual meeting was in the beautiful surroundings of Lysebu conference center, and included invited lectures, first by prof. Reimar Thomsen, Dep. of Clinical Epidemiology, Aarhus University Hospital, Denmark, who talked about “Changes in type 2 diabetes incidence and mortality associated with introduction of HbA1c as diagnostic option. Another was by prof. Tom Hemming Karlsen, who gave an overview of his work in the Lancet Commission on Liver Diseases, and of how to protect the next generation of Europeans against fatty liver disease.

A second highly stimulating seminar was initiated by our post.doc Gunn-Helen Moen and entitled: “Pregnancy exposures, genetics and epigenetics - short and long-term health outcomes for women and child”. Prominent invited lecturers from abroad included among others prof. David Evans (University of Queensland, Brisbane, Australia), prof. Deborah Lawlor (University of Bristol, UK), and prof. Allan Vaag (University of Copenhagen, Denmark and Lund Diabetes Center, Sweden).

We had also presentations from many of our own researchers and had a very interesting 2-day seminar discussing the importance of environment and genetics for the Developmental Origins of Health and Disease (DOHaD).

Our literature list counts 92 publications, which makes me very proud to chair a center with som many enthusiastic, clever and great researchers. Many of the articles with first-authors from our center were published in highly prestigious journals like the Lancet Diab & Endocrinol (Senior researcher Lars Chr. Stene), Diabetes (Ph.D. students Nicolas Fragoso-Bargas and Archana Sharma), Diabetologia (Senior researchers Lars Krogvold and Paz Ruiz), Cardiovasc Diabetol (PhD student Maryam Saeed), J Clin Endocrinol Metab (Senior researcher Christine Sommer) and J Intern Med (Senior researcher Kari Anne Sveen).

Prof. Anne Karen Jenum, who has been very productive in designing and conducting big studies with public health impact like the MoRO and the STORK-Groruddalen studies, chose to step down and enter status as prof. emerita this year. We thank you for your great engagement in our center and in diabetes research, and trust that many of your collaborators will bring the work further, most probably still for many years in close collaboration with you.

Finally, I want to express my sincere thanks to Petra Susanne Hedberg who served as our administrative co-ordinator while Nina Maagaard Holm was in maternity leave. You rapidly picked up the necessary knowledge about our center and helped us a lot, Petra, thanks! And I am very glad to welcome Nina back; you are invaluable to the center, helping us to work together, you maintain the overview and keep track of all the details!

I want to thank and acknowledge all our collaborators in Norway and internationally, our sponsors, and in particular, we value the close collaboration with and continuous support from the Norwegian Diabetes Association. We will also thank all the participants in our clinical studies for their enthusiasm, sharing their time and support to our efforts that we ultimately hope will improve prediction, prevention and treatment for diabetes.

Oslo June, 2023

Kåre I. Birkeland
Chair

PRIMARY INVESTIGATORS


Anne-Marie Aas


Tore Julsrud Berg


Kåre I. Birkeland


Esben Selmer Buhl


Knut Dahl-Jørgensen


Trond Geir Jenssen


Geir Joner


Svein Olav Kolset


Lars Krogvold


Tove Lekva


Benedicte A. Lie


Hanna Dis Margeirsdottir


Gunn-Helen Moen


Anne Pernille Ofstad


Elisabeth Qvigstad


Hanne Scholz


Torild Skrivarhaug


Line Sletner


Christine Sommer


Lars Christian Mørch Stene


Kari Anne Sveen


Per M. Thorsby


Line Wisting


Christin Wiegels Waage

PROJECT REPORTS

PI: ANNE-MARIE AAS

DIACHIEVE - AN E-HEALTH LIFESTYLE PROGRAM FOR IMPROVED SELF-MANAGEMENT, PREVENTION AND REMISSION OF TYPE 2 DIABETES

Primary Investigator: Anne-Marie Aas, Associate Professor, PhD

Background: Recent evidence suggest that T2D may be preventable and reversible if intensified lifestyle measures are implemented successfully. However, whether durable effects can be obtained in a large, national, population-based cohort, is not known. Furthermore, limited resources are allocated to preventive initiatives in primary care in Norway. Emerging evidence demonstrates the benefit of telemedicine and internet-based services for diabetes prevention and the management of T2D.

Aim: We will develop an effective, comprehensive and secure e-health program to guide and support people with T2D to obtain a healthy lifestyle and weight, ensuring secure and easy communication between participants in the program and health care providers or lifestyle coaches. The program will be designed in close collaboration with people with T2D, Primary Health care and the health-tech industry. We will perform a randomized controlled trial of lifestyle intervention with or without support of the e-health program to assess whether the program increases remission of T2D.

News from 2022
In 2022 we have started a qualitative pre-study, DiaMestring, where we are investigating user needs and preferences for an e-health program through focus group interviews with patients with T2D (1). Several focus group meetings, feasibility studies, and tests will be made throughout the preparation phase in 2023-24, before the RCT starts in 2025, to ensure the e-health program is user-friendly, safe, motivational, and perceived as useful for all participating stakeholders. Our industry partner Abel Technologies has already developed a mobile application for lifestyle intervention and digital follow-up in general, and our technical research partner at the University of Tromsø has experience from designing several health apps, whereof the previous "Diabetes Diary" app is strongly related to our aims in this project.

Based on previous diabetes and self-management studies from our project group, and results from the qualitative pre-study so far, we plan that the e-health program will include:

1) an educational digital course module that can be tailored to the users' individual needs and interactive webinars accessible through the program, hosted by health specialists.
2) individual digital coaching by trained health care personnel through video conference tools, chat, and phone.
3) A mobile phone-based motivational self-management app. This app will offer the user relevant data and information from sensors and devices according to the users' needs and preferences (physical activity and sleep sensors, weight scales, blood glucose monitors, etc.), as well as easy ways for recording dietary intake, and other parameters.

We are currently seeking funding to complete the development of the e-health program and to test it in a nationwide RCT in collaboration with The Norwegian Primary Care Research Network (Praksisnett).

Co-investigators/participants:
Kåre I. Birkeland, Line Wisting, Kirsti Bjerkan

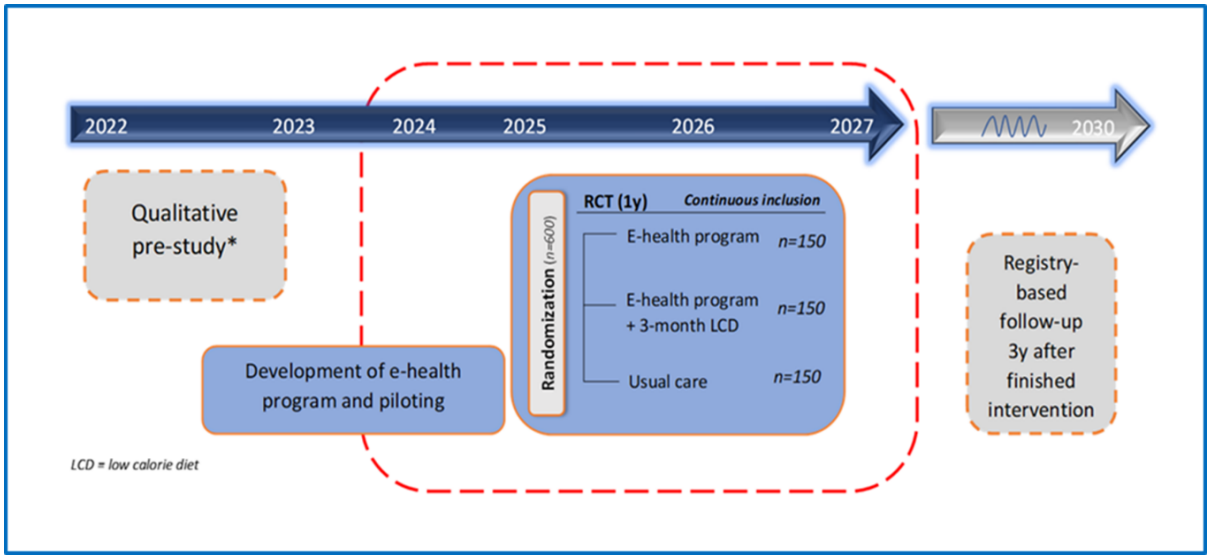
External collaborators:
University of Tromsø: Professor Eirik Årsand, Researcher Tina Rishaug, Professor Gunnar Hartvigsen, Associate Professor André Henriksen
Abel Technologies AS: Simon Laugsand, Rolf-Harald Haugen, Jorid Degerstrøm, Håkon Laugsand
The Norwegian Diabetes Association: Ragnhild Gjevre
Municipal health services: Dietitians Cathrine

Borchsenius (Bærum Municipality) and Trude Backer Mortensen (Nordre Follo M.) and GP Ståle Sagabråten (Nesbyen M.).

Scientific advisory board:
Professor Michael Lean, University of Glasgow, UK
Professors Ole Heljesen and Morten Hasselstrøm Jensen, University of Ålborg/ Steno Diabetes Center North Denmark, Denmark
Professor Rønnaug Ødegård and Ingrid Følling at Regional center of obesity research and innovation (ObeCe), NTNU, Trondheim
OsloMet: Professor Milada Cvancarova Småstuen, Statistician

Publications 2022:
Rishaug T, Henriksen A, **Aas A-M,** Hartvigsen G, Birkeland KI, Årsand E, editors. Designing an e-Health Program for Lifestyle Changes in Diabetes Care A Qualitative Pre-Study in Norway. The 18th Scandinavian Conference on Health Informatics; 2022; Tromsø: Linköping Electronic Conference Proceedings.

Massara P, Zurbau A, Glenn AJ, Chiavaroli L, Khan TA, Viguiliouk E, Mejia SB, Comelli EM, Chen V, Schwab U, Risérus U, Uusitupa M, **Aas AM**, Hermansen K, Thorsdottir I, Rahelić D, Kahleová H, Salas-Salvadó J, Kendall CWC, Sievenpiper JL. Nordic dietary patterns and cardiometabolic outcomes: a systematic review and meta-analysis of prospective cohort studies and randomised controlled trials. Diabetologia. 2022 Dec;65(12):2011-2031. doi: 10.1007/s00125-022-05760-z. Epub 2022 Aug 26. PMID: 36008559; PMCID: PMC9630197.



PI: TORE JULSRUD BERG

THE DIALONG STUDY - THE STATUS OF LONG-TERM SURVIORS OF TYPE 1 DIABETES

Primary Investigator: Tore Julsrud Berg, Professor, MD, PhD

Aims:
Long term follow up of patients with type 1 diabetes for more than 45 years. Cross-sectional study of 103 patients with type 1 diabetes and 75 control subjects. Study of glycaemic burden, diabetic macrovascular and non-vascular late complications.

Methods:
Coronary CT angiography, gene chip microarray analysis and Quality of Life measures, GCMS measurements of AGEs in skin collagen, serum AGE inflammatory markers and teleomeres and GWAS, mRNA expression of fat cells, metabolomics and GWAS.

News from 2022:
Tore Julsrud Berg has in the autumn semester been a Mary K. Iacocca Senior Visiting Research Fellow/Visiting Professor at the Joslin Diabetes Center, Harvard Medical School, Boston working with the Joslin Medalist Study in the group of Dr. George King.
Marte Narum MD has started as a PhD student on a grant given from the Norwegian South-East Health Authority named: «Discovering success factors for surviving with type 1 diabetes for more than 50 years without coronary artery disease. The Dialong study»

Co-investigators/participants:
Kari Anne Sveen
Kristine Bech Holte
Anne Karin Molvær
Marte Narum

External collaborators:
Marjolein M Iversen
Ingebjørg Seljeflot
Jannicke Igland
Mark Peyrot
Grethe Tell
Valeriya Lyssenko
Sverre Aukrust
Ragnhild Helseth
Trine Baur Opstad

Publications 2022:
Molvaer AK, Iversen MM, Igland J, Peyrot M, Tell GS, Holte KB, Monnier VM, Seljeflot I, Berg TJ. Metabolic predictors of pain, fatigue, depression and quality of life in people with long-term type 1 diabetes-the Dialong study. Diabet Med. 2023 Mar;40(3):e15009. doi: 10.1111/dme.15009. Epub 2022 Nov 29.

Aukrust SG, Holte KB, Opstad TB, Seljeflot I, Berg TJ, Helseth R NETosis in Long-Term Type 1 Diabetes Mellitus and Its Link to Coronary Artery Disease. Front Immunol. 2022 Jan 5;12:799539.

THE ROSA 4 SALTEN STUDY

Primary Investigator: Tore Julsrud Berg, Professor, MD, PhD

Project description
Sub-project of the ROSA 4 study investigating the prevalence of diagnose type 2 diabetes in the Salten municipalities, the interaction between primary and specialist care of these patients in Salten and the association between socioeconomic factors and vascular complications.

News from 2022:
- Of people with type 2 diabetes in Salten 16% were treated in specialist care. They had higher HbA_{1c} and more vascular complications. The use of a structured diabetes form (Noklus diabetes) and diabetes nurses seem to support type 2 diabetes follow-up in primary care.

- Kristina B. Slåtsve defended her PhD titled "Prevalence, vascular complications, and level of health care treatment in individuals with type 2 and type 1 diabetes mellitus" at the University of Tromsø 04.10.22 with Tore Julsrud Berg as the main supervisor https://uit.no/tavla/artikkel/788716/disputas_cand_med_kristina_barbara_slatsve

Co-investigators/participants:
PhD-student Kristina B. Slåtsve
Prof. Anne Karen Jenum
Prof. Knut Tore Lappegård
Dr Tor Claudi

External collaborators:
The ROSA 4 co-workers

Publications 2022:
Slåtsve KB, Claudi T, Lappegård KT, Jenum AK, Larsen M, Cooper JG, Sandberg S, Julsrud Berg T. The total prevalence of diagnosed diabetes and the quality of diabetes care for the adult population in Salten, Norway. Scand J Public Health. 2022 Mar;50(2):161-171.

Slåtsve KB, Claudi T, Lappegård KT, Jenum AK, Larsen M, Nøkleby K, Tibballs K, Cooper JG, Sandberg S, Buhl ES, Løvaas KF, Berg TJ. Level of education is associated with coronary heart disease and chronic kidney disease in individuals with type 2 diabetes: a population-based study. BMJ Open Diabetes Res Care. 2022 Sep;10(5): e002867.

PI: KÅRE I. BIRKELAND

DAPHNE - A RETROSPECTIVE NATIONWIDE COHORT STUDY TO INVESTIGATE THE TREATMENT OF DIABETES IN ADULTS IN NORWAY

Primary investigator: Kåre I. Birkeland, Professor, MD, PhD

Background/Rationale: The prevalence of diabetes has been increasing dramatically during the last 50 years, and although no exact number is available, it is estimated that there are approximately 350 000 patients living with diabetes in Norway. Data from the Norwegian prescription registry shows that 170,000 people used anti-diabetic drugs in 2014. A range of new therapeutic modalities have been introduced on the market in the recent years.

Research question and objectives: The purpose is to explore treatment of diabetic patients in Norway, especially their use of glucose lowering drugs and to elucidate the patient characteristics for treatment choices as well as the progression of the disease in terms of comorbidities, diabetic complications and drug treatments.

Study design: Descriptive retrospective study using nationwide data from the Norwegian National Registers.

Study setting and population: The study population consists of patients over the age of 18 years with a diabetes diagnosis or a prescription dispensed for use of any blood glucose-lowering drugs.

Data sources: The source population will be identified from the Population Registry (PR) (Statistics Norway), the Norwegian Patient Registry (NPR) or a prescription dispensed of any blood glucose-lowering drugs from the Norwegian Prescription Database (NorPD). Follow-up information will be requested from NPR, NorPD as well as the Norwegian Cause of Death Register (NCoDR) (2004-2014).

Exposure(s): Glucose lowering treatments

Outcome(s): Patient characteristics (age, gender), co-morbidities (e.g. CVD, GI, cancer), diabetic complications (e.g. nephropathy and neuropathy), mortality, drug utilisation patterns.

News from 2022:
This study uses information collected in national health registers in Norway: The Norwegian Patient Register, the National Prescription Database and The Causes of Death Register. The Regional Ethics Committee has approved exemption from individual informed consent for the studies. In 2022 we have conducted new analyses and published two papers. We will receive updated data in 2023 and perform new analyses that in particular will cover the relationship between heart and kidney failure in patients with and without diabetes.

Co-investigators/participants:
Kari-Anne Sveen
Trond G. Jenssen

External collaborators:
Anna Norhammar, Cardiology Unit, Department of Medicine, Solna, Karolinska Institutet and Capio Saint Göran Hospital, Stockholm, Sweden
Jan W. Eriksson and Robin Kristofi Department of Medical Sciences, Clinical Diabetes and Metabolism, Uppsala University, Uppsala, Sweden
David Nathanson, Department of Medicine, Huddinge, Karolinska Institutet, Stockholm, Sweden
Thomas Nyström, Department of Clinical Science and Education, Södersjukhuset, Karolinska Institutet, Stockholm, Sweden
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Urban Olsson, Statisticon
Hilja Brorsson, Statisticon
Fabian Söderdahl, Statisticon
Anna Carlsund, Statisticon
Johan Bodegaard, Astra Zeneca
Susanna Jerström, Astra Zeneca

Publications 2022:

Prevalence, outcomes, and cost of chronic kidney disease in a contemporary population of 2·4 million patients from 11 countries: The CaReMe CKD study. Sundström J, Bodegard J, Bollmann A, Vervloet MG, Mark PB, Karasik A, Taveira-Gomes T, Botana M, **Birkeland KI**, Thuresson M, Jäger L, Sood MM, VanPottelbergh G, Tangri N; CaReMe CKD Investigators.Lancet Reg Health Eur. 2022 Jun 30;20:100438. doi: 10.1016/j.lanepe.2022.100438. eCollection 2022 Sep.PMID: 36090671

Cost of healthcare utilization associated with incident cardiovascular and renal disease in individuals with type 2 diabetes: A multinational, observational study across 12 countries. Norhammar A, Bodegard J, Eriksson JW, Haller H, Linssen GCM, Banerjee A, Karasik A, Mamouris P, Tangri N, Taveira-Gomes T, Maggioni AP, Botana M, Thuresson M, Okami S, Yajima T, Kadowaki T, **Birkeland KI**; CaReMe Cardiorenal Investigators.Diabetes Obes Metab. 2022 Jul;24(7):1277-1287. doi: 10.1111/dom.14698. Epub 2022 Apr 19.PMID: 35322567

PHOTO: OSLO DIABETES RESEARCH CENTRE

THE DIASA RESEARCH PROGRAMME: DIABETES IN SOUTH ASIAN IMMIGRANTS – PATHOPHYSIOLOGY, PERCEPTIONS, PREVENTION AND TREATMENT

Primary investigator: Kåre I. Birkeland, Professor, MD, PhD

Primary objectives: To find effective means to improve diabetes prevention, treatment and care in SA, thereby improving metabolic regulation and preventing diabetic complications, morbidity and mortality.

DIASA 1: Find the prevalence of impaired glucose tolerance (IGT), impaired fasting glucose (IFG) and T2D in SA and NO women with pGDM 1-2 years after childbirth. Study insulin sensitivity, insulin secretion and glucose metabolism in pGDM. Study perceptions about health, disease risk, possibilities for and barriers against diabetes prevention in pGDM.

DIASA 2: Compare SA and NO women with IGT/IFG to reveal possible differences in liver and whole body insulin sensitivity, glucose and lipid metabolism, lipidomics, fatty infiltration in liver and visceral adipose tissue.

DIASA 3: In SA women with IGT/IFG, to test the effect of four different oral antidiabetic agents (OAD) on liver and whole body insulin sensitivity, glucose/lipid metabolism, lipidomics, fatty infiltration in liver and visceral adipose tissue.

DIASA 4: Establish and follow a SA T2D cohort in General Practice to assess glucose regulation, treatment and complications.

News from 2022:
We have completed inclusion of 279 participants in DIASA 1 and published 2 papers describing important numbers of prevalence of prediabetes and diabetes in South Asian and Nordic women after GDM, and novel pathophysiological characteristics that helps explain the differences. DIASA 2 is almost completed and will be finished early 2023, and DIASA 3 (RCT) has recruited 11 participants, but has encountered significant challenges with recruitment.

Co-investigators/participants:
Archana Sharma, Anita Suntaralinguam Kvist, Sindre Lee-Ødegaard, Elisabeth Qvigstad, Anh Thi Tran, Christine Sommer, Hanne K. Gulseth, Ingrid Nermoen, Stina Sollid, Åse Halsne, Ellen Hillestad

External collaborators:
Naveed Sattar, University of Glasgow
Jason Gill, University of Glasgow

Senter for pasientmedvirkning og samhandlingsforskning:
Lise Solberg Nes
Cecilie Varsi

Stovner Legesenter:
Hallstein Netland

Avdeling for forskning og utvikling, klinikk for radiologi og nukleærmedisin
Heidi B. Eggesbø
Anne Cathrine T. Martinsen

Publications 2022:
β-Cell Function, Hepatic Insulin Clearance, and Insulin Sensitivity in South Asian and Nordic Women After Gestational Diabetes Mellitus.
Sharma A, Lee-Ødegård S, Qvigstad E, Sommer C, Sattar N, Gill JMR, Gulseth HL, Sollid ST, Nermoen I, **Birkeland KI.**Diabetes. 2022 Dec 1;71(12):2530-2538. doi: 10.2337/db22-0622.PMID: 36112815

High prevalence and significant ethnic differences in actionable HbA_{1C} after gestational diabetes mellitus in women living in Norway.
Sharma A, Nermoen I, Qvigstad E, Tran AT, Sommer C, Sattar N, Gill JMR, Gulseth HL, Sollid ST, **Birkeland KI.**BMC Med. 2022 Sep 23;20(1):318. doi: 10.1186/s12916-022-02515-w.PMID: 36138475

DISCOVER - NORDIC

Primary Investigator: Kåre I. Birkeland, Professor, MD, PhD

Background and Aims:
Previous research has shown similarities and differences between type 2 diabetes (T2D) patients in general practice in the Nordic countries. The aim is to describe and compare patient populations, treatment modalities, complications and comorbidities in the Nordic countries, and follow the development over time.

Materials and Methods:
Electronic medical records (EMR) data on all T2D patients will be extracted once yearly from 60 primary care clinics in DK, NO and SE, and linked with national Prescribed Drug-, National Patient- and Cause of Death Registry data in the respective country. The number of patients below targets was also greatest in DK compared to the other countries. Norway and Sweden demonstrated similar target patterns.

News from 2022:
No activity in the project this year, but plans for further analyses next year.

Co-investigators/participants:
Kristian Furuseth, Solli Klinikk, Jessheim, Norway

External collaborators:
Frederik Persson and Søren Tang Knudsen, Steno Diabetes Center Aarhus, Aarhus University Hospital, Aarhus, Denmark
Anders Lindh Åkersberga, Sweden
Peter M. Nilsson Lunds University, Lund, Sweden
Michael Alvarsson Karolinska University Hospital, Stockholm, Sweden
Marit Eika Jørgensen Steno Diabetes Center Copenhagen, Gentofte, Denmark
Jens Søndergaard University of Southern Denmark, Odense, Denmark
Marcus Thureson, Statisticon
Johan Bodegaard, Astra Zeneca
Susanna Jerström, Astra Zeneca

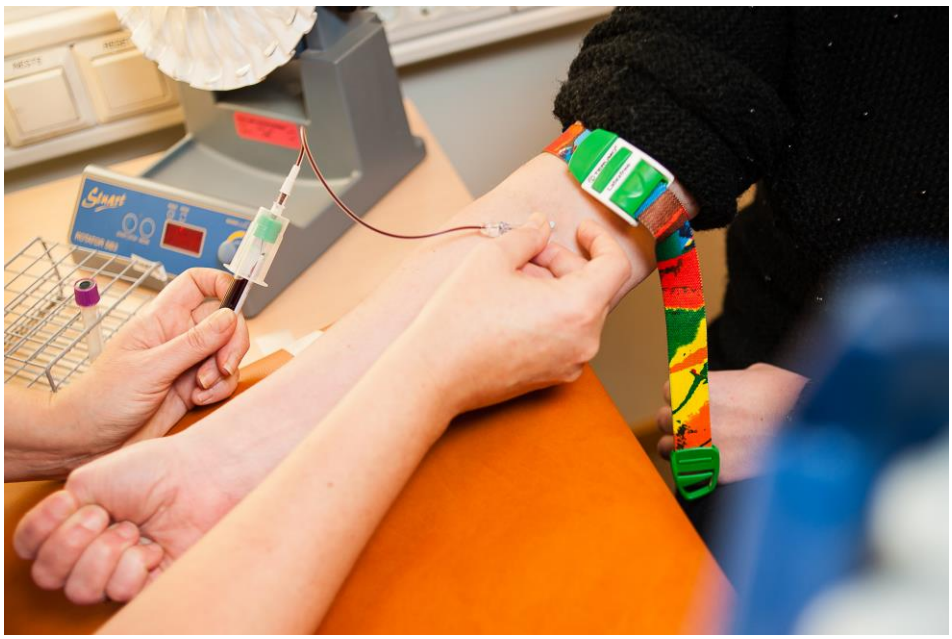

PHOTO: ØYSTEIN HORGMO, UIO

MYOGLU – PHYSICAL ACTIVITY, MYOKINES AND GLUCOSE METABOLISM

Primary Investigator: Kåre I. Birkeland, Professor, MD, PhD

Background:
Skeletal muscles account for ~ 40 % of body weight and normal glucose uptake and metabolism in skeletal muscles are essential to keep blood glucose within normal range. Hence, impaired skeletal muscle glucose uptake is a major cause of the insulin resistance in type 2 diabetes, and therefore physical activity is essential for health. The term myokine is used to describe proteins secreted from skeletal muscle that can execute important biological functions locally in the muscle (paracrine) or in other organs like the brain, liver, pancreas and intestines (endocrine).

Aims of the present study:
We want to quantify the effect of combined strength and endurance training on metabolic health among subjects with normal and elevated glucose levels, and explore potential myokines that can explain the effects of exercise.

Methods:
We will perform an intervention concerning physical activity among subjects with overweight (BMI in the range of 27 to 32 kg/m2) and abnormal glucose metabolism, evaluated by oral glucose tolerance test (OGTT), and compare their phenotypic changes with healthy, normal weight control subjects (BMI in the range of 19 to 25 kg/m2). The intervention will include strength as well as endurance training, lasting 8 weeks and we will recruit 12 subjects in each group (with abnormal glucose metabolism and control subjects). All the test individuals will be exposed to training by personal coaches four times weekly for 8 weeks and to extensive examinations before and after the training period. Muscle strength, aerobic capacity, insulin sensitivity (glucose clamp), fat- and muscle biopsies as well as extensive serum markers will be measured before and after the intervention period.

News from 2022:
We have published a review based partly on knowledge created in this study. Further analyses of collected samples are ongoing and publications are planned.

Co-investigators/participants:
Prof. em. Christian Drevon, Institute of basic medical sciences, University of Oslo
Prof. Jørgen Jensen, Norwegian School of Sports Medicine
Director of Department, Hanne L. Gulseth, Norwegian Institute of Public Health
Post.doc. Sindre Lee Ødegaard, Institute of Clinical Medicine, University of Oslo

External collaborators:
Ass. Prof. Frode Norheim, researcher Torgrim Langleite, prof. Helga Refsum, post.doc. Thomas Olsen, all Institute of basic medical sciences, University of Oslo

Publications 2022:
Potential Mechanisms for How Long-Term Physical Activity May Reduce Insulin Resistance.
Lee-Ødegård S, Olsen T, Norheim F, Drevon CA, **Birkeland KI.** Metabolites. 2022 Feb 25;12(3):208. doi: 10.3390/metabo12030208.PMID: 35323652

PI: ESBEN SELMER BUHL

Outcomes & Multi-morbidity In Type 2 diabetes (OMIT) – a national registry-based observational cohort with focus on care and treatment of key high-risk groups in Norway

Primary Investigator: Senior researcher Esben Selmer Buhl (MD, PhD) with Prof. Emeritus Anne Karen Jenum (MD, PhD) as co-PI

The "Outcomes & Multi-morbidity in Type 2 Diabetes" (OMIT) study was established to study high-risk patients with type 2 diabetes who are often omitted from prospective clinical trials (hence the acronym OMIT).

Patients treated in Norwegian general practice or at out-patient hospital clinics are identified in a linkage between the ROSA-4 register and the Norwegian Diabetes Register for Adults (NDR-A) (2006-2019, N=52,935) in order to study high-risk groups (1) young onset diabetes, 2) elderly, 3) ethnic minorities and 4) low socio-economic status) in relation to key clinical topics: 1) multi-morbidity, 2) real-life anti-diabetic drug utilization and performance, and 3) variability in disease control.

To analyse confounders, exposures and outcomes in observational data, ROSA4/NDR-A is linked to the Norwegian Prescription Database, the Norwegian Population Register, Statistics Norway and data from the Norwegian Directorate of Health.

Status: one postdoc and one PhD-candidate are working on the project, with two papers in preparation.

Co-investigators/Participants:

Rachel Bedenis Forster[1], Ragnhild Bjarkøy Strandberg[2], Katrina Tibballs[1], Kjersti Nøkkleby[1], Tore Julsrud Berg[3,4], Tor Iversen[4], Terje Hagen[4], Kåre Rønn Richardsen[5], John Cooper[6,7], Tor Claudi[8], Sverre Sandberg[6,9], Karianne Fjeld Løvaas[6], Roy Miodini Nilsen[2], Marjolein M.Iversen[2], Anne Karen Jenum[1] and Esben Selmer Buhl[1] †

[1]General Practice Research Unit (AFE), Department of General Practice, Institute of Health and Society, University of Oslo, Norway
[2]Department of Health and Caring science, Western Norway University of Applied Sciences (HVL) (Norway)
[3]Institute of Clinical Medicine , Oslo University (UiO) (Norway)
[4]Department of Endocrinology, Oslo University Hospital (OUS) (Norway)
[4]Institute of Health and Society, Department of Health Management and Health Economics, Oslo University (UiO) (Norway)
[5]Department of Physiotherapy, Falculty of Health Sciences Oslo Metropolitan University (OsloMet)(Norway)
[6]Norwegian Quality Improvement of Laboratory Examinations, Haraldsplass Deaconess Hospital, Bergen (HDS) (Norway)
[7]Division of Medicine, Stavanger University Hospital (SUS) (Norway)
[8]Medical Centre, Nordland Hospital (NLSH) (Norway)
[9]Department of Global Public Health and Primary Care, University of Bergen (UiB) (Norway)

Publications 2022:

Cohort profile: Outcomes & Multi-morbidity In Type 2 diabetes (OMIT) - a national registry-based observational cohort with focus on care and treatment of key high-risk groups in Norway. Forster RB, Strandberg RB, Bø Tibballs KL, Nøkleby K, Berg TJ, Iversen T, Hagen TP, Richardsen KR, Cooper J, Sandberg S, Løvaas KF, Nilsen RM, Iversen MM, Jenum AK, Buhl ESS.BMJ Open. 2022 May 11;12(5):e054840. doi: 10.1136/bmjopen-2021-05484

Lower education and immigrant background are associated with lower participation in a diabetes education program - Insights from adult patients in the Outcomes & Multi-morbidity In Type 2 diabetes cohort (OMIT). Strandberg RB, Nilsen RM, Pouwer F, Igland J, Forster RB, Jenum AK, Buhl ES, Iversen MM.Patient Educ Couns. 2023 Feb;107:107577. doi: 10.1016/j.pec.2022.107577. Epub 2022 Nov 2

PI: KNUT DAHL-JØRGENSEN

DIABETES VIRUS DETECTION STUDY (DIVID)

Primary Investigator: Knut Dahl-Jørgensen, Professor Emeritus, MD, PhD

DiViD started in 2009 and is the first study to provide pancreatic tissue biopsies of unique quality in 6 patients at the time of diagnosis. Of all the pancreatic islets, one third contained insulin, with several resembling completely normal islets. Inflammation in the pancreas which is typical for diabetes (called insulitis) was seen in all patients, and the immune cells were characterized in detail. Live insulin producing cells from all patients were examined in the laboratory and in some patients the insulin production improved when kept in a non-diabetic milieu. This shows a considerable reserve capacity of insulin production at the time of diagnosis. Most important a low-grade chronic enteroviral infection in the insulin producing pancreatic islets has been demonstrated with new sensitive assays in all cases: Live replicating enteroviruses viruses, virus RNA and Virus capsid protein (VP1). The results were confirmed in various laboratories. Antiviral tissue responses were detected by various methods: Increased expression of class I HLA molecules was found in the pancreatic islets of all patients. Gene expression studies revealed increased expression of genes that handle viral infections and gave evidence of increased cellular stress, which may induce production of neo-antigens. Furthermore they detected increased interferon response and increased levels of cytokines that may contribute to cell death. Nearly twenty different international laboratories are involved using these biopsies to study the pathogenesis of type 1 diabetes. At present 39 original articles are published and frequently cited. These results is the basis for the DiViD Intervention Trial with antiviral treatment in newly diagnosed patients with type 1 diabetes.

News from 2022
Detection of a low grade chronic infection with live enteroviruses in the pancreas at onset of type 1 diabetes.

Co-investigators/participants:
Lars Krogvold, Ass. Professor. Consultant, UiO/OUS
Bjørn Edwin, Professor, UiO/OUS
Trond Buanes, Professor, UiO/OUS

External collaborators:
Heikki Hyöty, University of Tampere, Finland
Gun Frisk, University of Uppsala, Sweden
Olle Korsgren, University of Uppsala, Sweden
Oskar Skog, University of Uppsala, Sweden
Decio Eizirik, University of Bruxelles, Belgium
Karsten Buchard, University of Copenhagen, DK
Johnny Ludvigsson, University of Linköping, SE
Noel Morgan, University of Exeter, UK
Sara Richardsson, University of Exeter, UK
Bart Roep, Leiden University, Netherlands
Mikael Knip, University of Helsinki, Finland
Gunilla Westermark, University of Uppsala, SE
Yuval Dor, University of Jerusalem, Israel
Antonio Toliono, University of Varese, Italy
Ben Giepmans, University of Groningen, NL
Riitta Lahesmaa, University of Turku, FI
Matthias von Herrath, La Jolla, USA
Ian Lipkin, Columbia University, New York, USA
Ivan C. Gerling, Memphis, USA
Shiva Reddy, Auckland University, New Zealand
Malin Thulin-Flodstrøm, Karolinska Institutet, SE
Mark Peakman, Kings College, London, UK
Mark Atkinson, University of Florida, USA
Alberto Pugliese, University of Miami, USA Francesco Dotta, University of Siena, Italy

Publications 2022

Krogvold L, Genoni A, Puggioni A, Campani D, Richardson SJ, Flaxman CS, Edwin B, Buanes T, Dahl-Jørgensen K, Toniolo A. Live enteroviruses, not other viruses, detected in human pancreas at the onset of type 1 diabetes in the DiViD-study. Diabetologia. 2022 Dec; 65(12):2108-2120. doi: 10.1007/s00125-022-05779-2

Krogvold L, Leete P, Mynarek I, Russell MA, Gerling IC, Lenchik NI, Matthews C, Richardson SR, NL Morgan, Hanssen KF, Dahl-Jørgensen K. Detection of antiviral tissue responses and increased cell stress in the pancreatic islets of newly diagnosed T1D patients: Results from the DiViD study. Front Endocrinol (Lausanne). 2022 Jul 26;13:881997. doi: 10.3389/fendo.2022.881997

Välikangas T, Lietzén N, Jaakkola MK, Krogvold L, Eike MC, Kallionpää H, Tuomela S, Mathews C, Gerling IC, Oikarinen S, Hyöty H, Dahl-Jorgensen K, Elo LL, Lahesmaa R. Pancreas Whole Tissue Transcriptomics Highlights the Role of the Exocrine Pancreas in Patients With Recently Diagnosed Type 1 Diabetes. Front Endocrinol (Lausanne). 2022 Apr 13;13:861985. doi: 10.3389/fendo.2022.861985. eCollection 2022. PMID: 35498413

Josefsen K, Krogvold L, Gerling IC, Pociot F, Dahl-Jørgensen K, Buschard K. Development of Type 1 Diabetes may occur through a Type 2 Diabetes mechanism. Front Endocrinol (Lausanne). 2022 Dec 14;13:1032822. doi: 10.3389/fendo.2022.1032822. eCollection 2022. PMID: 36589856.

Tekin H, Josefsen K, Krogvold L, Dahl-Jørgensen K, Gerling I, Pociot F, Buschard K. PDE12 in type 1 diabetes. Sci Rep. 2022 Oct 28;12(1):18149. doi: 10.1038/s41598-022-22890-x. PMID: 36307540.

DIABETES VIRUS AND INTERVENTION TRIAL (DiViDInt) - EudraCT Number: 2015-003350-41

Primary Investigator: Knut Dahl-Jørgensen, Professor Emeritus, MD, PhD

Co-PI: Lars Krogvold, Associate Professor, MD, PhD

Accumulating evidence suggest that viruses may be an important factor in the pathogenesis of type 1 diabetes. We recently demonstrated a lowgrade, persistent enterovirus infection in the pancreatic islets of Langerhans of live patients at the diagnosis of T1D, and that about one third of the islets still produced insulin. We now want to test whether antiviral treatment may stop the disease process and maintain residual insulin production. Patients 5-16 years of age participate in a randomized, double blinded, placebo controlled trial of antiviral treatment with the combination of oral Pleconaril and Ribavirin. Study sites: Oslo and Copenhagen. All patients receive modern, intensified insulin treatment with insulin pumps or pens. Study drug treatment or placebo started within three weeks after diagnosis of T1D and last for 6 months. Follow-up at 3, 6, 12, 24, and 36 months. In October 2020 we included the last of the 96 patients according to protocol.

Endpoints: Change in mean residual insulin secretion measured by stimulated C-peptide (MMTT) and number of patients with clinical significant C-peptide.

Fasting and meal stimulated C-peptide from blood sampled monthly at home. Insulin dosage. HbA1c. Hypoglycemic events. Proinsulin/c-peptide ratio in serum as a measure of beta cell stress. Change in presence of Enterovirus in nose, blood and stool.

If antiviral treatment is effective, it will add proof to the concept that type 1 diabetes in its origin may be a viral disease. This would be an important milestone in medical research and be a breakthrough to the understanding of the ethiopathogenesis of autoimmune diseases. It may promote the development of vaccines to prevent the disease.

News 2022
Primary endpoint analysis completed, and publication in preparation.

Co-investigators/participants:
Ida Mynarek, Physician, PhD student. Pediatric Dept. Oslo University Hospital
Trine Roald, Study Nurse, Pediatric Dept. Oslo University Hospital
Erica Ponzi, Statistician, PhD, Oslo University Hospital
Kristian F. Hanssen, Senior Professor, University of Oslo

External collaborators:
Jesper Johannesen, Professor, Pediatric Dept. Herlev Hospital, Steno Center, Copenhagen
Heikki Hyöty, Professor, Dept of Virology, University of Tampere, Finland
Johnny Ludvigsson, Professor, Dept. of Pediatrics, University of Linköping, Sweden
Mikael Knip, Professor, Dept. of Pediatrics, University of Helsinki, Finland
Peter Barker, Professor, University of Cambridge, UK
Adrian Mander, Statistician, Professor, University of Cardiff, UK
Freja Barrett Mørk, Physician, PhD student, Pediatric Dept. Herlev Hospital, Steno Center, Copenhagen
Trine Witzner Hessel, Physician, PhD student, Pediatric Dept. Herlev Hospital, Steno Center, Copenhagen

INNODIA - TRANSLATIONAL APPROACHES TO DISEASE MODIFYING THERAPY OF TYPE 1 DIABETES: AN INNOVATIVE APPROACH TOWARDS UNDERSTANDING AND ARRESTING TYPE 1 DIABETES

Primary investigators (Norwegian site):

Knut Dahl-Jørgensen, Professor Emeritus, MD, PhD, Torild Skrivarhaug, Associate Professor, MD, PhD, Geir Joner, Professor Emeritus, MD, PhD and Lars Krogvold, Associate Professor, MD, PhD

INNODIA assembles a comprehensive, complementary consortium of leading clinicians overseeing T1D registries and large clinical trial centres, aligned with basic science experts in beta-cell pathophysiology, immunology, biomarker discovery, bioinformatics, systems biology and trial design. INNODIA will accelerate understanding of T1D via coordinated studies of unique clinical samples and translation-oriented preclinical models delivering novel biomarkers and interventions for testing. Participants will be consented to recall, creating a 'living biobank'.

In Norway we recruit first degree family members (aged 5-40 years) of patients with type 1 diabetes. First a blood test of autoantibodies is performed and if positive prediabetes is diagnosed with a high risk for developing clinical type 1 diabetes, these participants undergo an organized follow-up and may be eligble for studies aiming to prevent clinical type 1 diabetes. Such prevention studies will start recruiting participants in the two years to come. Newly diagnosed patients are now enrolled in the DiViDInt Trial, which is affiliated to INNODIA.

Co-investigators/participants:
Kristin Namtvedt Tuv, Consultant pediatrician, Sørlandet Hospital, Norway

External collaborators:
INNODIA is a global partnership between 31 academic institutions, 6 industrial partners, a small sized enterprise and 2 patient organizations.

See www.innodia.eu

LONG TERM VASCULAR CHANGES IN TYPE 1 DIABETES CLINICAL ASPECTS AND BIOLOGICAL MARKERS – 30 YEARS FOLLOW-UP OF THE OSLO STUDY

Primary Investigators: Knut Dahl-Jørgensen, Professor Emeritus, MD PhD and Kari Anne Sveen, MD, PhD

The Oslo Study was planned by Professor Kristian F. Hanssen and Knut Dahl-Jørgensen fourty years ago. In 1980-81 forty-five type 1 diabetes patients aged 18-42 years with diabetes duration 13 years, were block-randomized to either insulin pump treatment (CSII), multiple injections or standard treatment with two daily mixed insulin injections for four years.

This was the first study in the world to compare these three regimens and to explore if intensive insulin treatment was superior to standard treatment. Insulin pumps were superior with near normal blood glucose values and less hypoglycemia compared to multiple injections with pens, and both better then two daily insulin regimens. After 4 years the randomization all patients offered intensified treatment, because early retinopathy, nephropathy and neuropathy were retarded by intensified treatment regimens. Later the DCCT study confirmed these findings.

The Oslo Study patients were followed prospectively for 30 years. After 18 years an unexpected high frequency and degree of atherosclerosis in the coronary arteries of the heart was detected by intravascular ultrasound in patients without symptoms of cardiovascular disease. Jakob Larsen made his thesis on these 18 years follow up results. The degree of atherosclerosis correlated with cholesterol and also long term blood glucose control, underlining the importance of optimal blood glucose control in preventing cardiovascular death.

Kari Anne Sveen performed the 30 years follow-up and worked to unravel the biochemical mechanism for why high blood sugar is so harmful to blood vessels and nerves, and studied how the changes in the proteins due to high blood glucose, measuring Advanced Glycation Endproducts (AGEs), is linked to late complications. She is now continuing using the Oslo Study materials for more in depth studies on progression of atherosclerosis and its prognostic factors as AGEs and circulating autoantibodies against modified lipids and epigenetic factors influencing the development and progression of late diabetes complications.

Co-investigators/participants:
Kristian F. Hanssen, Sen. Professor, Dept. of Endocrinology, OUS
Jakob Larsen, Consultant, Pediatric Dept. OUS

External collaborators:
Vincent Monnier, Cleveland, Ohio, USA.
Jan Nilsson, CRC, Universitetet i Lund
Eva Bengtsson, CRC, Universitetet i Lund
Ingebjørg Seljeflot, OUS
Harald Arnesen, OUS

PI: TROND GEIR JENSSEN

MAGNESIUM AND CALCIFICATION INDEX (T50) IN RENAL TRANSPLANT RECIPIENTS

Primary investigator: Trond Geir Jenssen, Professor, MD, PhD

Newly diagnosed Post-transplant diabetes mellitus (PTDM) occurs in 10-15% of kidney transplant recipients. PTDM doubles the risk of cardiovascular death during the first 10 post-transplant years. Low magnesium levels are frequently present in these patients due to loss of magnesium in the urine. Hypomagnesemia may be associated both with development of PTDM and also with cardiovascular disease.

Low magnesium leads to desensitization of the glucose sensor in the beta cell and promotes insulin resistance in peripheral tissues. Furthermore, low magnesium may also promote calcification processes in the arteries assessed by the T50 test in serum samples.

The T50 test assesses the ability of the blood to prevent formation of toxic calcification particles (CCP2) from calcium and phosphate. The test (T50) reports the time, which is necessary to convert 50% of the precursor CCP1 into CPP2. Low T50 is probably a strong predictor for future cardiovascular death in renal transplant patients. Low T50 may also be associated with reduced mineralization of bone tissue.

PHOTO: UNSPLASH

In a study on more than 634 renal transplant patients we want to:

1. Assess if low levels of magnesium are associated with development of PTDM over the first post-transplant year and also low T50.
2. Assess if levels and change in magnesium and T50 over the first post-transplant year are associated with arterial stiffness and death.
3. Assess if levels and change in magnesium and T50 over the first post-transplant year are associated with low bone mineral density.

Any role of magnesium in these conditions may advocate prophylactic use of magnesium supplements in kidney transplant recipients in the future.

News from 2022:
All analyses of blood samples for T50 were completed by the end of 2021. The results will be published in 2023.

Co-investigators/participants:
Rasmus Kirkeskov Carlsen, MD, PhD Student
Anders Aasberg, PhD, Professor of Pharmacy
Kåre I Birkeland, MD PhD, Professor of Medicine

External collaborators:
My Svensson, MD PhD, Professor of Medicine, Akershus University Hospital
Iain Bressendorft, MD PhD, Hillerød Hospital, Denmark
Hanne Løvdahl Gulseth, Section Director, Norwegian Institute of Public Health

MAGNESIUM AND HYPERGLYCEMIA AFTER KIDNEY TRANSPLANTATION: A NEW TARGET FOR TREATMENT

Primary investigator: Trond Geir Jenssen, Professor, MD, PhD

Post-transplant (new onset) diabetes (PTDM) occurs in 10-15% of all patients undergoing kidney transplantation. Hypomagnesemia occurs in most of these patients due to use of calcineurin inhibitors and in some cases loop-diuretics. Both induce urinary excretion of magnesium. Furthermore, magnesium is central for normal function of the insulin receptor, and induced hypomagnesemia reduces both insulin secretion and action in normal persons.

This project has three work packages:
Wp 1. We have a database of 1300 kidney transplant recipients who have undergone oral glucose tolerant tests (OGTTs) 8 and 52 weeks after transplantation. We will address whether hypomagnesemia 8 weeks after transplantation predicts fasting and post-challenge hyperglycemia 52 weeks after transplantation.

Wp 2. This is a cross-sectional study of kidney transplant recipients undergoing an OGTT 52 weeks after kidney transplantation with blood sampling for glucose, insulin and C-peptide measurements at 0,30 and 120 min after glucose intake. Through modelling we will assess whether low fasting magnesium levels are associated with impaired insulin release (1st phase and AUC) and/ or insulin resistance.

Wp 3. A 24-week randomized blinded study will be undertaken in 40 patients receiving either oral magnesium tablets or placebo. Only patients with measured magnesium <0,7 mmol/l will be included. The primary end-point will be the ability of retaining magnesium after oral medication, assessed by an intravenous magnesium retention test before and after treatment. The secondary end-point will be change in glycemia as assessed by a 2-hr OGGT test with blood sampling for glucose, insulin and C-peptide every half hour.

This the PhD project of Rasmus Kirkeskov Carlsen, and will be completed in 2023.

News from 2022:
Wp 1 is completed was presented at the annual meeting of European Renal Association and also the Eurpean Association for the Study of Diabetes in 2022. The manuscript will be submitted for publication.

Wp 2: Data are collected and analyzed. Ready to be published.

Wp 3: The study is ongoing, and was delayed for recruitment due to the covid pandemic. It is expected to be finished in the fall of 2022.

Co-investigators/participants:
Rasmus Kirkeskov Carlsen, MD, PhD Student
Anders Aasberg, PhD, Professor of Pharmacy
Kåre I Birkeland, MD PhD, Professor of Medicine

External collaborators:
My Svensson, MD PhD, Professor of Medicine, Akershus University Hospital
Iain Bressendorft, MD PhD, Hillerød Hospital, Denmark

SGLT2 INHIBITION AS RENOPROTECTIVE TREATMENT IN KIDNEY TRANSPLANT RECIPIENTS

Primary Investigator: Trond Geir Jenssen, Professor, MD, PhD

We have previously shown that the SGLT2 inhibitor (SGLT2i) empagliflozin can be safely used as glucose lowering therapy in kidney transplant recipients. This new project received funding from Helse SørØst in 2021 and will start to run in 2022.

Rationale:
Half-life of transplanted kidneys is restricted to 15-18 years. Non-immunological mechanisms may be responsible for this. SGLT2 inhibitors (SGLT2i) delay the fall in GFR in native kidneys with chronic disease.

Question:
Will use of an SGLT2i (dapagliflozin) prolong the half-life of transplanted kidneys in patients with or without diabetes?

Study:
330 kidney transplanted patients will be randomized to use of dapagliflozin or placebo 6 weeks after transplantation. Kidney transplant biopsies will be performed before and 72 weeks after randomization, and eGFR will be assessed 4 times/year for a total of 150 weeks after randomization.

Primary endpoint:
Difference in slope of eGFR over 3 years.

Secondary endpoint:
Difference in inflammation, fibrosis and nephron loss assessed in biopsies after 72 weeks (n=140 patients). mRNA sequencing and proteomics will be analyzed in a subset of the biopsies.

Tertiary endpoints:
Difference in urinary albumin excretion
Difference in body mass composition assessed by DXA
Difference in 24-h blood pressure measurements

News from 2022:
A grant was received from KLINBEFORSK to finance the whole study. AstraZeneca provides the active drug and placebo.

Co-investigators/participants:
Anders Aasberg, PhD, Professor
Charlotte Kongerud, MD
Ivar A. Eide, MD PhD, Consultant
Melinda Miraki, MD PhD
Karsten Midvedt, MD PhD, Consultant
Kaare I Birkeland, MD PhD, Professor
Jens Bollerslev, MD PhD, Professor
Clara Hammarstrom, MD

WHAT IS THE LONG-TERM OUTCOME OF SINGLE PANCREAS VS. COMBINED PANCREAS-KIDNEY TRANSPLANTATION?

Primary Investigator: Trond Geir Jenssen, Professor, MD, PhD

Oslo University Hospital Rikshospitalet is the national competence center for whole organ transplantation in Norway, serving the whole country. Some 15-20 patients with type 1 diabetes mellitus undergo whole organ pancreas transplantation every year, either as a single pancreas transplant alone (PTA) in patients with preserved renal function, or as a simultaneous pancreas and kidney transplantation (SPK) in patients with end-stage renal disease. We have previously reported graft and patient survival for all transplantations performed in the period 2012-2016 (Lindahl et al. Am J Transplant 2018;18:154-162). Patient survival was nearly 100% for both groups of patients, but pancreas graft survival was inferior in the PTA group.

Refinement of follow-up procedures and early diagnosis of rejections have improved over the last 3 years, and the assumption is that graft survival with PTA may approach the graft survival numbers for SPK.

This work started in 2019, and was delayed due to the covid-19 pandemic in 2020. Our aim is to complete the project in 2023.

News from 2022:
A substuy has been published.

Co-investigators/participants:
Jørn Petter Lindahl, MD PhD, Consultant
Espen Nordheim, MD PhD, Associate professor
Anders Aasberg, PhD, Professor of Pharmacy

Publications 2022:
Kjøsen G, Horneland R, Nordheim E, Aandahl EM, Line PD, Rydenfelt K, Jenssen TG, Tønnessen TI, Haugaa H. Validating the US pancreas donor risk index in a Norwegian population, a retrospective observational study. Scand J Gastroenterol 2022; 57;345-52

PHOTO: UNSPLASH

PI: GEIR JONER

CARDIOVASCULAR DISEASE AND END-STAGE RENAL DISEASE IN TYPE 1 DIABETES WITH ONSET BEFORE 15 YEARS OF AGE AND LONG DURATION

Primary investigator: Geir Joner, Professor Emeritus, MD, PhD

Approximately 330 children aged 0-15 years are diagnosed with type 1 diabetes (T1D) in Norway yearly. Diabetic nephropathy (DN) is a severe complication in T1D, leading to end-stage renal disease (ESRD) and renal replacement therapy (RRT). Risk of CVD is increased in T1D, and DN is a major predictor of CVD morbidity and mortality.

In this cohort study based solely on register-data, the aims are to estimate long-term cumulative incidence of ESRD, the increased risk of CVD in long-standing T1D compared with the background population and to study the risk factors for ESRD and CVD and specifically the role of inflammation. The follow-up cohort is all newly diagnosed cases of T1d < 15 y in Norway 1973-2017.

News 2022:
The PhD-candidate has been on maternity leave most of the year, but two papers have been published and the project has been presented in various forums.

Co-investigators/participants:
Maryam Saeed, MD, PhD-student, Dept. of Pediatrics, Oslo University Hospital and Institute of Clinical Medicine, University of Oslo.
Torild Skrivarhaug, MD, PhD, Dept. of Pediatrics, Oslo University Hospital and Institute of Clinical Medicine, University of Oslo.
Lars Chr. Stene, PhD, Senior researcher, Norwegian Institute of Public

External collaborators:
Anna Varberg Reisæter, MD, PhD, Section of nephrology, Dept. of Transplantation Medicine, Oslo university hospital. Chair of the Board, Norwegian Nephrology Register
Trond G. Jenssen, Professor, Dept. of Organ Transplantation, Oslo university hospital
Grethe S. Tell, MD, Professor, Department of Global Public Health and Primary Care, University of Bergen
Ingebjørg Seljeflot, Center for Clinical Heart Research, University of Oslo and Oslo university hospital
Inger Ariansen, MD, PhD, senior researcher, Norwegian Institute of Public Health
German Tapia, PhD, senior researcher, Norwegian Institute of Public Health

Publications 2022:
Saeed M., Stene L. C., Reisæter A. V., Jenssen T. G., Tell G. S., Tapia, G., Joner G., Skrivarhaug T. (2022). End-stage renal disease: incidence and prediction by coronary heart disease, and educational level. Follow-up from diagnosis of childhood-onset type 1 diabetes throughout Norway 1973–2017. Ann Epidemiol. 2022 Dec; 76:181-187.

Saeed M., Stene L. C., Ariansen I., Tell G. S., Joner G., Skrivarhaug T. (2022). Nine-fold higher risk of acute myocardial infarction in subjects with type 1 diabetes compared to controls in Norway 1973-2017. Cardiovasc Diabetol. 2022 Apr 27;21(1):59.

PI: SVEIN OLAV KOLSET

EXTRACELLULAR MATRIX AND DIABETIC NEPHROPATHY

Primary Investigators: **Svein O. Kolset, Professor, PhD and Trond Jenssen, Professor, PhD**

To improve diagnostics and increase the understanding of kidney complications in diabetes, we focus on the development of inflammation and tissue repair/fibrosis in the diabetic kidney. Our group is also involved in studies on inflammation and fibrosis in adipose tissue in obese patients and in studies of the regulation of epithelial – mesenchymal transition. All studies involve similar targets and methods and complement each other in several ways.

In the kidney project, we focus on proteomics analyses of kidney biopsies with inflammation and fibrosis targets. In relation to fibrosis, we focus on the proteoglycans, serglycin and the syndecan family.

Co-investigators/participants:
Knut Tomas Dalen
Frode Norheim

External collaborators:
Gunnar Pejler, Uppsala University
Erik Knutsen, University of Tromsø

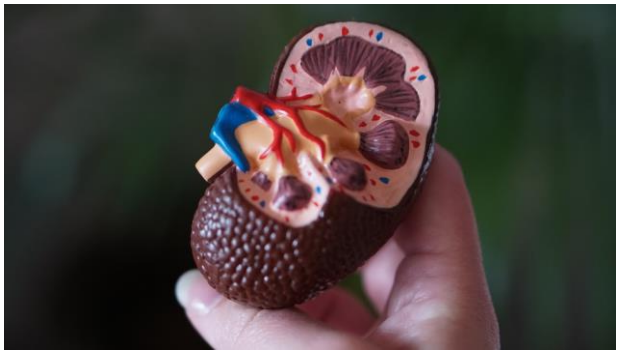

PHOTO: UNSPLASH

Publications 2022:

Doncheva AI, Norheim FA, Hjorth M, Grujic M, Paivandy A, Dankel SN, Hertel JK, Valderhaug TG, Böttcher Y, Fernø J, Mellgren G, Dalen KT, Pejler G, Kolset SO. Serglycin Is Involved in Adipose Tissue Inflammation in Obesity. J. Immunol. 2022, 208121-132. doi: 10.4049/jimmunol.2100231. Epub 2021 Dec

Kristiansen O, Roland MC, Zucknick M, Reine TM, Kolset SO, Henriksen T, Lekva T, Michelsen T.J Maternal body mass index and placental weight: a role for fetal insulin, maternal insulin and leptin. Endocrinol Invest. 2022 Jul 4. doi: 10.1007/s40618-022-01842-2.

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Geir Hetland, Magne Kristoffer Fagerhol, Veselka Petrova Dimova-Svetoslavova, Mohammad Reza Mirlashari, Nhan Trung Nguyen, Andreas Lind, Svein Olav Kolset, Arne Vasli Lund Søraas & Lise Sofie Haug Nissen-Meyer (2022) Inflammatory markers calprotectin, NETs, syndecan-1 and neopterin in COVID-19 convalescent blood donors, Scandinavian Journal of Clinical and Laboratory Investigation, DOI: 10.1080/00365513.2022.2123387

PI: TOVE LEKVA

PREGNANCY AS A "STRESS TEST FOR LIFE"- A LONGITUDINAL EXTENSION OF THE STORK COHORT

Primary investigator: Tove Lekva, MSc, PhD, Researcher

The STORK project is a prospective cohort study following 1031 pregnant Norwegian women from week 12-14 until the first week post-partum, included at Oslo University Hospital, Rikshospitalet. The participants (300 women) have been re-evaluated 5 years post-partum.

Investigating early development and mechanisms of gestational diabetes mellitus associated with later metabolic complications and cardiovascular disease may gain important information about women's later health and increase chances to prevent further progression of these diseases.

To reach our goals we perform translational research, using our well-defined clinical cohort investigating blood samples, placenta biopsies and
performing in-vitro studies exploring mechanistic functions and regulations.

News from 2022:
The STORK study contributed to show that

the BMI-placenta weight association is non-linear and may involve leptin. Maternal early pregnancy insulin and fetal insulin at term were associated with placenta weight.

multi-ancestry genome-wide association study of gestational diabetes mellitus highlights genetic links with type 2 diabetes.

Co-investigators/participants:
Thor Ueland
Marie Cecilie Paasche Roland
Jens Bollerslev
Tore Henriksen
Elisabeth Qvigstad
Kristin Godang
Annika E. Michelsen
Pål Aukrust

External collaborators:
Errol R. Norwitz

Publications 2022:
Contributed to the following relevant papers:

-Kristiansen O, Roland MC, Zucknick M, Reine TM, Kolset SO, Henriksen T, Lekva T and Michelsen T. 2022. Maternal body mass index and placental weight: a role for fetal insulin, maternal insulin and leptin. Journal of Endocrinological Investigation 45: 2105–2121.

- Pervjakova N, Moen GH, Borges MC, Ferreira T, Cook JP, Allard C, et.al. 2022. Multi-ancestry genome-wide association study of gestational diabetes mellitus highlights genetic links with type 2 diabetes. Human Molecular Genetics 31: 3377–3391.

PI: BENEDICTE A. LIE

FUNCTIONAL STUDIES OF THYMUS AND T CELLS WITH RELATION TO AUTOIMMUNITY

Primary Investigator: Benedicte A. Lie, Professor, Dr. philos

In addition to working on specific diseases, we aim to understand central mechanisms of autoimmunity particularly related to establishment of self-tolerant T cells in thymus. Tolerogenic and regulatory T cells represent a putative path to inhibit self-reactive T cells in order to prevent autoimmunity, including type 1 diabetes. To prevent autoimmunity, thymocytes expressing self-reactive T cell receptors are negatively selected, however, divergence into tolerogenic, agonist selected lineages represent an alternative fate. As thymocyte development, selection, and lineage choices are dependent on spatial context and cell-to-cell interactions. We have performed single cell sequencing and spatial transcriptomics of paediatric human thymus. Thymocytes expressing markers of strong TCR signalling diverged from the conventional developmental trajectory prior to $CD4^+$ or $CD8^+$ lineage commitment, while markers of different agonist selected T cell populations (CD8αα(I), CD8αα(II), $T_{(agonist)}$, T_{reg}(diff), and T_{reg}) exhibited variable timing of induction. Expression profiles of chemokines and co-stimulatory molecules, together with spatial localisation, supported that dendritic cells, B cells, and stromal cells contribute to agonist selection, with different subsets influencing thymocytes at specific developmental stages within distinct spatial niches. Understanding factors influencing agonist T cells is needed to enable future clinical use of their immunoregulatory effects.

Additionally, we have been involved in a study on the immune receptors KIR (killer cell immunoglobulin-like receptor) and in particular determination of KIR3DL1/S1 genotypes for medical application, which is hampered by complex sequence and structural variation. We therefore developed a model for imputing these genotypes from surrounding polymorphisms, and we plan to apply this method in future investigations of the role of KIR variants in autoimmune diseases.

Co-investigators/participants:
Siri T. Flåm (Medical Laboratory Scientist)
Hanne Hjorthaug (Medical Laboratory Scientist)
Dina Aronsen (Researcher)
Marte Heimli (PhD student)
Fatima Heinicke (PhD student)
Anne Rydland (PhD student)
Teodora Ribarska (Researcher)

External collaborators:
Arnt Fiane, OUS
Mary Carrington, US
Alberto Pugliese, US
Sarah Teichmann, UK

Publications 2022
We have several publications on different autoimmune diseases. The publications relevant to type 1 diabetes this year is:

Heimli M, Flåm ST, Hjorthaug HS, Trinh D, Frisk M, Dumont KA, Ribarska T, Tekpli X, Saare M, Lie BA. Multimodul human thymic profiling reveals trajectories and cellular milieu for T against selection. Front Immunol 2023, 13, 1092028. doi: 10.3389/fimmu.2022.1092028

Harrison, G.F., Leaton, L.A., Harrison, E.A., Kichula, K.M., Viken, M.K., Shortt, J., Gignoux, C.R., Lie, B.A., Vukcevic, D., Leslie, S., and Norman, P.J. “Allele imputation for the killer cell immunoglobulin-like receptor KIR3DL1/S1.” PLoS Comput Biol. 22;18 (Feb 2022):e1009059. doi: 10.1371/journal.pcbi.1009059.

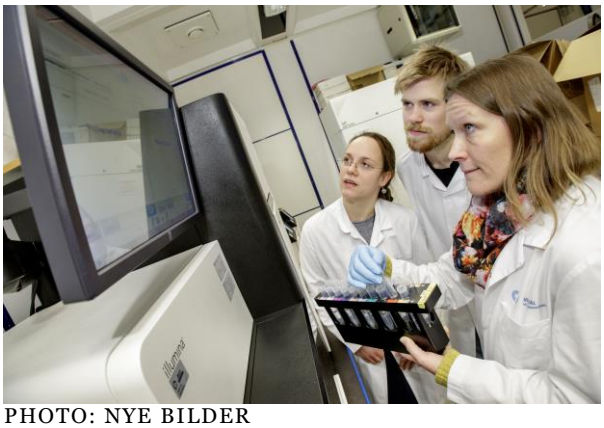
PHOTO: NYE BILDER

PI: HANNA DIS MARGEIRSDOTTIR

ATHEROSCLEROSIS AND CHILDHOOD DIABETES - ACD

Primary Investigator: Hanna Dis Margeirsdottir, MD, PhD

Background: Persons with type 1 Diabetes (T1D) have increased mortality due to cardiovascular disease (CVD). More scientific evidence is needed to justify aggressive early interventions during childhood. To address this, the ACD study was initiated in 2006.

Aims: To detect early signs of atherosclerosis, its progression and predisposing factors in childhood onset T1D compared to healthy controls.

Methods: This is a prospective study with follow-up every 5th year. Two of the most widely accepted surrogate markers of atherosclerosis, carotid intima media thickness (cIMT) and CRP are measured, as well as various biochemical markers of atherosclerosis and AGE`s, plus CVD risk factor analysis and clinical data collection. Cardiac ultrasound was performed at base-line, and ophthalmologic examination at 10-year.

Subjects: At baseline 324 persons with T1D aged 8-18 years from one health-region in Norway, were included together with 118 healthy controls. 80% participated again in the 5-year follow-up and 60% in the 10-year follow-up.

Progression: The baseline, 5- and 10-year follow up has all been completed and early stage atherosclerosis and low grade inflammation is observed despite short disease duration and intensive insulin treatment. The ophthalmologic examination performed at the 10-year follow up revealed that 32 % of the diabetic patients had diabetic retinopathy. We found that oxygen saturation in retinal arterioles and venules increased and vessel density in the macula decreased with increasing grade of nonproliferative retinopathy.

News from 2022:
The project is still ongoing.

Co-investigators/participants:
Knut Dahl-Jørgensen, Professor emeritus, Oslo Diabetes Research Center, UiO
Martin Heier, MD, PhD, Pediatric Department, OUS, Ullevål
Aida Simeunovic, Phd student, OUS, Ullevål
Ingebjørg Seljeflot, Professor. Center for Clinical Heart Research, dep of Cardiology, OUS
Cathrine Brunborg, Department of Biostatistics and Epidemiology, OUS
Nina Charlotte Veiby, MD, PhD, Department of Opthalmology, OUS
Goran Petrovski, Professor, Department of Opthalmology, OUS
Mario Gaarder, sonographer, Norwegian Institute of Public Health

External collaborators:
Torild Skrivarhaug, leader Norwegian Childhood Diabetes Registry, OUS
Kirsten Bjørklund Holven, Department of Nutrition, University of Oslo

PI: GUNN-HELEN MOEN

WHY DOES LOW BITHWEIGHT INCREASE THE RISK OF TYPE 2 DIABETES AND OTHER CARDIOMETABOLIC DISEASES? A STUDY OF GENETIC FACTORS IN HUNT.

Primary Investigator: Gunn-Helen Moen, PhD, Post doc.

There is a robust and well-documented relationship between lower birthweight and higher risk of cardiometabolic disease in later life, including Type 2 Diabetes.

Two major hypotheses have been put forward to explain this association. The first is the Developmental Origins of Health and Disease hypothesis (DOHaD), which posits that adverse intrauterine environments result in fetal growth restriction and increased future risk of cardiometabolic disease through developmental compensation.

In contrast, the Fetal Insulin Hypothesis postulates that the same genetic factors that alter intrauterine growth also affect future risk of disease. Broadly speaking, diabetes risk alleles in the mother result in higher levels of circulating glucose - increase offspring birthweight.

However, many of the same loci in the fetus decrease sensitivity to insulin (an important growth factor for the baby), decreasing offspring birthweight, which also predisposes the child to Type 2 Diabetes in later life.

By applying innovative statistical techniques to mother-offspring genome-wide association studies (GWAS) data from the Norwegian HUNT cohort, we investigate the relationship between birthweight and cardiometabolic disease.

News from 2022:
In 2022 we finished this project and published the last planed paper where we investigated the Genetic Covariance Between Birthweight and Cardiometabolic Risk Factors.

Publications 2022:
Moen, GH., Nivard, M., Bhatta, L. *et al.* Using Genomic Structural Equation Modeling to Partition the Genetic Covariance Between Birthweight and Cardiometabolic Risk Factors into Maternal and Offspring Components in the Norwegian HUNT Study. *Behav Genet* **53**, 40–52 (2023). https://doi.org/10.1007/s10519-022-10116-9

Co-investigators/participants:
Kåre I. Birkeland

External collaborators
David Evans (University of Queensland)
Nicole Warrington (University of Queensland)
Ben Brumpton (NTNU)
Bjørn Olav Åsvold (NTNU)

WHY DOES LOW BITHWEIGHT INCREASE THE RISK OF TYPE 2 DIABETES AND OTHER CARDIOMETABOLIC DISEASES? A STUDY OF GENETIC FACTORS IN HUNT.

Primary Investigator: Gunn-Helen Moen, PhD, Post doc.

There is growing evidence suggesting that environmental exposures, such as maternal diet, alcohol consumption and smoking during pregnancy may have long-term biological consequences across multiple generations, potentially playing a role in disease susceptibility.

Transgenerational effects may be defined as long term effects of environmental exposures that are transmitted down pedigrees and affect the health not only of an individual's children, but that of subsequent generations as well (i.e., grandchildren and beyond).

The aim of this project is to develop and apply three different statistical approaches to test for the existence of transgenerational inheritance of environmental exposures in human populations, as an alternative to conducting randomized controlled trials.

The focus will specifically be on the potential causal effect of grandparental environmental exposures on their grandchildren's birthweight.

News from 2022:
In 2022 we started this project and recruited our PhD student, Hanan Musa which started in November of 2022. We are looking forward to starting analysis in 2023!

Co-investigators/participants:
Hanan Musa (PhD student)

External collaborators
David Evans (University of Queensland)
Ben Brumpton (NTNU)
Bjørn Olav Åsvold (NTNU)
Deborah Lawlor (University of Bristol)

PHOTO: UNSPLASH

PI: ANNE PERNILLE OFSTAD

THE HUNT FOR HEART FAILURE RISK SCORE

Anne Pernille Ofstad, MD, PhD (Bærum Sykehus, Boehringer Ingelheim)

Co-primary: Håvard Dalen (NTNU, St Olavs)

Background:
Strategies to improve early detection and enable early treatment of heart failure (HF) are urgently needed. Currently no risk score for utilization in a general population is available for regular use. We aimed to develop such a tool to predict the 10-year risk for incident HF.

Methods:
Participants in the third wave (2006-08) of the Trøndelag Health Study (HUNT3) were included if they reported no known HF at baseline. In case of hospital diagnoses during follow-up of either heart failure, cardiomyopathy or hypertensive heart disease the medical records were reviewed and HF events validated according to the ESC 2016 guideline.

Results/conclusions:
We identified 12 clinical variables that independently predicted 10-year HF risk. This could be translated to a practical, online risk score which can be used for HF risk assessment in general practice.

PHOTO: UNSPLASH

News from 2022:
Analyses for the main risk score finalized and article submitted and rejected. Revised for new submission.

Co-investigators/participants:
Lars Gullestad (OUS-RH)
Lars Erik Laugsand (St Olavs)
Bjørn Mørkedal (Sykehuset i Vestfold)
Cathrine Brunborg (OUS)
Morten W. Fagerland (OUS)

External collaborators
Boehringer Ingelheim

PI: ELISABETH QVIGSTAD

REPRODIA: FERTILITY IN PREDIABETES AND DIABETES IN NORWAY

Primary investigator: Elisabeth Qvigstad, Associate Professor, MD, PhD

Background:
Infertility, contraceptive use and pregnancy outcomes are important health concerns for women and men with diabetes.
Obesity, Type-2 diabetes and infertility is increasing in young adults, and could influence risk for cardiovascular and diabetes-related disease and offspring health.
Recent Danish analyses indicate an increased risk of birth defects in the offspring of men using metformin during spermatogenesis.

Aims:
To improve understanding and treatment of reproductive health in women and men with diabetes in Norway.

Methods:
Complete analyses of interviews of women with Type-1 diabetes on family planning, sexual health and pregnancy.
Use national register data (prescriptions, births, diagnoses) to
1a) estimate rates of contraceptive use, and effect on number of pregnancies and pregnancy complications in women with diabetes.
1b) estimate rates of assisted reproductive therapy (ART), live births and pregnancy complications after ART.
2) investigate whether diabetes treatment of expecting fathers influences the risk for birth defects in the offspring.

News 2022:
Analysis of the IVF cohort presented at poster session at the EASD meeting in Stockholm, manuscript in preparation.
The interview project in good progress, interviews completed Feb 2023, with subsequent transcription, coding and analysis, submission of Master thesis: May 2023 for J.Anaruthan.
Project plans: Analysis of parental use of medications and pregnancy outcomes during Spring 2023.
Received support from the Odd Fellow Research Foundation, NOK 90 000.

Project participants:
Cecilie Varsi, RN, PhD. OUH and University of South-Eastern Norway. Co-supervisor.
Paz Lopez-Doriga Ruiz MD, PhD, NIPH.Co-supervisor.
Jesini Anurathan, RSN, Master candidate, Department of Endocrinology, OUH.
Kari Furu, MScPharm, MPH, PhD, senior researcher. Center for Fertility and Health, NIPH.
Jacqueline M Cohen, PhD, senior researcher Center for Fertility and Health. NIPH.
T. Lekva, post doc, MSc, PhD, Research Institute for Internal Medicine, UiO.
M-C.P. Roland MD, PhD, Dept of Clinical Biochemistry/Dept of Obstetrics and Gynecology, OUH.
S. Steintorsdottir, MD, MSc, junior consultant, Department of Endocrinology, OUH
Kristin Godang, Dept. of Endocrinology, OUH
Siri Eldevik Haaberg MD, MPH, PhD, research director, deputy head of Center for Fertility and Healt, NIPH.
H.L. Gulseth, MD, PhD, Research director, Dept. of Chronic Diseases and Ageing, NIPH.
J.R. Mellembakken MD, PhD, Senior Consultant in Gynecology and Obstetrics, the Fertility center at Rikshospitalet, OUH.
Line Wisting, Researcher, PhD, Division of Mental Health, OUH.

External collaborators:
Marjolein Memelink Iversen, Professor, PhD, RSN and Ragnhild Bjarkøy Strandberg, Post doc, PhD, RSN. Western Norway University of Applied Sciences Bergen
K Berntorp, MD, PhD, Dept. of Endocrinology, Skåne University Hospital, Malmö, Sweden.

POPULATION BASED STUDIES OF SOCIAL INEQUALITIES IN DIABETES DIAGNOSIS, INCIDENCE, MORTALITY AND TREATMENT (POSDIT)

Primary investigator: Elisabeth Qvigstad, Associate Professor, MD, PhD

The POSDIT study is a public health epidemiology and health service project targeting diabetes. The overall purpose is comprehensive analysis of time trends and social inequality in undiagnosed diabetes, incidence of type 2 diabetes across the lifespan, treatment and mortality among patients with type 2 diabetes in Norway.

News 2022:
During 2022, a paper from the HUNT study on undiagnosed diabetes has been published.

We have participated in a multicountry project organized by the Baker Heart and Diabetes Institute in Australia. A paper on mortality trends in type 1 diabetes (without data from Norway) has been published in the Diabetologia. A paper on all-cause mortality and another on lifetime risk, life expectancy, and years of life lost to type 2 diabetes in type 2 diabetes have been published in the Lancet Diabetes and Endocrinology in 2022.

We have collaborated with the IDF Diabetes Atlas in the group on undiagnosed diabetes.

Co-investigators/participants:
Norwegian Institute of Public Health:
Hanne L. Gulseth, Lars Christian Stene, Paz Lopez-Doriga Ruiz, German Tapia, Øystein Karlstad

Oslo University Hospital:
Kåre Birkeland

External collaborators:
Laila A. Hopstock, Inger Njølstad, Guri Grimnes, Anne Elise Eggen and Sameline Grimsgaard, Tromsø study, University of Tromsø

Bjørn Olav Åsvold, Norwegian University of Science and Technology (NTNU)

Dianna Magliano, Baker Heart and Diabetes Institute, Melbourne, Australia

Publications 2022:
Dunya Tomic, et al. «Lifetime risk, life expectancy, and years of life lost to type 2 diabetes: a global study of 23 jurisdictions» The Lancet Diabetes & Endocrinology (2022)

Vik Bjarkø, Vera et al. "Undiagnosed diabetes: Prevalence and cardiovascular risk profile in a population-based study of 52,856 individuals. The HUNT Study, Norway" Diabetic Medicine (2022)

Ruiz, Paz LD, Lei Chen et al. " Mortality trends in type 1 diabetes: a multicountry analysis of six population-based cohorts" Diabetologia (2022)

Magliano, D. J., et al "Trends in all-cause mortality among people with diagnosed diabetes: a multi-country analysis of aggregate data from 21 million deaths in diabetes in high-income settings" The Lancet Diabetes & Endocrinology (2022)

Ogurtsova, Katherine et al "IDF Diabetes Atlas: Global estimates of undiagnosed diabetes in adults for 2021" Diabetes Research and Clinical Practice (2022)

PI: MARIE CECILIE PAASCHE ROLAND

STORK - MATERNAL METABOLIC SYNDROME, MACROSOMIC NEWBORN AND PREGNANCY COMPLICATIONS

Primary investigators: Marie Cecilie Paasche Roland, MD, PhD and
Elisabeth Qvigstad, Associate Professor, MD, PhD

Background:
The STORK study was initiated to address the observed increase in proportions of large babies in Norway and the growing acknowledgement that birthweight and fetal growth have consequences for health and disease both in short and long term. In Norway the proportion of babies with high birthweight/macrosomia (>4000 g) increased from approximately 17 % in 1990 to 22 % around the year 2000 when the study was planned.

Aims:
The STORK study was designed to study maternal risk factors for macrosomia as reflected in the acronym STORK "store barn og komplikasjoner", which translates into large babies and complications. The overall aim was to study associations between maternal factors and fetal growth.

Methods:
The STORK study is a prospective, longitudinal cohort study performed in the period 2001-2008. A total of 1031 healthy pregnant women who gave birth at Oslo University Hospital, Rikshospitalet were included in the study. Data included clinical, biochemical and fetal growth measurements.

News 2022:
We have used new technology to investigate the composition of lipids in maternal plasma at different time points in pregnancy in relation to fetal growth and pregnancy complications like preeclampsia. The results from these analyses were presented at The society for Reproductive Investigations, Colorado, March 2022.

Co-investigators/participants:
Tove Lekva
Kristin Godang
Jens Bollerslev
Tore Henriksen
Thor Ueland
Camilla Friis
Nanna Voldner
Kathrine Frey Frøslie
Gunn-Helen Moen
Sandra Steintorsdottir

External collaborators:
We are part of the Maternal-Fetal Interaction Group at Oslo University Hospital, lead by professor Guttorm Haugen and collaborate on several projects linking maternal metabolism and placental physiology. We take part in a national collaboration on gestational diabetes together with researchers from Oslo (STORK Groruddalen), Trondheim and Kristiansand. International collaborators include the GenDIP consortium, an international consortium on genetics in gestational diabetes and dr. Jansson and dr. Powell at University of Denver, USA.

Publications 2022:
Degnes ML, Westerberg AC, Zucknick M, Powell TL, Jansson T, Henriksen T, Roland MCP, Michelsen TM. Placenta-derived proteins across gestation in healthy pregnancies-a novel approach to assess placental function? BMC Med. 2022 Jul 1;20(1):227. doi: 10.1186/s12916-022-02415-z. PMID: 35773701; PMCID: PMC9248112

Kristiansen O, Roland MC, Zucknick M, Reine TM, Kolset SO, Henriksen T, Lekva T, Michelsen T. Maternal body mass index and placental weight: a role for fetal insulin, maternal insulin and leptin. J Endocrinol Invest. 2022 Nov;45(11):2105-2121. doi: 10.1007/s40618-022-01842-2. Epub 2022 Jul 4. PMID: 35781790; PMCID: PMC9525437.

Skytte HN, Christensen JJ, Gunnes N, Holven KB, Lekva T, Henriksen T, Michelsen TM, Roland MCP. Metabolic profiling of pregnancies complicated by preeclampsia: A longitudinal study. Acta Obstet Gynecol Scand. 2023 Mar;102(3):334-343. doi: 10.1111/aogs.14505. Epub 2023 Jan 16. PMID: 36647289; PMCID: PMC9951333

PI: HANNE SCHOLZ

ADVANCING BETA CELL REPLACEMENT THERAPY FOR TYPE 1 DIABETES: CURRENT CLINICAL AND EXPERIMENTAL PROJECTS

Primary Investigator: Hanne Scholz, PhD, Senior Researcher

Project background:
We develop and establish new cell therapies for treating diabetes focus on experimental, translational and clinical studies. The research focused on developing beta cell replacement therapy for type 1 diabetes and understanding human islet cell biology. The human islet consists mainly of insulin-producing beta cells and glucagon producing alpha cells responsible for the fine-tune regulation of our blood glucose level in our body. The laboratory aims to improve the care for diabetic patients and has a clear and strong focus on clinical translation based on experimental research. Scholz is head of the Cell Therapy Laboratory for islet isolation and mesenchymal stromal/stem cell preparation which holds international standards. The group work in close collaboration with the Nordic Network for Clinical Islet transplantation and Uppsala group (led by Prof. Olle Korsgren). The research group is integrated in the Centre of Excellence -Hybrid Technology Hub at Institute of Basic Medical Sciences, UiO for developing organoids and the organ on a chip technology. The lab is funded by the Research Council of Norway, UiO:Life Science, South-Eastern Norway Regional Health Authority, University of Oslo, The Norwegian Diabetes Association, Oslo Diabetes Research Center, Novo Nordisk Fonden.

A short list of ongoing activities:
- Clinical beta cell replacement therapy program
- Adipose-derived stromal cells preserve pancreatic islet function in a 3D bioprinted scaffold
- Generation of beta cells from human pluripotent stem cells (hPSCs)
- Determination of insulin secretion from islet organoids
- Development of a novel cell therapy based on decidual stromal cells (DSC) for treatment of patients with type 1 diabetes
- Deep learning-based analysis of stem cell differentiation pathways (islets)
- Create metabolism on the chip using islets and liver clusters

News from 2022
NRK radio Hanne Scholz was a guest on the Abels Forgård radioshow and podcast talking about 3D printing of organs.
https://radio.nrk.no/podkast/abels_taarn/sesong/202203/l_1e994fa7-9813-4a47-994f-a798138a478e

Co-investigators/participants:
Prof. Trond Geir Jenssen, MD, PhD UiO/OUS
Prof. Kåre Birkeland, MD, PhD, UiO/OUS
Shadab Abadpour MSc, PhD, Postdoctoral OUS/UiO
Chencheng Wang, PhD student, UiO
Essi Niemi, PhD student, UiO
Franziska Schoeb, PhD student, UiO
Ragnhild Fjukstad, Biomedical Laboratory Scientist OUS
Marina Katavic, MSc, Biomedical Laboratory Scientist, OUS
Merete Høyem, Research Technician, OUS
Section for Transplantation Surgery, OUS (Morten Hagness, MD, PhD, Kristine Fasting, MD)
Anne Waage, MD, PhD, OUS

External collaborators:
- The Nordic Network for Clinical Islet transplantation and Uppsala University, Uppsala, Sweden. Main researcher: Prof. Olle Korsgren
- Chalmers University of Technology, Gotenburg, Sweden. Main researcher: Prof. Paul Gatenholm
- MERLN Institute for technology-inspired regenerative medicine, Maastricht University. Main researcher: Dr. A.A van Apeldoorn
- European Pancreas and Islet Transplant Association Consortium (EPITA)

Publications 2022:
S Abadpour, EM Niemi, LS Orrhult, C Hermanns, R de Vries, LP Nogueira, HJ Haugen, D Josefsen, S Krauss, A Apeldoorn, P Gatenholm, H Scholz. Adipose-derived stromal cells preserve pancreatic islet function in a

transplantable 3D bioprinted scaffold, bioRxiv doi: https://doi.org/10.1101/2022.05.30.494035

Berney T, Andres A, Bellin MD, de Koning EJP, Johnson PRV, Kay TWH, Lundgren T, Rickels MR, Scholz H, Stock PG, White S, International Islet Transplant Centers (2022) A Worldwide Survey of Activities and Practices in Clinical Islet of Langerhans Transplantation Transpl Int, 35, 10507 DOI 10.3389/ti.2022.10507

C Olsen, E Wiborg, E Lundanes, S Abadpour, H Scholz, SR Wilson. On-line reduction of insulin disulfide bonds with photoinduced radical reactions, upstream to nano liquid chromatography-mass spectrometry. Separation Science Plus (2022) https://doi.org/10.1002/sscp.202200022

Ghila L, Furuyama K, Grey ST, Scholz H, Chera S. Editorial: Beta-Cell Fate: From Gene Circuits to Disease Mechanisms. Front Genet. 2022 Feb 25;13:822440. doi: 10.3389/fgene.2022.822440. eCollection 2022.

Carrasco M, Wang C, Søviknes AM, Bjørlykke Y, Abadpour S, Paulo JA, Tjora E, Njølstad P, Ghabayen J, Nermoen I, Lyssenko V, Chera S, Ghila LM, Vaudel M, Scholz H, Ræder H (2022) Spatial Environment Affects HNF4A Mutation-Specific Proteome Signatures and Cellular Morphology in hiPSC-Derived β-Like Cells Diabetes, 71 (4), 862-869 DOI 10.2337/db20-1279

Ward C, Odorico JS, Rickels MR, Berney T, Burke GW 3rd, Kay TWH, Thaunat O, Uva PD, de Koning EJP, Arbogast H, Scholz H, Cattral MS, Stratta RJ, Stock PG; International Pancreas and Islet Transplant Association Beta-Cell Replacement Therapy Monitoring Task Force. International Survey of Clinical Monitoring Practices in Pancreas and Islet Transplantation. Transplantation. 2022 Jan 10. doi: 10.1097/TP.0000000000004058. PMID: 35019897.

PHOTO: MARIUS DIDRIKSEN

PI: TORILD SKRIVARHAUG

THE NORWEGIAN CHILDHOOD DIABETES REGISTRY (NCDR) AND BIOBANK

Primary Investigator: Torild Skrivarhaug, Professor, MD, PhD

Norwegian Childhood Diabetes Registry and Biobank. A nationwide population based registry with 98% ascertainment, sampling blood and standardized clinical data from the onset of diabetes in children < 18 years, and later annually until the age of 18 years. NCDR is increasing with more than 400 children with new-onset diabetes a year, including type 1 diabetes, type 2 diabetes, genetic diabetes and secondary diabetes. By following over 12000 patients with childhood-onset diabetes, we can identify changes in incidence and clinical status at onset. We also present changes in diabetes treatment, quality of care, prevalence of acute and late complications, quality of life. NCDR is a major contributor to different research projects.

The main research focus in NCDR:
1) Epidemiology in childhood-onset diabetes, focusing on incidence, prevalence, classification of childhood-onset diabetes in Norway, genetics, ethnicity, long-term complications and
mortality.

2) Quality in childhood diabetes care – a nationwide prospective population-based study for research and quality improvement by means of benchmarking.

3) Clinical childhood diabetes, especially focusing on quality of life, diabetes treatment, co-morbidity, eating disorders and the transition from paediatric to adult diabetes care.

News from 2022:
An increasing number of children and adolescents are diagnosed with diabetes in 2022.

Co-investigators/participants:
Geir Joner, Senior professor, MD, PhD
Knut Dahl-Jørgensen, Senior professor, MD, PhD
Kristian F. Hanssen, Senior professor, MD, PhD
Pål R. Njølstad, Prof., MD, PhD, University of Bergen, Haukeland University Hospital
Lars Christian Stene, PhD, senior researcher, Norwegian Institute for Public Health
Siv Janne Kummernes, RN, MSc
Osman Gani, PhD, statistician
Hanna Dis Margeirsdottir, MD, PhD
Maryam Saeed, MD, PhD student
Håvard Hatle, MD, PhD student
Heiko Bratke, MD, PhD student
Line Wisting, PhD, senior researcher
Nicolai A. Lund-Blix (postdoc), PhD
Per M. Thorsby, Ass. Professor, MD, PhD
Kristin Hodnekvam, MD, researcher
Nina Gjerlaugsen, MSc
Egil Midtlyng, psychologist
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External collaborators
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Karin Åkeson, MD, PhD, Dep. Pediatrics, Jønkøbing Hospital, Sweden
Ragnar Bjarnason, Prof., MD, PhD, Dep. Pediatrics, Landspitali University Hospital, Iceland
Hilde Hestad Iversen, PhD, Norwegian Institute of Public Health
Ragnar Hanås, Prof. Dr. med, Department of Paediatrics, NU Hospital Group, Uddevalla, Sweden and the Sahlgrenska Academy, Institute of Clinical Sciences, University of Gothenburg, Gothenburg, Sweden
Reinhard Holl, Prof. Dr. med. Institut für Epidemiologie und medizinische Biometrie, Universitaet Ulm

Publications 2022:

J Svensson, E.H. Ibfelt , Carstensen, A. Neu, O. Cinek, T. Skrivarhaug, B. Rami-Merhar, R.G. Feltbower, C. Castell, D. Konrad, K. Gillespie, P. Jarosz-Chobot, D. Marčiulionytė, J. Rosenbauer, N. Bratina, C. Ionescu-Tirgoviste, F. Gorus , M. Kocova, C.E. de Beaufort, C.C. Patterson **(2022)** *Age-period-cohort modelling of Type 1 diabetes incidence rates among children included in the EURODIAB 25-year follow-up study.* Acta Diabetologica 2022 Oct 7. PMID:36205797.IF:4.28

Niels H Birkebaek, Clemens Kamrath, Julia M Grimsmann, Karin Akesson, Klemen Dovc, Carine de Beaufort, Aveni Haynes, **Torild Skrivarhaug**, Mary White, Craig Jefferies, Martin De Bock, Zdenek Sumnik, Jannet Svensson, Justin T Warner, John W Gregory, Valentino Cherubini, Osman Gani, Thomas Hörtenhuber, Rosaria Gesuita, Riccardo Schiaffini, Ragnar Hanas, Reinhard W Holl, Ondrej Cinek **(2022)** *Long-term trends in the frequency of diabetic ketoacidosis at onset of paediatric type 1 diabetes and impact of the COVID-19 pandemic in 2020 and 2021 – An international multicentre study using 13 national diabetes registries from three continents* Lancet Diabetes and Endocrinology Oct. 2022. IF: 44.867

Lanzinger S, Zimmermann A, Ranjan AG, Gani O, Perez S. P, Akesson K, Majidi S, Witsch M, Hofter S, Johnson S, Pilgaard K.A, Kummernes S.J, Robinson H, Eeg-Olofsson K, Ebekozien O, Holl R.W, Svennson J, Skrivarhaug T, Warner J, Craig M.E, Maahs D **(2022)** *A collaborative comparison of international pediatric diabetes registries.* Pediatric Diabetes 2022 Sep;23(6):627-640. IF: 3.488

HOW DO YOUNG PEOPLE WITH TYPE 1 DIABETES (T1D) EXPERIENCE TRANSITION FROM PEDIATRIC TO ADULT HEALTH CARE?

A national, population-based cohort study from the Norwegian Childhood Diabetes Registry (NCDR)

Primary Investigator: Torild Skrivarhaug, Professor, MD, PhD

Objectives:
To explore the experiences of young people with T1D on transition from pediatric to adult health services.

Methods:
A questionnaire based on a mixed-method model was developed and sent to 784 adolescents/ young adults with T1D, registered in NCDR and transferred to adult-health services within the last 2-4 years. Psychometric evaluation included explorative factor analysis, tests of intern reliability, test-retest reliability. The questionnaire addressed experiences with health-personnel, consultations, organization of services and preparedness for transfer. Most items had a five-point scale. Demographic data, questions on treatment-regimens and comorbidity are included.

Results:
321 (41.4%) answered the questionnaire. 57.6% of the respondents, 36.0% of the non-respondents were female. Mean HbA1C at time of transfer was 8.8% in respondents, 9.1% in non-respondents. Significant differences in patient experiences of pediatric and adult health care were found for continuity in services ($p<0,001$), interval between consultations ($p<0,001$), confidence in caretakers ($p<0,001$), all-in-all satisfaction ($p<0,001$).

Co-investigators/participants:
Kristin Hodnekvam, M.D. (research fellow)

External collaborators:
Hilde Hestad Iversen, PhD, Norwegian Institute of Public Health
Cathrine Brunborg, Oslo Centre for Biostatistics and Epidemiology, Research Support Services, Oslo University Hospital, Norway
Osman Gani, PhD. Ass. Professor, Faculty of Medicine, UiO

News from 2022:
Submitted to Diabetic Medicine 07.04.2022, the paper: *Do adolescents and emerging adults receive the diabetes care they truly need? A nationwide study of the quality of diabetes health care during the transition from paediatric to adult care.*

THE USE OF INSULIN PUMPS (CSII) AND CONTINUOUS GLUCOSE MONITORING (CGM): DOES IT MAKE A DIFFERENCE?

Data from the Norwegian Childhood Diabetes Registry (NCDR).

Primary Investigators: **Heiko Bratke, MD, PhD. student**
Torild Skrivarhaug, Professor, MD, PhD (main supervisor)

Objective
The primary aim was to analyse the association between diabetes-specific health-related quality of life (HRQOL) and HbA1c in children and adolescents with type 1 diabetes. The secondary aims were to evaluate the associations between diabetes-specific HRQOL and age, sex, diabetes duration, and the use of diabetes technology in diabetes treatment.

Research Design and Methods
Children with type 1 diabetes (10-17 years, *N* = 1,019) and parents (children <10 years, *N* = 371; 10-17 years, *N* = 1,070) completed the DISABKIDS diabetes-specific questionnaire (DDM-10) as part of the 2017 data collection for the Norwegian Childhood Diabetes Registry. The DDM-10 consists of two subscales—'impact' and 'treatment'—with six and four items, respectively. In the linear regression models, the items and subscales were outcome variables, while HbA1c, age, sex, diabetes duration, insulin pump use, and continuous glucose monitoring (CGM) system use were predictor variables.

Results
Lower HbA1c measurements and male sex were associated with higher HRQOL scores on both DDM-10 scales in the age group 10-17 years, but not in children under 10 years. Parents gave lower HRQOL scores than children in the 10-17 age group. Insulin pump and CGM use were not significantly associated with HRQOL on the impact and treatment scale.

Conclusions
Low HbA1c and male sex are significantly associated with high HRQOL in children aged 10-17 with type 1 diabetes, but the use of diabetes technology is not positively associated with HRQOL. Differences in child- and parent-reported scores imply that parents might both over- and underestimate their child's HRQOL.

News from 2022:
Low HbA1c and male sex are significantly associated with high HRQOL in children aged 10-17 with type 1 diabetes, but the use of diabetes technology is not positively associated with HRQOL. Differences in child- and parent-reported scores imply that parents might both over- and underestimate their child's HRQOL.

Co-investigators/participants:
Eva Biringer, MD, Senior researcher, The Department of Research and Innovation, Helse Fonna HF
Hanna Dis Margeirsdottir, MD, Oslo University Hospital
Pål R. Njølstad, MD, PhD, Professor, University of Bergen, Haukeland University Hospital, Bergen, Norway
Jorg Assmus, PhD, Haukeland University Hospital, Bergen, Norway

Publications 2022:
Heiko Bratke, Eva Biringer, Hanna D Margeirsdottir, Pål R Njølstad, Torild Skrivarhaug **(2022)** *Relation of Health-Related Quality of life with glycemic control and use of diabetes technology in children and adolescents with type 1 diabetes: Results from a national population based study.* Journal of Diabetes Research 2022 Nov 3; 2022: 8401328. IF: 4.011

DOES NORMAL BLOOD GLUCOSE (TIME-IN-RANGE) PRESERVE INSULIN PRODUCTION IN CHILDREN WITH NEWLY DIAGNOSED TYPE 1 DIABETES?

Primary Investigator: Torild Skrivarhaug, Professor, MD, PhD

T1D is not a homogeneous disease. At onset of diagnosis, most patients still have some insulin-production left. The rate of the immune-mediated destruction of β-cells varies. Some patients lose their β-cell function soon after diagnosis; others maintain insulin production for years. Reports from several studies have shown that preservation of β-cell function results in better metabolic control, as evaluated by HbA1c, lower daily insulin-dose, reduction of long-term micro- and macro-vascular complications, and reduction of acute complications. The remaining insulin production seems to make the blood glucose more stable and the diabetes treatment less complicated.
The remaining insulin-production in the β-cells can be measured by using C-peptide, an excellent marker for residual β-cell activity. All children with new onset T1D in 2022 in Norway will be invited to participate in this study.

Our objectives:

1) To develop a digital, user friendly, educational tool to motivate and to increase the use of Time In Range (TIR) on a daily basis in children and adolescents with new-onset T1D.
2) Implement this tool as a part of daily diabetes care, close to onset of T1D, and follow the children with a standardized approach the first year of T1D.
3) To show that the use of CGM and increased TIR will preserve insulin production from the onset of T1D, measured as C-peptide.

News from 2022:
The recruiting of children and adolescents started in March 2022. By the end of 2022 about 90 subjects were recruited.

Co-investigators/participants:
Kristin Namtvedt Tuv, MD (research fellow)
Knut Dahl-Jørgensen MD, PhD, Senior professor
Osman Gani, PhD
Per Medbøe Thorsby, MD, PhD, Ass. Professor
Lars Krogvold MD, PhD

PHOTO: UNSPLASH

ADHD IN CHILDREN AND ADOLESCENTS WITH TYPE 1 DIABETES; DO THEY HAVE AN INCREASED RISK OF DIABETIC COMPLICATIONS?

Primary Investigator: Torild Skrivarhaug, Professor, MD, PhD

Attention Deficit Hyperactivity Disorder (ADHD) and type 1 diabetes (T1D) are diverse disorders with separate causes and treated by different health care professionals. Individuals with comorbidity of ADHD and T1D are reported to have poor metabolic control compared to T1D patients without ADHD. Maintaining adequate treatment adherence and glycaemic control in T1D requires the ability to organize several critical daily management tasks; frequent blood glucose monitoring, carbohydrate counting, insulin dose calculation and administration. Successful treatment of T1D requires good planning and organizing skills and impulsivity may be a challenge. Research on this comorbidity is still scarce. How many children in Norway that are diagnosed with both T1D and ADHD are not known. Our objectives are to find the number of children with the comorbidity of T1D and ADHD in Norway and to investigate whether these children have an increased health risk compared to children with only T1D.

Co-investigators/participants:
Kristin A Bakke, MD, paediatrician, Norwegian Centre of Expertise for Neurodevelopmental Disorders and Hypersomnias, Division of Paediatric and Adolescent Medicine, OUS
Egil Midtlyng, psychologist, Norwegian Centre of Expertise for Neurodevelopmental Disorders and Hypersomnias, Division of Paediatric and Adolescent Medicine, OUS
Osman Gani, PhD, Norwegian Childhood Diabetes Registry, Division of Paediatric and Adolescent Medicine, OUS

PHOTO: UNSPLASH

PI: LINE SLETNER

ARE EPIGENETIC MODIFICATIONS OF KEY GENES IN PLACENTA IMPORTANT LINKS BETWEEN MOTHER'S LIFESTYLE AND FETAL PRE- AND POSTNATAL GROWTH PATTERNS AND FUTURE DIABETES RISK?

Primary Investigator: Line Sletner, Associate Professor, MD, Phd

Background:
In utero exposures are possible mediators of risk for obesity, type 2 diabetes and cardiovascular disease in adulthood, by modulating placental function and early life development and growth.

Aims:
Our aim is to examine if variations methylation of growth-related hormones and morphology in placental tissue mediates effects of maternal factors on offspring growth from mid pregnancy until pre-school age.

Methods:
High quality maternal data collected from pregnancy, birth and postpartum and later routine anthropometric measurements of the children in the STORK-Groruddalen cohort is used. Placental epigenetic modifications are assessed using Formaline-Fixed-Paraffine-Embedded placental (FFPE) tissue.

News from 2022:
A pilot test of genome-wide metylation analyses (n=8) has been performed, with promising results. Analyses in a larger sample (n=96) has now started. Two papers exploring 1) the associations between maternal metabolic factors- and placental size and phenotype and 2) the potential mediating role of placental anthropometry on the associations between of maternal metabolism on offspring body composition at birth, is in progress.

Co-investigators/participants:

Ahus/Epigen:
Yvonne Böttcher (Professor)
Aina Fossum Moen (Researcher)
Baoyan Bai (PhD)

UiO:
Anne Karen Jenum (Professor Emerita)
Kåre I. Birkeland (Professsor)

OUS:
Christine Sommer (PhD)
Gitta Turowski (MD, PhD)

External collaborators:
India, Pune: Chittaranjan S. Yajnik

PREDICTION OF GESTATIONAL DIABETES FROM FOUR NORWEGIAN STUDIES (PREGEDIAB4N)

Primary Investigator: Line Sletner, Associate Professor, MD, PhD

Background:
National data about the prevalence of gestational diabetes (GDM) by different criteria, the effect on outcomes and how to best identify these women are needed.

Aims:
1) develop prediction models to improve screening strategies for GDM, balancing benefits and harms for women and health care
2) develop new sub-projects with other outcomes

Methods:
Our national Consortium with individual participant data from four Norwegian pregnancy cohorts collected 2002-2013 holds information from 3300 women followed 2-3 times during pregnancy and offered OGTT one or more times.

News from 2020:
The second paper in Rai's PhD, examining the risk of adverse perinatal outcomes in women who were identified with GDM by different criteria, has been in review (accepted 2023). The third paper, exploring alternative screening procedures for GDM is in progress and is nearly ready for submission.

A master project assessing seasonal variation in GDM-prevalence has been finalized and a research paper presenting the same results has been finalized (published 2023).

Co-investigators/participants:
UiA/Sørlandet sykehus:
Linda Reme Sagedal (MD, PhD),
Anam Shakil Rai (PhD-student)

UiO:
Anja Lyche Brænd (MD, Ass. Prof)
Anne Karen Jenum (Prof. Emerit.)

OUS:
Elisabeth Qvigstad (MD, Ass. Prof)
Marie-Cecilie Paasche-Roland (MD, PhD)

External collaborators:
NTNU:
Signe Stafne (PhD)
Siv Mørkved (Prof)

UiA/Sørlandet sykehus:
Are Pripp (PhD, Stat.)

Høyskolen på Vestlandet:
Marjolein M. Iversen (Prof)
Ragnhild B. Strandberg (Ass. Prof)
Astrid Stalheim (Master-student)

Australia (Brisbane):
David McIntyre (Prof)

PI: CHRISTINE SOMMER

THE EPIPREG PROJECT

Genetics and epigenetics in a population-based, prospective cohort of pregnant women

Primary Investigator: Christine Sommer, MSc, PhD, project leader

Background:
Since insulin resistance increases naturally in all pregnancies, pregnancy is a valuable model to study type 2 diabetes and other cardiometabolic diseases related to insulin resistance.

Aim:
discover epigenetic marks with potential to prevent or delay onset, or improve treatment of diabetes and other cardiometabolic diseases or trait and understand more about the underlying mechanisms.

Methods:
We have quantified epigenome-wide DNA methylation (Infinium methylationEPIC beadchip) in all Europeans (n=312) and South Asians (n=168) in the STORK Groruddalen cohort. We perform Epigenome-wide association studies (EWAS) to explore associations between a trait and DNA methylation at CpG sites across the entire genome, follow-up analysis such as methylation quantitative trait loci (mQTL), GO enrichment, and further lookups in publicly available summary data (such as expression quantitative trait methylation - eQTM).

News from 2022:
In 2022, our statistician Riccardo Parviero helped us by evaluating different models and methods for trans-ethnic epigenome-wide association studies. Our PhD student Nicolas Fragoso Bargas was very successful in publishing his epigenome-wide association study (EWAS) of insulin resistance in pregnancy in the prestigious journal Diabetes, and also published an EWAS of serum folate. He plan to submit his PhD early in 2023. Teresa Linares Pineda had a 3 months research stay in the EPIPREG research group as a part of her PhD project, working with methylation risk scores in the EPIPREG sample.

Co-investigators/participants:
Gunn-Helen Moen
Sindre Lee
Julia Onsrud Opsahl
Kåre I. Birkeland
Elisabeth Qvigstad
Anne Karen Jenum
Line Sletner
Nicolas Fragoso-Bargas
Riccardo Parviero

External collaborators:
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Lars Christian Mørch Stene
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Sonsoles Morcillo
Teresa Linares Pineda

Publications 2022:
Pervjakova N, Moen GH, Borges MC, Ferreira T, Cook JP, Allard C, Beaumont RN, Canouil M, Hatem G, Heiskala A, Joensuu A, Karhunen V, Kwak SH, Lin FTJ, Liu J, Rifas-Shiman S, Tam CH, Tam WH, Thorleifsson G, Andrew T, Auvinen J, Bhowmik B, Bonnefond A, Delahaye F, Demirkan A, Froguel P, Haller-Kikkatalo K, Hardardottir H, Hummel S, Hussain A, Kajantie E, Keikkala E, Khamis A, Lahti J, Lekva T, Mustaniemi S, Sommer C, Tagoma A, Tzala E, Uibo R, Vääräsmäki M, Villa PM, Birkeland KI, Bouchard L, Duijn CM, Finer S, Groop L, Hämäläinen E, Hayes GM, Hitman GA, Jang HC, Järvelin MR, Jenum AK, Laivuori H, Ma RC, Melander O, Oken E, Park KS, Perron P, Prasad RB, Qvigstad E, Sebert S, Stefansson K, Steinthorsdottir V, Tuomi T, Hivert MF, Franks PW, McCarthy MI, Lindgren CM, Freathy RM, Lawlor DA, Morris AP, Mägi R. Multi-ancestry genome-wide association study of gestational diabetes mellitus highlights genetic links with type 2 diabetes. Hum Mol Genet. 2022 Sep 29;31(19):3377-3391. doi: 10.1093/hmg/ddac050.

DIASA DIET – IMPROVING DIETARY ASSESSMENT IN INDIVIDUALS OF SOUTH ASIAN ORIGIN LIVING IN NORWAY

Primary Investigator: Christine Sommer, MSc, PhD, project leader

Background:
Individuals of South Asian origin living in Norway have high rates of type 2 diabetes, and diet may play a role in challenging blood glucose management seen in this group. However, we have limited knowledge about the role of diet in blood glucose management in South Asians living in Norway.

Aims:
To develop valid dietary assessment methods for South Asians living in Norway, to stimulate further research into the role of diet in cardiometabolic disease and risk factors in South Asians living in Norway.

Methods:
We want to assess and compare the results obtained by a web-based food frequency questionnaire (FFQ) and a 24h-recall interview (by telephone) in South Asian women that participate in the DIASA-1 study.

News from 2022:
In 2022, we have finalized all the interviews. Results are being analysed and prepared for publication.

Co-investigators/participants:
Kåre Birkeland
Hanne Løvdal Gulseth
Radhika Kumar
Therese ML Lensnes

External collaborators:
Monica Carlsen
Torunn Totland

PI: LARS CHRISTIAN STENE

THE PAGE STUDY: PREDICTION OF AUTOIMMUNE DIABETES AND CELIAC DISEASE IN CHILDHOOD BY GENES AND PERINATAL ENVIRONMENT

Primary investigator: Lars Christian Stene, PhD, Senior Researcher

PAGE is an acronym for «Prediction of Autoimmune diabetes and celiac disease in childhood by Genes and perinatal Environment». The overall goal is to gain new knowledge about environmental risk factors for type 1 diabetes and celiac disease, which in the future may be translated into preventive interventions. It is a substudy in the Norwegian Mother, Father and Child Cohort study (MoBa), which recruited pregnant women throughout the country from 1999-2008 and continues to follow the offspring.

Type 1 diabetes and celiac disease are common chronic diseases in children, associated with serious complications and reduced quality of life. Genes (HLA-DQ2 and -DQ8) strongly predispose for both diseases. Consumption of wheat products is necessary for expression of celiac disease, but most of the susceptible children do not develop disease. Increasing incidence over the past decades suggests involvement of non-genetic factors which are yet to be identified.

The early onset of both diseases, and other lines of evidence, suggest that in utero and early postnatal exposure is important. By following 100 000 pregnancies in the Norwegian Mother, Father and Child Cohort Study (MoBa), we have identified children who later develop type 1 diabetes and celiac disease, yielding the world's largest pregnancy cohort of this kind. Stored blood samples from the mother during pregnancy and from the umbilical cord has been tested for selected markers of perinatal environment to investigate whether these can predict future development of celiac disease and type 1 diabetes, together with genetic factors. These include vitamin D metabolites, circulating immune mediators, and quantity of maternal cells in the fetal circulation (maternal microchimerism). We also test the potential influence of several exposures of the mother during pregnancy and of the child in early life, based on information collected in questionnaires. These include frequencies of infections, smoking habits, use of medication and dietary intake. Some sub-studies are done in collaboration with a similar large cohort: The Danish National Birth Cohort.

The project is run by the Norwegian Institute of Public Health, in close collaboration with collaborators at several institutions, including Oslo University Hospital, Haukeland University hospital and University of Bergen, University of Southern Denmark, Statens Serum institut in Denmark, University of Bristol, and University of Colorado.

A number of specific research questions have been answered:

* PERINATAL VITAMIN D. The hypotheses that maternal and perinatal vitamin D predicts lower risk of type 1 diabetes or celiac disease, were not supported by our data. We also found a possible complex interaction of vitamin D and its binding protein with genes in the aetiology of type 1 diabetes.

* PERINATAL SYSTEMIC INFLAMMATION. The hypothesis that maternal or perinatal circulating immunological mediators predict future risk of celiac disease in childhood was not supported, but there was a potential relation between selected markers and risk of type 1 diabetes in children, which requires further study to provide conclusive evidence.

* INFECTION FREQUENCY. While gastrointestinal infections have long been hypothesized to influence the risk of celiac disease, there are few studies of this. PAGE found that frequency of infections (as reported by the mother) was associated with a slightly higher risk of celiac disease. A novel and interesting finding was that this was also the case for respiratory infections. This

indicates supports that infections may contribute towards disease risk, together with the established influence by genetic factors and gluten intake, and that this is not confined to gastrointestinal infections. While infections have also been hypothesized to influence the risk of type 1 diabetes, data from PAGE did not support this.

* INFANT GROWTH. Increased infant and early childhood weight gain is related to a statistically significant, but yet quite modest increase in risk of type 1 diabetes. For celiac disease, it is well established that affected children on average has lower weight and height for age at diagnosis, because of intestinal malabsorption. The PAGE study found, however, that linear growth deficits can be traced back to the second year of life, which is earlier than expected from current knowledge of when the disease process starts.

* MATERNAL MICROCHIMERISM. MMc is the transfer of small quantities of maternal cells to the fetus in utero, but the physiological functions of this process is still unclear. It has been proposed that this is associated with a state of tolerance. Measuring maternal DNA in the fetal circulation, a complex and time-consuming, process, was done for cases of T1D and controls. The main conclusion was that the quantity of maternal cells (DNA) in the fetal circulation at birth, was not associated with risk of type 1 diabetes in children. Our hypothesis that a larger quantity of maternal cells would protect the child from T1D was therefore not supported.

* DIETARY FIBRE: maternal dietary fibre during pregnancy intake was not associated with type 1 diabetes in children, despite very similar design and harmonized analysis with a previous study in the BMJ from the Danish National Birth Cohort study. In addition, we contributed with data on the child's intake of fibre (estimated quantity of gluten intake per day) during early childhood, and higher intake was associated with higher risk of type 1 diabetes. The results were published in PloS Medicine:
https://pubmed.ncbi.nlm.nih.gov/32119659/

SUMMARY. The study has contributed important new knowledge regarding early environmental exposures in the aetiology of type 1 diabetes and celiac disease. The funding from The Research Council of Norway has created a set of data and network of investigators that will continued harvesting of new knowledge from these unique resources.

News from 2022:
Two MSc student from Tromsø have successfully completed their master theses based on the PAGE study (main supervisor Nicolai Lund Blix)

Co-investigators/participants:
Geir Joner
Torild Skrivarhaug
Benedicte A. Lie
German Tapia
Nicolai A. Lund-Blix
Marte K. Viken
Ketil Størdal
and others, see list on project website:
https://www.fhi.no/en/studies/page/forskere-og-samarbeidspartnere-i-page/

External collaborators:
Pål R. Njølstad, Bergen
C. Legido-Quigley, T. Suvitaival and L. Ahonen, Steno Diabetes Center Copenhagen
List of collaborators at project website:
https://www.fhi.no/en/studies/page/forskere-og-samarbeidspartnere-i-page/
Publications 2022:
Abstract/conference presentation:
Øien MZ, Stene LC, Tapia G, Skrivarhaug T, Joner G, Njølstad PR, Størdal K, Lund-Blix NA. Vitamin A consumption in pregnancy and risk of offspring type 1 diabetes (Abstract). European Diabetes Epidemiology Group (EDEG) 56th Annual Meeting, Crete, Greece, April 2-5, 2022.

MIDIA: ENVIRONMENTAL CAUSES OF TYPE 1 DIABETES

Primary Investigator: Lars Christian Stene, PhD, Senior Researcher

MIDIA aims to find environmental risk factors or factors associated with lower risk of islet autoimmunity or type 1 diabetes (T1D). The study recruited over 900 newborns throughout Norway between 2001 and 2007, after screening nearly 50 000 newborns to identify those with the HLA genotype associated with highest T1D risk (HLA DQ8/2). Children with this susceptibility genotype had an expected absolute risk of T1D around 6-8%, and were followed longitudinally with screening for islet autoantibodies (anti-insulin, -GAD and IA2), questionnaires, blood samples and fecal samples (See Stene et al. J Autoimmun 2007 for detailed description of study design). A primary focus has been intestinal viral infections, but few consistent associations have been detected, including with enteroviruses. Recently, we have also investigated celiac disease in this cohort, for which we have discovered an association with higher frequency of enteroviruses (C. Kahrs, et al. BMJ 2019). Other novel discoveries in the MIDIA study includes the finding that respiratory infections were associated with higher risk of islet autoimmunity (Rasmussen et al. 2011) and that maternal obesity was associated with higher risk of islet autoimmunity (Rasmussen, Diabetes Care 2009), findings that have subsequently been corroborated in other cohort studies. Updated analyses of autoimmunity dynamics and risk of progression to type 1 diabetes are planned for 2023.

News from 2022:
No diabetes-publications from MIDIA in 2022, but results were presented in invited presentation of “Genes vs environment in the development of type 1 diabetes” at the EASD annual meeting in Stockholm.

Co-investigators/participants:
Kjersti S. Rønningen (founder and former PI)
German Tapia
Nicolai A. Lund-Blix
Ketil Størdal
Finn Erik Aas
Torild Skrivarhaug

External collaborators:
Ondrej Cinek, Motol University Hospital and Charles University, Prague, The Czech Republic
MIDIA also participates in the HEDIMED project, see separate description there.

Publications 2022:
Stene LC, Rasmussen T, Aas FE, Tapia G, Magnus P, Skrivarhaug T, Rønningen KS. Differential impact of family history of type 1 diabetes on incidence of islet autoimmunity and progression to clinical type 1 diabetes: the MIDIA study (Abstract). European Diabetes Epidemiology Group (EDEG) 56th Annual Meeting, Crete, Greece, April 2-5, 2022. (oral)

PHOTO: COLORBOX

HEDIMED: HUMAN EXPOSOMIC DETERMINANTS OF IMMUNE MEDIATED DISEASES

Primary Investigator: Lars C. Stene, PhD, Senior Researcher (Norwegian site; the consortium coordinator/PI is Heikki Hyöty; Tampere)

The project is based on a data and biological samples from cohorts constituting the largest clinical resource in this field including 350.000 pregnant women, 28.000 children prospectively followed from birth and 6.600 children from cross-sectional studies.

HEDIMED focuses on type 1 diabetes, celiac disease, allergies and asthma. Exposomic disease determinants and the underlying biological pathways will be identified by comprehensive characterization of both external and internal exposomic factors, and using advanced omics and multiplex technologies combined with cutting–edge data mining technologies. Particular emphasis is put on intrauterine and early childhood exposures since the disease process is known to start early.

HEDIMED also include cell and organ culture models to help the identification of causal associations.

The project period is 2020-2024. This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 864764 HEDIMED.

News 2022:
We have published a description of the study, finalized all the necessary infrastructure with ethical permissions, data protection impact assessments, agreements and HEDIMED platform for data storage analysis and visualization. Analyses are underway, and we have secured funding for a postdoc to work with us at Oslo University hospital, primarily on studies of celiac disease.

Co-investigators/participants:
The Norwegian Institute of Public Health (NIPH) is one of 22 partner institutions, and contributes with our two ongoing cohort studies MIDIA and MoBa/PAGE (described as separate projects). Among the collaborating scientist at ODRC are: German Tapia, Nicolai A. Lund-Blix, Geir Joner, Torild Skrivarhaug, Benedicte A. Lie, Marte K. Viken, Ketil Størdal

External collaborators:
The consortium consists of 22 partner institutions in 11 countries, and is led by Prof. Heikki Hyöty at University of Tampere. See project website for list of partners https://www.hedimed.eu/.

Publications 2022:
Laiho JE, Laitinen OH, Malkamäki J, Puustinen L, Sinkkonen A, Pärkkä J, Hyöty H, the HEDIMED Investigator Group (incl. LC Stene). Exposomic determinants of immune-mediated diseases. Environmental Epidemiology. 2022;6(3):e212. doi: 10.1097/EE9.0000000000000212. PMID: 35702504. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9187189/

Stene LC, Haynes A. Trending now: modelling global epidemiology of type 1 diabetes. Lancet Diabetes Endocrinol 2022 10(12):828-829. doi: 10.1016/S2213-8587(22)00306-0. PMID: 36372071. (solicited commentary on Ward et al. DOI: 10.1016/S2213-8587(22)00276-5) https://pubmed.ncbi.nlm.nih.gov/36372071/

Rantala AK, Tapia G, Magnus MC, Stene LC, Jaakkola JJK, Størdal K, Karlstad Ø, Nystad W. Maternal antibiotic use and infections during pregnancy and offspring asthma: the Norwegian Mother, Father and Child Cohort Study and a nationwide register cohort. Eur J Epidemiol 2022 37(9):983-992. doi: 10.1007/s10654-022-00897-y. PMID: 35939140.

PI: PER MEDBØE THORSBY

METABOLOMIC PROFILING OF HYPERGLYCEMIC CLAMP IN HUMANS

Primary Investigator: Per Medbøe Thorsby, MD, PhD

Nearly 90% of the genomically inherited risk of type 2 diabetes is in genes regulating beta cell function. Understanding the relationship between these findings and the pathophysiological development of type 2 diabetes is important. It has been reported that different metabolites are important for GSIS in humans.

We use untargeted metabolomic and proteomic profiling in samples form humans - both with and without type 2 diabetes - to investigate the difference in metabolomic and proteomic profiling between patients and healthy controls during hyperglycemic and euglycemic clamps.

Co-investigators/participants:
Milaim Pepaj, Mcs, PhD - Senter for psykofarmakologi, Diakonhjemmet sykehus

PHOTO: ØYSTEIN HORGMO, UIO

GENE EXPRESSION OF GLUCOSE AND VITAMIN D STIMULATED RODENT AND HUMAN ISLETS

Primary Investigator: Per Medbøe Thorsby, MD, PhD

Experiments on isolated pancreatic islets have elicited positive effects of 1,25(OH)2vitamin D on glucose-induced insulin secretion.

Our previous study showed direct effects of 25(OH)vitamin D and 1,25(OH)2vitamin D on insulin secretion in INS1E cells when combined with glucose. In addition, in vivo studies in rodents have also given support to the beneficial effect of vitamin D on pancreatic function.

We have recently reported the genomic effects of 25(OH)vitamin D and 1,25(OH)2vitamin D in INS1E cells. Both vitamin D metabolites significantly changed expression of genes, especially genes concerning apoptosis and beta cell survival were found to be upregulated.

Results from other studies on rodents and human islets support this, but to our knowledge none have yet investigated the effect of both 25(OH)vitamin D and 1,25(OH)2vitamin D on GSIS and gene expression in in rodent and human islets.

The aim of the present study is to find out whether both 25(OH)vitamin D and 1,25(OH)2vitamin affected glucose-induced insulin secretion in mouse and human islets and whether transcriptional changes investigated with array techniques could explain the positive link between vitamin D and GSIS.

News from 2022:
Mette E Bornstedt defended her PhD with the title: "The effect of vitamin D metabolites on glucose-stimulated insulin secretion (GSIS) and gene expression in murine insulin producing β-cells and pancreatic islets – an experimental study"

Co-investigators/participants:
Mette Eskild Bornsted, MD - Hormone laboratory, OUS
May Kristin Lyamouri Bredahl, Msc, PhD - Hormone laboratory, OUS
Jens Petter Berg, MD, PhD - Dep. Medical Biochemistry, OUS

External collaborators:
Hanne Scholz, Mcs, PhD - Dep. of Surgical Research, OUS
Ole Kristoffer Olstad, PhD - Dep. of Medical Biochemistry, OUS

TMEM27- MARKER FOR ß-CELL MASS

Primary Investigator: Per M. Thorsby, MD, PhD

Background
The total amount of secreted insulin depends on the absolute number of the ß-cells (ß-cell mass), and the output of each of these cells (ß-cell function). In both T1D and T2D significant amounts of ß-cell mass are lost. A more comprehensive understanding of how ß-cell mass changes during the course of diabetes may allow more targeted therapy strategies. However, today no biomarkers are available to monitoring ß-cell mass.

Aims
To develop Tmem27 as a circulating biomarker for assessing ß-cell mass.

Methods
Both Liquid chromatography coupled to Mass spectrometry (LC-MS) and ELISA will be used for measuring the levels of Tmem27 in blood.

Co-investigators/participants:
Milaim Pepaj, Mcs, PhD - Senter for psykofarmakologi, Diakonhjemmet sykehus
Kari Julien, Hormone laboratory, OUS
Nina Gjerlaugsen, Hormone laboratory, OUS

PI: CHRISTIN WAAGE

WOMEN AND THE RISK OF TYPE 2 DIABETES

Primary Investigator: Christin Waage, PhD, Post doc.

Background:
High prevalence of type 2 diabetes (T2D) among minority women in Norway. Gestational diabetes (GDM) is an early marker of disturbances in the glucose metabolism, linked to T2D. We found a high prevalence of GDM in the STORK Groruddalen study (STORK-G1).

Aim:
To assess the prevalence of prediabetes and T2D (measured by HbA1c) and to explore ethnic differences in development of T2D.

Method:
11 years follow-up study of 823 pregnant women, 59% ethnic minorities (STORK-G1).

News from 2022:
The data collection was completed in March 2022. We have achieved a participation rate of 53% of those eligible at the 11-year follow-up with extensive clinical data collected during the Covid pandemic. Many women had moved out of the area, some were no longer living in Norway, some were not possible to reach by phone, and many women struggled with time constraints. We have dried blood spots from 94% of those who met, and fasting venous samples from 56%. A total of 85% attended the full-scale data collection. 76% of the participants used an accelerometer (Actigraph).

Co-investigators/participants:
Senior researchers:
Anne Karen Jenum (PI), MD, PhD/Prof
Kåre I. Birkeland, MD, PhD/Prof
Kåre Rønn-Richardsen, PhD
Nilam Shakeel, MD, PhD
Line Sletner, MD, PhD
Nina Køpke Vøllestad, Dr. scient, Prof.
Hilde Stendal Robinson, PhD
Research fellows:
Karin Elisabeth Bennetter, PhD student

External collaborators
Active collaborators over the past year (2022): Child health clinics in Stovner and Bjerke district in Oslo

Publications 2022:
Waage, C. W., Mdala, I., Stigum, H., Jenum, A. K., Birkeland, K. I., Shakeel, N., ... & Sletner, L. (2022). Lipid and lipoprotein concentrations during pregnancy and associations with ethnicity. *BMC Pregnancy and Childbirth*, *22*(1), 1-12.

PHOTO: UNSPLASH

PI: LINE WISTING

TYPE 1 DIABETES AND DISTURBED EATING BEHAVIOR

Primary Investigator: Line Wisting, PhD, Senior Researcher

Background: The prevalence of eating disorders among young females with type 1 diabetes is 2-3 times higher compared to their peers without diabetes. This comorbidity is associated with poor glycemic control and increased rates of morbidity and mortality. Yet, there is a lack of knowledge about how to prevent eating disorders in individuals with type 1 diabetes.

Aims: This project aims to investigate the effect of the body acceptance- and eating disorder prevention program Diabetes Body Project compared to a psychoeducational control condition over 2-years of follow-up in a multi-site RCT.

Methods: 280 young females with type 1 diabetes aged 14-35 years will be recruited across four sites in three countries (Norway, the Netherlands, and USA).

Outcomes: Main outcomes include eating disorder risk factors (body dissatisfaction, thin-ideal internalization, negative affect, and dietary restraint), eating disorder symptoms, eating disorder onset, HbA1c and time-in-range (TIR), diabetes distress, and diabetes-specific quality of life.

News from 2022
In collaboration with Stanford University, Joslin Diabetes Center, and Amsterdam University Medical Centers we received a research grant from the Juvenile Diabetes Research Foundation to investigate the effect of the Diabetes Body Project to reduce eating disorder risk factors and symptoms, eating disorder onset, glycemic control, and diabetes psychological aspects among young females with type 1 diabetes (2022-2026).

Read more: www.bodyproject.no/diabetes

Co-investigators/participants:
Severina Haugvik, Pediatric Department and Regional Department for Eating Disorders, OUS
Torild Skrivarhaug, Pediatric Department and the Norwegian Childhood Diabetes Registry, OUS
Knut Dahl-Jørgensen, Pediatric Department, OUS

External collaborators:
Eric Stice, Stanford University, USA
Maartje deWit, Amsterdam University Medical Centers, the Netherlands
Elena Toschi, Joslin Diabetes Center, USA

THESES 2022

Mette Bornstedt
"The effect of vitamin D metabolites on glucose-stimulated insulin secretion (GSIS) and gene expression in murine insulin producing β-cells and pancreatic islets – an experimental study"

Oddrun Kristiansen
"Nutritional environment of the unborn child: The role of the human placenta in the maternal-fetal interaction; A study of uncomplicated pregnancies"

Kristina B. Slåtsve
"Prevalence, vascular complications, and level of health care treatment in individuals with type 2 and type 1 diabetes mellitus"

Therese Weider
"Autoimmune Thyroid Diseases: Traces of Viral Infection"

PUBLICATIONS

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