A reduced-carbohydrate diet high in monounsaturated fats in type 2 diabetes
A six-month study of changes in metabolism, liver- and cardiovascular function (reduction)
Gram-Kampmann, Eva-Marie; Olsen, Michael Hecht; Krag, Aleksander; Beck-Nielsen, Henning

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Abstract Book
Diet, Diabetes and the Metabolic Syndrome

25th – 26th August 2016
The Novo Nordisk Foundation,
Tuborg Havnevej 19, Hellerup,
Copenhagen
Organising committee

Bjørn Richelsen, Professor, Aarhus University

Jens Meldgaard Bruun, Consultant, Aarhus University Hospital

Mette Pedersen, Dietitian, Chair of The Danish Dietetic Association

Tore Christiansen, Danish Diabetes Academy

Tina Hansen Barbisan, Danish Diabetes Academy

thb@rsyd.dk

Welcome

This symposium will give a comprehensive update of the newest research focusing on the impact of diet on the development, prevention, and treatment of diabetes (type 1 and type 2) and metabolic diseases. Several of the more controversial questions concerning the effects of dietary proteins and carbohydrates on body weight regulation and glucose metabolism will be covered by internationally esteemed researchers.

Danish Diabetes Academy
Funded by the Novo Nordisk Foundation
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### Thursday 25 August

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<td>08:45 – 09:25</td>
<td>Registration including coffee and rolls</td>
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<td>09:25-09:30</td>
<td>Welcome</td>
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<td><strong>Bjørn Richelsen</strong>, Professor, Aarhus University</td>
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<tr>
<td>09:30 – 10:10</td>
<td><strong>Session 1 – Carbohydrates</strong></td>
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<td></td>
<td>Chair: <strong>Bjørn Richelsen</strong>, Professor, Dept. of Endocrinology,</td>
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<td>Aarhus University Hospital</td>
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<tr>
<td>09:30 – 10:10</td>
<td>“Carbohydrates and diabetes – review and status”</td>
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<td><strong>Jim Mann</strong>, Professor, Dunedin School of Medicine, University of Oto</td>
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<td>go, New Zealand</td>
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<td>09:30 – 10:10</td>
<td>“Low vs high-carbohydrate diet for patients with type 2 diabetes”</td>
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<td><strong>Grant Brinkworth</strong>, Assoc. Professor, Commonwealth Scientific and</td>
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<td>Industrial Research Organisation (CSIRO) – Food and Nutrition,</td>
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<td></td>
<td>Australia</td>
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<td>10:50 – 11:10</td>
<td>Coffee break</td>
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<tr>
<td>11:10 – 11:50</td>
<td>“Whole grain cereals and type 2 diabetes”</td>
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<td><strong>Knud Erik Bach Knudsen</strong>, Professor, Dept. of Animal Science, Aarhus</td>
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<td></td>
<td>University, Denmark</td>
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<td>11:50-12:30</td>
<td>“Carbohydrate quality and risk of type 2 diabetes”</td>
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<td><strong>Vasanti Malik</strong>, ScD, Research Scientist, Harvard School of Public</td>
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<td>Health, dept. of Nutrition, Boston, US</td>
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<tr>
<td>12:30 – 14:00</td>
<td>Lunch &amp; Poster Session</td>
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<td>14:00 – 14:40</td>
<td>“Intake of sugar and fat liver”</td>
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<td><strong>Bjørn Richelsen</strong>, Professor, Aarhus University, Denmark</td>
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<td>14:40-15:20</td>
<td>“Sugar consumption, metabolic disease and obesity: The state of the</td>
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<td>controversy”</td>
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<td><strong>Kimber L Stanhope</strong>, PhD, Assoc. Researcher, Dept. of Nutrition, University of California, Davis, USA</td>
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<tr>
<td>15:20-15:35</td>
<td>Coffee break</td>
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<tr>
<td>15:35-16:00</td>
<td>“Carbohydrate counting in the treatment of type 1 diabetes”</td>
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<td><strong>Birgit Schelde</strong>, Clinical Dietitian, RD, Aarhus University Hospital,</td>
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<td>Denmark</td>
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<td>16:00-16:45</td>
<td>“High vs low glycemic load diet for obesity and type 2 diabetes:</td>
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<td>Novel insight and concepts from intervention studies”</td>
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<td></td>
<td><strong>Arne Astrup</strong>, Professor, Dept. of Nutrition, Exercise and Sports,</td>
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<td>University of Copenhagen, Denmark</td>
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## Friday 26 August

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<tbody>
<tr>
<td>08:30-09:05</td>
<td>Coffee and rolls</td>
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<tr>
<td>09:05-09:15</td>
<td>Poster awards</td>
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<tr>
<td><strong>Session 2</strong></td>
<td>Chair: Kjeld Hermansen, Professor</td>
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| 09:15-09:55   | “Dairy products for metabolic syndrome and type 2 diabetes. Good or bad?”  
Peter Clifton, Professor, School of Pharmacy and Medical Sciences, University of South Australia |
| 09:55-10:35   | “Dietary gluten and the development of type 1 diabetes”              
Julie Antvorskov, Post Doc, The Bartholin Institute, Rigshospitalet, Denmark |
| 10:35-10:55   | Break                                                                |
| 10:55-11:35   | “Mediterranean and Nordic diet – effects and possibilities in diabetes”  
Kjeld Hermansen, Professor, Aarhus University, Denmark |
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Chair: Vasanti Malik, Research Associate |
Matti Uusitupa, Professor Emeritus, Inst. Of Public Health and Clinical Nutrition, University of Eastern Finland |
| 12:15-13:00   | Lunch                                                                |
| 13:00-13:40   | Polyunsaturated fatty acids and risk of diabetes”                    
Maria Lankinen, Post Doc, Inst. of Public Health and Clinical Nutrition, University of Eastern Finland |
| 13:40-14:20   | Panel Discussion and closing remarks                                 
Bjørn Richelsen, Professor, Aarhus University, Denmark |
1. Orphan G protein–coupled receptor GPR56 and pancreatic β-cell function

Israa Mohammed Al-Amily, Pontus Dunèr, Arvind Soni, Olof Asplund, Fateme Safi, Peter Storm, Lief Groop, Stefan Amisten and Albert Salehi.

Department of Clinical Science, Malmö, Division of Islets Cell Physiology, Jan Waldenströmaga 35, Building 91, floor 11, SE-205 02 Malmö, Sweden.

Aim
The functional role of G-protein coupled receptor 56 (GPR56) in pancreatic islets and in the pathogenesis of diabetes is unclear. We explored the influence of GPR56 on insulin secretion in mouse and human isolated pancreatic islets.

Material and methods: RNA-seq data confirmed by qPCR, confocal microscopy and Western blot in islets showed an abundant expression of GPR56 protein in β-cells.

Results
Diabetic islets showed a reduced GPR56 expression which coincided with an attenuated glucose-stimulated insulin secretion. Long-term culture of islets at high glucose concentration reduced GPR56 expression and islet cell viability. Ablation of Gpr56 in INS-1 832/13 cells was associated with reduced glucose-stimulated insulin secretion, reduced cell proliferation, reduced cell viability, reduced cell adhesion to collagen III coated matrix and increased apoptosis measured by PARP cleavage. Down-regulation of Gpr56 in isolated mouse islets was associated with disrupted cAMP-production and insulin secretory response to glucose. Further functional studies showed that collagen type III potentiates glucose-stimulated cAMP-generation and insulin release in islets with normal Gpr56 expression, supporting the idea that collagen type III is an agonist for Gpr56. RNA-seq data showed a positive correlation of GPR56 expression with insulin, WFS1, ABCA3, ATP2A2, TMEM198, RASD1, GTF3C, SLC7A4 and C19orf59 and a negative correlation with EGFR and VEZT.

Conclusion
Taken together, our data demonstrate that the highly expressed GPR56 in human and rodent pancreatic β-cells plays an important role in β-cell function. We propose that GPR56 might be a potential novel target for the development of new drugs for the treatment of type 2 diabetes.

2. Pre-meal of whey protein induces differential effects on glucose and lipid metabolism in subjects with the metabolic syndrome

Ann Bjørnshave1,2; Jens Juul Holst3 and Kjeld Hermansen1.

1Department for Endocrinology and Internal Medicine, Aarhus University Hospital, Denmark, 2Danish Diabetes Academy, Odense, Denmark, 3Endocrinology Research Section, University of Copenhagen, Denmark.

Objective
Whey protein (WP) is a potent insulinotropic secretagogue. Consumption of WP as pre-meal reduces postprandial glycemia after a subsequent meal and induces an early insulinemic response. No studies have examined, if a pre-meal of WP influences the subsequent postprandial lipemia. Therefore, we examined if the triglyceride (TG) and ApoB-48 responses to the second meal were dose-dependently affected by a WP pre-meal prior to a fat-rich test meal in subjects with metabolic syndrome (MeS).

Methods
We performed an acute, randomized, cross-over study with three arms. At the test day fasting data were collected (blood, urine, anthropometric measurements and visual analogue scale (VAS)). A 200ml pre-meal containing 0, 10 or 20 g WP was served at -15 min. A fat-rich breakfast (second meal) was served at 0 min. The subjects were then observed for 360 min after the second meal and VAS was carried out every 30 min.

Results
Twenty subjects (8 women and 12 men) with MeS completed the study. We observed no effects of the pre-meal on TG or ApoB-48. The response of insulin was increased after consumption of 20 g WP compared to 10 g (P<0.001) and placebo (P<0.0001). Likewise, the postprandial glucagon response was higher after 20 g WP compared to 10 g WP (P<0.0001) and 0 g WP (P<0.0001) as pre-meals. Consumption of 20 g of WP as pre-meal generated a lower blood glucose response (P<0.05) and a higher GLP-1 response (p<0.05) compared to 0 g. A pre-meal of WP had neither effect on GIP, FFA or appetite (VAS).

Conclusion
Consumption of a pre-meal of WP prior to a fat-rich second meal caused a differential impact on lipid and glucose responses. No change was observed in the postprandial lipid responses, whereas WP stimulated insulin and glucagon secretion while blood glucose remained low in subjects with MeS.
3. The effects of proteins and medium-chain fatty acids from milk on body composition, insulin sensitivity and blood pressure in abdominally obese adults

Mette Bohl1, Ann Bjørnshave, Mette K. Larsen, Søren Gregersen, and Kjeld Hermansen

1Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Aarhus, Denmark. Mette.Bohl.Larsen@aarhus.rm.dk

Aim
To investigate whether intake of whey protein and butter naturally enriched in medium-chain fatty acids (MC-SFAs) (C6-C12) affected the body composition, insulin sensitivity, diurnal blood pressure (BP) and plasma cholesterol.

Material and methods
A 12-week randomised, double-blinded, intervention study was completed in 52 abdominally obese adults. Subjects were assigned to one of four dietary supplementations: 63 g/day of milk fat with either high (8.5 g/day) or low MC-SFA (6.9 g/day) content combined with 60 g/day of whey or casein. We examined changes in body composition by Dual-Energy X-ray Absorption scan, insulin sensitivity, diurnal blood pressure (BP) and plasma cholesterol. Two-factor ANOVA was used to examine the impact of MC-SFA content and protein type.

Results
We observed that the lean body mass increased by 981 g (95% CI: 248, 1713; P = 0.010) after high-MC-SFA compared with low-MC-SFA supplementation. Consequently, the composition of dairy fat should be considered when evaluating the impact of dairy products on body composition.

4. High expression of organic cation transporter 3 (oct3) in human bat-like adipocytes. Implications for extraneuronal norepinephrine uptake

Peter Breining, Steen Benlekke Pedersen, Arunas Pikelis, Lars Rolighed, Elias Immanuel Sundelin, Niels Jessen, Bjarne Richelsen

Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Tage-Hansens Gade 2, 8000 Aarhus C, Denmark. peter.breining@clin.au.dk

Aim
In this study we aimed at examining whether OCT3 is present and plays a role in norepinephrine (NE) uptake in adipose tissue (AT) and whether the presence is correlated to commonly accepted thermogenic markers, most notably UCP1. Brown adipose tissue (BAT) carries the potential of reducing blood glucose and body weight by oxidation of sugar and fat in heat production.

Material and methods
Human subcutaneous AT and deep-neck AT biopsies were obtained during neck surgery (thyroid- and parathyroid surgery). Gene expression was analyzed by qPCR and UCP1 protein was assessed by immunohistochemistry. The in vitro norepinephrine uptake study was performed on isolated brown adipocytes collected from the interscapular depot from male Sprague Dawley rats. Cells were incubated with 3H-NE, propranolol and inhibitors of NE degradation enzymes. Selective blockage of OCT3 was obtained with corticosterone.

Results
When comparing deep-neck AT with subcutaneous AT from 57 individuals we found that UCP1 expression was largely confined to the deep-neck AT depot. OCT3 was 2.5±0.16 fold higher in the deep-neck AT compared to the subcutaneous AT and the correlation between UCP1 and OCT3 within the deep-neck AT was highly significant. Lastly, we were able to reduce NE uptake in isolated brown adipocytes by OCT3 blockage.

Conclusion
OCT3 is highly expressed in BAT and selective blockage of OCT3 inhibits NE uptake in brown adipocytes. This suggests that the brown adipocyte has the potential to reduce its own activation upon sympathetic stimulation. A self-regulatory mechanism is intriguing because it carries a potential of a future drug development targeting OCT3 in UCP1-rich adipocytes. A pharmacological reduction of OCT3 in BAT may increase energy expenditure through BAT activation leading to lowering of blood glucose and weight loss in type two diabetics.
5. A reduced-carbohydrate diet high in monounsaturated fats in type 2 diabetes: a six-month study of changes in metabolism, liver- and cardiovascular function (reduction)

Eva Marie Gram-Kampmann1, Michael Hecht Olsen, Aleksander Krag, Henning Beck-Nielsen

1Department M, Diabetic Research, Kloevervaenget 10, 6th floor, 5000 Odense C.
Eva.Gram-Kampmann@rsyd.dk

Aim
Lately, attention has increasingly been directed towards low-carbohydrate diets (LCD) for patients with diabetes mellitus type 2 (DM2). There is confusion amongst researchers and health professionals whether a LCD is appropriate diet for these patients or not. Recent studies suggest that LCD is safe and effective over short-term, with significant improvements in weight and glycemic control compared to other diets. However, there is still a lack of understanding of pathophysiology and metabolic changes in reported research.

The aim of this study is to investigate impact of six months of LCD with high fraction of fat, compared to a regular diabetic diet (RDD), on glycemic control, metabolic changes in reported research.

Material and methods
With continuous enrollment, 135 patients with DM2 will be randomized 2:1 to either a ketogenic LCD or RDD for six months. Anthropologic measurements, fat distribution, and complications associated with diabetes. Also, impact on endothelial dysfunction, non-alcoholic fatty liver disease (NAFLD) associated with diabetes, gut dysbiosis and quality of life will be evaluated.

Results
Both positive and negative results will be published. It is expected that the trial will lead to several publications in leading journal in the field of Endocrinology and Hepatology. Results will also be reported as part of a Ph.D. thesis. Scientific and social perspectives

By investigating the mechanisms behind the consequences of LCD in diabetes, diabetc complications and NAFLD, the study is expected to impact future guidelines and daily clinical practice both in diabetology, hepatology and cardiovascular medicine.

6. Large reductions in prescription drug used for metabolic syndrome-related diseases after gastric bypass surgery: a nationwide cohort study

Sigrid Bjerre Grisbøl, MD 1,2, Reimar Wernich Thomsen, PhD 1, Dóra Kőrmenőné Farkas, MSc 1, Henrik Toft Sørensen, DMSc 1, Bjarne Richelsen, DMSc 1, Elisabeth Svensson, PhD 1

1Department of Endocrinology and Internal Medicine, Aarhus University Hospital
2Department of Clinical Epidemiology, Aarhus University Hospital

Aim
After Roux-en Y Gastric Bypass (RYGB) surgery, metabolic syndrome-related diseases such as diabetes, dyslipidemia and hypertension may improve or remit with concomitant reduction of complications associated with disorders. While relapse of complications may occur, studies with long-term follow-up are sparse. Furthermore, little is known about the overall prescription drug use before and after RYGB. We aimed to evaluate changes over time in drug use among patients undergoing RYGB surgery and a matched comparison cohort.

Material and methods
Nationwide population-based cohort study, including all 9,908 patients undergoing RYGB in Denmark during 2006–2010 and 99,080 matched general population members. We calculated prevalence ratios (PRs) comparing prescription drug use 36 months after RYGB/index date with use 6 months prior to this date (baseline).

Results
In the RYGB cohort (median age 40 years, 22% men), large, sustained decreases (up to 70% reduction) occurred for treatment of metabolic syndrome-related conditions including any glucose-lowering drug: 16.5% users at baseline, PR after 3 years=0.82; 95% confidence interval (CI)=[0.75-0.89]; lipid-modifying drugs: 14.4% users at baseline, PR after 3 years=0.50; 95% CI=[0.46-0.55]; and antihypertensive drugs: 43.2% users at baseline, PR after 3 years=0.61; 95% CI=[0.59-0.64]. At baseline, more RYGB patients used a prescription drug (82.0% versus 50.8%), after three years, the PR was 0.93; 95% CI=[0.92-0.94] versus PR=1.04; 95% CI=[1.03-1.05] among comparisons. Use of inhalants for obstructive airway diseases [PR=0.79; 95% CI=[0.74-0.85)] also decreased. Use of neuropsychiatric drugs was two-fold higher at baseline in the RYGB cohort (22.8% versus 10.9%) and increased similarly after RYGB [PR=1.16; 95% CI=[1.10-1.21] versus PR=1.13; 95% CI=[1.11-1.16)].

Conclusions
Three years after RYGB surgery, we found large reductions in the use of treatment of metabolic syndrome-related conditions and inhalants for obstructive airway diseases with little indication of relapse during this time period. In contrast, frequent use of neuropsychiatric drugs did not decrease.
7. Hedonic changes in food choices following roux-en-y gastric bypass

Thea Toft Hansen1, Tine Anette Jakobsen1, Mette Søndergaard Nielsen1, Anders Sjödin1, Carel le Roux1, Julie Berg Schmidt1
*Contributed equally in conducting the manuscript
1Department of Nutrition, Exercise and Sports (NEXS), Faculty of Science, University of Copenhagen, Rolighedsvej 26, Dk-1958 Frederiksberg C; 2Odense University Hospital, The Danish Diabetes Academy, Sdr Boulevard 29, 5000 Odense C, Denmark; 3Imperial College, London
Phone: +45 28708653 or +45 35334754, E-mail: tha@nexs.ku.dk

Aim
Roux-en-Y gastric bypass surgery (RYGB) seems to lead to a shift in food choices in the direction of less energy-dense foods, which may be explained by decreased hedonic drive to consume highly palatable foods. Literature on hedonic changes in food choices following RYGB is reviewed with the hypothesis that RYGB changes several factors that collectively lead to a decreased hedonic drive to consume highly palatable, energy dense foods. This may play an important role in changing food choices towards a diet with a lower energy density. Yet, human behaviors are complex, and sociological and psychological factors are very likely to affect eating behavior outside an experimental setting.

Conclusion
The majority of studies discussed, indicate that RYGB changes several factors that collectively lead to a decreased hedonic drive to consume highly palatable foods. This may play an important role in changing food choices towards a diet with a lower energy density. Yet, human behaviors are complex, and sociological and psychological factors are very likely to affect eating behavior outside an experimental setting.

Material and methods
An automated literature search using the Medical subheadings (MeSH terms) Gastric bypass and appetite in PubMed was conducted on the 13th of January 2016 identifying 11 papers fulfilling the criteria.

Results
Questionnaires indicate that patients decrease food seeking of highly palatable foods after RYGB. Results from behavioral tests are conflicting with one study suggesting that the rewarding value of chocolate candy is decreased following RYGB, while an interim analysis from our own group using an ad libitum buffet meal show no changes in food choices. Studies on brain activity and signaling in dopaminergic pathways in response to highly palatable food cues indicate that these are altered after RYGB; however results are not entirely consistent.

8. Epigenome-wide changes in DNA methylation and risk of cardio-metabolic disease in 9-14 years old offspring of GDM women and controls

Line Hjort1,2, Louise G Grunnett, Anders H Olsson1, David Martino1, Frank B Hu1, Cuilin Zhang5, Richard Saffery1,3, Sjurur F Olsen1 and Allan A Vaag1,2
1Dept. of Endocrinology (Diabetes and Metabolism), Copenhagen University Hospital, Denmark
2Danish Diabetes Academy, Odense, Denmark
3Cancer and Disease Epigenetics Group; Murdoch Children’s Research Institute (MCRI); Royal Children’s Hospital; Parkville, VIC Australia
4Harvard Medical and Public Health school, Boston, USA
5National Institute of Child Health and Human Development, Bethesda, USA
6Dept. of Paediatrics, Melbourne University, Parkville, Australia
7Centre for Fetal Programming, Statens Serum Institut, Copenhagen, Denmark

Aims
Offspring of women with Gestational Diabetes Mellitus (GDM) are at increased risk of developing Type 2 Diabetes later in life. A growing number of studies implicate the time in utero as playing a key role in regulating later diabetes risk with potential effects mediated by epigenetic variation in the offspring at birth. However, whether these epigenetic changes are persistent, and are associated with risk of cardio-metabolic disease in later life, remains unknown. Using an epigenome-wide approach, we aimed to investigate DNA methylation profiles in blood from 9-14 year old offspring of GDM women relative to matched non-GDM controls.

Methods
We recruited 608 GDM and 623 control offspring from the Danish National Birth Cohort. DNA from 92 GDM offspring and 94 controls were analyzed for genome-wide DNA methylation profiles using the Infinium HumanMethylation450 BeadChip platform.

Results
BMI, height, total body fat percentage, fasting plasma glucose and insulin levels were higher among GDM offspring compared to controls (p<0.001). We identified 76 significant differentially methylated positions (DMPs) between the groups at the genome-wide level (adjusted p<0.05). DMPs were primarily located within exons, with the majority showing lower methylation in GDM offspring (92%), and several have previously been reported associated with diabetes and ageing.

Conclusions
Offspring of GDM pregnancies present prediabetes traits and altered DNA methylation profiles in blood at age 9-14 years. This supports a role for DNA methylation in fetal programming of metabolic health and suggests that GDM has long-term effects on offspring epigenetic profile. Stable marks may serve as interesting sites in investigation of causal relation to the increased T2D risk later in life. Validation studies are in progress in the entire cohort of 1,240 children.
9. Neonatal vitamin D3 and risk of type 1 diabetes in Danish children

Ramune Jacobsen, Peder Frederiksen, Berit L. Heitmann
Research Unit for Dietary Studies, The Parker Institute, Frederiksberg Hospital, Nordre Fasanvej 57, 2000 Frederiksberg, Denmark; email: ramune.jacobsen@regionh.dk

Aim
The aim of the study was to assess the association between the levels of vitamin D3 in neonatal blood (25(OH)D3) and the later risk of type 1 diabetes (T1D) in Danish children up to age of 18 years.

Material and methods
A case-cohort study was designed. A random sub-cohort of 3600 individuals born in Denmark in the period 1981-2002 was selected from the Danish Civil Registration system. Additionally, a random sample of 1100 individuals developing T1D until age of 18 years and diagnosed until 2012 was selected from the Danish Childhood Diabetes Register. Neonatal 25(OH)D3 levels were measured using the punches from the Dried Blood Spots (PKU cards), which are stored at the National Neonatal Specimen Bank and contain the blood samples routinely taken from the heel of all newborn babies in Denmark. The statistical analysis were based on quintiles of 25(OH)D3 levels in the sub-cohort, and weighted Cox regression models were run adjusting for birth weight, gestational age, mother’s age, diabetes diagnosis, ethnicity, education and job situation.

Results
In all, 3778 individuals had valid vitamin D3 measurements, 912 were diagnosed with T1D. Neonatal serum 25(OH)D3 concentrations in individuals from the random sub-cohort varied from 0.0 to 130.3 nmol/l with the median (25-75% range) being 23.8 (13.5-36.7) nmol/l. Gestational age per week: HR (95%CI)=0.96 (0.93-1.00); mother’s diabetes diagnosis versus non-diagnosis: HR (95%CI)=1.67 (1.20-2.33); and ethnicity: HR (95%CI) for non-Western versus Danes=0.39 (0.25-0.61) - were associated with the T1D risk. There was no association between levels of neonatal serum 25(OH)D3 and the T1D risk: HR (95%CI) for 1st, 2nd, 4th and 5th, versus 3rd quintile were: 0.85 (0.66-1.10), 0.95 (0.75-1.22), 0.86 (0.67-1.10), 0.96 (0.76-1.21), respectively.

Conclusion
Our large-scale study shows that vitamin D3 around time of birth is not associated with the risk T1D up to age 18 years.

10. Effects of 12 weeks high dose vitamin D3 treatment on insulin sensitivity, beta cell function, and metabolic markers in patients with type 2 diabetes and vitamin D insufficiency – a double-blind, randomized, placebo-controlled trial

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Aim
Vitamin D insufficiency is common in subjects with type 2 diabetes. Observational studies suggest that vitamin D plays a role in the pathogenesis of type 2 diabetes. However, results of intervention studies have been inconsistent. We investigated the effects of improving vitamin D status on insulin sensitivity, insulin secretion, and inflammatory markers in patients with type 2 diabetes.

Materials and Methods
A double blind, randomized, placebo controlled trial was conducted. Sixteen patients with type 2 diabetes and hypovitaminosis D were recruited. Eight patients received colecalciferol (280μg daily for 2 weeks, 140μg daily for 10 weeks) and 8 patients received identical placebo tablets for 12 weeks. Before and after intervention, patients underwent an IVGTT, a hyperinsulinemic euglycemic clamp, assessment of baseline high-frequency insulin pulsatility, glucose-entrained insulin pulsatility, DXA scans, 24-Hour-Ambulatory Blood Pressure Monitorings, and fasting blood samples.

Results
Serum-25(OH) vitamin D was also significantly higher in the vitamin D group compared to the placebo group (p = 0.02) after intervention. Although no significant changes in insulin sensitivity, inflammation, blood pressure, lipid profile, or HbA1c were found, we observed borderline (p between 0.05 and 0.10) improvements of insulin secretion, in terms of c-peptide levels, first phase incremental AUC insulin and insulin secretory burst mass.

Conclusions
Improvement in vitamin D status does not improve insulin resistance, blood pressure, inflammation or HbA1c, but might increase insulin secretion in patients with established type 2 diabetes.
11. The effects of eucaloric saturated and polyunsaturated high fat diets on insulin sensitivity and metabolism in healthy men

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The effect of dietary fatty acid content and quality on insulin sensitivity and molecular metabolism is not clear, and well controlled dietary intervention studies in healthy subjects are required. The Aim of the present study was to evaluate peripheral and hepatic insulin sensitivity, health related parameters and molecular metabolism before and after eucaloric 6 weeks high-fat diets (64 E% fat). The intervention was divided in two, one diet enriched in polyunsaturated fatty acids (PUFA) and one diet enriched in long-chain saturated fatty acids (SFA). The intervention was divided in two, one diet enriched in long-chain saturated fatty acids (SFA) and after eucaloric 6 weeks high-fat diets (64 E% fat). The intervention was divided in two, one diet enriched in polyunsaturated fatty acids (PUFA).

Materials and methods
18 untrained healthy men (age 33±1 years, BMI 26±1, VO2peak 39±1 ml·min⁻¹·kg⁻¹) completed the study (n=9 in each group). The hyperinsulinemic-euglycemic clamp was applied and [6.6-2H2] glucose was infused to evaluate hepatic glucose production. Skeletal muscle and subcutaneous adipose tissue biopsies were obtained.

Results
The glucose infusion rate and insulin-stimulated leg glucose uptake were not changed after the high fat diets. Fasting respiratory exchange ratio (RER) was markedly decreased after both interventions (p<0.001), but the increase in RER with insulin (i.e. metabolic flexibility) was intact compared to baseline. The basal hepatic glucose Ra was lower after both interventions (p<0.01), and the suppression of glucose production with insulin was not changed. Fasting plasma insulin (p<0.01) and plasma triacylglycerol (p<0.01) was lower after both interventions, while total cholesterol (p<0.01) and LDL cholesterol (p<0.06) concentration was lower after PUFA. In skeletal muscle, the capacity for FA uptake was increased after the interventions, evidenced by increased cluster of differentiation 36 (CD36), fatty acid transport protein 1 (FATP1) and fatty acid transport protein 4 (FATP4) protein content, concomitant with a lowering of TBC1 domain family member 1 (TBC1D1) protein, which might play a role for the observed increase in fat oxidation.

Conclusion
A high-fat diet is not detrimental to insulin action, as long as subjects are in energy balance, and polyunsaturated fat may have beneficial effects on lipoprotein metabolism.

12. effect of intake of extra protein high in ketogenic amino acids (e.g. Leucine) together with resistance training for four month in elderly individuals. Implications for physical function, muscle and bone.

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Aim
The objective of this study was to determine whether chronic supplementation of whey protein with extra leucine improves physical function such as six-minute walk distance and four-meter gait speed and whether this treatment affects the body composition in elderly men and women.

Materials and methods
The study was a 4 month randomized single blinded placebo controlled intervention study, including 47 women and 10 men between 60-85 years of age with osteopenia (t-score<-1.0 by DEX scan). The subjects were assigned to receive daily supplementations of 45.8 g whey protein with 6.14 g leucine (n=24), 45.8 g soy protein with 3.1 g leucine (n=23) or an isocaloric placebo product with maltodextrin and no protein (n=10). Concurrently with the supplementation, the subjects conducted a guided resistance-training program three times a week. Body composition was determined by DEX scan before and after the intervention.

Results
Six-minute walk distance was increased significantly in the whey group with high leucine (p<0.05) compared to the soy group (low leucine) by 3.5%. There was, however, no effect on four-meter gait speed. Surprisingly, the ratio of LBM/FM was significantly increased in the soy group compared to the whey group (p<0.05). Weight and BMI were increased within the whey and placebo groups (all p<0.05), and LBM was increased within the soy group (p<0.05). Plasma glucose, insulin and HOMA index increased within the whey group (all p<0.05) without any changes in the two other groups.

Conclusion
Four month of whey protein supplementation with extra leucine and concurrently resistance training significantly increased six-minute’ walk distance in elderly individuals. Surprisingly, the ratio of LBM/FM increased significantly only in the soy protein group with the lower amount of leucine (3.1 g vs 6.1 g daily).
13. changes in the hedonic component of taste does not predict food preferences assessed by an ad libitum meal 6 month post roux-en-y gastric bypass or sleeve gastrectomy surgery

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Aim
The effect of Roux-en-Y gastric bypass (RYGB) and Sleeve gastrectomy (SG) surgery on food preferences has never been investigated by means of direct behavior. A proposed mechanism for the effect of surgery on food preferences includes post-operative changes in the hedonic component of taste. Using an ad libitum buffet meal we investigated if RYGB and SG surgery leads to changes in food preferences, and whether this was associated with post-operative changes in fat perception and sweet taste.

Material and methods
Forty-one diabetic (n=10) and non-diabetic (n=31) subjects (BMI: 24.5±1.8 kg/m2) randomly completed one week of high (HCD) (≥250 g daily) vs low (LCD) (≤50 g daily) carbohydrate diets. A proposed mechanism for the effect of surgery on food preferences includes post-operative changes in the hedonic component of taste. Using an ad libitum buffet meal we investigated if RYGB and SG surgery leads to changes in food preferences, and whether this was associated with post-operative changes in fat perception and sweet taste.

Material and methods
Forty-one diabetic (n=10) and non-diabetic (n=31) subjects (BMI: 24.5±1.8 kg/m2) completed a sensory preference test and consumed an ad libitum buffet meal before and 6 month after RYGB (n=31) or SG (n=10). Ratings of preference for sweet taste and fat perception were registered for 4 variations of apple juice (5, 10, 15 and 20 g sucrose/L) and 5 variations of cocoa milk (0.4, 1.5, 3, 10 and 38% fat) on a 9-point hedonic scale. An index was calculated as the sum of log-concentration multiplied with the rating. Twenty food items organized equally into the following food categories: high-fat-savory (HFS), low-fat-savory (LFS), high-fat-sweet (HFSW) and low-fat-sweet (LFSW) were represented on the buffet. The subjects were instructed to eat ad libitum and according to their preferences. Relative energy intake from each category was calculated.

Results
Relative intake (% of total energy intake) from each of the 4 food categories did not change following surgery (all P>0.20). Postoperative changes in fat perception and sweet taste were not associated with changes in relative intake of fat (HFSW: R2=0.06; HFSW: R2=0.04; HFSW and HFSW: R2=0.08; all P>0.29) or sweet (HFSW: R2=0.04; LFSW: R2=0.04; HFSW and LFSW: R2=0.07, all P>0.19) from the buffet meal. Food preferences assessed at the buffet meal did not differ between surgery groups (all P>0.30) or between diabetes and non-diabetics (all P>0.18), justifying combining data in one pooled analysis.

Conclusion
Our data do not support the hypothesis that RYGB and SG surgery leads to changes in food preferences, or that post-operative changes in the hedonic component of taste predicts changes in food preferences, or that post-operative changes in the hedonic component of taste predicts changes in food preferences.

14. Low Carbohydrate Diet Reduces the Glycaemic Response to Glucagon in Patients with Type 1 Diabetes

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Background and aims
Dual hormone pump treatment with insulin and glucagon reduces the risk of mild hypoglycaemia. However, the efficacy of glucagon to elevate plasma glucose (PG) when liver glycogen stores are partly depleted is unknown.

This two-way crossover randomized clinical study investigated the effect of low-dose glucagon to restore PG from mild hypoglycaemia in patients on high (HCD) (≥250 g daily) vs low (LCD) carbohydrate diets (≤50 g daily).

Materials and methods
Ten patients with insulin pump treated type 1 diabetes (median±SD age 48±10 years, HbA1c 6.9±2.7 %, diabetes duration 22.5±7 years, and BMI 24.5±1.8 kg/m2) randomly completed one week of HCD and one week of LCD. Each week ended with a study visit, where fasting patients received subcutaneous insulin bolus estimated to reduce PG to 3.0 mmol/l. When PG ≤ 3.9 mmol/l, 100 µg glucagon was given subcutaneously followed by 500 µg glucagon after two hours.

Results
The PG time course after glucagon differed between HCD vs LCD (repeated measurement ANOVA: time x studyvisit, p=0.003). HCD had higher peak rises after both first (2.7±0.4 vs 1.3±0.3 mmol/l, p=0.003) and second glucagon bolus (5.6±0.5 vs 4.4±0.3 mmol/l, p=0.006). Similar, HCD had higher PG level two hours after the first (4.1±0.3 vs 3.1±0.2 mmol/l, p=0.01) and the second glucagon bolus (8.5±0.6 vs 5.9±0.5 mmol/l, p=0.005). However, the difference of the area under the glucose curve between the first and second glucagon dose after HCD was similar to LCD (366±53 vs 234±58, p=0.06). Further, the time to peak was similar after the first (31.9±2 vs 28.1±2.3 min, p>0.05) and second glucagon bolus (48.1±14 vs 44±14 min, p>0.05).

Conclusion
We conclude that LCD may impair the treatment effect of glucagon on mild hypoglycaemia. However, the first glucagon dose may not additionally reduce the LCD induced effect on a second glucagon bolus. Thus, patient’s carbohydrate intake should be assessed when low doses of glucagon are used in open loop and maybe also in closed loop settings.
15. Steno abc: advanced carbohydrate counting with or without an automated bolus calculator in type 1 diabetes

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Background
Advanced carbohydrate counting (ACC) improves metabolic control in patients with type 1 diabetes (T1D).

Aim
The aim of this study was to test whether concomitant use of an automated bolus calculator (ABC) would induce further improvements.

Material and Methods
In a 12-month, randomized, parallel group, open-label, single-centre, investigator-initiated clinical trial, we enrolled ACC-naïve adults with multiple daily insulin injections-treated T1D and HbA1c 64-100 mmol/mol. In a 1:1 ratio, participants were randomized to receive training in either ACC using mental calculations (MC-group) or ACC using an ABC (ABC-group) during a 3.5-hour group training course. For 12 months post training, patients attended a specialized diabetes centre quarterly. The primary outcome was change in HbA1c from baseline to 12 months.

Results
Between August 2012 and September 2013, 168 participants (96 men, 72 women) were recruited and randomly assigned to the MC-group (n=84) and the ABC-group (n=84). Drop-out rates were 23.8% and 21.4%, respectively (p=0.712 (between-group difference)); 130 participants completed the study. Baseline HbA1c was 7.7±4 mol/mol in the MC-group and 7.4±8 mmol/mol in the ABC-group. At 12 months, change in HbA1c was significant within both groups; MC-group -2 mmol/mol/year (95% CI -4 to -1, p=0.017) and ABC-group -5 mmol/mol/year (95% CI -6 to -3, p<0.0001). However, HbA1c reductions were significantly greater in the ABC-group (p=0.033). No episodes of severe hypoglycaemia were reported.

Conclusion
T1D patients initiating ACC obtained significantly greater HbA1c reductions when guided by an ABC.

16. High fat diet-induced changes of mouse hepatic transcription and enhancer activity are reversed by subsequent weight loss


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Epigenetic factors have been suggested to play an important role in metabolic memory by trapping and maintaining initial metabolic changes within the transcriptional regulatory machinery. However, there is considerable controversy regarding the permanency of these changes after intervention. The aim of this study was to identify hepatic epigenetic and transcriptional changes associated with intake of a high fat diet (HFD) followed by subsequently weight loss. We fed mice (C57BL6) a HFD for seven weeks followed by additional five weeks of chow to identify HFD-mediated changes to the hepatic transcriptional program. Mice fed a HFD displayed increased fasting insulin levels, hepatosteatosis and major changes in hepatic gene transcription associated with modulation of H3K27ac at enhancers, but no major changes in chromatin accessibility, indicating that HFD regulated gene transcription is exclusively controlled by alteration of pre-established enhancer activity. After return to the same body weight as chow fed control mice, the fasting insulin, glucose, and hepatic TG levels of the formerly obese mice were restored. Moreover, HFD-regulated H3K27Ac and mRNA levels returned to similar levels as chow fed mice. These data provide strong evidence, that the transcription regulatory landscape in liver induced by HFD is highly dynamic and can be reversed by weight loss. This provides hope for efficient treatment of early obesity-associated changes to hepatic complications by simple weight loss intervention without significant persistent reprogramming of the liver transcriptome.

17. Adipose Tissue Storage Enzymes and Postprandial Lipemia in Type 2 Diabetes

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Background and aims
Ectopic lipid storage is associated with insulin resistance and development of type 2 diabetes. In accordance with the adipose tissue expandability hypothesis, this may be a consequence of impaired postprandial adipose tissue storage capacity. Therefore, we measured enzyme activity of enzymes involved in adipose tissue lipid storage: Lipoprotein lipase (LPL) (hydrolyzes triglyceride (TG) from lipoproteins), acyl-CoA synthetase (ACS) (activation of fatty acids for anabolic or catabolic pathways) and diacylglycerol acetyltransferase (DGAT) (final step in TG synthesis). We hypothesized, that men with type 2 diabetes have preserved postprandial adipose tissue storage enzymes, which may contribute to their greater postprandial lipemia.

Materials and methods
11 men with type 2 diabetes and 10 weight-matched healthy men were included. Postprandial LPL, ACS and DGAT enzyme activity was measured in abdominal and femoral adipose tissue biopsies five hours after an oral fat tolerance test (FTT). Postprandial VLDL-TG storage was measured after a bolus of ex-vivo labeled [3H]-triolein VLDL-TG.

Results
No differences were observed between type 2 diabetic and healthy men in LPL activity (Abdominal: 0.7 (0.4-1.5) vs 0.7 (0.4-1.3) (p=0.75); Femoral: 0.6 (0.4-1.6) vs 0.6 (0.5-1.0) (p=0.87) μmol FFA/g/hr), ACS activity (Abdominal: 60±14 vs 69±21 (p=0.34); Femoral: 49±9 vs 65±26 (p=0.09) pmol/mg lipid/min) or DGAT activity (Abdominal: 7.7±2.1 vs 7.7±2.4 (p=0.94); Femoral: 5.3±1.6 vs 6.6±3.3 (p=0.31) pmol/mg lipid/min). LPL (p=0.04), ACS (p=0.09) and DGAT (p<0.01) activity was greater in abdominal compared to femoral adipose tissue. Abdominal ACS activity was inversely related to the peak total TG (R²=0.29, p<0.01) and VLDL-TG (R²=0.66, p<0.01) plasma concentration after the FTT. Femoral LPL activity (R²=0.57, p<0.02) was inversely related to the peak plasma VLDL-TG after the FTT. Postprandial VLDL-TG storage rate was not associated with the activity of any of the storage enzymes.

Conclusion
Men with type 2 diabetes have preserved postprandial adipose tissue storage enzyme activities, which, therefore, do not explain their increased ectopic lipid storage. However, LPL and ACS activity may affect the extent of postprandial lipemia and the lipid amount available for ectopic fat storage irrespectively of type 2 diabetes.

18. Association between sugar intake and coronary event risk in the malmö diet and cancer cohort

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Aims
Previous studies have suggested that a high intake of sugar-sweetened beverages is positively associated with the risk of a coronary events. However, few studies have examined the association between sucrose (i.e., sugar) and incident coronary events. The aim of the present study was, therefore, to examine the associations between sucrose intake and coronary event risk in a large cohort.

Materials and methods
We performed a prospective analysis on 26,190 individuals (62% women) free from diabetes and without a history of cardiovascular diseases from the Swedish population-based Malmö Diet and Cancer cohort. Over an average of 17 years of follow-up, 2,493 incident cases of coronary events (fatal or non-fatal myocardial infarction or death attributable to ischemic heart disease) were identified from registers. Sucrose intake was obtained from an interview-based diet history method, including 7-day records of prepared meals and cold beverages and a 168-item diet questionnaire covering other foods. Cox proportional hazards regression was used to model the association between sucrose intake and coronary event risk adjusted for gender, age, energy intake, dietary method, season, smoking, waist, alcohol consumption, physical activity, educational level, intake of fruit and vegetables, whole grains, coffee, fermented milk, meat, and fish. A restricted cubic spline was computed to examine the shape of the association between sucrose intake and coronary event risk.

Results
Participants who consumed more than 15% of their energy intake (E%) from sucrose (five percent of this population) had a 37% (95% CI=13-66%) increased risk of a coronary event compared with the lowest sucrose consumers (<5 E%). In addition, we observed a non-linear association indicating that the risk increased above the median intake (8.2 E%), and no benefit of having a lower sucrose intake was observed.

Conclusion
The results indicated that high sucrose consumption is associated with an increased risk of a coronary events.