Berzelius symposium no 96

23–25 MAY 2018 IN MALMÖ, SWEDEN

Diabetes and the cardiovascular risk challenge – mechanisms, epidemiology and treatment aspects

Programme · General information · Abstracts

Svenska Läkaresällskapet

LUND UNIVERSITY

Karolinska Institutet

U.E.M.S.

The symposium has been granted 12 European CME credits (ECMEC) by the European Accreditation Council for Continuing Medical Education, EACCME®

Welcome to the symposium on

**Diabetes and the cardiovascular risk challenge
– mechanisms, epidemiology and treatment aspects**

The Berzelius symposia are the most prestigious scientific meetings organised by the Swedish Society for Medicine (SSM), this time in collaboration with Lunds Universitet (LU) and Karolinska Institutet (KI). The symposium will focus on mechanisms and clinical aspects of the relationship between diabetes and cardiovascular disease in the light of new studies and trial data that expand our understanding of this relationship and new treatment possibilities. An abstract book and proceedings will be published.

The conference is open to all clinicians and basic science representatives from the Nordic area, international guests and lecturers, as well as representatives from pharma and device manufacturers.

We hope that you will join us for the Berzelius symposium on 23–25th May 2018 and look forward to your active participation. There will be a number of oral presentations but also a possibility to submit abstracts for poster presentation.

Welcome to the conference!

Organising Committee:
Peter M Nilsson, Professor, MD, PhD, Lund University (chair)
Margrét Leosdottir, MD, PhD, Lund University
Lars Rydén, Senior Professor, MD, PhD, Karolinska Institute (co-chair)
Linda Mellbin, MD PhD, Karolinska Institute
Carl Johan Östgren, Professor, MD, PhD, Linköping University
Stig Attvall, Associate Professor, MD, PhD, Sahlgrenska Academy

Contact information:
Peter M Nilsson (chair), peter.nilsson@med.lu.se, phone +46-40-33 24 15
Lars Rydén (co-chair), lars.ryden@ki.se, phone +46-70-7292171
Camilla Key, Symposium secretariat, camilla.key@med.lu.se, phone +46-40-33 23 01
Annie Melin, Symposium secretariat, annie.melin@sls.se , phone: +46-8-440 88 78

EACCME accreditation granted EACCME #940
The Berzelius symposium 96 Diabetes and the cardiovascular risk challenge – mechanisms,epidemiology and treatment aspects, Malmö, Sweden, 23/05/2018-25/05/2018 has been accredited by the European Accreditation Council for Continuing Medical Education (EACCME®) with 12 European CME credits (ECMEC®s). Each medical specialist should claim only those hours of credit that he/she actually spent in the educational activity.

Partners

Hjärt Lungfonden

AMGEN

Boehringer Ingelheim

AstraZeneca

MSD

SANOFI

novo nordisk

Programme

Wednesday May 23rd, 2018

11.00–13.00   Registration at Jubileumsaulan, Malmö

13.00   Opening of symposium
Stefan Lindgren, President, the Swedish Society of Medicine
Jan Nilsson, Chair of the scientific board, HLF Foundation
Peter M Nilsson, Chair, Organizing committee, Malmö

Session 1   **Definition of diabetes and origins of cardiovascular complications**
Chair: *Francesco Cosentino*, Stockholm

13.10–13.30   Diabetes – a disease with many faces. *Leif Groop*, Malmö
13.30–13.50   Lifestyle interventions in the context of precision medicine.
Tuomas Oskari Kilpeläinen, Denmark
13.50–14.10   The red blood cell in diabetes. *John Pernow*, Stockholm
14.10–14.30   The gene-diet-microbiota-metabolism link. *Marju Orho-Melander*, Malmö

14.30–15.00   **Coffee, Posters**

Session 2   **Epidemiology and trends**
Chair: *Annika Rosengren*, Göteborg

15.00–15.20   Life course perspectives. The Finnish experience. *Johan Eriksson*, Helsinki, Finland
15.20–15.40   Early life programming of cardiometabolic disease – Global perspectives.
Chittaranjan Yajnik, Pune, India
15.40–16.00   Factors contributing to the global rise in type 2 diabetes and impaired glucose regulation.
William Knowler, Phoenix, USA
16.00–16.20   Global trends in cardiovascular disease – increased disease burden, but not everywhere.
Helena Nordenstedt, Stockholm

Session 3   **State-of-the-Art 1**
Chair: *Leif Groop*, Malmö

16.20–16.50   Personalized medicine to treat patients with diabetes. *Andrew Hattersley*, Exeter, UK

16.50–17.00   **Best poster abstract 1.**

17.15   Welcome Reception

Thursday May 24th, 2018

Session 4   **Diabetes – the clinical spectrum**
Chair: *Anna Norhammar*, Stockholm

08.30–08.50   Diabetes complications: impact of metformin. *John Petrie*, Glasgow
08.50–09.10   Testosteron, diabetes and cardiovascular disease. *Anne Wang*, Stockholm
09.10–09.30   Identifying novel biochemical pathways as possible drug targets for the prevention and treatment of diabetes. *Martin Magnusson*, Malmö
09.30–09.50   Endocrine disturbances in diabetes and cardiovascular diseases. *Olle Melander*, Malmö

09.50–10.20   **Coffee, Posters**

Session 5   **State-of-the-Art 2**
Chair: *Marju Orho-Melander*, Malmö

10.20–10.50   Lifestyle as the first step for prevention and treatment of diabetes. *Mai-Lis Hellenius*, Stockholm

Session 6   **Primary prevention of CVD complications in diabetes**
Chair: *Peter Rossing*, Copenhagen

10.50–11.10   Glycaemic control. *Katarina Eeg-Olofsson*, Göteborg
11.10–11.30   Lipid control. *Mats Eriksson*, Stockholm
11.30–11.50   Blood pressure control. *Karin Manhem*, Göteborg
11.50–12.10   Cardio-renal protection. *Per-Henrik Groop*, Helsinki, Finland

12.10–13.00   **Lunch, Posters**

Session 7   **Secondary prevention of CVD complications in diabetes**
Chair: *Linda Mellbin*, Stockholm

13.00–13.20   The importance of a target driven multifactorial approach. *Lars Rydén*, Stockholm
13.20–13.40   New lipid-lowering treatment and goals. *Olov Wiklund*, Göteborg
13.40–14.00   Arterial stiffness – A new treatment target? *Peter M Nilsson*, Malmö

Pro-Pro debate
14.00–14.40   Second-line treatment for type 2 diabetes
– incretin active drugs or SGLT2 inhibitors as first choice?!
Pro incretin drugs: *Anders Frid,* Malmö
Pro SGLT2 drugs: *Jan Eriksson*, Uppsala

14.40–15.10   **Coffee, Posters**

Session 8   **The role of guidelines for prevention of cardiovascular complications**
Chair: *Lars Rydén*, Stockholm

15.10–15.30   European perspective. *Francesco Cosentino*, Stockholm
15.30–15.50   Transatlantic perspective. *William M Herman*, USA
15.50–16.10   Swedish perspective. *Carl Johan Östgren*, Linköping

Session 9   State-of-the Art 3
Chair: *Lars Rydén,* Stockholm

16.10–16.40   Integration of basic and clinical science for prevention of diabetes complications – focus on the incretin system. *Eberhard Standl*, Germany

16.40–17.00   **Best poster abstract 2 and 3**

19.00   Symposium Dinner at the Scandic Triangeln in Malmö
Pre-registration is necessary.

Friday May 25th, 2018

Session 10   Quality Assessment and Developments, Registers
Chair: *Emil Hagström*, Uppsala

08.30–08.50   The National Diabetes Register, Sweden. *Soffia Gudbjörnsdottir*, Göteborg
08.50–09.10   SWEDEHEART, Sweden. *Bertil Lindahl,* Uppsala
09.10–09.30   SEPHIA Register, Sweden. *Margrét Leosdottir*, Malmö
09.30–09.50   EUROASPIRE . *Viveca Gyberg*, Stockholm

09.50–10.20   **Coffee, Posters**

Session 11   The role of Patients, Relatives and the Health Care Organisation
Chair: *Mona Landin-Olsson*, Lund

10.20–10.40   Swedish Diabetes Association. *Fredrik Löndahl*, Helsingborg
10.40–11.00   Patient centered health care. *Åsa Hörnsten*, Umeå
11.00–11.20   Primary Health Care. *Carl Johan Östgren*, Linköping
11.20–11.40   The Steno Diabetes Centre Concept. *Allan Flyvbjerg*, Copenhagen, Denmark

Panel debate: Quality of diabetes care – New challenges for 2020!
Chair: *Anders Frid,* Malmö

11.40–12.30   Panelists: *Karin Wikblad, Fredrik Löndahl, Carl Johan Östgren, Allan Flyvbjerg, Soffia Gudbjörnsdottir, Viveca Gyberg, Stig Attvall*

12.30–12.40   Closing remarks. *Lars Rydén* and *Peter M Nilsson*

General information

Jubileumsaulan – the conference hall

Malmöhus Castle

Skåne University Hospital, Malmö

Skåne University Hospital, Malmö.
Central building with Emergency

Venue
23–25 May 2018 at the Jubileumsaulan, Medicinskt forskningscentrum (MFC), Skåne University Hospital at Jan Waldenströms gata 3–5 in Malmö.

Lunch and coffee
Lunch on 24 May, a lunchbaguette on 25 may and coffee on 23–25 May are included in the participation fee and will be served outside the Jubileumaulan.

Social events
Welcome reception on Wednesday 23 May at 17.15, outside Jubileumsaulan.
Faculty dinner on Wednesday 23 May at 19.00 Restaurang Wega, Malmöhus Castle (pre-reservation is mandatory).
Symposium dinner on Thursday 24 May at 19.00, Restaurant Scandic Triangeln (pre-reservation is mandatory).

Abstracts from the symposium
All congress documents will be handed out to the participants at registration outside the symposium hall from 11 a.m on Wednesday 23 May, 2018.

Symposium website
http://www.sls.se/diabetes

Speakers abstracts

Diabetes – a disease with many faces

Leif Groop, Lund University Diabetes Centre, Finnish Institute for Molecular Medicine (FIMM), Helsinki University

During the past 100 years we have been diagnosing diabetes by measuring only one metabolite, glucose. During the same time the prevalence of diabetes in Europe has increased from less than 1% to more than 7–8% and much more in other parts of the world. Today >90% of all diabetic patients are considered to have T2D. While the phenotype of T1D and T2D way back were quite distinct, early-onset lean insulin-deficient patients vs. obese adult-onset patients, the situation today with the explosion of T2D is more complex. Do they all have the classical characteristic form of T2D? From clinical experience this is likely not the case, therefore a refined classification could provide a powerful tool individualize treatment regimens and identify individuals with increased risk of complications already at diagnosis.

To address this we applied a data-driven cluster analysis in > 20,000 mostly newly diagnosed diabetic patients from 4 Nordic cohorts using six variables (GAD-auto antibodies, age at diagnosis, BMI, HbA1c, HOMA2-B and HOMA2-IR), and related to health registries. We thereby identified 5 replicable clusters of diabetes patients, with significantly different patient characteristics and risk of diabetic complications. Particularly, individuals in the most insulin-resistant cluster 3 had significantly higher risk of diabetic kidney disease, but had been prescribed similar diabetes treatment compared to the less susceptible individuals in clusters 4 and 5. The insulin deficient cluster 2 had the highest risk of retinopathy. In support of the clustering, genetic associations to the clusters differed from those seen in traditional T2D.

This new sub-classification may help to tailor and target early treatment to patients who would benefit most, thereby representing a first step towards precision medicine in diabetes.

Lifestyle interventions in the context of precision medicine

Tuomas Oskari Kilpeläinen, Associate Professor, University of Copenhagen, Section for Metabolic Genetics

Randomized controlled trials have shown that reducing body weight, increasing physical activity, and improving dietary quality decreases the risk of type 2 diabetes. However, these studies have focused on the average estimated effects in the studied populations and have not accounted for the fact that susceptibility to lifestyle risk factors and responses to interventions vary between individuals. Precision medicine approaches could make lifestyle therapies more effective by using a person's genomic and other omic chararacteristics to tailor interventions individually. Genetic information is a particularly attractive tool for personalizing lifestyle interventions as genome-wide genotypes can now be assessed accurately and at low cost. However, studies aiming to predict individual susceptibility to lifestyle risk factors or differential response to lifestyle interventions based on genetic variants have not been successful. New approaches are needed to facilitate the discovery of genetic variants and other biomarkers linked to lifestyle response phenotypes. Recent studies applying machine learning algorithms to interrogate omic data layers have shown promise in predicting individual responses to foods. Mobile technologies may help assessing lifestyle behaviors among participants of large biobanks in order to identify genetic markers that modify individual susceptibility to lifestyle risk factors. Eventually, utilizing novel biomarkers linked to intervention responses in disease prevention requires specific efforts for clinical translation, which remains a further challenge ahead.

The red blood cell in diabetes

John Pernow, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden

The mechanisms underlying the development of cardiovascular complications in patients with type 2 diabetes (T2DM) are complex and far from understood. Due to this gap in knowledge, specific therapies targeting such mechanism are lacking. Existing evidence suggest that endothelial dysfunction is a key factor behind development of atherosclerosis in T2DM. This change involves reduced bioavailability of endothelium-derived nitric oxide (NO) and increased formation of reactive oxygen species which results in activation of pro-inflammatory and pro-atherosclerotic processes. Recent data indicate that red blood cells (RBCs) may play a role in the regulation of cardiovascular function and that their function is altered in T2DM. We have investigated the ability of RBCs to induce endothelial and cardiac dysfunction in T2DM. These RBCs have increased activity of the enzyme arginase which results in increased oxidative stress. RBCs from patients with T2DM markedly impair endothelial function via a mechanism that involves reduced production of endothelial cell NO. Pharmacological interventions that target the altered function of the RBCs results in improved endothelial function. The data obtained demonstrate a novel disease mechanism in T2DM whereby altered function of RBCs drives the development of vascular dysfunction.

Life course perspectives – the Finnish experience

Johan G Eriksson, Professor, Helsinki, Finland

Several non-communicable diseases, including cardiovascular disease (CVD) and type 2 diabetes (T2D), seem to have their origins in early life. This is believed to work through the mechanism of early programming taking place at sensitive periods of development. Studies based upon findings from the longitudinal Helsinki Birth Cohort Study (HBCS), including 13345 men and women, born 1934-44 in Helsinki, Finland, have shown the importance of prenatal and early postnatal growth in relation to CVD and T2D and will be further described and discussed. Also, the long-term health impact of maternal adiposity during pregnancy will be discussed. Potential underlying factors and mechanisms explaining the associations will be discussed as well as preventive measures.

Early life programming of cardiometabolic disease – Global perspectives

Chittaranjan S Yajnik, KEM Hospital & Research Centre, Pune, India

Conventional model of cardiometabolic risk proposes a genetic susceptibility and precipitation by accumulation of adverse lifestyle factors. Given the polygenic and non-modifiable nature of genetic susceptibility, majority of prevention trials have concentrated on reduction of risk factors. This usually happens in post-reproductive adults. Research in last few decades has proposed a modifiable susceptibility linked to early life exposures (pre- , peri- and post-conceptional) which is presumably epigenetic. Maternal nutrition and metabolism are some of the many factors which can permanently alter the structure and function in a developing embryo which persists for the rest of life, this is called programming. Both undernutrition (of macro- and micro-nutrients) and overnutrition (maternal obesity and diabetes) increase the risk of future adiposity and diabetes. This reflects in the U shaped association between birth weight and subsequent diabetes. In a rapidly transiting country like India, there is a combination of macro-nutrient excess and micro-nutrient deficiency which could contribute to the rapidly rising epidemics of diabetes and other cardiometabolic disorders. Indeed, India is one of the world's capitals of diabetes and cardiovascular disease.

Research in Pune demonstrated that short and undernourished mothers gave birth to small and thin babies which were more adipose than the English babies (thin-fat), suggesting programming of body composition and metabolism. The mothers ate only moderate quantities of macro-nutrients (predominantly carbohydrates) and were deficient in a number of micronutrients (iron, vit B12, vit D), folate appeared adequate. Majority worked on the farms and had large energy expenditure. The children have grown on average 5 cm taller than their parents, are relatively thin but 28% of them have prediabetes at 18 years of age. Prediabetes is predicted by lower birth weight but higher BMI at 18 years, they had lower B-cell function since early childhood. Low maternal vit B12 and vit D during pregnancy but higher concentrations of red cell folate predicted higher adiposity in these children.

In summary, we now have a new 'primordial' model for prevention of non-communicable disease which is intergenerational. In the lifecycle it is never too early and never too late to start prevention. Maternal nutrition, metabolism and related factors appear appropriate targets for intervention.

Factors contributing to the global rise in type 2 diabetes and impaired glucose regulation

William C. Knowler, MD, DrPH, National Institute of Diabetes and Digestive and Kidney Diseases, Phoenix, AZ, USA

Overview. Type 2 diabetes and impaired glucose regulation, defined as abnormal plasma glucose concentrations not severe enough for a diagnosis of diabetes, are caused by a combination of inadequate insulin secretion and insulin action in the body. The major known contributors to these abnormalities and their changes over time will be discussed.

Relevance to the congress. Because diabetes is a major risk factor for cardiovascular disease, its increasing incidence presents new challenges to the prevention of cardiovascular diseases. Type 2 diabetes can be prevented or delayed in high risk persons, but there is limited evidence that such prevention also prevents cardiovascular disease or extends life.

Key learning points. The incidence of type 2 diabetes is increasing in many parts of the world, especially among youth, owing to many familial and environmental factors.

References

Pettitt DJ, Baird HR, Aleck KA, Bennett PH, Knowler WC. Excessive obesity in offspring of Pima Indian women with diabetes during pregnancy. *N Engl J Med* 308:242-245, 1983.

Hales CN, Barker DJ, Clark PM, Cox LJ, Fall C, Osmond C, Winter PD. Fetal and infant growth and impaired glucose tolerance at age 64. *British Medical Journal.* 303(6809):1019–22, 1991.

Lindsay RS, Dabelea D, Roumain J, Hanson RL, Bennett PH, Knowler WC: Type 2 diabetes and low birth weight: the role of paternal inheritance in the association of low birth weight and diabetes. Diabetes 49: 445–449, 2000.

Pavkov ME, Hanson RL, Knowler WC, Bennett PH, Krakoff J, Nelson RG: Changing patterns of type 2 diabetes incidence among Pima Indians. *Diabetes Care* 30: 1758–1763, 2007.

Mayer-Davis EJ, Lawrence JM, Dabelea D, Divers J, Isom S, Dolan L, Imperatore G, Linder B, Marcovina S, Pettitt DJ, Pihoker C, Saydah S, Wagenknecht L; SEARCH for Diabetes in Youth Study. Incidence Trends of Type 1 and Type 2 Diabetes among Youths, 2002-2012. *N Engl J Med* 376:1419–1429, 2017.

Knowler WC, Crandall JP, Chiasson JL, Nathan DM: Prevention of type 2 diabetes. Chapter 38 in *Diabetes in America*, 3rd ed. Cowie CC et al, Eds. Bethesda, MD, National Institutes of Health, NIH Pub No. 17-1468, 2017 (in press).

Global trends in cardiovascular disease – increased disease burden, but not everywhere

Helena Nordenstedt, Karolinska Institutet and Gapminder

The number of people with cardiovascular diseases globally is increasing and in both the popular media and in scientific articles dire warnings of this emerging giant disease burden are common. To encounter this burden we need to understand the underlying driving factors. Is it the so-called Western lifestyle, with unhealthy diet and sedentary habits that is taking its toll when spreading to all corners of the world? Or is it that people in some parts of the world are more susceptible to cardiovascular diseases? The story behind the increasing cardiovascular disease burden is also the history of humankind in the past 100 years, and the story will be told using animated statistics from free online tools. (www.gapminder.org and www.healthdata.org)

Diabetes complications: impact of metformin

John R Petrie, Professor, BSc MBChB PhD FRCP(Ed) FRCPSG
Professor of Diabetic Medicine, Institute of Cardiovascular and Medical Sciences, BHF Glasgow Cardiovascular Research Centre, University of Glasgow

Diabetes carries a risk of complications (retinopathy, nephropathy and neuropathy) that are unique to the condition, while others are premature forms of those affecting the general population (e.g. myocardial infarction, stroke and peripheral artery disease). Despite undoubted advances in care and management, contemporary population-based data from the Scottish Diabetes Research Network indicate that period life expectancy is still reduced by 4–5 years in type 2 diabetes and by 11–13 years in type 1 diabetes.

Absolute rates of acute myocardial infarction are falling in people with and without diabetes but remain much higher in those with diabetes because rates were so much higher before the start of this trend. A doubling of incidence and tripling of prevalence of type 2 diabetes in the past 20 years (in part due to increased longevity), has translated to a rise in the overall proportion of coronary artery disease in the population that is attributable to diabetes. On a more positive note, since 2014 diabetes is no longer the leading cause of working-aged blindness, at least in developed countries.

Long term glucose control (although difficult to achieve) is effective in preventing the complications unique to types 1 and 2 diabetes. However, it but has much less impact on premature cardiovascular disease, at least in type 2 diabetes. A multifactorial approach to the management of risk factors (obesity, blood pressure, dyslipidaemia, smoking) is effective in type 2 diabetes, and probably also in middle-aged (and older) adults with type 1 diabetes. In addition, metformin and some of the newer glucose-lowering agents (e.g. empagliflozin, liraglutide) may reduce rates of cardiovascular disease by mechanisms that are not entirely dependent on glucose-lowering.

In this lecture, I will highlight the effects of metformin on cardiovascular disease in diabetes, focusing particularly on recent data from the REMOVAL trial (NCT01483560) in type 1 diabetes. The potential for other adjunct agents within future therapeutic strategies will also be discussed.

Testosteron, diabetes and cardiovascular disease

Anne Wang, MD, PhD student, Unit of Cardiology, Department of Medicine, Solna, Karolinska Institutet, Stockholm Sweden

People with type 2 diabetes mellitus (T2DM) are more prone to develop cardiovascular disease (CVD) and their prognosis is more dismal than that of people without T2DM. Reasons for this increased risk are not fully understood. Observational studies suggest a low testosterone in males as part of the explanation, based on reports of low testosterone levels being associated with CVD risk factors including insulin resistance as well as increased cardiovascular events and all-cause mortality. However, the current data is inconsistent and whether testosterone is a marker for poor health or a causal risk factor remains unclear. The presentation aims at providing an overview of the effect of endogenous and exogenous testosterone on the cardiometabolic system.

Key learning points:
- Why testosterone is an interesting hormone in glucose perturbations and CVD.
- The controversy surrounding testosterone substitution and cardiac safety.
- The effects of testosterone substitution on glucometabolic measures and the cardiovascular system.

References:

Gencer B, Mach F. *Testosterone: a hormone preventing cardiovascular disease or a therapy increasing cardiovascular events?* European Heart Journal. 2016.

Cheung K et al. *Testosterone level in men with type 2 diabetes mellitus and related metabolic effects: A review of current evidence.* Journal of Diabetes Investigation. 2015.

Identifying novel biochemical pathways as possible drug targets for the prevention and treatment of diabetes

Martin Magnusson, Associate professor, Lund University

Using mass spectrometry–based metabolomics approaches and multiplex proteomic platforms we have identified several associations between small molecules and diabetes independent of established traditional risk factors, but although these circulating biomarkers associated with disease represent possible useful markers of disease susceptibility, their causal involvement and directionality of any causal effect is less certain (due to possible reversed causality and/or unknown factors affecting disease). In this talk I will discuss the clinical importance of assessing causality between circulating biomarkers and disease and present two novel possible drug targets.

We have published data showing low plasma levels of dimethylgycine (DMG), a byproduct of the metabolism of choline, to be associated with high glucose levels. In addition, in the genome wide association study (GWAS), a genetic variation (major allele of rs2431332) within the dimethylglycine dehydrogenas (DMGDH) locus was genome wide associated with lower DMG concentrations, higher blood glucose, increased insulin resistance as well as with increased risk of incident diabetes in three independent large cohorts (1). These data implicate that DMG is causally associated with diabetes development and urges for further studies examining if a possible inhibition of DMHDH or supplementation of DMG might prove useful for the treatment/ prevention of diabetes.

Furthermore, we have also been able to show that low levels of the well know cardio-protective and antihypertensive natriuretic peptides (e.g. atrial natriuretic peptide (ANP)) (2), as well as a genetic variation at the natriuretic peptide precursor A (NPPA) locus gene (minor allele of rs5068), GWAS associated with lower levels of circulating ANP (3), are associated with increased risk of diabetes development, implicating a causal role for ANP in diabetes and a supplement of natriuretic peptides as a potential drug target.

1. Magnusson M, Wang TJ, Clish C, Engstrom G, Nilsson P, Gerszten RE, Melander O: Dimethylglycine Deficiency and the Development of Diabetes mellitus. Diabetes 2015;

2. Magnusson M, Jujic A, Hedblad B, Engstrom G, Persson M, Struck J, Morgenthaler NG, Nilsson P, Newton-Cheh C, Wang TJ, Melander O: Low plasma level of atrial natriuretic Peptide predicts development of diabetes: the prospective malmo diet and cancer study. J Clin Endocrinol Metab 2012;97:638–645

3. Jujic A, Nilsson PM, Engstrom G, Hedblad B, Melander O, Magnusson M: Atrial natriuretic peptide and type 2 diabetes development--biomarker and genotype association study. PLoS One 2014;9:e89201

Endocrine disturbances in diabetes and cardiovascular diseases

Olle Melander, Professor of Internal Medicine, Lund University, Malmö

Given the increasing burden of obesity and type 2 diabetes, novel ways of prevention of diabetes-related cardiovascular disease (cardiometabolic disease) are needed. Individuals with high levels of the two hormones neurotensin and vasopressin are at markedly increased risk of cardiometabolic disease and premature mortality, however, recent data suggests that cardiometabolic disease related to excess neurotensin and vasopressin can be prevented.

Neurotensin promotes intestinal absorption and central storage of fat, an evolutionary conserved trait which was beneficial in times of insufficient food access but instead has become harmful in our Western societies with obesity, liver steatosis, diabetes and cardiovascular disease as consequences. Antibody-based blockade of neurotensin as well as inhibition of intestinal fat absorption and neurotensin secretion with orlistat are promising candidate therapies.

Under stable (non-acute) conditions, the most important cause of high vasopressin secretion is low fluid/water intake. Compensatory high levels of vasopressin aimed at retaining water through action on the renal vasopressin-2 receptor also stimulates ACTH and cortisol secretion through vasopressin-1B receptors. Subjects with high vasopressin levels have a mild "Cushing-like" phenotype and are at high risk of diabetes and cardiovascular disease. Importantly, the approximately 25% of the population who are at risk due to high vasopressin are typically low water drinkers and respond with prompt vasopressin reduction when supplemented with water; pointing out a simple promising life-style therapy suitable for risk reduction in 25% of the population, i.e. water supplemention.

Specific preventive actions to individuals with high cardiometabolic risk due to high levels of neurotensin and vasopressin are promising examples of personalized primary prevention.

Lifestyle as the first step for prevention and treatment of diabetes

Hellénius M-L, MD, PhD, Professor
Department of Medicine, Karolinska University Hospital, Solna
SE-171 76 Stockholm, Sweden

The knowledge of the importance of a healthy lifestyle for prevention and treatment of type 2 diabetes, as well as cardiovascular disease, has increased considerably in recent decades, and today lifestyle interventions form the basis of both prevention and treatment of type 2 diabetes. Findings from epidemiological studies have now been confirmed in both primary and secondary preventive lifestyle trials.

Despite the fact that many are exercising, sedentary time has increased and total physical activity has decreased in most populations. Sedentary time is, according to a large number of prospective studies, an independent risk factor for type 2 diabetes and cardiovascular diseases and also common cancers. Furthermore, dietary factors (unhealthy dietary patterns) are according to Global Burden of Disease the most prominent risk factor for total mortality and non-communicable diseases like type 2 diabetes.

In randomized controlled lifestyle intervention trials from for example China, USA and Finland, it has been shown that dietary intervention in combination with increased physical activity, can radically reduce the risk of type 2 diabetes in individuals at increased risk. Long-term follow-up investigations after 23 years of the participants in the Chinese trial, demonstrate significantly reduced incidence of type 2 diabetes, as well as reduced cardiovascular and total mortality.

In the randomized controlled cardiovascular primary prevention study PREDIMED (n 7447), it could be shown within 4,8 years that a mediterranean diet with additional supplements of extra virgin olive oil or supplements of nuts and almonds could prevent every second case of type 2 diabetes in healthy risk individuals aged 55-80 years. With new molecular genetics and molecular biology techniques, we better understand the underlying mechanisms regarding the protective effects of a healthy lifestyle.

Knowledge from prospective epidemiological studies as well as controlled randomized clinical trials, needs to be more effectively translated into clinical practice to achieve its full impact.

Primary prevention of CVD complications in diabetes – Focus on glycaemic control

Katarina Eeg-Olofsson, Sahlgrenska University Hospital, Gothenburg

Glycaemic control is a corner stone in diabetes treatment for persons with both type 1 diabetes and type 2 diabetes. The goal is high quality of life and to avoid both acute and chronic diabetes complications. Over the last decades the risk of cardiovascular disease (CVD) in diabetes has decreased but is still higher in persons with diabetes than in the general population. Results from the DCCT and the EDIC follow-up in type 1 diabetes as well as the UKPDS and follow-up of newly diagnosed type 2 diabetes persons show that glycaemic control is important in primary prevention of CVD complications. These results are supported by observational data. The effect of glycemia on CVD risk takes time and we need to individualize treatment targets. Extra focus and strict treatment targets should be given younger persons with many years with diabetes ahead. In the new era with continuous glucose monitoring, other measures of glycaemia than HbA1c, focusing more on effects of glycaemic variability might add insights in the role of glycaemia on CVD risk. Multifactorial risk factor treatment and control including glycaemic control is of paramount importance in primary prevention of CVD complications in diabetes.

Lipid control

Mats Eriksson, Professor, Senior consultant, Department of Endocrinology, Metabolism and Diabetes, Karolinska University Hospital, Stockholm

Statins are the main treatment for prevention of cardiovascular disease (CVD) reducing the synthesis of cholesterol. Ezetimibe inhibit cholesterol absorption. The combination of statin and ezetimibe has in two randomized trials, SHARP and IMPROVE-IT resulted in additional reduction of cholesterol and in cardiovascular events. In the Sharp study 1/5 of the patients had diabetes mellitus (T2DM). The positive result of the IMPROVE-IT was mainly the result of reducing atherosclerotic events in participating patients with T2DM. Patients with T2DM with high-risk for CVD are characterized by increased remnant-cholesterol. Especially T2DM with end-stage disease as albuminuria and peripheral artery disease are at very high risk. Remnant-cholesterol has clearly been shown to be good predictor for CVD in epidemiological studies. The combination of simvastatin and ezetimibe decrease the remnants in addition to a decrease of cholesterol and low density lipoprotein (LDL) cholesterol. The combination seems to be especially effective in patients with T2DM.

PCsk-9 is an enzyme reducing the LDL receptors and thus increase the plasma level of LDL cholesterol. Antibodies against Pcsk-9 on top of statin decrease the LDL cholesterol and the remnant particles to very low plasma levels. Two huge outcome studies with PCsk-9 antibodies have shown remarkable good effects. The sub-population of patients with T2DM in responds in the same manner as other high-risk patients with reductions in CVD morbidity and mortality.

Conclusion: Recent data from several high quality randomized clinical studies clearly indicate that most of the patients with diabetes mellitus ought to be treated with lipid lowering agents for the prevention of CVD.

Blood pressure control

Karin Manhem, Professor/Chief physician, University of Gothenburg

High blood pressure (HT) and diabetes mellitus type 2 (DM 2) have a high degree of coexistence. For example, HT occurs in approximately 80% of the adult population with DM 2, and HT is twice as common in patients with DM 2 as in healthy matched controls. In the adult population, almost every third adult person has HT, and at 70 years age , almost two thirds of the population has HT.

There are limited data from RCTs regarding a specific target blood pressure in DM. However, there are data from RCTs that confirm that patients with HT and DM type 2 benefit from a more intensive HT treatment. UKPDS showed in the late 1990th that more intensive blood pressure treatment reduced the risk of macro and microvascular complications, but compared to today's blood pressure targets, the intensively treated group was relatively poorly treated. HOT and ABCD are examples of other historical RCTs that show increased treatment benefit with a lower blood pressure, but these RCTs included patients with diabetes based on more conservative (higher) glucose levels. Other RCTs cannot proof any benefit with lower blood pressure targets, but among these studies there are several factors that make the evaluation problematic. In some trials there was a clear problem with power (ACCORD) (INVEST) and in other presented trials the data was based on subgroup analyzes (ONTARGET). The SBU report concludes in 2004 that "Available studies on blood pressure reduction and reduced risk of progressive kidney damage motivate a target blood pressure of 130/80 mm Hg or lower for patients with diabetes mellitus, but the effects on cardiovascular disease and death have not been studied. "Thus, these data on reduced renal damage contributed to the target blood pressure <130/80 mm Hg. In 2014 the Swedish Medical Products Agency wrote in its recommendations that patients with HT and DM 2 should aim for a target blood pressure of <140/85 mm Hg, and the reason for this was two folded. First there was inevitably a lack of conclusive results from RCTs. Second there was a worry regarding intensive blood pressure reduction in older patients with HT and DM 2 since these patients often have several coexisting diseases, are subject to polypharmacy and are generally fragile.

During 2016–2017, no less than 9 meta-analyzes were published on the topic of intensive versus less intensive blood pressure treatment. None of these studies, however, are based on individual data and the same RCTs are naturally occurring in several of the meta-analyzes. The results are reported in different ways, but the majority conclude that a more intensive blood pressure treatment is of value. The new guidelines from AHA/ACC recommend the lower blood pressure level (<130/80) to all patients with HT and high risk, regardless of the presence of DM 2 or not.

In conclusion, treatment of patients with HT and DM 2 should be individualized. In older individuals with a long duration of illness, the overall picture may determine how intensively blood pressure should be treated, but at younger ages and in individuals with short duration of illness, one should aim at a lower target blood pressure level.

Cardio-renal protection

Per-Henrik Groop, professor, Helsinki, Finland

The prevalence of type 2 diabetes (T2D) is increasing with epidemic proportions all over the world. A substantial proportion of individuals with T2D develop diabetic complications with grim consequences such as increased risk of premature mortality, cardiovascular disease, heart failure, renal disease and high risk of ending up on dialysis. The presence of renal disease increases the risk of cardiovascular disease manifold and cardiovascular disease increases the risk of renal disease substantially. Such a close relationship between the heart and the kidney is not unexpected given the shared risk factor profiles. Consequently, cardiovascular and renal disease need to be monitored and treated in concert.

Recent landmark randomized controlled trials such as the EMPA REG OUTCOME trial, the LEADER trial and the CANVAS program have provided unprecedented treatment options for individuals with T2D and established cardiovascular disease with profound effects on the prognosis. In the EMPA REG OUTCOME trial exposure to 10 or 25 mg of the SGLT2-inhibitor empagliflozin compared to placebo reduced the primary composite endpoint, 3P-MACE, by 14%, and in the CANVAS program exposure to 100 or 300 mg of canagliflozin was associated with a similar 14% reduction in the primary 3-P MACE endpoint. In the LEADER trial exposure to 1.8 mg of the GLP1 agonist liraglutide was associated with a 13% reduction in the primary 3P-MACE endpoint. Notably, the two SGLT2-inhibitor trials showed not only immediate reductions in the risk of cardiovascular death, but also in the risk of hospitalization for heart failure as well as remarkable reductions in the risk of progression of renal disease. These cardio- and renoprotective effects of the SGLT2-inhibitors have been accompanied by similar beneficial effects of the GLP1-agonist liraglutide. The presentation will highlight the cardio- and renoprotective effects of these novel glucose-lowering medications, and will also dig deeper into the potential mechanisms behind the beneficial effects of these novel medications.

# The importance of a target driven multifactorial approach

Lars Rydén, Senior Professor, FoU - Tema Hjärta och Kärl, S1:02
Karolinska University Hospital/Solna

The association between cardiovascular disease and type 2 diabetes (T2DM) is complex involving many potential pathophysiological pathways. Among them are dysglycaemia (even before the formal onset of diabetes), hypertension, dyslipidaemia, inflammatory activation, oxidative stress, endothelial dysfunction and hypercoagulability. If T2DM develops by the age of 40–45 years it means a shortening of future life expectancy by six-seven years. Risk factors e.g. a too high blood pressure or lipids are considerably more serious in people with than among those without T2DM and therefore in need of early detection and strict management. As many as 90% of people with T2DM are overweight or obese, 66% have hypertension and 70% dyslipidaemia. The combination of two or more risk factors multiplies rather than adds to the future cardiovascular risk.

A multifactorial disease demands a multifactorial management. European and national guidelines recommend careful control of blood pressure, dyslipidaemia, glycaemia and in the presence of cardiovascular disease antiplatelet therapy, and they bring forward strict treatment targets. It is underlined that life-style measures are the fundamental platform for management and that pharmacological treatment usually is needed in addition. The recommendations include advice on the use of appropriate drugs and their combinations. Examples on improved prognosis by means of a holistic multifactorial approach to T2DM has been brought forward e.g. from the Euro Heart Survey on Diabetes and the Heart, the Danish Steno 2 study and more recently from the Swedish Diabetes Registry.

New and important is that agents, originally launched as glucose lowering drugs, reduce cardiovascular events, some also protecting from heart failure in T2DM patients with established atherosclerotic disease. Accordingly the prevailing glucocentric approach to glycaemic control, "the lower the better", should be abandoned and glucose lowering treatment chosen with the ambition not only to manage glycaemia but also to protect from cardiovascular events.

The evolution of the (glycaemic) management of T2DM can be illustrated as in the figure:
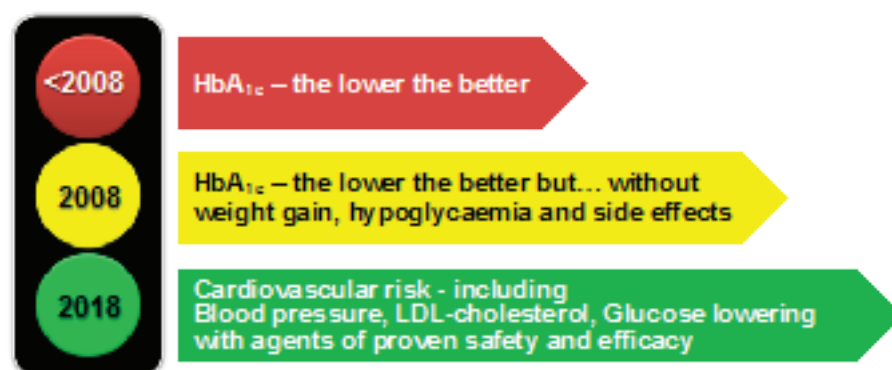
New Lipid lowering treatment and goals

Olov Wiklund, professor em., Wallenberg Laboratory, Sahlgrenska Academy at University of Gothenburg, Sweden

LDL-lowering with statin treatment is now the clinical routine to reduce cardiovascular events among patients with diabetes. Current treatment goals are based on the results from a large number of randomized controlled studies and meta-analyses. These goals are challenged by recent trials suggesting a benefit from LDL-reduction to lower levels, than currently recommended (1, 2). Furthermore recent data emphasize the importance of triglyceride-rich lipoproteins and their remnants for the development of atherosclerosis (3, 4). Since moderately elevated triglycerides often is a component of diabetic dyslipidaemia new treatment options against high triglycerides may be of special relevance in diabetes.

In the future new LDL-cholesterol goals will be considered, using cholesterol absorption inhibitor or PCSK9 inhibitors in addition to statin treatment. Treatment should go beyond LDL cholesterol and target triglyceride rich lipoproteins and their remnants.

New drugs to reduce plasma triglyceride levels are being developed targeting apoCIII, angiopoetin like protein and also new fibrate derivatives. These drugs are now being tested in clinical trials.

1. Giugliano RP, Cannon CP, Blazing MA, Nicolau JC, Corbalan R, Spinar J, et al. Benefit of Adding Ezetimibe to Statin Therapy on Cardiovascular Outcomes and Safety in Patients With vs. Without Diabetes: Results from IMPROVE-IT. Circulation. 2017.

2. Sabatine MS, Leiter LA, Wiviott SD, Giugliano RP, Deedwania P, De Ferrari GM, et al. Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: a prespecified analysis of the FOURIER randomised controlled trial. Lancet Diabetes Endocrinol. 2017;5(12):941–50.

3. Olkkonen VM, Sinisalo J, Jauhiainen M. New medications targeting triglyceride-rich lipoproteins: Can inhibition of ANGPTL3 or apoC-III reduce the residual cardiovascular risk? Atherosclerosis. 2018;272:27–32.

4. Taskinen MR, Boren J. Why Is Apolipoprotein CIII Emerging as a Novel Therapeutic Target to Reduce the Burden of Cardiovascular Disease? Curr Atheroscler Rep. 2016;18(10):59.

Arterial stiffness – A new treatment target?

Peter M Nilsson, MD, PhD, Lund University, Dept. Clinical Sciences, Skåne University Hospital, Malmö, Sweden

For many years the interest in atherosclerosis, primarily affecting the arterial intima layer, has been growing and mechanism leading to cardiovascular events well described and defined. However, prior to this in time is a period in early life with stiffening of the large elastic arteries, primarily affecting the arterial media, a phenomenon that has been shown to be an important risk marker for future cardiovascular events and mortality beyond well-known cardiovascular risk factors [1]. Measurement of arterial stiffness is preferably performed by use of carotid-femoral Pulse Wave Velocity (c-f PWV) according to a consensus document [2]. This can be done directly by devices such as SphygmoCor® or Complior®, or indirectly by devices such as Arteriograph® or Mobil-o-Graph®, etc. There are also other ways to investigate the arterial distensibility by ultrasound technologies. A value of arterial stiffness with c-f PWV more than 10 m/s is a risk marker based on European consensus.

Arterial stiffness is known to be strongly associated with age, hypertension and diabetes [3]. The arterial ageing is tightly inter-correlated with blood pressure and causes the increase in pulse pressure seen in aged individuals. In some individuals, the arterial stiffening seen with increasing age is more pronounced and occurs earlier in life, a phenomenon described as Early Vascular Ageing (EVA) [4]. A number of non-haemodynamic components are thought to affect the arterial ageing, among the markers of glucose metabolism and insulin resistance influencing dyslipidaemia. Several cross-sectional studies have shown an association between arterial stiffness and diabetes as well as with markers of impaired glucose metabolism. Individuals with end-stage renal disease (ESRD) are also known to exhibit an increased central arterial stiffness but results from studies investigating the association between arterial stiffness and stages of chronic kidney disease have presented conflicting results. Results from a prospective study showed that central obesity predicts arterial stiffness over a time period of 16 years [5], whereas a 20-years follow-up study including men indicates that heavy smoking, c-reactive protein (CRP) and pulse pressure (PP) are predictors of arterial stiffness. New intervention studies test the benefits of reducing arterial stiffness in a targeted way, for example the SPARTE study in France.

In summary, EVA is a new concept to explain some of the increased cardiovascular risk also in patients with diabetes. New interventions are needed to address the role of glycaemia and Advanced Glycaemic End (AGE) products for promoting EVA. It is possible to assess arterial stiffness, both with direct and indirect methods.

References:
1. Ben-Shlomo Y, Spears M, Boustred C, May M, Anderson SG, Benjamin EJ, *et al*. Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17,635 subjects. J Am Coll Cardiol. 2014;63(7):636–646.

2. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, *et al*. Expert concencus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J. 2006;27:2588–2605.

3. Stehouwer CD, Henry RM, Ferreira I. Arterial stiffness in diabetes and the metabolic syndrome: a pathway to cardiovascular disease. Diabetologia. 2008;51(4):527–539.

4. Nilsson PM, Boutouyrie P, Cunha P, Kotsis V, Narkiewicz K, Parati G, *et al*. Early vascular ageing in translation: from laboratory investigations to clinical applications in cardiovascular prevention. J Hypertens. 2013;31(8):1517–1526.

5. Johansen NB, Vistisen D, Brunner EJ, Tabak AG, Shipley MJ, Wilkinson IB, *et al*. Determinants of aortic stiffness: 16-year follow-up of the Whitehall II study. PLoS One. 2012;7(5):e37165.

The role of guidelines for prevention of cardiovascular complications. European perspectives

Francesco Cosentino, Unit of Cardiology, Karolinska Institute and Karolinska University Hospital, Stockholm

Type 2 diabetes (T2D) mellitus portends a high risk of adverse cardiovascular outcomes, including death, translating into an estimated reduction in life expectancy of 12 years. Despite this alarming risk, 30 to 50% of patients with diabetes do not meet guideline-recommended treatment goals for glycated haemoglobin (HbA1c) and other cardiovascular risk factors such as blood pressure, or cholesterol. Providing patients with optimal cardioprotection treatment strategies thus remains a major unmet need in this population. Addressing this treatment gap is imperative because of the burdensome prevalence of T2D, which impacts an estimated 58 million people in Europe, and it is expected to reach 439 million globally by 2030.

The growing awareness of the strong biological relationship between T2D and CVD rightly prompted two large European organizations to collaborate to generate guidelines relevant to their joint interests, the first of which were published in 2007.

Now, the third joint effort of the European Society of Cardiology (ESC) and European Association for the Study of Diabetes (EASD) to write guidelines on the management of diabetes mellitus (DM), pre-diabetes, and cardiovascular disease (CVD), is ongoing. During the last decade an interdisciplinary approach between cardiologists and diabetologists has been strongly advocated in Europe. Indeed, the collaboration across specialty borders is crucial to improve CV health in patients with T2D. The last guidelines on this subject were presented at the ESC meeting in Amsterdam and published in the European Heart Journal in 2013. Some assert that too many guidelines are being produced but, in this burgeoning field, the development of both basic and clinical science and, most of all, the exciting results of recent CV outcome trials have made necessary to update the previous guidelines.

From a European perspective, how to promote evolution in guidelines to best empower clinicians to integrate evidence-based therapies into practice is today's challenge.

The Role of Guidelines for the Prevention of Cardiovascular Complications. A Transatlantic Perspective

William H. Herman, MD, MPH

Over the past decade, North American diabetes clinical practice guidelines have increasingly emphasized individualized treatment goals and a more holistic approach to cardiovascular risk reduction. Recommendations for glycemic management now reflect the results of recent cardiovascular outcome trials that have demonstrated that people with type 2 diabetes and atherosclerotic cardiovascular disease (ASCVD) benefit from GLP-1 receptor agonists and SGLT-2 inhibitors. Recommendations for lipid management focus on moderate intensity statin therapy for all diabetic patients ≥40 years of age, moderate or high intensity statin therapy for diabetic patients with ASCVD risk factors, and high intensity statin therapy for all diabetic patients with established ASCVD. The addition of non-statin LDL lowering therapies is also now recommended for patients with diabetes and ASCVD who have LDL-cholesterol levels ≥70 mg/dl (1.8 mmol/l) despite maximally tolerated statin therapy. A target blood pressure of <140/90 mmHg is recommended for diabetic patients with hypertension but the classes of recommended anti-hypertensive agents have been expanded to include all of those demonstrated to reduce adverse cardiovascular outcomes. Finally, guidelines continue to focus on smoking prevention and cessation and aspirin therapy for secondary and primary cardiovascular disease prevention as part of a comprehensive approach to the prevention of cardiovascular complications.

The role of guidelines for prevention of cardiovascular complications. Swedish perspective

Carl Johan Östgren, Professor, Department of Medical and Health Sciences (IMH), Linköping University

There is now extensive evidence on the optimal management of diabetes, offering the opportunity of improving the immediate and long-term quality of life and reduce the risk for cardiovascular complications of those with diabetes. Furthermore, there is currently an increasing number of other classes of antihyperglycemic agents, including insulin, that may be added to metformin, or used in combination with each other, if glycemic targets are not met. This imposes demands on increased competence and knowledge of the primary care physicians, which in most cases are responsible for the treatment of type 2 diabetes in a population. Guidelines are one important part of a process, which seeks to address those problems. Many guidelines have appeared internationally, nationally, and more locally in recent years. Ideally, a guideline should be evidence based but also sensitive to resource and cost-effectiveness issues. The talk will give a brief overview of the Swedish guidelines focusing on glycemic targets and choice of antihyperglycemic agents.

Integration of basic and clinical science for prevention of diabetes complications – focus on the incretin system

Eberhard Standl, Forschergruppe Diabetes eV at Munich Helmholtz Centre

Incretin based therapies have matured to established therapies, especially in combination with metformin. They have been proven to be safe by dedicated, usually FDA mandated large scale cardiovascular outcome trials (CVOTs), some of them, in particular therapy with the GLP-1 receptor agonist liraglutide, to indeed reduce cardiovascular events and all-cause mortality in high risk patients with type 2 diabetes (T2D) and coexisting cardiovascular complications. Incretin based therapies by virtue of their mode of action of enhancing GLP-1 levels or action, release more insulin in a glucose dependent manner and reduce inadequately elevated glucagon levels. GLP-1 receptor agonists (GLP-1 RA) also delay gastric emptying and increase satiety by effects on the brain. Incretin based therapies mainly target postprandial hyperglycemia, longer acting GLP-1 agonists also lower fasting glucose concentrations. Unlike as with sulfonylureas, there is very little risk of hypoglycemia or weight gain. On the contrary, DPP4 inhibitors regularly induce some weight loss despite better glucose control, treatment with GLP-1 agonists is usually associated with a more marked weight loss of around three kilograms or more. Other favorable cardio-metabolic actions comprise beneficial effects on blood pressure and components of dyslipidemia, more marked though with GLP-1RAs. DPP-4 inhibitors are well tolerated, GLP-1 agonists may cause some nausea and other gastrointestinal side effects upon initiation of therapy, symptoms which usually subside longer term. Controversy exists whether all GLP1 RAs are able to decrease cardiovascular complications in patients with established cardiovascular disease with a number of CVOTs still ongoing. In all CVOTs showing a cardiovascular benefit also a reduction of renal endpoints was seen by secondary outcome analysis. None of the DPP4 inhibitors thus far has been able to demonstrate cardiovascular benefit in appropriate CVOTs, in contrast to earlier hopes based on limited short term studies. Moreover, there is currently no evidence for primary prevention with any glucose lowering agent, so this should not influence treatment choice for T2D patients without evidence of cardiovascular disease. Increased risk of hospitalization for heart failure was noted in a CVOT with a DPP4 inhibitor as an unexpected finding, but without likely explanation this being related to the inhibition of the DPP4 enzyme. GLP1 RAs showed no heart failure related signals in CVOTs, as did the DPP4 inhibitor sitagliptin.

SWEDEHEART, Sweden

Bertil Lindahl, professor, University of Uppsala

The vision for the Swedish Quality Registries is that "the National Quality Registries are used in an integrated and active way for *continuous learning, improvement, research and management* to create the best possible health and care together with the individual". The SWEDEHEART registry (Swedish Web-system for Enhancement and Development of Evidence-based care in heart disease Evaluated According to Recommended Therapy) is a national quality registry for cardiovascular care (RIKS-HIA), coronary angiography and percutaneous coronary intervention (SCAAR), cardiac surgery, and secondary prevention (SEPHIA) and cardio-genetic diseases, which was formed in 2009 by the merging of 4 different existing registries. After that, the cardiogenic and percutaneous valve implantation sub-registries have been added.

The goal for the SWEDEHEART registry is to respond to all aspects of the vision for the National quality registers. During my presentation, I will give examples how the register has been used successfully for continuous learning, improvement, research and management and the impact this has had on cardiac care in Sweden. Furthermore, I will discuss the possibilities and challenges ahead for the registry.

SEPHIA Register, Sweden

Margrét Leosdottir, MD, PhD, Chair of the SEPHIA Registry

The Secondary Prevention after Heart Intensive Care Admission (SEPHIA) registry provides detailed information on the quality of cardiac rehabilitation care in Sweden. Since the start of the registry in 2005 approximately 77.000 patients have been registered in SEPHIA with high national coverage at a hospital level (>95%). As such, the registry represents an internationally unique cardiac rehabilitation cohort of patients who have suffered a myocardial infarction (MI), both in terms of size and national representability.
According to the registry 26% of patients with MI in 2017 had a diagnosis of diabetes at one-year post-MI, which is somewhat lower than reported in the latest EUROASPIRE survey. The range between hospitals, however, is wide (17–50%), indicating lack of adequate diagnostics at sites with low numbers. There is also a wide variation in prescribed treatment and routines for care of patients with diabetes between hospitals, with considerable room for improvement. More detailed variables on prescribed diabetes treatment, which are being introduced in the registry in 2018, will provide more details on the quality of care for MI patients with diabetes.

Key learning points

- Diabetes among MI patients is underdiagnosed at many Swedish hospitals

- There is a large variation in how MI patients with diabetes are treated within cardiac rehabilitation

- Care for MI patients with diabetes also varies largely, with considerable room for improvement

References
www.swedeheart.se

EUROASPIRE

Viveca Gyberg, Department of Medicine, Solna, Karolinska University Hospital

The European Society of Cardiology has published guidelines six times since 1994 describing state-of-the art in preventing cardiovascular disease. The implementation of these guidelines has been evaluated by the cross-sectional survey EUROASPIRE since the mid 1990's. The results show that the risk factor management is suboptimal and that many patients do not reach the treatment targets for blood pressure, blood lipids and blood glucose. Over time the EUROASPIRE-studies reveal a negative trend regarding life style oriented care with an increase in obesity, central obesity and diabetes but an improvement regarding the control of blood pressure and blood lipids. It is likely that the negative life style trend counteracts the positive trend regarding improved pharmaceutical treatment. This knowledge underlines the importance of further efforts to implement multifactorial preventive programs to reach the most effective cardiovascular disease prevention.

Patient centered care

Åsa Hörnsten, Umeå University

Patient- or person-centred care was introduced with the aim to move the focus away from a strict biomedical view on disease to a more comprehensive perspective on patients, viewed as whole persons. Health care of today should be patient-centred according to law and several guidelines. However, in international comparisons and evaluations of quality in health care, patients in Sweden have scored lower levels of satisfaction in patient-centred issues. It has been suggested that a problem is that Swedish health care is organized for administrative convenience rather than patient or even provider convenience.

The evidence for patient-centred care on health outcomes are increasing, but still weak. Systematic reviews evaluating effects report mixed effects on health behaviour and health status among patients. Several single randomized controlled studies have though reported effects on health outcomes in shorter and longer terms among patients with e.g. acute coronary syndrome and type 2 diabetes. Our own intervention studies among people with type 2 diabetes in primary health care have shown satisfying results on HbA1c and these are presented in this session.

In conclusion, these results are promising even if some staff still seem to me ambiguous regarding patient centred care in clinical practice. In addition, patients as well as caregivers have reported improved wellbeing from a person centred approach in health care.

Learning points
- Health care of today should be patient-centred according to law and several guidelines.
- The evidence for patient-centred care on health outcomes are weak but increasing.
- Our own studies evaluating patient centred care among people with type 2 diabetes in primary health care are very promising even if some staff still are ambiguous.

References

1. Boström E, Isaksson U, Lundman B, Lehuluante A, Hörnsten Å. Patient-centred care in Type 2 Diabetes- an altered professional role for diabetes specialist nurses. Scandinavian Journal of Caring Sciences 2014; 28(4): 675–82.
2. Hörnsten Å, Sandström H, Stenlund H, Lundman B. Metabolic improvement after intervention focusing on personal understanding in type 2 diabetes. Diabetes Research and Clinical Practice 2005; 68: 65–74.
3. Hörnsten Å, Stenlund H, Lundman B, Sandström H. Improvements in HbA1c remain after 5 years – a follow-up of an educational intervention focusing on patients' personal understandings of type 2 diabetes. Diabetes and Research in Clinical Practice 2008; 81(1): 50–55.
4. Jutterström L, Hörnsten Å, Sandström H, Stenlund H, Isaksson U. Nurse-led patient-centered self-management support improves HbA1c in patients with type 2 diabetes – A randomized study. Patient Education and Counseling 2016; 99(11):1821-1929.

The role of Patients, Relatives and the Health Care Organisation – Primary Health Care

Carl Johan Östgren, Professor, Department of Medical and Health Sciences (IMH), Linköping University

Appropriate diabetes care is particularly important at the primary care level, where most people with type 2 diabetes are treated and therefore, where a healthcare team trained on best practice for type 2 diabetes is vital for success. The task is not easy, since the limited amount of time to solve a great variety of medical problems makes it very difficult for the primary care physician to personalize care for every patient with type 2 diabetes considering individual needs and barriers. It becomes even more difficult when having to choose among the increasing number of new medications that may have added benefits, but also risks. The challenge for the healthcare team is thus to develop a treatment strategy that can lower blood glucose levels as much as possible for as long as possible while reducing the risk of hypoglycemia and to address the numerous cardiovascular risk factors present in any given patient.

The Steno Diabetes Centre Concept

Allan Flyvbjerg[1,2]
[1]Steno Diabetes Center Copenhagen, Capital Region of Denmark,
Niels Steensens Vej 2, DK-2820 Gentofte, Denmark and
[2]Department of Clinical Medicine, Faculty of Health and Medical Sciences,
University of Copenhagen, Blegdamsvej 3B, DK-2200 Copenhagen,
Denmark. allan.flyvbjerg@regionh.dk

Brief Overview: Non-communicable diseases (NCD's), including diabetes, are a global burden towards the population, the healthcare system and -e. In order to manage NCD's today and in the future, we need to move from traditional healthcare structures towards more cross-sectorial orientated collaborations.

The relevance: In this presentation a Public Private Partnership (PPP)-like collaborative structures, i.e. the Steno Diabetes Center Copenhagen (SDCC), will be presented as a new model to facilitate an individualized, cross-sectorially orientated collaborative structure within diabetes.
In order to improve the quality of diabetes healthcare within the Capital Region of Denmark (CRD), a collaboration was established between CRD, the Novo Nordisk Foundation (NNF) and Novo Nordisk A/S to form SDCC. For the period 2017-2029, a grand total of 0.6 billion € (4,3 billion DKK) has been allocated to form SDCC, with focus on clinical treatment, clinical research, education and healthcare promotion activities within diabetes, with 0.2 billion € (1.35 billion DKK) coming from the CRD and 0.4 billion € (2,95 billion DKK) given as a donation from NNF to CRD.

Key point: Public Private Partnership (PPP)-like collaborative structures, like SDCC, may be a new way to facilitate a more agile and effective cross-sectorial collaboration within diabetes.

Reference: www.sdcc.dk

Poster abstracts

Lyfestyle and dietary determinants of weight change between baseline and 5-year examination in the Malmö Diet and Cancer (MDC) cohort

Joana A. Dias, Emily Sonestedt

Background: Lifestyle factors such as smoking and physical activity, as well as dietary habits and obesity, are known to influence the risk of developing non-communicable diseases such as cardiovascular diseases (CVD) and type 2 diabetes (T2D). However, assessing prevalent factors cross-sectionally might not be sufficient to establish meaningful associations; longitudinal associations between change in dietary habits and physical activity and weight change has been shown to give more robust results than cross-sectional correlation with prevalent dietary habits. It is, thus, important to investigate changes prospectively. The aim of this study is to examine the associations between several baseline lifestyle and dietary factors, as well as changes, and weight change after 5-year follow-up.

Methods: Participants of the MDC study (n=30,446), with baseline measurements between 1991 and 1996, took part in a second re-examination 5 years later (n=22,367). Baseline examinations included a questionnaire regarding socioeconomic and lifestyle factors, anthropometric measurements, and a modified diet history tool for reporting dietary habits (that included a 7-day food diary, a 168-item semi-quantitative diet his-tory questionnaire, and an interview). During the re-examination, participants answered a new questionnaire, similar to the baseline, and reported their weight and change in dietary intake.

Annual weight change (AWC) was calculated by dividing the subtraction of weight at the 5-year re-examination to the weight at baseline by each person's follow-up time. AWC was further divided into quintiles, and lifestyle factors at baseline investigated across those quintiles. Partial correlations between dietary factors at baseline and AWC were examined with a stepwise exclusion using a linear regression model. The mean AWC was also investigated across categories of reported dietary intake change, as well as categories of change in physical activity, smoking behavior and BMI.

Results: The mean weight at re-examination was slightly, but significantly, lower than at baseline (-0.13kg). Mean weight, BMI, waist circumference, and age decreased across quintiles of AWC, both in men and women. A higher proportion of male smokers and a smaller proportion of female non-smokers was found in the higher quintiles of AWC.

In full and mutually adjusted model, the baseline consumption of fruits, grains, cream, fruit juice, SSB, and wine was negatively associated with AWC, whereas processed meat, ice cream, oil/dressing/mayonnaise, sweets, coffee and ASB were positively associated with AWC. Overall, despite significant, correlation coefficients were quite low; the highest was observed for oil/dressing/mayonnaise, r=0.026.

People who were moderately physically active at baseline and increased their levels of PA after 5 years suffered the greatest weight reduction (-0.089 kg), whereas smokers at baseline that quit after 5 years, suffered the greatest weight increase (0.60 kg). People who have reported to have decreased the consumption of the majority of several food items (22) after 5 years, lost weight overall compared to non-changers, whereas the ones who reported to have increased the consumption of vegetables, fruits, fiber-rich foods, milk and eggs have also lost weight. In contrast, women who reported to consume more bread, margarine spreads, coffee bread/biscuits and food in general have increased their weight compared to non-changers.

Conclusion: Several lifestyle and dietary factors assessed at baseline, as well as changes, were associated with weight change after 5-years re-examination. However, the correlation coeficients for dietry factors were low, which is in line with previous research. Nevertheless, these results should be taken into consideration when investigating prospectively the associations between prevalent exposures and diseases such as CVD and T2D.

Characteristics and Prognosis of Healthy Severe Obesity (HSO) Subjects – The Malmo Preventive Project

Erasmus Bachus[1,5], Maximilian Tremmel[2], Valeriya Lyssenko[1], Bengt Zöller[3], Gunnar Engström[1], Martin Magnusson[1,4], Olle Melander[1], Peter M Nilsson[1,5]

[1]Department of Clinical Sciences, Lund University, Malmö
[2]Institute for Medical Informatics, Biometry and Epidemiology (IBE), LMU Munich, Germany,
[3]Center for Primary Health Care Research, Lund University, Malmö
[4]Department of Cardiology, Skåne University Hospital, Malmö
[5]Department of Internal Medicine, Skåne University Hospital, Malmö

Background: The characteristics and prognosis of healthy obesity (HO) still remain unclear. We aimed to examine the characteristics of healthy severe obesity (HSO), defined by a novel approach, with a focus on self-reported physical activity (PA) and a genetic risk score for type 2 diabetes (GRS DM2).

Methods: A cross-sectional analysis was carried out in a subsample of severly obese subjects (BMI≥35 kg/m2; n=809) selected from the population-based Malmo Preventive Project (MPP). Subjects with HSO (n=57) were defined by having no records of hospitalisation in the Swedish Hospital Discharge Register during a time period of 33.4±3.9 years between baseline (1974-1992) and the end of follow-up (31st of December 2014). They were compared to subjects with unhealthy severe obesity (USO; n=752), as well as age- and sex-matched non-obese controls (n=1618).

Results: Subjects with HSO had a significantly lower GRS DM2 (HSO 40.4±3.7 vs. USO 41.8±3.8, p=0.007). Compared to subjects with USO, the HSO subjects reported significantly more leisure-time physical activity, PA (p=0.016). There were no significant differences between HSO and USO subjects in the distribution of fat mass or obesity-associated gene phenotypes (*FTO* gene; variant rs9939609; p=0.8).

Conclusion: Higher PA and lower GRS DM2 might be protective factors against all-cause hospitalisation in subjects with severe obesity. These findings support the concept of HO being fat but fit. Still, it remains unclear whether higher PA is causally related to HSO, and which role environmental factors such as PA play in the interaction with genetic factors such as GRS DM2.

Keywords: *Epidemiology; Genetic risk score; Diabetes; Hospitalisation; Healthy severe obesity; Obesity; Physical activity*

Correspondence: Erasmus Bachus MD, PhD, FHFA
Department of Internal Medicine
Skane University Hospital, Ruth Lundskogs gata 3, 5th floor
S-205 02 Malmo/Sweden
erasmus.bachus@med.lu.se

Random plasma glucose predicts long-term mortality in patients with heart failure without previously known diabetes – insights from the Swedish heart failure registry (SwedeHF)

I. Johansson[1], U. Dahlström[2], M. Edner[1], P. Näsman[3], L. Rydén[1], A. Norhammar[1]

[1]Karolinska Institutet, Cardiology Unit, Department of Medicine K2, Stockholm, Sweden

[2]Department of Cardiology and Department of Medical and Health Sciences, Linköping University, Linköping, Sweden.

[3]Royal Institute of Technology, KTH, Centre for Safety Research, Stockholm, Sweden

Background: Dysglycaemia often coexists with heart failure and adversely impacts long-term prognosis. A random, elevated plasma glucose (RPG) during hospitalisation for an acute coronary syndrome or stroke often reflects undetected dysglycaemia and is associated with a poor prognosis.

Purpose: To investigate the association between RPG and long-term prognosis in real world patients with heart failure with and without a reported diabetes (DM) diagnosis.
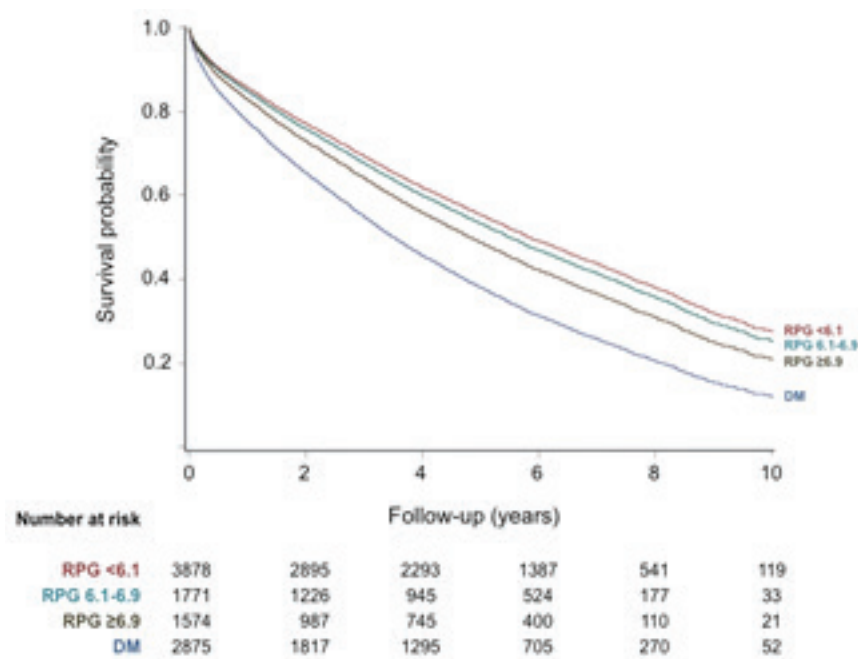
Methods: Patients with and without previously known DM included in the Swedish national heart failure registry (SwedeHF) between 2003–2011 and with a reported RPG (n=10098) were followed for all cause mortality until December 31, 2014 (median 4.4 (IQR 2-6) years). Mortality was analysed by DM diagnosis or by glycaemic levels as follows: RPG <6.1 mmol/L; 6.1-6.9 mmol/L; ≥7.0 mmol/L (the latter = DM cut off level for fasting glucose according to WHO). Hazard ratios (HR) were calculated in a Cox regression model adjusting for age, gender, renal function and heart failure care (hospitalisation or out patient clinic-visit).

Results: The number of patients without reported DM was 7223 of whom 22% (n=1574) had an RPG ≥7.0 mmol/L, 25% (n=1771) 6.1-6.9 mmol/L and 54% (n=3878) <6.1 mmol/L. DM was reported in 28% (n=2875). The mean age was lowest in patients with known DM (76 years) while it increased with higher RPG category; 77 (<6.1 mmol/L); 79 (6.1-6.9 mmol/L) and 80 (≥7.0 mmol/L) years respectively (p<0.0001). Left ventricular ejection fraction did not differ across the groups, (≈22% with LVEF ≥50%; p=0.81). Age adjusted survival by RPG category compared with known DM is depicted in Figure 1. Mortality increased by increasing RPG in patients without known DM and was highest in those with known DM (log-rank p=0.0001). Known DM was associated with an increased risk of mortality vs. the lowest RPG category (<6.1 mmol/L; adjusted HR 95% CI 1.51:1.42-1.60). The highest RPG category was associated with increased mortality even among those without known DM (adjusted HR 1.17, CI 1.08-1.25 comparing ≥7.0 vs. <6.1 mmol/L). There was no increased mortality risk comparing the slightly elevated vs. lowest RPG category (6.1-6.9 vs. <6.1 mmol/L; adjusted HR 1.04:0.96-1.11).

Conclusions: In patients with heart failure without previously reported DM

increased levels of RPG were associated with greater risk of long-term mortality compared with lower RPG levels. DM was as expected associated with the highest mortality risk. These findings highlight the importance of searching for previously undetected dysglycemia and DM in heart failure populations.

Figure 1. Age adjusted survival by RPG or DM in HF

Number at risk						
RPG <6.1	3878	2895	2293	1387	541	119
RPG 6.1-6.9	1771	1226	945	524	177	33
RPG ≥6.9	1574	987	745	400	110	21
DM	2875	1817	1295	705	270	52

Added sugar intake and micronutrient dilution in a large Swedish population

Esther González Padilla, Lund University

Introduction: The awareness of the detrimental effects of high intake of sugar on cardiovascular disease has increased during the last decade. Diets high in sugar might indicate a diet low in micronutrients, which could be involved in the development of cardiovascular disease. However, reliable data to support the association between the dietary composition of added sugar and intake of micronutrients in large populations is scarce. The aim of this study was to investigate the association between added sugar and micronutrient intake in a large Swedish population.

Methods: Data was obtained for 12,238 individuals (45% males, aged 45 to 68 years) from the population-based Malmö Diet and Cancer Study, with extensive collection of dietary information. The levels of daily intake of nine micronutrients were analysed across six strata of added sugar intake, expressed as percentage of energy intake, for men and women separately. The model was adjusted for age, BMI and energy intake. The percentage of individuals with micronutrient intakes below the Average Requirements (AR) and the Recommended Intake (RI) for the six intake groups were also analysed.

Results: Inverse associations was observed between the levels of added sugar and all micronutrient intake, except vitamin C, for both men and women. The percentage of individuals with intake levels below AR and RI were most remarkable for folate, selenium and vitamin D. We found difference between the lowest and highest added sugar groups ranging from 10% to 40% difference in males and around 25% in females for all three micronutrients. Moreover, half or more of the females with the highest level of added sugar did not meet the daily AR of these three micronutrients.

Conclusions: Our study shows a consistent association between high levels of added sugar and micronutrient dilution, which helps to further understand the effect that added sugar has on cardiovascular disease.

Early life origins of type 2 diabetes and cardiovascular diseases: The Malmö Birth Data Cohort (MBDC) and the LifeGene cohort

Shantanu Sharma, Research student, Louise Bennet, Associate Professor, Peter M Nilsson, Professor. Department of Clinical Sciences, Lund University, Skane University Hospital, Malmö, Sweden

Early life programming has been the subject of interest since 40 years for associations with the onset and prognosis of non-communicable diseases in adulthood, such as cardiovascular disease (CVD), hypertension, obesity and type 2 diabetes (T2D) [1], but also breast cancer, prostatic cancer, etc. The growing interest in this cohort-based epidemiology comes from the rapidly escalating epidemics of these non-communicable diseases and consequently staggering economic losses annually. Most of the researches in this area are based on the cohorts with birth and early life data from high-income countries like Sweden, Finland, Norway, UK, etc. Sweden has a number of carefully sampled population-based cohorts and variety of high-quality national registries on morbidity and mortality since decades.

The rich databases from three Malmo cohorts (Malmo Birth Data Cohort, MBDC; Malmo Offspring Study, MOS), and the Lifegene cohort (mostly recruited from the Stockholm area) will be explored for the associations between factors in early life in relation to organ function, health and disease in adult life, including prediction of CVD and T2D. The MBDC includes data of 4,039 individuals with birth records from 1920-1950 consists of the information from two nested case-cohort studies within the Malmo Preventive Project (MPP) [2] and the Malmo Diet Cancer (MDC) study [3]. MOS (www.med.lu.se/mos) includes at present 3200 subjects, but aims for 6000 participants, consisting of children and grandchildren to index subjects in the MDC study. In MOS will be sampled data on health parameters such as information on diet, gut microbiota, cognition etc.

The third and the largest cohort, Lifegene (www.lifegene.se) includes data from 22,000 individuals that will be linked with early life data from the Medical Birth Register (MBR) of Sweden, for subjects born 1973 or later. The MBR includes details of early life factors (maternal and pregnancy characteristics) such as birth weight, length, gestational age, head circumference. Phenotypes can be calculated, for example small-for-gestational-age (SGA) following intrauterine growth retardation, and ponderal index. During follow-up, phenotypes available in mid-life include cardiovascular risk factors and results from oral glucose tolerance test (OGTT available in MPP), renal function, blood pressure, lipid metabolism, lung function, etc. The incidence of non-fatal coronary events, stroke and diabetes, or total mortality, will be tracked as outcomes until end of 2016. We will look for the association between early life factors and adult organ function or incident disease manifestations in mid-life using different statistical models like proportional hazard analysis, multi-regression analysis, competing risk, etc.

In summary, we will be able to analyze the association between early life factors and adult health and disease in Swedish subjects, some representing birth cohorts from 1920-1950 (MBDC, MPP, MDC) and some from 1970–2000 (MOS, LifeGene). This will contribute to a better understanding of the risk of hyperglycaemia/T2D as well as of risk factors and events related to CVD in relation to different birth cohort characteristics. These are examples of early life programming of health and disease.

References

1. Gluckman PD, Hanson MA, Cooper C, *et al.* Effect of in utero and early-life conditions on adult health and disease. *N Engl J Med*. 2008;359:61–73.

2. Gerdtsson A, Poon JB, Thorek DL, *et al.* Anthropometric Measures at Multiple Times Throughout Life and Prostate Cancer Diagnosis, Metastasis, and Death. *Eur Urol*. 2015;68:1076–82.

3. Lahmann PH, Gullberg B, Olsson H, *et al.* Birth weight is associated with postmenopausal breast cancer risk in Swedish women. *Br J Cancer*. 2004;91:1666–8.

Plasma proneurotensin and diabetes risk in a highly insulin resistant population: The MEDIM population-based study of Iraqi immigrants

Ayesha Fawad, Peter M Nilsson, Olle Melander, Louise Bennet. Department of Clinical Sciences, Lund University, Skane University Hospital, S-20502 Malmö, Sweden

Background: Type 2 diabetes (T2D) is highly prevalent among Middle Eastern populations that represent the largest non-European immigrant group in Sweden today. As proneurotensin (PNT) predicts T2D, the aim of this observational study comparing Iraqi and Swedish born populations, was to investigate differences across ethnicities in PNT levels and its associations with glucose regulation and T2D.

Methods: A total of 2155 individuals, aged 30 to 75 years and born in Iraq or Sweden, participated in the MEDIM study in Malmö [1]. Anthropometrics and fasting samples were collected and insulin secretion (disposition index; DIo) and insulin sensitivity (ISI) were assessed through blood sampling during an oral glucose tolerance test (OGTT; 75 gram glucose). PNT was analysed by a method, as previously described [2].

Results: Higher fasting PNT levels were observed in the Iraqi-born than in the Swedish-born population (137.5 vs. 119.8 pmol/L, p<0.001), data adjusted for age, sex and body mass index. Associations of plasma PNT with DIo, ISI and HbA1c levels respectively, were stronger in Iraqi compared to the Swedish-born population, which is reflected by significant interactions between country of birth and PNT ($P_{interaction\ ISI}$=0.048; $P_{interaction\ DIo}$=0.014; $P_{interaction\ HbA1c}$=0.029). Iraqi born individuals, in the highest tertile of the PNT distribution, had almost five times the odds of having T2D as compared to the reference group of Swedish born individuals within the lowest tertile of PNT.

Conclusion: The association between PNT levels on glucose regulation was significantly stronger in Iraqi immigrants compared to native Swedes. This supports the hypothesis that high PNT levels in Middle Eastern immigrants could contribute to their higher risk of developing T2D.

References:
1. Bennet L, Johansson SE, Agardh CD, Groop L, Sundquist J, Råstam L, Sundquist K. High prevalence of type 2 diabetes in Iraqi and Swedish residents in a deprived Swedish neighbourhood--a population based study. *BMC Public Health*. 2011; 11:303.

2. Fawad A, Bergmann A, Struck J, Nilsson PM, Orho-Melander M, Melander O. Proneurotensin predicts cardiovascular disease in an elderly population. *J Clin Endocrinol Metab*. 2018 Mar 13. doi: 10.1210/jc.2017–02424. [Epub ahead of print].

Growth differentiation factor 15 predicts incident diabetes mellitus in the general population: a population-based cohort study

Xue Bao, Department of Clinical Sciences, Malmö, Lund University

Background: Growth Differentiation Factor-15 (GDF-15) is an anti-inflammatory cytokine belonging to the transforming growth factor-β superfamily. Previous studies have revealed a positive association between GDF-15 and glucose metabolism among people with obesity or diabetes. However, evidence regarding the predictive role of GDF-15 in diabetes risk is scarce. The aim of this study was to explore whether GDF-15 can predict future diabetes in the general population.

Methods: During 1991–1994, GDF-15 was measured in 4,360 participants without diabetes from the Malmö Diet and Cancer-Cardiovascular Cohort (aged 57.4 ± 5.96 years, 38.6% men). After a mean follow-up of 19.0 ± 5.16 years, Cox proportional hazard regression was used to study baseline GDF-15 in relation to incident diabetes with adjustment for established confounders. Possible interactions between GDF-15 and confounders on diabetes risk factor were explored. C-reactive protein was additionally adjusted for in a sensitivity analysis.

Results: During follow-up, 621 subjects developed diabetes. The multivariate-adjusted hazard ratio (95% confidential interval) for diabetes was 1.43 (95% CI, 1.11-1.83; p for trend=0.007) in the 4th compared with the 1st quartile of GDF-15, and was 1.17 (95% CI, 1.07-1.28; $p<0.001$) per 1 standard deviation (SD) increase of GDF-15. Significant interaction was observed between GDF-15 and age (p for interaction<0.001). The association was considerably stronger in participants up to 55 years old as compared to those older than 55 years. Further adjustment for CRP eliminated the association between GDF-15 quartiles and diabetes risk (p for trend=0.061), but the association between GDF-15 (in SD units) and diabetes remained significant (HR, 1.12; 95% CI, 1.02–1.23; p=0.015).

Conclusion: The study demonstrated that elevated circulating levels of GDF-15 were associated with an increased risk of incident diabetes in the general population. The strength of association was influenced by chronic inflammation and biological age.

Keywords: diabetes mellitus; cardiovascular diseases; cohort study; inflammatory markers; competing risk analysis.

Who was Berzelius?

Jöns Jacob Berzelius, one of the most prominent natural scientists of the 19th century, was born in 1779 in Väversunda, in the county of Östergötland in southern Sweden, a region with rich cultural traditions.

Orphaned at an early age, he went to several foster-homes and received his schooling in nearby Linköping. After graduating in medicine at the University of Uppsala, he moved to Stockholm, where he became assistent master without pay at the so-called »Surgical School«, and earned his keep by working as a doctor for poor people. At the age of 28 he became professor of medicine and pharmacy.

In 1808 Berzelius was one of the seven men who founded The Swedish Society of Medicine »For the perfection of science through mutual mediation of knowledge and collective experience, for the promotion of friendly confidence between doctors«.

Berzelius have enriched our knowledge of nature of life phenomena, established the atomic weights of most of the known elements, presented his electrochemical theory for the understanding of the nature of chemical compounds and laid the foundation for the sciences of the chemistry of rock types.

He also found that elements combine with each other according to fixed numerical relationships. In addition to this, in his striving for order and method, with his talent for simplicity and clarity in expression, he created the chemical symbolic language in 1813, which since that time has been an essential instrument of chemistry.

With time he became a practised lecturer but preferred to express himself in writing and this he did superbly. Impressive are the great scientific works where he also demonstrated his interest and ability to spread knowledge about the latest advances of natural sciences.

Berzelius delight in research and debate was united with a great humility before the great scientific questions. Both his attitude and artistery of formulation is illustrated by the following passage in his Manual of Cheamistry (vol 3, 1818):

»All our theory is but a means of conistently conceptualizing the inward processes of phenomena, and it is presumable and adequate when all scientifically known facts can be deduced from it. This mode of conceptualization can equally well be false and, unfortunately, presumable is so frequently. Even though, at a certain period in the development of science, it may match the purpose just as well as a true theory. Experience is augmented, facts appear which do not agree with it, and one is forced to go in search of a new mode of conceptualization within which these facts can also be accomodated; and in this manner, no doubt, modes of conceptualization will be altered from age to age, as experience if broadened, and the complete truth may perhaps never be attained. But even if the goal can never be reached, let us never abondon our endeavor to get closer to it.«

Parts of this text is found in: Berzelius – Creator of the chemical language, by Carl Gustaf Bernhard, the Royal Swedish Academy of Sciences