JAARGANG 20 / NOVEMBER 2022

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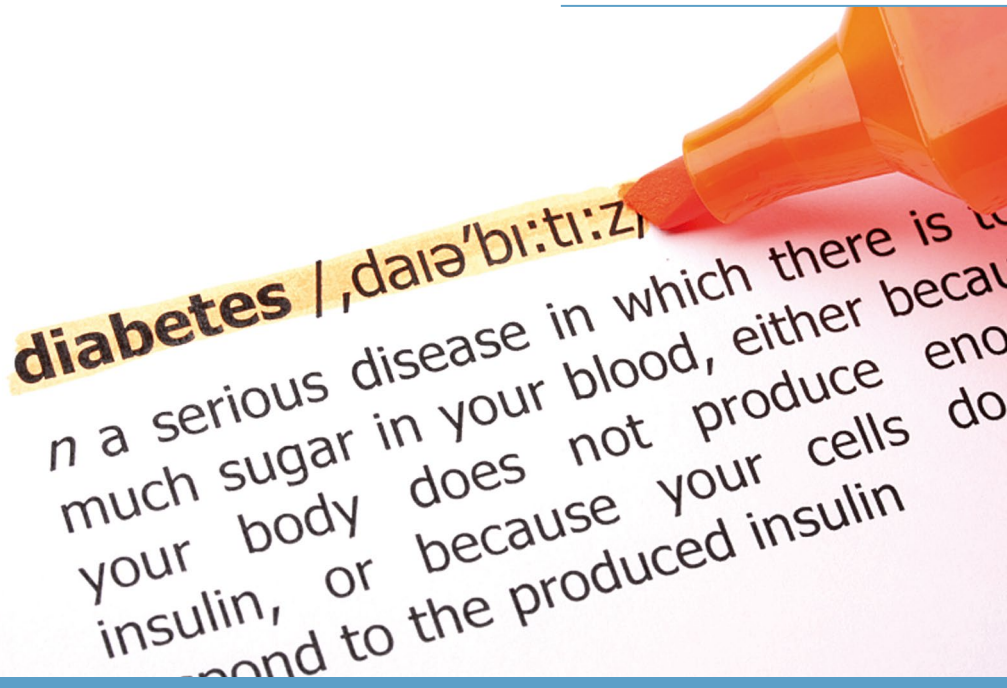
Nederlands Tijdschrift voor Diabetologie

Annual Dutch Diabetes Research Meeting 2022
3 & 4 november



Nederlands Tijdschrift voor Diabetologie

JAARGANG 20
NOVEMBER 2022
4

Beste lezer,

Traditiegetrouw is het vierde nummer van het Nederlands Tijdschrift voor Diabetologie volledig gewijd aan het programma van de *Annual Dutch Diabetes Research Meeting* (ADDRM).

Op donderdag 3 november en vrijdag 4 november 2022 vindt de 48e ADDRM plaats in Wageningen. Deze jaarlijkse bijeenkomst wordt georganiseerd door de Nederlandse Vereniging voor Diabetes Onderzoek (NVDO), in samenwerking met de Nederlandse Associatie voor de Studie van Obesitas (NASO), de Netherlands Diabetes Epidemiology Study
Group (NESDG), de Nederlands/Vlaamse Werkgroep PsychoSociale Aspecten van Diabetes (PSAD) en de Vereniging voor Neurovasculaire Complicaties van Diabetes (NVCD).

Na twee covid-jaren is de editie van 2022 weer een 'normale' ADDRM, waarbij iedereen van harte welkom is om deel te nemen aan het programma in het WICC in Wageningen.

Het wetenschappelijke programma heeft een herkenbare ADDRM-identiteit, met de traditionele highlights, zoals een sterk klinisch programma, de beste wetenschappelijke abstracts, internationale keynote lectures en natuurlijk de Terpstra en Gerritzen Awards.

Verderop in het blad vindt u het plenaire programma, met een keur aan nationale en internationale topsprekers. Ook alle abstracts zijn opgenomen in deze uitgave van het NTD.

Graag tot ziens in Wageningen!

Dr. Marten Engelse
Voorzitter Nederlandse Vereniging
voor Diabetes Onderzoek

Zustervereinigingen
PSAD
NDESG
NVCD
NASO

3 en 4 november 2022

ANNUAL DUTCH DIABETES RESEARCH MEETING

www.addrm.nl

PLENAIR PROGRAMMA

Donderdag 3 november

09:30 - 09:45	Plenary opening 48e ADDRM Dr. Marten Engelse, chair NVDO
09:45 - 10:45	**Niet-alcoholische leververvetting en diabetes mellitus type 2 – raakvlak tussen endocrinologie en hepatologie** Dr. Onno Holleboom Dr. Maarten Tushuizen
10:45 - 11:15	**ADA/EASD Position statement 2022: Management of Type 2 Diabetes** Prof. dr. Chantal Mathieu
11:15 - 11:45	Coffee break
11:45 - 12:45	**Nieuwe incretines: hoe werken ze en wat kunnen we verwachten?** Prof. dr. Patrick Rensen en dr. André van Beek
12:45 - 13:15	**Pompen en sensoren: zien we door de bomen bos nog?** Dr. Titia Vriesendorp
13:15 - 14:15	Lunch
14:15 - 15:00	**Complexe obesitas voor de internist** Prof. dr. Mireille Serlie
15:00 - 15:45	Diabeteskamer ALV
15:45 - 16:30	Break
16:30 - 17:15	**Adipose tissue in obesity: size, sites and cytes** Dr. Gijs Goossens
17:15 - 18:00	**Gerritzen Award for best thesis on diabetes research 2022**
18:00 - 18:15	Mini break
18:15 - 19:15	**Prof. dr. J. Terpstra Young Investigator Award 2022**
19:15 - 19:30	**Gerritzen Award Ceremony (with drinks)**
19:30	Walking dinner

Vrijdag 4 november

08:30 - 09:15	ALV NVDO
09:15 - 10:00	**Case report session**
10:00 - 10:45	**Mendelian randomisation and other emerging methodologies** Prof. dr. Harold Snieder
10:45 - 11:15	Break
11:15 - 12:00	**Nudging and prevention in the social domain** Prof. dr. Joline Beulens
12:00 - 13:00	**Best meeting abstracts session ADDRM 2022**
13:00	Closure

ABSTRACTS ADDRM 2022

1
Evaluation of Diabetes eHealth application CloudCare

Henk-Jan Aanstoot, Nico Riegman, Sander Last, Dick Mul, Arjen Hoogendam, Henk Veeze

Diabeter Nederland, Rotterdam, the Netherlands

BACKGROUND

Modern diabetes care shows an increasing importance of data from devices such as glucose meters, glucose sensors, insulin pumps and electronic pens. Getting these data to healthcare providers, into hospital EMR's and use them to provide patients with timely treatment advice is often complex and difficult.

METHODS

Diabeter developed a brand-agnostic CE-marked eHealth application, CloudCare, aimed to get these data to healthcare providers, into hospital EMR's and use them to provide patients with timely treatment advice. The first step was the development a 'closed data loop' between patients and healthcare providers (HCP) enabling uploading insulin and glucose device data from all used platforms/brands. These glucose values are displayed in a heat map, a visual also shared with the patient (allowing an overlook and proactive approach in glucose management). Insulin data can be added as well as additional information from the patient's EMR.

RESULTS

A previous version was applied 9 years in the Diabeter patient population and resulted more than 10.000 'data loops' annually. Using this, we showed improved HbA1c and a shift from live to remote contacts. As second step a decision-support system was build based on consensus data sets and published algorithms, servicing also devices and data that do not require manual uploads). This allows for glucose management based triage: Patients that are well regulated will be transferred to CloudCare for further glucose management, but patients with abberant trends and dysregulation will receive additional guidance. The aim is to use CloudCare to facilitate patient-centered, population-based glucose management, leading to enhanced patient outcomes and HCP satisfaction. The next evaluation includes a 3 months' retrospective period and a 6 months' prospective period. Primary outcomes include glucose control (A1c) and patient satisfaction and secondary outcomes include additional glucometrics, complications, costs, shifts in HCP worklflow and HCP satisfaction.

CONCLUSION

We will seek to include additional clinics in this evaluation. Solutions such as CloudCare will help to integrate modern diabetes treatment and improve outcomes.

2
Glucose variability impacts long-term immune alterations and hypoglycaemia-induced inflammation in people with type 1 diabetes

Mandala Ajie[1], Clementine Verhulst[1], Julia van Heck[1], Therese W Fabricius[2], Ulrik Pedersen-Bjergaard[2,3], Cees Tack[1], Rinke Stienstra[1,4], Bastiaan de Galan[1,5]

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BACKGROUND

Hypoglycaemia causes activation of the immune system and is linked to an increased risk for cardiometabolic disease. We set out to determine how glycaemic parameters based on continuous glucose monitoring (CGM) affect the immune response to a hypoglycaemic event.

METHODS

38 individuals with type 1 diabetes were recruited. Participants underwent a hyperinsulinaemic-normoglycemic (5.2 ± 0.1 mmol/L) hypoglycaemic (2.7 ± 0.0 mmol/L) glucose clamp. Venous blood was drawn during the normoglycaemic phase, hypoglycaemic phase, and one day after

the clamp to measure circulating immune cell composition and inflammatory markers. CGM data from 6 days prior to the clamp experiment were used to assess the relation between different glucose metrics with immune responses to experimental hypoglycaemia.

RESULTS

At baseline, innate immune cell counts and 6/72 circulating inflammatory markers were negatively associated with the frequency of CGM-recorded hypoglycaemia ($p < 0.05$). Hypoglycaemia caused an increased levels of circulating monocytes ($p < 0.01$), lymphocytes ($p < 0.01$), and inflammatory proteins like CRP (all $p < 0.05$), which were sustained until one day after the clamp. The increase in circulating immune cells were positively associated with CGM-recorded time spent on hyperglycaemia (TAR), whilst negatively associated with the time spent on hypoglycaemia (TBR). TBR was also positively associated with circulating inflammatory markers upon hypoglycaemia.

CONCLUSION

Glycaemic parameters based on CGM impact immune response to hypoglycaemia, with the TBR having an attenuating effect and the TAR a stimulating effect on hypoglycaemia-induced inflammation. Future studies are needed to identify drivers of these altered responses.

3
Sharp fall in prevalence of impaired awareness of hypoglycaemia in individuals with type 1 diabetes over the recent years

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BACKGROUNDS

Impaired Awareness of Hypoglycaemia (IAH) has been reported to affect up to a third of people with type 1 diabetes. Whether the increased use of sensor technology has changed its prevalence is unknown. The aim of this study was to investigate the current prevalence of IAH and its change over time in a cohort of individuals with type 1 diabetes.

METHODS

In this single-centre cohort study, the hypo awareness state was assessed using the modified Clarke questionnaire in people with type 1 diabetes, aged ≥ 16 years. Participants were recruited from the diabetes outpatient clinic from February 2020 through April 2021. The scores were compared to similar data collected during previous assessments in 2006, 2010 and 2016 respectively.

RESULTS

A total of 488 individuals (51.2% male) with a mean (± SD) age of 51.3 ± 15.9 years, median [IQR] diabetes duration of 30 [16-40] years and mean HbA1c of 60.3 ± 11.6 mmol/mol (7.7 ± 1.1%) were included. Sensors were used by 85% of the study population. IAH was present among 78 (16.0%) participants, whereas 86 (17.6%) participants had a history of severe hypoglycaemia. By comparison, the prevalence of IAH equalled 32.5% in 2006, 32.3% in 2010 and 30.1% in 2016 (p for trend < 0.001), while the proportion of individuals reporting severe hypoglycaemia equalled 21.2%, 46.7% and 49.8%, respectively (p for trend 0.010). Comparing sequential assessments over time, the proportion of individuals with persistent IAH decreased from 74.0% and 63.6% between 2006 and 2016 to 32.5% in 2020.

CONCLUSION

Among individuals with type 1 diabetes and high use of sensor technology, the current prevalence of IAH was 16%, about half lower as compared to previous years.

4
Amount and timing of physical activity in relation to sleep in the general population

Charlotte Andriessen[1], Jeroen van der Velde, Joris Hoeks, Andries Kalsbeek, Raymond Noordam, Frits Rosendaal, Diana van Heemst, Femke Rutters, Patrick Schrauwen, Renée de Mutsert[2]

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BACKGROUND

Physical activity plays an important role in aligning the internal circadian rhythm with the external day-night rhythm, and has been proposed to exert beneficial effects on sleep. We examined if the amount and timing of moderate-to-vigorous physical activity (MVPA) was associated with sleep quality and duration in the general population.

METHODS

In this cross-sectional analysis of the Netherlands Epidemiology of Obesity study, physical activity was measured with accelerometery for 4 days, and categorized in performing most MVPA (> 5% difference in MVPA) in the morning (06:00-12:00), afternoon (12:00-18:00), evening (18:00-00:00), or with an even distribution of MVPA over the day. Sleep characteristics were reported with the Pittsburgh Sleep Quality Index and dichotomized as good (reference) or poor. We estimated odds ratios of poor sleep with 95% confidence intervals using logistic regression analysis, adjusted for confounding (e.g. age, sex, BMI).

RESULTS

We analysed 739 participants (56% women), with a mean (SD) age of 56 (6) years and BMI 26.1 (4.2) kg/m^2; 20% performed most MVPA in the morning, 61% in the afternoon, 7% in the evening, and 12% evenly divided their MVPA over the day. The amount and timing of MVPA were not related to sleep quality, latency, duration, efficiency, and medication use, albeit with wide confidence intervals. The amount of MVPA was associated with a lower odds of fatigue-related dysfunction during daytime (OR: 0.54, 95% CI: 0.32-0.94 per hour of MVPA/day). Participants who performed most MVPA in the morning were less likely to experience sleep disturbances (0.23, 0.09-0.60) than participants with an even distribution of MVPA over the day.

CONCLUSION

These results suggest that the amount of MVPA is associated with functioning during daytime, whereas most MVPA in the morning was associated with less sleep disturbances. Larger studies need to verify these results.

5
The ubiquitin E3 ligase Rnf125 is a novel PPAR target gene in adipocytes

Rosalie Baak[1], Miguel Hernandez-Quiles[1], Ellen Jeninga[1], Soufian El Makrini[1], Vanessa Meyn[1], Arvind Wennberg[1], Robert van Es[1], Harm Jan Vos[1], Eric Kalkhoven[1]

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BACKGROUND

Peroxisome proliferator-activated receptor (PPAR), a member of the nuclear receptor superfamily of ligand inducible transcription factors, is viewed as the master regulator of adipocyte differentiation, function, and maintenance. Thiazolidinediones (TZDs) like rosiglitazone are synthetic PPAR ligands that display effective anti-diabetic activity, but their clinical use is limited because of serious undesired side effects. Detailed studies of PPAR action will not only expand our fundamental understanding of adipocyte biology but also reveal the possibilities and limitations of PPAR as an anti-diabetic drug target.

METHODS

We identified the E3 ubiquitin ligase Rnf125 as a novel PPAR target gene. Both Rnf125 mRNA and protein expression significantly increased during 3T3-L1 differentiation and ChIP-seq experiments showed that PPAR binds at three potential enhancer sites in the Rnf125 locus together with its heterodimeric partner RxR . Subsequent analyses showed that two of these enhancers are functional, supporting the classification of Rnf125 as a novel PPAR target gene. Interestingly, RNA-seq on purified adipocytes collected from subcutaneous samples of insulin sensitive and resistant human subjects reveals that RNF125 mRNA expression is significantly decreased in insulin resistant patients (GEO: GSE174475). Moreover, in patients with

acquired obesity, RNF125 negatively correlated with adipocyte size and metabolic derangements, but positively with adiponectin and adipocyte number (Heinonen et al., 2014; Nature).

RESULTS

To identify the role of Rnf125 in adipocyte biology we next aimed to identify substrates, which are expected to be degraded by the ubiquitin-proteasome system (UPS). Using different mass spectrometry-based methods, we identified multiple potential substrates including the metabolic enzyme Glutamine Synthetase (Glul). Interestingly, Glul converts glutamate to glutamine, which levels inversely correlate with fat mass and inflammation in human WAT (Petrus et al., 2020; Cell Metabolism).

CONCLUSION

Taken together, we identified Rnf125 as a novel PPAR target gene and show that the UPS may represent a level of spatiotemporal regulation in adipocyte biology and metabolism that has remained understudied so far.

6
Glyoxalase 1 overexpression reduces cognitive decline in diabetic mice

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**Shared last-authorship*

BACKGROUND

Diabetes is associated with cognitive impairment, however, the underlying mechanism remains unclear. Methylglyoxal (MGO) is a small but highly reactive molecule, which arises from the breakdown of glucose and is increased in diabetes. MGO is associated with microvascular dysfunction in diabetes. We hypothesise that MGO accumulation in diabetes causes cognitive impairment and can be prevented by overexpression of *glyoxalase 1 (Glo1)*; the enzyme involved in the breakdown of MGO.

METHODS

8-9 week old Glo1 overexpressing C57Bl/6 mice and wild-type littermates (WT) were used. Diabetes was induced by streptozotocin injection (STZ, 50mg/kg IP) on 5 consecutive days, resulting in 3 groups (WT/control, WT/diabetes, Glo1/diabetes). Fasting blood glucose was measured at 13 weeks. Mouse cognitive function was tested around 6 and 15 weeks using various cognitive tests. Animals were sacrificed at 17 weeks and brain GLO1 activity was measured in the cortex ex vivo.

RESULTS

Glucose levels in WT/diabetes (25.6 ± 3.0 mM, n = 11) and Glo1/diabetes (23.6 ±2.7 mM, n = 12) were increased compared to WT/control (7.0 ± 1.0 mM, n = 12) ($p < 0.0001$). The cortical GLO1 activity was increased 2.5-fold in Glo1/diabetes compared to WT/control ($p < 0.0001$) and GLO1 activity was decreased 1.1-fold in WT/diabetes compared to WT/control ($p = 0.03$). A decreased long-term memory was observed in WT/diabetes mice, compared to WT/control, which was normalised in the Glo1/diabetes group.

CONCLUSION

We found that diabetes impairs long-term memory in mice which can be prevented by overexpression of Glo1. These data suggests that MGO accumulation in the brain in diabetes has an effect on impaired cognitive function. The impact of MGO on the cerebral microvasculature is currently being investigated.

7
Cold-induced thermogenesis shows a diurnal variation, that unfolds differently in males and females

Mariëtte R. Boon[1], Maaike E. Straat[1], Borja Martinez-Tellez[1], Aashley Sardjoe Mishre[1,2], Magdalena M. A. Verkleij[1], Mirjam Kemmeren[1], Iris C. M. Pelsma[1], Juan M. A. Alcantara[3], Andrea Mendez Gutierrez[4], Sander Kooijman[1], Patrick C. N. Rensen[1]

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BACKGROUND

Cold exposure mobilizes lipids to feed thermogenic processes in organs, including brown adipose tissue (BAT). In rodents, BAT metabolic activity exhibits a diurnal rhythm, which is highest at the start of the wakeful period. Here, we studied whether cold-induced thermogenesis displays diurnal variation in humans and differs between sexes.

METHODS

This randomized crossover study included 24 young and lean males (n = 12) and females (n = 12) who underwent 2.5 hour personalized cooling in the morning (7:45 am) and evening (7:45 pm), with 1 day in between. We measured energy expenditure (EE) and supraclavicular skin temperature in response to cold exposure.

RESULTS

In males, cold-induced EE was higher in the morning than in the evening (+54% vs +30%; p = 0.05) but did not differ between morning and evening in females (+37% vs +30%; p = 0.42). Only in males, supraclavicular skin temperature upon cold increased more in morning than evening (+0.2°C vs -0.2°C; p = 0.05). In males, circulating free fatty acid (FFA) levels were increased after morning cold exposure, but not evening (+90% vs +9%; p < 0.001). In females, circulating FFA (+94% vs +20%; p = 0.006), but also triglyceride (+42% vs +29%, P = 0.01) and cholesterol levels (+17% vs 11%; p = 0.05) were more increased after cold exposure in the morning than in the evening.

CONCLUSION

Cold-induced thermogenesis is higher in the morning than the evening in males; however, lipid metabolism is more modulated in the morning than the evening in females.

8
Alpha cells exhibit beta cell-like stress during inflammation, but show resistance to oxidative stress

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BACKGROUND

Inflammation is associated with β cell loss in both type 1 and type 2 diabetes, but little is known about the effect on α cells under these same circumstances. Whilst there are reports of hyperglucagonemia in both T1D and T2D, the mechanisms of α cell dysfunction remains largely unknown. Here, we aim to model α cell failure in vitro in order to investigate underlying mechanisms.

METHODS

AlphaTC1 Clone 6 cells (mαTC, murine α-cell line) were incubated for 24h with pro-inflammatory cytokines (a combination of IFNy (5, 50, or 100ng/mL) and IL-1b (0.1, 1 or 10ng/mL), IFNy only (50ng/mL), or IL-1b only (1ng/mL)), or with oxidative stressor H2O2 (1, 10, 50, 100, 200 uM). Gene expression was assessed by qPCR. Calcium activity was measured with Cal520-dye at a DragonFly500 spinning-disk confocal. Primary human islets were incubated with pro-inflammatory conditions (IFN-y (50ng/mL) and IL-1b (1ng/mL)) for 24h, and checked for glucagon (GCG) gene expression and secretion by dynamic glucose stimulation.

RESULTS

Pro-inflammatory conditions trigger an upregulation of ER stress genes Chop (1.3-1.5x, p < 0.05; IFN-y+IL-1b, IFNy, n = 6) and Atf3 (2.6-7.7x, p < 0.05, IFN-y+IL-1b, IFNy, n = 3), and oxidative stress gene Nrf2 (1.5x, p < 0.05, IFN-y+IL-1b, n = 3), as well as a decrease in Gcg (0.7x, p < 0.05, IFN-y+IL-1b, n = 6) in mαTC. In contrast, oxidative stress did not show any significant changes. Decrease in GCG after pro-inflammatory conditions was confirmed in human islets (0.6x, p < 0.05, n = 5). In contrast, dynamic glucose

stimulation resulted in an increase in glucagon secretion after cytokine treatment in human islets (n = 1). Similarly, calcium activity was increased during high glucose in cytokine-treated mαTC ($p < 0.05$, n = 3).

CONCLUSION

An inflammatory environment induces ER and oxidative stress genes in α cells, similar to that in β cells, as well as downregulation of their main identity marker glucagon. Nonetheless, calcium activity and secretory data suggest an increase in glucagon secretion after cytokine treatment, which is in line with physiological evidence of hyperglucagonemia. In contrast to inflammation, induction of oxidative stress did not warrant upregulation in any stress-related genes, and no changes in identity genes in the α cells. This suggests that α cells have internal defense mechanism protecting them from oxidative stress.

9

The association between social jetlag and parameters of Metabolic Syndrome and Type 2 Diabetes: a systematic review and meta-analysis

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BACKGROUND

We aimed to determine the association between social jetlag and parameters of the Metabolic Syndrome and Type 2 Diabetes (T2D) in a systematic review and meta-analysis.

RESULTS

A systematic literature search was conducted in PubMed/Embase/Scopus until May 2022. Included studies described an association between social jetlag and parameters of the Metabolic Syndrome and/or T2D, were available full text and written in English or Dutch. Data extraction and quality assessment was performed on pre-piloted forms independently by two reviewers. Results were meta-analyzed using random-effects analysis. 6290 titles/abstracts were screened, 176 papers were read full-text, 68 studies were included.

METHODS

Three studies were rated as low quality, 27 were moderate, and 38 were high quality. High quality studies showed that having social jetlag compared to no social jetlag was significantly associated with higher BMI (0.49 kg/m^2, 95%confidence interval 0.21; 0.77; $I^2 = 100\%$) in 20 studies, higher waist circumference(1.11 cm, 0.42; 1.80; $I^2 = 25\%$) in seven studies, higher systolic blood pressure (0.37 mmHg, 0.00; 0.74; $I^2 = 94\%$) in ten studies and higher HbA1c (0.42%, 0.12; 0.72; $I^2 = 100\%$) in 12 studies. No statistically significant associations were observed for obesity, abdominal obesity, High and Low Density Lipoprotein (HDL, LDL) levels, cholesterol, triglycerides, diastolic blood pressure, hypertension, fasting glucose, HOMA, Metabolic Syndrome or T2D. Sensitivity analyses on health status and statistical quality did not reduce heterogeneity.

CONCLUSION

Despite substantial heterogeneity, social jetlag is associated with certain parameters of the Metabolic Syndrome and T2D, but not with prevalent Metabolic Syndrome or T2D. These findings should be interpreted with caution as the level of evidence is low, longitudinal studies are needed to further assess the direction of causality.

10

Dual RNA-sequencing to understand host-pathogen interactions in *Mycobacterium tuberculosis*-infected macrophages from people with diabetes mellitus

Julia Brake[1], Valerie A.C.M. Koeken[1,4], Jodie A. Schildkraut[2], Rinke Stienstra[1], Cees J. Tack[1], Jakko van Ingen[3], Reinout van Crevel[1]

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BACKGROUND

Since diabetes mellitus (DM) and tuberculosis (TB) are co-emerging diseases, the control of TB is threatened by DM as a well-known risk factor. Evidence suggests that altered availability of metabolic substrates in DM induces

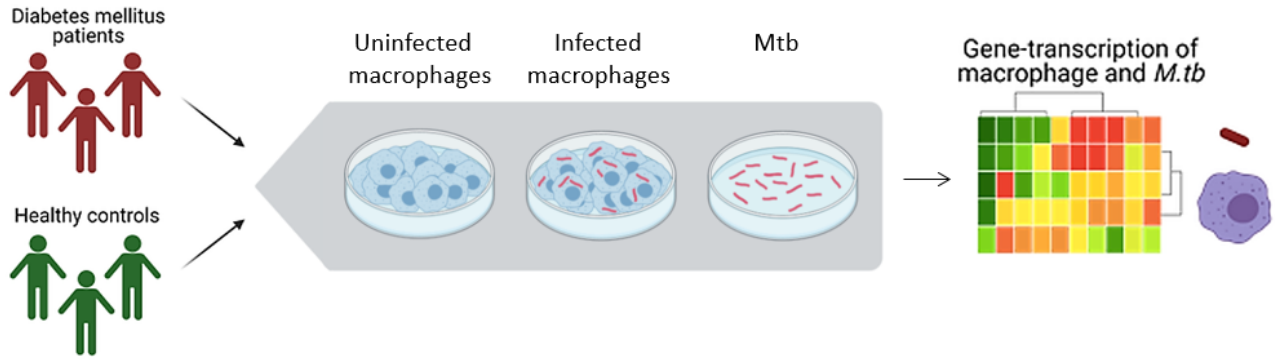

Figure 1. Human monocyte-derived macrophages were infected with Mtb strain H37Rv, followed by mycobacterial transcript enrichment and RNA sequencing.

immunometabolic changes in macrophages, resulting in an impaired immune response and a preferred niche for Mycobacterium tuberculosis (Mtb). Up until now, the exact biological mechanisms underlying the increased susceptibility to TB are unclear.

METHODS

Previous research only focused on one side of the story; either the response of the host or the pathogen upon infection. To get a grasp on the host-pathogen interaction, comprehensive knowledge of gene expression changes in both species is required. First, we optimized a protocol for dual RNA sequencing and performed a pilot study with two healthy participants. Human monocyte-derived macrophages were infected with Mtb strain H37Rv, followed by mycobacterial transcript enrichment and RNA sequencing.

RESULTS

Results show that RNA sequencing reads are of high quality and quantity, which allows for transcriptional profiling of host and pathogen. Next, we will apply this optimized dual RNA sequencing workflow to macrophages derived from individuals with DM (n = 20) and age and sex-matched healthy controls (n = 20). In addition, cytokine production upon infection and mycobacterial load in macrophages will be measured. This approach is a unique way of getting deeper insights into what exactly the macrophage and Mtb are telling each other during infection in the context of diabetes.

CONCLUSION

We aim to get a better understanding of the increased susceptibility to tuberculosis in people with DM and to identify leads for additional host-directed therapy.

11
Pressure-relieving effect of different insole top covers in people with diabetes at high risk of foot ulceration

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BACKGROUND

Appropriate pressure-relieving footwear helps prevent foot ulcers in people at high risk of ulceration, and many footwear design elements contribute to this effect. We aimed to assess the offloading effect of commonly used (combinations of) materials as insole top cover.

METHODS

We measured 20 participants with diabetes and neuropathy (all IWGDF risk 2 or 3) for in-shoe peak pressures (pedar-X) in 8 different insole top covers while walking in prescribed footwear. Top covers were assessed in random order and consisted of either a 3 mm or 6 mm thick open-cell foam or a combination of closed-cell and open-cell foams (**Figure 2**). We again measured in-shoe plantar pressure after one month of wearing the top cover. Results are reported for a region of interest (ROI, i.e. previous ulceration or high baseline pressure). Repeated measures ANOVA with Greenhouse-Geisser correction was used to compare insoles.

RESULTS

Participants were 17 males, 17 with diabetes type 2, mean age 71 (SD 7) years, and 18 with ulcer history. Mean peak pressure at the ROI varied between 167 (SD 56) and 186

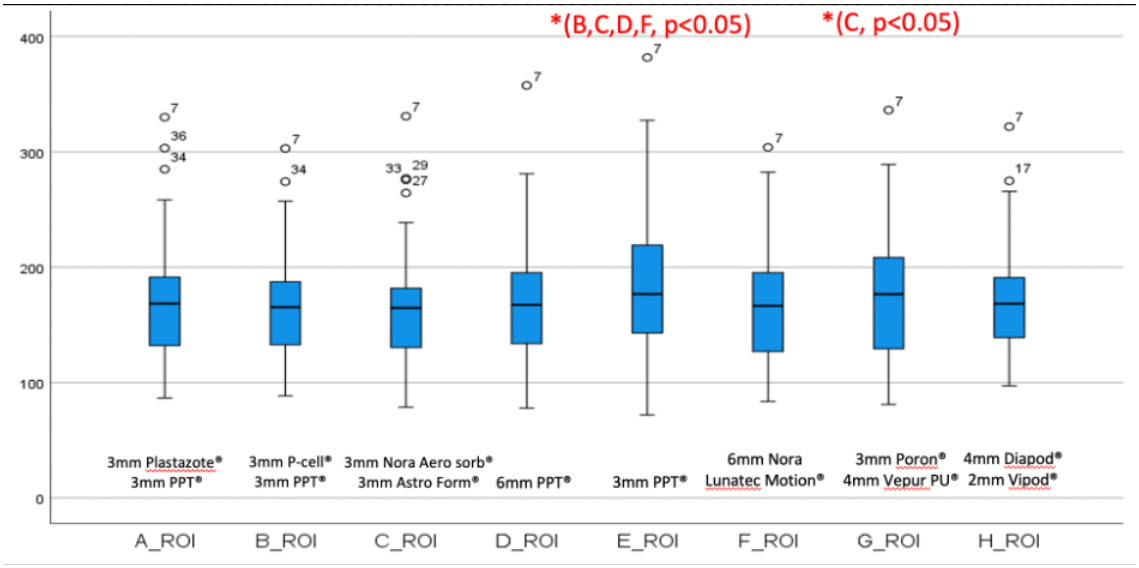

Figure 2. Top covers were assessed in random order and consisted of either a 3 mm or 6 mm thick opencell foam or a combination of closed-cell and open-cell foams.

(SD 65) kPa across top covers. The single 3-mm thick top cover (open-cell foam) showed significantly higher in-shoe peak pressures than four 6-mm thick top covers (**Figure** 2). Across all 6-mm thick top covers, only two showed to be significantly different in peak pressure. One month wearing changed in-shoe peak pressures from -2.7 to 47.8 kPa across conditions, with only the three single density foams showing a reduction.

CONCLUSION

Compared to a 3 mm thick open-cell foam, 6 mm thick open-cell foams and combinations of 3 mm open and 3 mm closed cell foams provide more pressure relief when walking in high-risk people with diabetes. The 6 mm thick open-cell foams seem to retain their offloading capacity more effectively than combined materials.

12

The HMO 2'-fucosyllactose in combination with resistant starch increased distal colonic short-chain fatty acid production in lean men and in men with prediabetes and obesity

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BACKGROUND

Clinical trials demonstrated that distal colonic infusions of the microbial metabolites short-chain fatty acids (SCFA) beneficially affect human substrate metabolism. Here, we hypothesized that the combination of the fermentable human milk oligosaccharide 2'-fucosyllactose (2-FL) with resistant starch (RS) increases distal colonic SCFA production and improves metabolic parameters in lean men and men with overweight/obesity and prediabetes.

METHODS

In this double-blind, placebo-controlled, randomized, crossover study, 10 lean men and 9 men with prediabetes and overweight/obesity were supplemented with either 2-FL, 2-FL+RS or placebo one day prior to a clinical investigation day (CID). During the CIDs, blood samples were collected fasted and after consumption of a liquid high-fat mixed meal to determine plasma SCFA acetate, butyrate and propionate concentrations (primary outcomes). Secondary outcomes were fasting and postprandial plasma insulin, glucose, free fatty acid (FFA), glucagon-like peptide 1 and peptide YY concentrations. In addition, fecal SCFA and microbiota composition, breath hydrogen excretion, and energy expenditure and substrate oxidation (indirect calorimetry) were determined.

RESULTS

In lean men, supplementation of 2-FL increased postprandial plasma acetate ($p < 0.017$) and fasting hydrogen excretion ($p < 0.041$) compared to placebo. Postprandial plasma butyrate increased after 2-FL and 2FL+RS supplementation compared to placebo ($p < 0.05$) in both metabolic phenotypes. Additionally, 2-FL+RS decreased fasting and postprandial plasma FFA compared to placebo ($p < 0.05$) in lean men.

CONCLUSION

Supplementation of 2-FL with or without RS the day prior to investigation increased the essential microbial metabolites SCFA in the systemic circulation in lean men and in men with prediabetes and obesity. The combination of 2-FL with RS showed an additional beneficial metabolic effect by lowering plasma FFA in lean men. Future research should investigate the metabolic health effects after prolonged supplementation in particular in the prediabetic, obese phenotype.

13

Impaired endothelial-dependent systemic microvascular function is associated with higher risk of heart failure with preserved ejection fraction in women with type 2 diabetes

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BACKGROUND

Endothelial microvascular dysfunction (MVD) is common in subjects with type 2 diabetes (T2D) and might trigger the development of left ventricular diastolic dysfunction (LVDD) and heart failure with preserved ejection fraction (HFpEF). However, the clinical relevance of MVD and its association with HFpEF remains unclear. Further, the influence of sex on MVD and on its association with HFpEF needs further investigation.

METHODS

We aimed to characterize systemic MVD in T2D, and investigate its association with markers of LVDD/HFpEF. Furthermore, we aimed to test the effect of sex on the association between MVD and LVDD/HFpEF. 77 men and 75 women from the Hoorn Diabetes Care System Cohort underwent in vivo evaluation of MVD, echocardiography and blood sampling. MVD was assessed by laser speckle contrast analysis combined with iontophoresis of insulin, acetylcholine and sodium nitroprusside (SNP). The association between indices of MVD and markers of LVDD/HFpEF was assessed by multivariable linear regression analysis adjusted for confounders. Probability of HFpEF was estimated with the H2PEFF score.

RESULTS

Mean age was 65 ± 6y, mean HbA1c 7.5 ± 1.2%. Comorbidities and biomarkers did not significantly differ between the sexes. Women had smaller LV mass index (82.8 ± 18.1 vs 99.2 ± 20.3 g/m^2) and higher E/E' (13.4 ± 4.4 vs 11.3 ± 2.8) than men. No significant differences between the sexes were observed in terms of MVD indices. A lower relative perfusion change from baseline to plateau due to insulin and acetylcholine was associated with higher H2PEFF score, independently of cardiovascular risk factors and medications, in women but not in men (1% increase in perfusion associated to 0.5 and 0.6% decrease of the H2PEFF score respectively). No significant associations were observed between SNP and the H2PEFF score.

CONCLUSION

Impaired endothelial-mediated vasodilation in response to insulin and acetylcholine confers a higher risk of HFpEF in women with T2D. In vivo measures of systemic MVD could represent novel cardiovascular risk markers, for refined risk prediction of HFpEF.

14

12-week oral GABA supplementation reduces fasting glucose concentration but does not change postprandial glucose response in adults with prediabetes: A double-blind, randomized, placebo-controlled trial

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BACKGROUND

Rodent studies have shown beneficial effects of oral gamma-aminobutyric acid (GABA, traditionally known as a neurotransmitter) on glucose homeostasis and cardiovascular health. Aside from endogenous synthesis, GABA is

also present at high concentrations in for example fermented foods and tomatoes. However, it is currently unknown whether oral GABA is capable of improving glucose homeostasis in humans.

METHODS

The aim of this study was to investigate whether oral GABA supplementation can improve glucose homeostasis in individuals at risk of developing type 2 diabetes. In a 12-week, randomized, placebo-controlled, double-blind, parallel-arm trial, 52 individuals with prediabetes (impaired glucose tolerance and/or fasting glucose) between 50 and 70 years old with a BMI ≥ 25 kg/m^2 were randomized to receive either 500 mg GABA 3 times daily, or a placebo. As primary outcome, the effect of the intervention on the glucose response after an oral glucose tolerance test was assessed. As exploratory secondary outcomes, parameters of glycaemic control (HbA1c, insulin, glucagon, and mean amplitude of glycaemic excursions and standard deviation as measured with flash glucose monitoring) and cardiovascular health (blood pressure, 24 hr blood pressure, and circulating triglycerides, cholesterol and markers of inflammation) were measured.

RESULTS

GABA supplementation, compared with placebo, led to a significant decrease in fasting plasma glucose (-0.22 mmol/L, 95% CI: -0.397, -0.045) but did not change the postprandial glucose response. No significant group differences were observed for the other parameters of glycaemic control and cardiovascular health. In addition, no significant changes in fasting plasma GABA concentration were found.

CONCLUSION

12-weeks GABA supplementation reduced fasting glucose concentration in individuals at risk of developing type 2 diabetes. The participants were relatively healthy, and therefore future research may focus on assessing the health effects of GABA in diabetic and hypertensive individuals.
Registered at www.clinicaltrials.gov as NCT04303468.

15
PPAR-α/γ modulation on non-invasive tests of liver steatosis and fibrosis in T2DM

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BACKGROUND

Peroxisome proliferator-activated receptor (PPAR) agonists might have favourable outcomes in NAFLD patients, and dual agonists of PPAR-α/γ have been suggested to reduce inflammation in T2DM patients. NAFLD has close bidirectional relations with T2DM, yet the effect of PPAR agonists on NAFLD has been understudied in clinical tri-

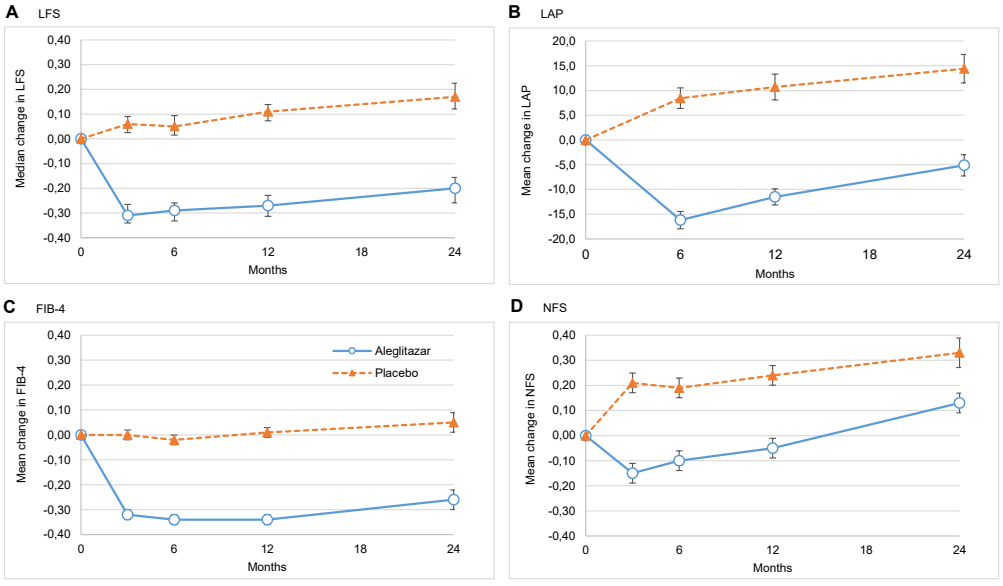

Figure 3. Change in NITs of liver steatosis and fibrosis from baseling.
Value at baseline for A: median LFS of 0.60 for placebo and 0.63 for aleglitazar, B: mean LAP of 69.5 for placebo and 67.8 for aleglitazar, C: mean FIB-4 of 1.40 for placebo and 1.44 for aleglitazar, D: mean NFS of -0.50 for placebo and -0.41 for aleglitazar. Error bars indiate 95% CIs. Change from baseline is significantly different in the aleglitazar and the placebo group at all timepoints ≥3 months for all proxies (all $p < 0.001$).

als. This study serves as proof of concept to evaluate whether dual PPAR-α/γ agonists improve non-invasive tests of liver steatosis and fibrosis in a cohort or T2DM patients.

METHODS

Post-hoc analysis of a randomized, double-blind, placebo-controlled, multi-centre trial including 7226 patients with T2DM and recent coronary syndrome randomized to receive aleglitazar, a PPAR-α/γ agonist, or placebo for two years (AleCardio trial). Main outcomes were changes from baseline of indicators of NAFLD: the Liver Fat Score (LFS), Liver Accumulation Product (LAP), Fibrosis-4 (FIB-4), and NAFLD Fibrosis Score (NFS).

RESULTS

All indicators for steatosis and fibrosis (LFS, LAP, FIB-4, NFS) showed a steep decrease in the treatment group at 3-6 months, followed by a slow gradual increase over time (**Figure 3**). However, all indicators remained to be significantly lower in the treatment group throughout follow-up (24 months), whereas in the placebo group they remained the same or increased ($p < 0.001$). In the treatment group more participants showed improvement by shifting to a lower FIB-4 and NFS category compared to the placebo group (FIB-4: 22% vs. 11% and NFS: 12% vs. 8% for aleglitazar vs. placebo ($p < 0.001$)).

CONCLUSION

In this analysis T2DM patients showed improvement of liver steatosis and fibrosis indicators after starting PPAR-α/γ agonist treatment compared to placebo, adding evidence from a large trial that the PPAR pathway has potential for NAFLD/NASH treatment.

16
Alternative management in a pregnant woman with GCK-MODY

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BACKGROUND

Glucokinase Maturity-Onset Diabetes of the Young (GCK-MODY) is an autosomal dominant monogenetic cause of diabetes, resulting in hyperglycaemia but with normal insulin metabolism.
GCK-MODY does not require treatment and prognosis is good concerning long-term risks of cardiovascular complications. However during pregnancy the fetus carries an increased risk of fetal demise, growth restriction and macrosomia, with a miscarriage risk of up to 35% depending on fetal GCK status. In a GCK-MODY-positive fetus, no additional problems are expected, but active lowering of maternal glucose levels can lead to fetal growth restriction or even intrauterine fetal death. In a GCK-MODY-negative fetus, maternal hyperglycaemia increase the risk of macrosomia and fetal hyperglycaemia-related complications during pregnancy and at birth. Current practice is to monitor fetal growth by frequent ultrasound measurements from 20 weeks' gestation. A GCK-MODY-negative fetus is assumed once fetal growth exceeds the 75th percentile.

METHODS

A 38-year-old woman was referred to our outpatient clinic for GCK-MODY management during pregnancy. Her medical history includes subfertility, multiple early miscarriages, and one intrauterine fetal death after 38 weeks' gestation. In the previous two pregnancies she had elevated glucose at an early stage of pregnancy, wrongfully diagnosed as gestational diabetes. GCK-MODY was subsequently diagnosed.

RESULTS

In this pregnancy, after extensive counseling patient and partner agreed to testing of fetal DNA in amniotic fluid for the GCK c.386G>A, p.(Cys129Tyr) variant, which was negative. Insulin therapy was therefore started at 17 weeks' gestation, resulting in glucose levels within target range for pregnancy. Fetal growth remained stable at P55, with no pregnancy or therapy-related complications.

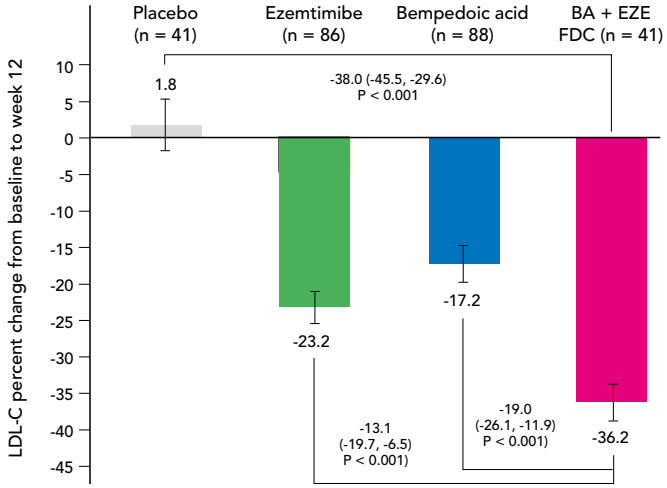
CONCLUSION

This case illustrates the testing of fetal DNA in amniotic fluid for the GCK c.386G>A, p.(Cys129Tyr) variant. Fetal genetic testing is currently not common practice, mainly due to the risk of miscarriage following amniocentesis (1:1000). However in individuals who have undergone multiple pregnancy complications or previous intrauterine fetal death for example, fetal genetic testing could be considered to support initiation of early insulin therapy if the fetus is GCK-MODY negative.

staat." De combinatie bempedoïnezuur + ezetimibe zonder statine levert een LDL-C verlaging van ca. 45% op.[3] "Ik zie daar dan ook duidelijk de grootste potentie", aldus Schatz. De LDL-C verlaging die bereikt wordt door toevoeging van de fixed-dose combinatie (FDC) van bempedoïnezuur + ezetimibe boven op een statine is ongeveer 35%, waarbij Schatz opmerkt dat een FDC goed is voor de therapietrouw (figuur 2).[3]

FIGUUR 2

LDL-C verlaging na behandeling met FDC bempedoïnezuur + ezetimibe[3]



Veiligheid bempedoïnezuur

Behandelaren moeten alert zijn op de combinatie bempedoïnezuur met simvastatine, stelt Schatz. "Er is een kleine interactie omdat ze beiden de OATP1B1-transporter gebruiken. Praktisch gezien komt het erop neer dat de dosis simvastatine niet hoger mag zijn dan 40 mg. Dit speelt niet bij de andere statines, het is echt specifiek voor simvastatine."

Een ander punt van aandacht zijn patiënten met jicht aangezien bempedoïnezuur het urinezuur kan verhogen (een transporter gemedieerde bijwerking). Dit is overigens volledig reversibel. "Voor patiënten die niet goed onder controle zijn en elke paar maanden een jichtopvlamming hebben, is bempedoïnezuur niet het middel van keuze", vindt Schatz. "Los daarvan wordt bempedoïnezuur over het algemeen goed verdragen."

DE HELE PODCASTSERIE BEKIJKEN?

Scan nu de QR-code om meer te weten te komen over bempedoïnezuur

www.mednet.nl/nieuws/podcast-de-nieuwe-orale-lipideverlager-bempedoinezuur

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BEM/22/0564

17

Playing your Diabetic Life: Personalized Data-Driven Game for Diabetes Self-Management Education

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BACKGROUND

Adequate glycemic control supplemented with multifactorial risk-reduction strategies is essential to prevent acute complications, reduce long-term risks, and increase the quality of life of patients with diabetes mellitus. This requires patients to persistently self-monitoring their disease. However, a considerable group of patients struggle to comprehend the complexity of the many facets affecting diabetes, let alone to manage continuously and effectively. Therefore, we are creating a personalized data-driven game focused on educating and empowering patients through interactive playful learning.

METHODS

A pilot clinical study was conducted in which glucose, insulin, and C-peptide concentrations, along with fasting and anthropometric measurements, were measured of 55 patients (type 1 and 2) consuming three standardized meals over a full day with antidiabetic medication. Subsequently, currently a 14-day free-living conditions study is conducted that utilizes wearable technologies (CGM, smartwatch, smartphone applications) to collect data to be used to personalize the game. Additionally, a mathematical physiological model is being developed that integrates the collected data to describe patient-specific blood glucose dynamics due to food intake, physical activity, stress, and antidiabetic medication.

RESULTS

Figure 4 shows the project structure and data from the pilot and free-living study, demonstrating the extent of collected measurements and inter-meal and inter-individual heterogeneity. An internal evaluation following the pilot study, which provided a set of predefined user profiles, indicated a perceived lack of personalization and inadequate correspondence to the patient's own diabetes regulation.

CONCLUSION

Therefore, the ongoing study aims to personalize the game and ultimately assess the effects on patient empowerment and glycaemic control.

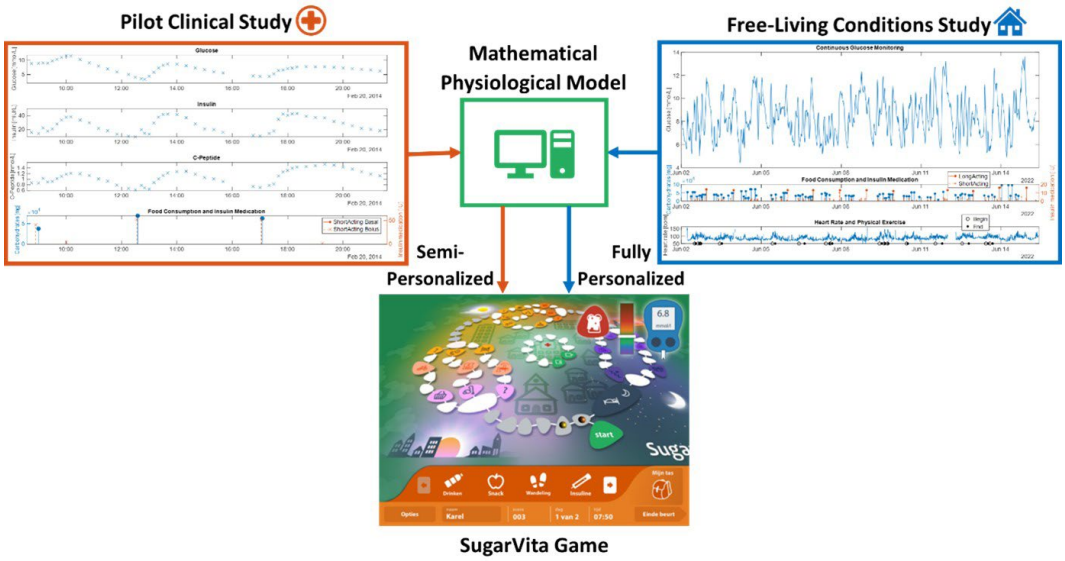

Figure 4. Structure and data from the pilot and free-living study.

18
Enhanced BMP signalling alters human β-cell identity and function

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BACKGROUND

We reported earlier that the immunosuppressive drug tacrolimus has a detrimental effect on human β-cell identity and function through the activation of BMP signalling. Inflammation contributes to the pathophysiology of different types of diabetes and islet transplantation. We hypothesize that BMP-signalling is associated with inflammation-induced β-cell failure.

METHODS

Human donor islets were treated (24h & 72h) with IL-1β (1 ng/ml), IFNγ (50 ng/ml) and IFNα (1000 U/ml) and processed for single-cell transcriptomics (scRNAseq). Gene expression of human islets and INS-1E cells exposed to cytokines was assessed by qPCR. Further, gene expression and insulin secretion (72h) were assessed in human islets and INS-1E treated with recombinant human BMP2 (50 ng/ml), BMP4 (50 ng/ml) and/or the BMP pathway inhibitor LDN193189 (120 nM).

RESULTS

ScRNAseq data showed tendency to increase BMP target genes ID1-4 in primary human β-cells treated with IL-1β+IFNγ and IFNα (1.25, 1.44, 1.32-fold, ID1, ID3, ID4, respectively, $p < 0{,}009$). Induction of the BMP signalling pathway was confirmed by qPCR in cytokine-treated islets (1.7, 1.5, 1.7-fold, ID1, ID2, ID4, respectively, $p < 0{,}01$) and INS-1E (4.7, 29-fold, ID1, ID3, respectively). Direct upregulation of BMP2, but not of the ID-genes, was seen 2h after IL-1β and IFNγ treatment, indicating upregulation of ID-genes through BMP2 activation (2.5, 11-fold, islets, INS-1E, respectively, $p < 0{,}04$). Preliminary data indicates IFNα-enhanced ID-gene expression through BMP4 activation (24h: 1.7-fold; $p = 0.02$). Inhibition of the BMP pathway was not sufficient to prevent 72h inflammation-induced β-cell dysfunction or changes in identity gene expression. However, treatment of human islets and INS-1E with recombinant BMP impaired glucose-stimulated insulin secretion (SI = 0.5, 0.3 vs. control, islets, INS-1E, respectively). This effect was associated with ER-stress (XBP1s/u: 1.53-fold, $p = 0.004$) and reduced expression of key β-cell maturity genes (0.6, 0.5-fold for MAFA, INS respectively, $p < 0.005$).

CONCLUSION

The BMP signalling pathway is activated in primary human β-cells upon inflammation. Enhanced BMP signalling induces β-cell dysfunction, which is associated with maturity marker loss and ER-stress activation. Altogether, these data indicate that inhibition of BMP-signalling could be a target to preserve β-cell identity and function in a pro-inflammatory environment.

19
No long-acting insulin dose adjustment required after aerobic exercise for people with type 1 diabetes on insulin degludec; the ADREM study

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BACKGROUND

Widely recognized guidelines recommend to reduce basal insulin doses after exercise to reduce the risk of post-exercise nocturnal hypoglycaemia. It is unknown whether such adjustments are required for insulin degludec.

METHODS

Using a randomized controlled cross-over study design, we compared 40% insulin degludec dose reduction (D40) or 8-hour postponement and 20% dose reduction (D20-P) to no adjustment (CON), after a 45-minute exercise test among adults with type 1 diabetes at elevated risk of hypoglycaemia. All participants wore blinded continuous glucose monitors for 6 days. The primary outcome was the time spent below range (TBR, glucose < 3.9 mmol/l) in minutes (median [IQR]) during the night (00:00-05:59h) following the exercise test.

RESULTS

We recruited 18 participants (6 women, mean ± SD age 38 ±

13 years, HbA1c 56 ± 8 mmol/mol). There were no differences between the treatment regimens in nocturnal TBR after exercise. During the subsequent whole day, TBR was lower in D40 compared to CON (0 [0-23] vs 18 [0-55] min, p = 0.043), whereas time above range (glucose > 10 mmol/l) was greater in D20-P compared to CON (mean±SEM 584 ± 81 vs 364 ± 66 min, p = 0.001) and D40 (385 ± 72 min, p = 0.003). During the second day, TBR was greater in D20-P than in D40 (28 [4-46] vs 0 [0-41] min, p = 0.019).

CONCLUSION

Adjustment of degludec after exercise has no effect on the risk of nocturnal hypoglycaemia in people with type 1 diabetes, although a 40% dose reduction reduces the risk of next-day hypoglycaemia without increasing the risk of hyperglycaemia. These data argue against standard degludec dose adjustment after a single exercise bout, including for those at elevated risk for hypoglycaemia.

20

The efficacy and safety of a hybrid closed loop insulin delivery system in patients with type 1 diabetes mellitus with poor glycaemic control

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BACKGROUND

This study aimed to investigate, in a real-life setting, the efficacy and safety of a hybrid closed loop insulin delivery system (HCL) in patients with type 1 diabetes mellitus (T1DM) who had (very) poor glycaemic control despite using multiple daily insulin injections (MDI) or continuous subcutaneous insulin infusion (CSII) in combination with intermittent scanning glucose monitoring (ISGM). While the improved and adequate glycaemic results of HCL systems have been investigated predominantly in relatively well controlled compliant patients, the key clinical question for this study was whether an HCL system is robust enough in a patient population with poor self-management, i.e. misjudging or skipping pre-meal boluses.

METHODS

Prospectively, we aimed to start a HCL system (Medtronic MiniMed 780G hybrid closed loop insulin pump using Guardian 4 real time glucose monitor, Medtronic, USA) in ten patients for the purpose of value based health care. Patients were treated within the scope of clinical care and started on HCL upon shared decision making with their treating physician. Poor glycaemic control was defined as either an HbA1c value > 64 mmol/mol and/ or hypoglycaemia unawareness. All patients were treated at the Groene Hart Ziekenhuis (Gouda, The Netherlands). A retrospective patient outcome data analysis was performed. For this analysis, we included ten T1DM patients (six male, four female). Study endpoints were glycated haemoglobin level (HbA1c), time-in-glucose-range (TIR) and time-below-glucose-range (TBR). Endpoints were assessed at baseline and follow-up. Data are presented as mean values. Change between baseline and follow-up was tested for statistical significance using a paired samples t test.

RESULTS

We included ten patients (six male, four female, mean age 38 years). At the start of the study, nine patients were on MDI and one patient used CSII. All patients used ISGM (Freestyle Libre Sensor, Abbott, USA). At baseline HbA1c was 74 mmol/mol, TIR was 36% and TBR was 6%. One patient had an adverse hypoglycaemic event during a remote instruction in the pump starting week requiring admission. This patient decided not to proceed with the HCL pump. The remaining nine patients started using HCL successfully and continued during the follow-up period. At follow up after 3-9 months the mean HbA1c was 55 mmol/mol (p = 0.02) with a TIR of 72% (p = 0.004) and TBR of 1% (p = 0.05). Safety: one patient was admitted with diabetic keto-acidosis after having ignored alarms indicating a pump-stop, and subsequently fully recovered. Another patient had progression of retinopathy requiring treatment, probably caused by a rapid decline in HbA1c.

CONCLUSION

The hybrid closed loop system resulted in improved glycaemic control in this group of T1DM patients with poor self-management advocating high robustness of the algorithm guiding automated insulin dosing. However, within one year after pump-start, two patients were admitted with acute glycaemic events related to erroneous pump-use, highlighting the challenges diabetes management in a real-life setting.

21

MyDiaMate: Implementing Self-Guided Web-Based Support For Mental Health In Type 1 Diabetes

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BACKGROUND

Diabetes-related distress and fatigue are highly prevalent in people with type 1 diabetes (T1D) and complicate diabetes self-management. MyDiaMate is a self-guided, web-based application designed to assist in preserving/improving mental vitality. Since March 2021 the application is offered freely to Dutch speaking adults with T1D via the Minddistrict platform. Here we report on first results regarding usage and user profiles.

METHODS

Number of downloads and usage were analyzed using log-data for all participants (data extraction August 2022). Users could opt for participating in the user-profile study, providing self-reported socio-demographics, diabetes-distress (PAID-5), emotional wellbeing (WHO-5) and fatigue (CIS). Single item question scores (0-10) on worrying about diabetes, mood and energy were compared before and after completion of the start module by paired t-tests.

RESULTS

N = 963 persons downloaded MyDiaMate. 734 persons (76.2%) opened the start module 'Diabetes in Balance', of whom 27% completed the module. In-depth modules 'My Mood' and 'My Energy' were opened by 14.7% and 16.5% participants respectively, of whom 24.6% and 22% completed these modules. The module Eating and Emotions was opened by 24.6% of the users, of whom 43.9% completed the module. N = 334 participated in the user-profile study. Mean age was 43 years (SD = 15), 63.7% females, and 57.5% higher educated. The majority was not receiving psychological treatment (78.2%). Of the 334 participants, 61.2% persons reported low emotional wellbeing (WHO-5 ≤ 50), 64.3% elevated diabetes-distress (PAID-5 ≥ 8) and 50.9% were severely fatigued (CIS ≥ 35). Those who reported high Worries (> 5), low Mood (< 6) and low Energy (< 6) improved their score after completing 'Diabetes in Balance' (see **Table 1**).

CONCLUSION

Results 16 months after launching MyDiaMate show a clear interest from the target group. Participants report relatively low well-being and high fatigue scores, indicating a need for (additional) psychosocial support. Log-data showed a wide variety of user behaviors, indicating a spectrum of individual support needs. There were indications for improvement in worrying, mood and energy after completing Diabetes in Balance. Further data collection is ongoing.

Table 1. Paired samples t-tests for pre-post scores on Worrying about diabetes, Mood and Energy.

	Pre Diabetes in Balance		Post Diabetes in Balance			
	M	*SD*	*M*	*SD*	*t*	*p*
Worrying about diabetes	7.50	1.19	6.19	2.73	t(104)=5.13	.001
Mood	3.29	1.48	3.98	2.12	t(85)=-2.75	.007
Energy	3.18	1.46	3.66	1.95	t(113)=-2.86	.008

22

Effect of motivational interviewing on adherence to wearing orthopaedic shoes: a multicentre cluster-randomized controlled trial

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BACKGROUND

Adherence to wearing orthopaedic shoes is a known problem in people with diabetes and neuropathy. Interventions to improve footwear adherence are needed. Motivational interviewing (MI) has been suggested, but never tested beyond pilot studies. The aim of this RCT was to evaluate the effectiveness of MI performed by a MI-trained podiatrist, in improving adherence to wearing orthopaedic shoes.

METHODS

People diagnosed diabetes mellitus type 1 and 2 with either loss of protective sensation or peripheral artery disease and

prescribed with orthopaedic shoes were included. Participants in the intervention group received usual care plus MI-conversation. Wearing time was continuously measured using a temperature sensor inside the footwear (Orthotimer®). Participants wore a wrist activity tracker (Misfit Shine 2™) for seven consecutive days at 3 months and 6 months. Adherence was determined as the percentage of steps taken while wearing the footwear. Participants were considered adherent when ≥ 80% of steps were taken in their orthopaedic shoes. Follow-up was 12 months. Analyses were based on intention-to-treat, with Chi-square and T-tests to compare intervention and control.

RESULTS

123 participants were included (mean (SD) age: 68.5 (8.6) years; females: n = 39; type 2 diabetes: n = 111; mean (SD) BMI: 30.6 (5.3); mean (SD) diabetes duration: 17.7 (12.3) years). 69 were allocated to the control group and 54 to the intervention group, with primary outcome available in 97 participants. Of the 43 participants in the intervention group, 18.6% (8/43) were adherent; of the 54 participants in the control group, 27.8% (15/54) were adherent (p = 0.29). Mean (SD) adherence was 49.2% (35.0) vs. 59.8% (32.4), respectively (p = 0.10); mean (SD) wearing time was 7.0 (5.8) hours vs. 8.3 (6.1) hours, respectively (p =0.16).

CONCLUSION

On the basis of intention-to-treat, MI did not result in higher adherence to wearing orthopaedic shoes in comparison to usual care. Per-protocol and subgroup analyses are currently being performed.

23
Mixed meal affect distinct pathways in adipose tissue in subjects with high and low liver fat

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BACKGROUND

Liver is an important organ for lipid metabolism. Excessive liver fat content is often related to some chronic metabolic diseases, such as non-alcoholic fatty liver disease (NAFLD) and type II diabetes. Adipose tissue is an important organ for adequate lipid metabolism and storage. To examine whether lipid metabolism and storage are differently regulated in people with high versus low liver fat, we investigate the differences in post-meal whole genome gene expression response in adipose tissue of people with different liver fat content.

METHODS

In this study, which is part of the Belly Fat Study, abdominal obese males and females received a high fat and high glucose mixed meal, adipose biopsies were taken before (fasted) and 4 hours after the mixed meal. Intrahepatic lipids values were determined using MRS. Intrahepatic lipid values were known for 66 of the 100 individuals that completed the study. Participants in the first tertile of intrahepatic lipids values (0.14-2.05) were classified as low liver fat group, and participants in the last tertile of intrahepatic lipids values (7.99-32.58) were classified as high liver fat group.

RESULTS

The postprandial responses of plasma glucose, insulin as well as triglycerides are significantly stronger in high liver fat group than in low liver fat group. At baseline, there were 2014 genes significantly differentially expressed between the two groups. 613 genes responded significantly different to the mixed meal between both groups. Preliminary analyzes showed that genes in the network 'TCA cycle' expressed lower in high liver fat group compared to low liver fat group. Oxidative phosphorylation was decreased postprandially in the low liver fat group compared to the high liver fat group.

CONCLUSION

Consumption of a mixed meal shake reduced lipolysis more and increased oxidatidative phosphorylation more in adipose tissue in the high liver fat group compared to the low liver fat group.

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A zebrafish model to address beta-cell stress following exocrine damage

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BACKGROUND

Dynamic microscopic analysis of molecules in a zebrafish model is a key approach for studying the pathophysiology of diseases like type 1 diabetes (T1D). The latter is caused by the autoimmune destruction of insulin-producing beta cells in the Islets of Langerhans. These islets are embedded in the exocrine pancreas that produces enzymes for the digestive tract. Despite recent advancements in the field, the initial trigger leading to T1D is not known, but recent evidence suggests that exocrine malfunction may precede beta cell stress: T1D patients exhibit 'intermediate cells' that have the characteristics of both hormone-producing cells as well as exocrine cells. Furthermore, pre-T1D patients exhibit reduced pancreatic volume compared to non-diabetic control.

METHODS

We aim to test whether a cause/consequence relationship in exocrine malfunction and beta cell stress exists. Therefore, a hybrid chemical and genetic ablation approach is achieved by expressing nitroreductase-caspase-dependent fluorescent reporter in exocrine cells of our transgenic model. Nitroreductase transforms a prodrug, called nifurpirinol into a cytotoxic DNA cross-linking drug, subsequently causing damage to exocrine cells. Moreover, morphology, ultrastructure, and histology alterations are examined to define the extent of damage in the exocrine compartment.

RESULTS

Ablated nitroreductase positive exocrine cells were observed as well as reduced pancreatic size in our transgenic model after exposure to nifurpirinol. Also, exocrine cells that have undergone apoptosis are initially observed as a result of the treatment before disappearing, displaying exocrine loss as a result of the nitroreductase-nifurpirinol combination.

CONCLUSION

Our zebrafish model provides a dynamic tool to modulate the exocrine pancreas. Above all, generating transgenic beta cell readout lines in conjunction with advanced light microscopies will disclose beta cell functionality and stress in the zebrafish larval pancreas at single cell resolution. Hence, this project will determine whether exocrine stress might cause beta-cell stress preceding T1D.

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Day-night rhythm in skeletal muscle mitochondrial network integrity is disturbed in older, obese metabolically compromised individuals

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BACKGROUND

Muscle mitochondrial dysfunction associates with insulin resistance. We have shown previously that muscle mitochondrial function is rhythmic in young healthy lean, but not in older obese metabolic compromised individuals. We here examined if rhythmicity in mitochondrial network integrity underlies the 24-hour rhythm in mitochondrial function. Thus, we studied mitochondrial network integrity in healthy lean young participants (Lean-Young) and in older obese metabolic compromised participants (Metab-Older) along with mitochondrial function.

METHODS

Five muscle biopsies were taken within 24h (8AM, 1PM, 6PM, 11PM and 4AM) from the m. vastus lateralis from 12 Lean-Young (22 ± 2 years, BMI: 22.4 ± 2.0) and 12 Metab-Older (65 ± 9 years, BMI: 30.3 ± 2.7, impaired glucose tolerance/low insulin sensitivity) men. Mitochondrial networks stained against TOMM20 were imaged with confocal microscopy, and quantified for the mitochondrial fragmentation index (MFI). Rhythmicity in network integrity and mitochondrial function was assessed using CircaCompare when a significant time effect was observed in these parameters.

RESULTS

Mitochondrial networks in the Metab-Older were fragmented compromised compared to Lean-Young indicated by a higher MFI in both fiber types (type I: 0.78 ± 0.07 vs. 1.61 ± 0.49, $p < 0.001$; type II: 1.17 ± 0.16 vs. 1.65 ± 0.52, $p < 0.01$). A significant time effect ($p < 0.05$) and rhythmicity in the MFI (CircaCompare: $p < 0.05$) was observed in the type I fibers of Lean-Young and this mirrored mitochondrial function. In type II fibers time effects, but no rhythmicity was observed (Lean-Young: $p < 0.01$; Metab-Older: $p < 0.01$). In Metab-Older, neither mitochondrial network integrity ($p = 0.407$) nor mitochondrial function ($p = 0.125$) displayed a 24-hour rhythm.

CONCLUSION

In Lean-Young individuals, the 24-hour rhythmicity in mitochondrial function is paralleled by mitochondrial network integrity. The fragmented mitochondrial networks and the lack of rhythmicity in these networks and mitochondrial function in Metab-Older suggests a role for mitochondrial network integrity in mitochondrial function and associated metabolic aberrations such as insulin resistance.

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Hepatic insulin resistance and muscle insulin resistance are characterised by distinct postprandial metabolite profiles

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BACKGROUND

The pathophysiology of insulin resistance (IR) is characterised by great heterogeneity, with inter-individual differences in IR severity in the various insulin target organs. Tissue-specific IR predominantly in the muscle (muscle-IR) or liver (liver-IR) has previously been linked to differential fasting metabolite profiles. We compared postprandial metabolite profiles in response to a high-fat mixed meal (HFMM) between individuals with predominant muscle-IR or liver-IR.

METHODS

This cross-sectional study included data from 230 men and women (age 40-75 years, BMI 25-40 kg/m^2) with predominant muscle-IR (n = 142) or liver-IR (n = 88). Tissue-specific IR was assessed using the muscle insulin sensitivity index (MISI) and hepatic insulin resistance index (HIRI), which were calculated from the glucose and insulin responses during a 7-point oral glucose tolerance test (OGTT). 164 metabolites including (apo)lipoproteins, cholesterol, triglycerides (TG), ketone bodies, and amino acids were quantified in plasma samples that were collected before and after (T = 30, 60, 120, 240 min) consumption of a HFMM using nuclear magnetic resonance spectroscopy.

RESULTS

Plasma concentrations of total TG ($p = 0.002$), very-low-density lipoprotein (VLDL) TG ($p = 0.002$), low-density lipoprotein (LDL) TG ($p = 0.041$), extra-large VLDL particles ($p = 0.019$), large VLDL particles ($p < 0.001$), medium LDL particles ($p = 0.007$), and saturated fatty acids ($p = 0.021$) were higher 1-4h after consumption of the HFMM in liver-IR compared to muscle-IR. Plasma branched-chain amino acid concentrations peaked earlier at 30 minutes postprandially in liver-IR, compared to at 60 minutes postprandially in muscle-IR ($p = 0.015$). The amino acid histidine showed a slower decrease back to fasting levels after the peak concentration in muscle-IR compared to liver-IR ($p = 0.041$).

CONCLUSION

Muscle-IR and liver-IR are characterised by distinct postprandial metabolite profiles, with liver-IR showing more pronounced postprandial metabolite responses compared to muscle-IR.

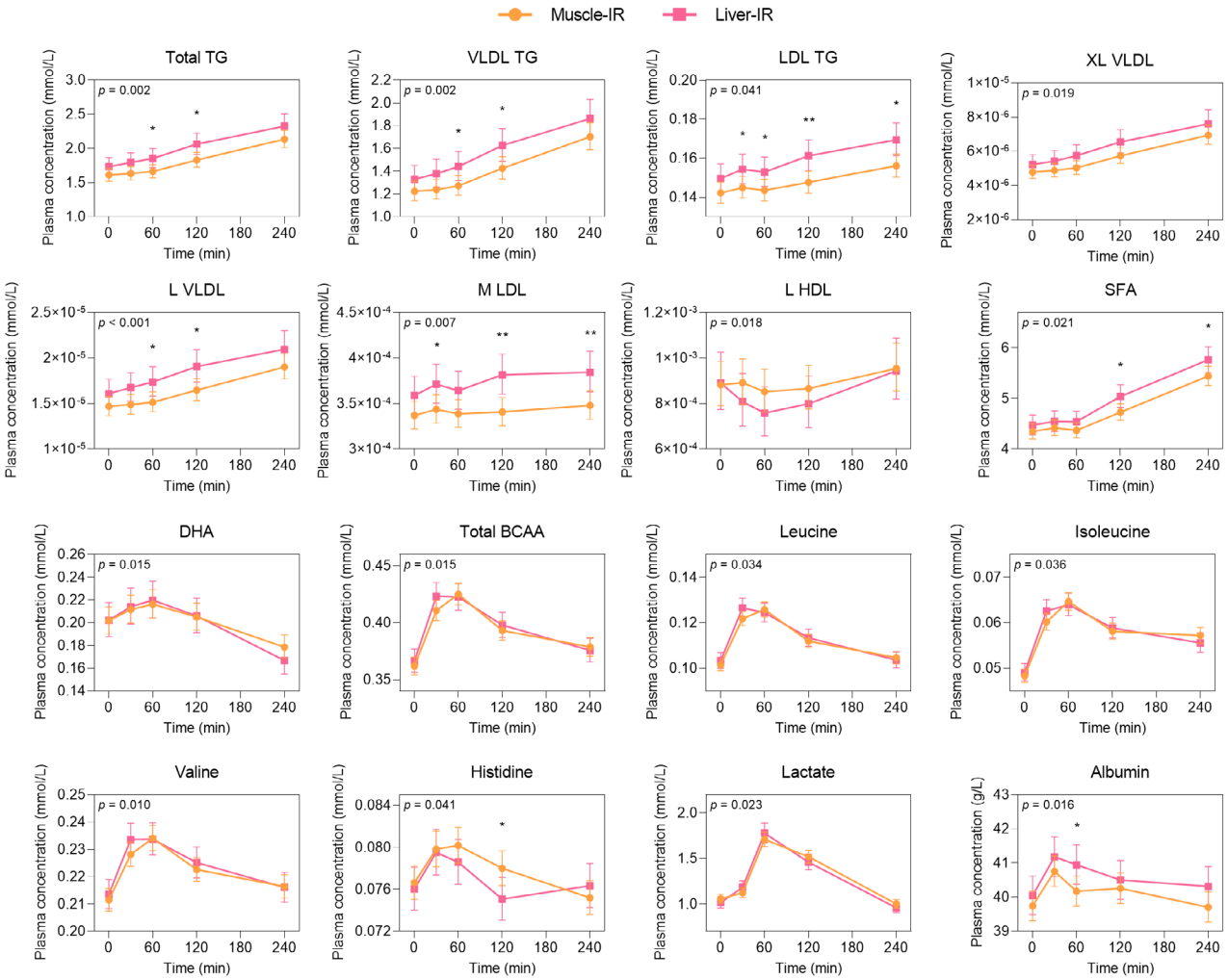

Figure 5. Differences in postprandial metabolite cocentrations upon a high-fat mixed meal between indivuals with muscle-IR (orange) or liver-IR (pink). Values are adjusted geometric mean with 95% confidence intervals. Differences in the postprandial metabolite responses between muscle-IR and liver-IR were tested using a linear mixed-effects model with the pstprandial timepoints as repeated measures, including study center, sex, age, BMI, and waist-tohip ratio as covariates and with LSD *post-hoc* testing. An asterisk indicates statistical significance for post-hoc muscle-IR vs. liver-IR difference in metabolite concentration (*p<0.05, **p<0.01, ***p<0.001).

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Oral Glucose Tolerance Test for the Screening of Glucose Intolerance Long Term Post-Heart Transplantation

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BACKGROUND

Post-transplant diabetes mellitus (PTDM) is a frequent complication post-heart transplantation (HT), however long-term prevalence studies are missing. The aim of this study was to determine the prevalence and determinants of PTDM as well as prediabetes long-term post-HT using oral glucose tolerance tests (OGTT). Also, the additional value of OGTT compared to fasting glucose and glycated hemoglobin (HbA1c) was investigated.

METHODS

All patients > 1 year post-HT seen at the outpatient clinic between August 2018 and April 2021 were screened with an OGTT. Patients with known diabetes, an active infec-

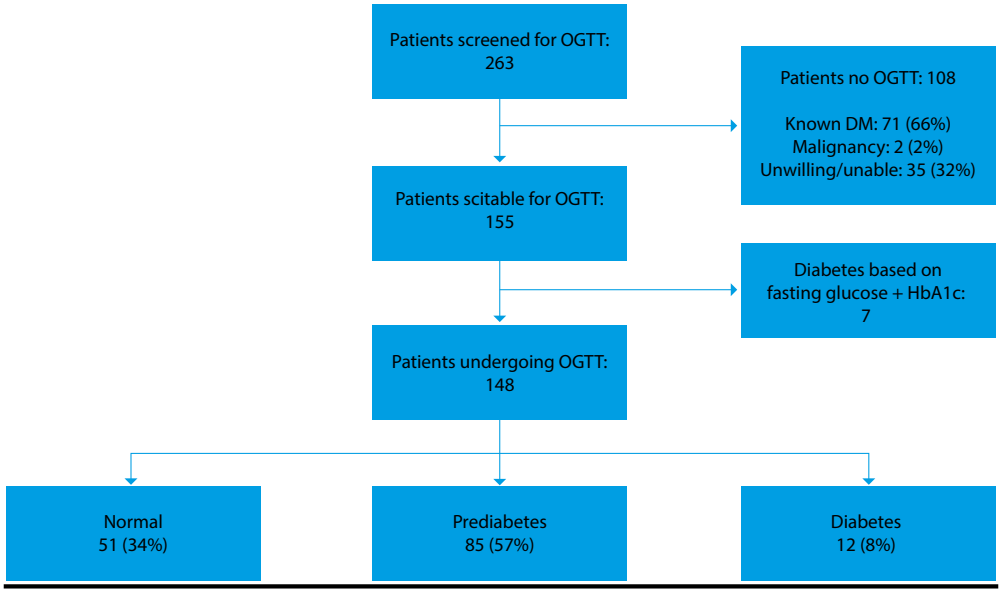

Figure 6. Results of Oral Glucose Tolerance Test for the Screening of Glucose Intolerance Long Term Post-Heart Transplantation.

tion/rejection/malignancy or patients unwilling or unable to undergo OGTT were excluded. An OGTT was performed according to the guidelines of the American Diabetes Association.

RESULTS

In total, 263 patients were screened, 108 were excluded. The included 155 patients had a median age of 54.3 [42.2-64.3] years, and 63 (41%) were female. Median time since HT was 8.5 [4.8-14.5] years. Overall, 51 (33%) had a normal range, 85 (55%) had a prediabetes range and 19 (12%) had a PTDM range test. OGTT identified prediabetes and PTDM in more patients (18% and 50%, respectively), than fasting glucose levels and HbA1c. Age at HT (OR 1.03 (1.00-1.06), p = 0.044) was a significant determinant of an abnormal OGTT.

CONCLUSION

Prediabetes as well as PTDM are frequently seen long-term post-HT. As such, systematic screening by OGTT is warranted for timely intervention as this may improve the long-term outcome. OGTT is the preferred screening method.

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The association between the levels of coagulation factors and the incidence of type 2 diabetes in the NEO study

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BACKGROUND

Coagulation factors are blood clotting proteins participating in hemostasis. By activating the production of inflammation markers, coagulation factors are suggested to associate with the pathogenesis of inflammation-related diseases, like type 2 diabetes mellitus (T2DM). Currently, it is unclear whether coagulation factors are associated with T2DM. We aim to investigate the associations between Factor (F) VIII, FIX, FXI, and fibrinogen levels as well as thrombin generation parameters (i.e., lag time, endogenous thrombin potentials [ETP], peak, time-to-peak, and velocity) and incident T2DM in middle-aged men and women.

METHODS

We calculated hazard ratios (HR) with 95% confidence intervals (CI) using Cox regression modeling the associations between the levels of FVIII, FIX, FXI, fibrinogen as well as all thrombin generation parameters and incident T2DM. Coagulation factor levels were analyzed continuously and in quartiles, with the first quartile as the reference except for lag time and time-to-peak with the last quartile as reference. We adjusted the crude HRs for age, sex, ethnicity, BMI, menopausal status, baseline fasting

glucose, physical activity smoking, cancer, oral contraceptive use, hormone replacement, family history for T2DM, hypertension, triglyceride, and high-density lipoprotein cholesterol.

RESULTS

Of 5722 participants, 53% were women. At baseline, the mean (SD) age of participants was 55 (6) years. During a median follow-up of 6.7 years, 297 newly diagnosed T2DM were detected. When analyzed continuously, four coagulation factors and all thrombin generation parameters were associated with an increased risk of T2DM, except for lag time and time-to-peak. Compared with the lowest quartiles, the HRs (95% CI) of the highest quartiles were 2.90 (1.75-4.80) for FIX, 1.49 (1.03–2.17) for FVIII, 1.72 (1.17–2.51) for ETP, 2.03 (1.36–3.03) for peak, and 1.71 (1.16-2.50) for velocity.

CONCLUSION

Increased levels of FVIII, FIX, and thrombin generation parameters are associated with an increased risk of T2DM, which suggests a novel T2DM biological pathway through hypercoagulability.

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Stimulation of the beta-2-adrenergic receptor with salbutamol activates human brown adipose tissue

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BACKGROUND

In rodents, brown adipose tissue (BAT) is activated by the beta-3-adrenergic receptor (ADRB3), while we showed that the ADRB2 is dominantly present and responsible for noradrenergic activation of human brown adipocytes in vitro (Cell Metab 2020). Therefore, we now aimed to assess whether ADRB2 agonist salbutamol activates human BAT in vivo.

METHODS

We performed a randomized double-blinded crossover trial in 10 young (age: 24.4 ± 4.3 years old) and lean (body mass index: 23.1 ± 2.3 kg/m^2) males over two study days with one week wash-out in between. Subjects received a single intravenous bolus of salbutamol (250 µg) with or without the ADRB1/2 antagonist propranolol (80 mg), followed by a dynamic 2-[^{18}F]fluoro-2-deoxy-D-glucose ([^{18}F]FDG) PET-CT scan.

RESULTS

Salbutamol, compared to salbutamol with propranolol, increased glucose uptake by BAT (67.1±87.0 vs. 16.2±5.2 nmol·g^{-1}·min^{-1}, p = 0.03), heart rate (+ 17 ± 11 vs. -3 ± 9 beats/min, p = 0.004) and whole-body energy expenditure (EE; +122 ± 168 vs. -192 ± 91 kcal/day, p = 0.003). The salbutamol-induced glucose uptake by BAT was positively associated with the increase in energy expenditure (Spearman rho = 0.73, p = 0.03). Notably, participants with high salbutamol-induced glucose uptake by BAT (n = 5) had a lower body fat mass (11.8 ± 1.3 vs. 16.9 ± 2.3 %, p = 0.008), waist-hip ratio (0.8 ± 0.02 vs. 0.9 ± 0.1, p = 0.03), and serum low-density lipoprotein cholesterol concentration (1.6 ± 0.4 vs. 2.7 ± 0.5 mmol/L, p = 0.02) compared to participants with low salbutamol-induced glucose uptake by BAT (n = 5).

CONCLUSION

Pharmacological stimulation of the ADRB2 with salbutamol acutely increases the rate of glucose uptake by human BAT in vivo, which is largely suppressed after blocking the ADRB1/2. Notably, individuals with a healthier metabolic profile show a higher salbutamol-induced glucose uptake by BAT.

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Cumulative plantar tissue stress and its association with foot ulcer recurrence in people with diabetes

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BACKGROUND

We aimed to understand the mechanisms for recurrence of plantar foot ulcers, which are common in people with diabetes. We focused on repetitive mechanical stress as causative factor for ulcer development, which consists of multiple components: plantar pressures during walking barefoot and shod and the amount of weight-bearing activity, such as with walking and standing. When these components are modelled together, the cumulative plantar tissue stress (CPTS) can be estimated. We investigated the association between CPTS with its underlying components and plantar diabetes-related foot ulcer recurrence.

METHODS

We monitored 53 participants with diabetes and neuropathy (all IWGDF risk 3) for 12 months. At baseline, we objectively assessed barefoot and in-shoe plantar pressures during walking and standing (Emed-X and Pedar-X), type and extent of weight-bearing activities during 7 days (MoveMonitor), and footwear adherence (Orthotimer). Our CPTS model included barefoot and in-shoe pressure-time integrals (PTI) for walking and standing (**Table 2**). We used Mann-Whitney U test in univariate analyses to compare people with and without a recurrent plantar foot ulcer during follow-up.

RESULTS

During a median 12.0 months follow-up, 16 out of 53 participants (30.2%) developed a plantar foot ulcer. CPTS was higher in people with than without an ulcer, although not statistically significant (Table 1). People who ulcerated had higher barefoot and lower in-shoe peak pressure while walking, although not significant. Standing duration was shorter, and average daily number of steps, variation in day-to-day number of steps and adherence were lower in those who ulcerated, although none significantly.

CONCLUSION

The interaction between CPTS components in ulcer development is complex and requires more investigation in larger populations. Also, other components not investigated may play a role, such as tissue properties and shear stress.

Table 2. Cumulative plantar tissue stress and its underlying components in people with and without a recurrent plantar foot ulcer.

	People with recurrent plantar ulcer (N = 16)	People without recurrent plantar ulcer (N = 37)	p-value
Cumulative plantar tissue stress (MPa s/day)a			
- Barefoot + In-shoe	762.4 [369.7, 1038.7]	695.1 [455.9, 1115.5]	0.394
- Barefoot	185.4 [112.9, 525.9]	322.9 [128.0, 547.3]	0.498
- In-shoe	356.7 [190.0, 628.6]	310.1 [193.3, 613.5]	0.877
Weight-bearing activity (per day)			
- Number of steps	4233 [1524, 7048]	6095 [3300, 8944]	0.157
- Day-to-day variation in steps	1619 [821, 2255]	1855 [992, 2963]	0.378
- Standing duration (h)	1.8 [1.1, 2.4]	2.0 [1.4, 2.3]	0.612
Barefoot peak plantar pressure (kPa)			
- Walking	1168.2 [823.4, 1275.0]	1043.8 [858.2, 172.5]	0.232
- Standing	171.3 [89.1, 313.1]	135.0 [95.1, 235.0]	0.452
In-shoe peak plantar pressure (kPa)			
- Walking	180.6 [143.6, 204.7]	197.2 [138.0, 261.2]	0.406
- Standing	59.5 [53.2, 89.9]	51.6 [44.4, 75.3]	0.312
In-shoe peak plantar pressure (kPa)			
- Walking	73.3 [54.8, 86.4]	76.5 [55.7, 89.2	0.656
- Standing	75.7 [53.2, 87.2]	74.7 [52.2, 84.6]	0.831

Continuous data are median [25th percentile, 75th percentile]. a = Cumulative plantar tissue stress model: (in-shoe walking PTI * total strides adherent to wearing footwear) + (barefoot walking PTI * total strides non-asherent to wearing footwear) + (in-shoe standing PTI * total time spent standing adherent to wearing footwea) + (barefoot standing PTI * total time spent standing non - adherent to wearing footwear).

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Design of the Dual Hormone Fully Closed Loop in Type 1 Diabetes: a Randomized (DARE) Trial

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BACKGROUND

Many type 1 diabetes mellitus (T1DM) patients fail to achieve their glycaemic treatment goals despite the increased number of advanced therapies such as continuous or flash glucose monitoring sensors (CGM or FGM) and hybrid closed loops (HCLs). Dual hormone fully closed loop (DHFCL) concepts with both insulin and glucagon infusion have shown promising results in small studies in T1DM patients. More extensive studies are needed on efficacy, tolerability, safety and cost-effectiveness.

METHODS

The DARE-study is a non-commercial 12 month open-label, two-arm randomised parallel-group trial study funded by the "Promising Care" programme from the Zorginstituut Nederland/ZonMw. The primary aim of this study is to determine the long-term effects on glycaemic control, PROMs and cost-effectiveness of treatment with the DHFCL compared to the currently most advanced technological care (i.e. HCL) and the currently most used care (i.e. multiple daily insulin injections (MDI)+FGM/CGM).

RESULTS

In this study, 240 adult T1DM patients are to be included in 14 hospitals in the Netherlands. In one arm, DHFCL is compared to HCL users (n = 170; most advanced care) and in the other arm against MDI (n = 70; at least once daily long-acting insulin and thrice daily short-acting insulin; most used care) treatment together with FGM or CGM. Both arms are to be randomised 1:1 on continuation of their current care or using the DHFCL.

CONCLUSION

Results of this large pivotal trial will expand knowledge on this novel dual-hormone approach in T1DM incorporating not only glycaemic outcomes but also PROMs and cost-effectiveness.

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Time-restricted feeding reprograms microglial day-night immunity in the hypothalamus

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BACKGROUND

The mediobasal hypothalamus (MBH) contains neurons that are key for controlling body weight and energy expenditure. Previously we found that microglial ramifications in the MBH mainly rise in the dark phase in animals fed with a chow diet. Nocturnal animals, like mice and rats, consume most of their food (i.e. 80-85%) during the dark phase, when on chow.

METHODS

In the current study, we investigated whether the elevated microglial ramification in the dark phase is driven by food intake. We performed a Time-Restricted Feeding (TRF) study to answer this question. Wistar rats fed with chow diet were divided into three groups, i.e. ad libitum, light-phase feeding or dark-phase feeding. After 4 weeks of TRF, rats were sacrificed every 4 hrs around the clock (Zeitgeber time (ZT) 2, 6, 10, 14, 18, 22) and hypothalamic microglial morphology was profiled.

RESULTS

During the 4 weeks of TRF feeding, both TRF groups showed a lower total food intake, with the light-feeding group showing a lower intake than the dark-feeding group. However, the light feeding-group lost less body weight than the dark-feeding group, indicating a higher feeding efficiency (higher weight gain on same food intake) in these animals.

CONCLUSION

These data confirmed that food intake during the regular

sleeping/resting period has detrimental metabolic consequences. In the ad libitum group, the highest number of microglial ramifications were found at ZT22, whereas in the light-feeding group, this peak had moved to ZT14. Intriguingly, in the dark-feeding group, microglial ramifications unexpectedly showed an even larger phase shift, with the highest levels appearing at ZT10. Our data indicate that microglial immune survey activity is affected by the time of the feeding, but is not only driven by the food intake per se. In the ongoing study, we are investigating the microglial intracellular signaling to search for the underpinning mechanism. Moreover, we are also studying how TRF of a hypercaloric diet affects microglial function.

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Hepatic fat and macrophages are increased in livers of diabetic patients without NAFLD

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BACKGROUND

Diabetes mellitus (DM) is strongly associated with non-alcoholic fatty liver disease (NAFLD), which increases risk of severe liver disease and extra-hepatic microvascular disorders. NAFLD is diagnosed in liver biopsies when fat accumulation, lymphocytes, ballooning of hepatocytes and/or fibrosis are found, but it is often diagnosed late due to diagnostic limitations and minor clinical manifestations during early development. This study aimed to analyse putative early changes in the liver of deceased DM patients without clinical diagnosis and histopathological characteristics of NAFLD, and analysed age/sex effects hereon.

METHODS

Liver tissue was obtained at autopsy from 24 DM patients and 66 non-diabetic control patients, without histopathological characteristics of NAFLD. Hepatic fat (percentage and number of cells) and inflammatory cells (CD45-positive lymphocytes and CD68-positive macrophages) were studied through (immuno)histochemical analysis.

RESULTS

We observed a 2-fold increase in fat percentage/mm^2 (0.7 ± 1.1%, p = 0.0007) and a near 5-fold increase in amount of fat cells/mm^2 in DM patients (94.6 ± 133.5, p < 0.0001) compared to the non-diabetic controls (0.4 ± 0.9 and 19.9 ± 47.8 respectively). Fat content was significantly higher in patients with type 2 DM compared to both patients with type 1 DM and non-diabetic controls, while the number of CD68+ cells/mm^2 was significantly elevated in both DM groups. Compared to their non-diabetic counterparts, only women with DM had an elevated fat percentage/mm^2 (p = 0.007), whereas the number of CD45+ cells/mm^2 was only lower in men with DM (p = 0.04). Age/sex and hepatic fat content/inflammation were not associated in patients with or without diabetes.

CONCLUSION

Hepatic fat and the number of macrophages are increased in the liver in patients with DM not yet diagnosed with NAFLD, which may reflect a higher risk on development of steatosis and steatohepatitis.

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The association between dietary total, animal, and plant-based protein intake and depressive symptoms in Dutch adults with type 2 diabetes: the Hoorn Diabetes Care System cohort

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BACKGROUND

This study aimed to investigate the cross-sectional associations between protein intake (total, animal, plant-based) and depressive symptoms in people with type 2 diabetes (T2D).

METHODS

We included 1137 individuals with T2D (aged 68.6 ± 9.0, 36% women) from the Hoorn Diabetes Care System cohort. Energy-adjusted protein intake was assessed using a validated Food Frequency Questionnaire. The nine-item

Patient Health Questionnaire (PHQ-9) was used to assess the prevalence of depressive symptoms (PHQ-9 ≥ 10 and/or use of anti-depressant medication) and depressive symptom severity (continuous PHQ-9 total score). Associations of quartiles of total, animal, and plant-based protein with depressive symptoms were analyzed using multiple logistic regression (prevalence) and linear regression (severity), adjusted for total energy intake and demographic, health-related, and lifestyle-related covariates.

RESULTS

143 participants were categorized as having depressive symptoms (12.6%).
Highest intake of total-, animal-, and plant-based protein were not significantly associated with prevalence of depressive symptoms, compared to lowest intake in the fully adjusted models (e.g., total protein, ORQ4vsQ1: 0.75, 95% CI 0.42; 1.32, p-for-trend = 0.21). For depressive symptom severity, highest total protein intake was significantly associated with a 1.13 times (ORQ4vsQ1: 0.87, 95% CI 0.75; 1.00) lower PHQ-9 total score, compared to lowest intake in the fully adjusted model (p-for-trend = 0.05). Energy-adjusted animal and plant-based protein intake were not significantly associated with depressive symptom severity.

CONCLUSION

In people with T2D, higher total protein intake was associated with reduced depressive symptom severity, but not with the prevalence of depressive symptoms. Further prospective research with a larger sample size is needed to confirm these associations.

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Concordance between culture, Molecular Culture and illumina 16S rRNA gene amplicon sequencing of bone and ulcer bed biopsies in people with diabetic foot osteomyelitis

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BACKGROUND

The diagnosis of diabetic foot osteomyelitis (DFO) relies on outcomes of cultures of bone or ulcer bed (UB) biopsies. Identification of bacteria in aseptically obtained bone specimens is the reference standard for osteomyelitis. The slow growth of some bacteria, or their fastidious nature, prevents accurate and expeditious detection and identification. Rapid molecular techniques may solve both issues, but their additional value for everyday practice is currently unknown.

METHODS

To investigate the concordance between conventional culture, the rapid molecular techniques Molecular Culture (MC), and illumina 16S rRNA gene amplicon (16S) sequencing in people with DFO. In the BeBoP trial, bone and UB biopsies were obtained from people with DFO who visited Amsterdam University Medical Centres. These low microbial biomass biopsies were analysed using 1) conventional culturing, 2) Molecular Culture (MC), a semi quantitative rapid broad range PCR which analyses length polymorphisms of the 16S-23S ribosomal interspace region, and 3) Illumina 16S amplicon sequencing (16S). We evaluated the concordance among culture, MC and 16S sequencing.

RESULTS

We analysed 20 samples (11 bone and 9 UB) of 18 people. A total of 84 species were identified, 45 (54%) by all techniques, and an additional 22 (26.5%) by both MC and 16S, the remaining 16 species were identified by culture and MC or 16S, or by a single method. MC and 16S sequencing identified anaerobes, not detected by culturing, in 5 samples, and the presence of bacteria in 7 out of 8 culture-negative (6 bone, 2 ulcer bed) samples

CONCLUSION

The high level of concordance between MC and 16S and the additional ability of molecular techniques to detect various bacteria not detected by culturing opens up prospects for routine use of fast molecular techniques , in clinical settings such as aseptically obtained bone samples.

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Insulin-Sparing Effects of Oral Semaglutide: An Analysis of PIONEER 8

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Dr. William van Houtum is presenting on behalf of the authors.

BACKGROUND

The PIONEER 8 (NCT03021187) trial demonstrated significant glucose-lowering efficacy of oral semaglutide vs placebo in patients with T2D inadequately controlled with insulin.

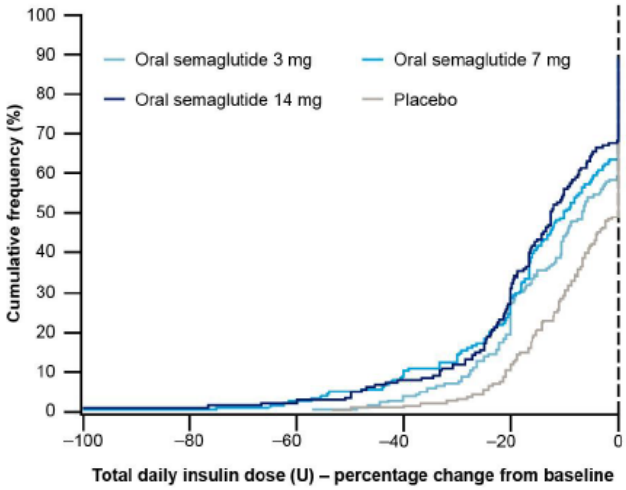
METHODS

Additionally, those assigned to oral semaglutide (7 or 14 mg daily) had a lower total daily insulin dose at end of treatment (week 52) relative to baseline, vs those treated with placebo, suggesting an insulin-sparing effect. This post-hoc analysis of PIONEER 8 aimed to characterize the transition of adding a GLP-1RA to insulin therapy and to quantify reductions in total insulin dose seen with the addition of oral semaglutide.

RESULTS

A 20% reduction in total daily insulin dose was recommended at randomization up to week 8. Total daily insulin was not to exceed pre-randomization dose between weeks 8 and 26, but was freely adjustable at the investigator's discretion from week 26 to 52. For all doses of oral semaglutide, a greater proportion of patients were able to maintain a greater level of insulin dose reduction vs placebo at week 26 (**figure 7**). Greater proportions of patients on oral semaglutide 3, 7, and 14 mg achieved ≥ 20% reductions in insulin vs those in the placebo group at both weeks 26 and 52 (Treatment policy estimand; 27.5%, 28.9%, 31.2% vs 12.4% and 19.5%, 25.0%, 32.0% vs 5.7%, respectively; $p < 0.001$ for all).

Figure 7. Proportion of patients achieving reductions in total insulin dose from baseline at week 26.



Data are from the in-trial observation period and according to the treatment policy estimand. Subjects with an increase in total daily insulin dose are outside the plotted range but do still contribute to the empirical distribution function.

CONCLUSION

Addition of oral semaglutide in patients with T2D permits a significant reduction in insulin dose, which may provide benefits (e.g. lower risk of hypoglycaemia and weight gain) long-term.

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Postprandial histidine levels and responses of IDL and SHDL to a liquid mixed meal are associated with incidence of type 2 diabetes

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BACKGROUND

Disturbed postprandial plasma metabolite levels and responses have been suggested as a risk factor for type 2 diabetes (T2D). However, this remains to be fully investigated.

METHODS

We leveraged The Netherlands Epidemiology of Obesity (NEO) study to examine the associations between postprandial metabolite levels and responses, and incidence of T2D.

We analyzed 5876 participants with a mean (SD) age of 56 (6) years, body mass index (BMI) of 29.8 (4.7) kg/m^2, 53% women, without T2D at baseline. In fasting and postprandial (t = 150 min after a liquid mixed meal; 400 ml with 2.5 MJ) plasma samples, 148 metabolites were measured using the Nightingale 1H NMR platform. A Cox proportional-hazard model was used to estimate hazard ratios (HR) of T2D, adjusted for age, sex, BMI and glucose levels. False discovery rate was applied in each meal state respectively.

RESULTS

Over a median follow-up of 6.7 years, 302 new cases of T2D were detected. After adjusting for glucose levels, higher postprandial histidine levels were associated with a lower risk of T2D (HR [95% CI]: 0.71 [0.63-0.81]), which was not found in fasting state. Similarly, IDL particle responses (HR between 0.78 and 0.80 for six different fractions) and SHDL particle responses (HR between 0.71 and 0.83) were associated with a lower risk of T2D.

CONCLUSION

In this middle-aged population, certain postprandial metabolite levels and responses were associated with incidence of T2D, independent of glucose levels, which suggests the clinical utility of postprandial measurements in predicting T2D progression.

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Metabolic effects and safety of glycodeoxycholic acid (gDCA) in healthy lean men: a proof of concept study

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BACKGROUND

Bile acids function as postprandial signaling molecules for lipid-, glucose- and energy metabolism via the activation of Takeda G protein-coupled receptor 5 (TGR5) and Farnesoid X receptor (FXR). A single dose of orally administered gDCA increased postprandial GLP-1, which implicates bile acid induced TGR5-activation. However, safety issues and side effects occur frequently in prolonged supplementation. In this study, we investigated metabolic effects and safety of gDCA (10 mg/kg bw/day) for 30 days in twenty healthy lean men.

METHODS

Participants were assigned to either regular or slow release (i.e. mimic physiological bile acid release) capsules. Metabolic effects were measured at baseline, day 15 and 31 by mixed meal testing. Side effects and liver functions tests were monitored at day 7, 15 and 31. A step-down-procedure was implemented in case of elevated liver function test (2-4x upper reference limit), by which dose was reduced to 5 mg/kg bw/day.

RESULTS

Plasma glucose levels were increased in the regular group while no effect was found in the slow release group. No effects on fasting and postprandial insulin levels were found. In both groups, gDCA reduced plasma lipid concentrations, which may be a FXR-dependent effect. Also, total bile acids and FGF19 responses were increased. gDCA administration is safe, but resulted in increased liver transaminases. A major part of the participants experienced gastrointestinal complaints, especially in the regular group.

CONCLUSION

Prolonged gDCA administration did not have lowering effects on postprandial plasma glucose and insulin levels in healthy lean mean. However, gDCA increased postprandial bile acid and FGF19 responses and inhibited bile acid synthesis. The most prominent metabolic effects were decrease in plasma cholesterol, LDL and HDL. gDCA increased liver transaminases and especially participants in the regular group experienced gastrointestinal complaints. More dose finding studies are warranted before gDCA can be considered as therapeutic option for cardio-metabolic diseases.

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Additional effects of exercise to hypocaloric diet on body weight, body composition, glycaemic control, and cardio-respiratory fitness in adults with overweight or obesity and type 2 diabetes: a systematic review and meta-analysis

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BACKGROUND

This systematic review and meta-analysis evaluates the additional effects of exercise to hypocaloric diet on body weight, body composition, glycaemic control, and cardio-respiratory fitness in adults with overweight or obesity and type 2 diabetes.

METHODS

Embase, Medline, Web of Science, and Cochrane Central databases were evaluated and 11 studies were included. Random-effects meta-analysis was performed on body weight and measures of body composition and glycaemic control, to compare the effect of hypocaloric diet plus exercise with hypocaloric diet alone.

RESULTS

Exercise interventions consisted of walking or jogging, cycle ergometer training, football training, or resistance training, and duration varied from 2 to 52 weeks. Body weight and measures of body composition and glycemic control decreased during both the combined intervention and hypocaloric diet alone. Mean difference in change of body weight (0.77 kg [95% CI: 2.03; 0.50]), BMI (0.34 kg/m^2 [95% CI 0.73; 0.05]), waist circumference (1.42 cm [95% CI: 3.84; 1.00]), fat-free mass (0.18 kg [95% CI 0.52; 0.17]), fat mass (1.61 kg [95% CI 4.42; 1.19]), fasting glucose (+0.14 mmol/l [95% CI 0.02; 0.30]), HbA1c (0.06 % [95% CI 0.25; 0.13]), and HOMA-IR (+0.01 [95% CI: 0.40; 0.42]) was not statistically different between the combined intervention and hypocaloric diet alone. Two studies reported VO2max and showed significant increases upon addition of exercise to hypocaloric diet.

CONCLUSION

Additional effects of exercise to hypocaloric diet in adults with overweight or obesity and type 2 diabetes were not shown for body weight, body composition, or glycaemic control, while cardio-respiratory fitness improves.

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Significant difference in glucometric outcome between automated insulin delivery (AID, 780G+RTCGM) versus traditional ‹playing pancreas› (780G+FGM) in adults with type 1 diabetes

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BACKGROUND

Outcomes of type 1 diabetes (T1D) still show only 20-50% of patients reaching target-A1c levels (< 7.0%; 53 mmol/mol). Until recently, therapy was based on self-management i.e. constant ‹manual› adjustments by the person with T1D, preferably as often as possible (‹playing pancreas›). This has also a substantial impact on their lives with psychosocial consequences. Automated insulin delivery (AID) overcomes this burden by reducing human input. Currently available technologies offer semi-automated insulin administration (i.e. hybrid closed loop) resulting in more patients reaching HbA1c targets without hypoglycemia.

METHODS

We analyzed (adult) patients who switched to a new

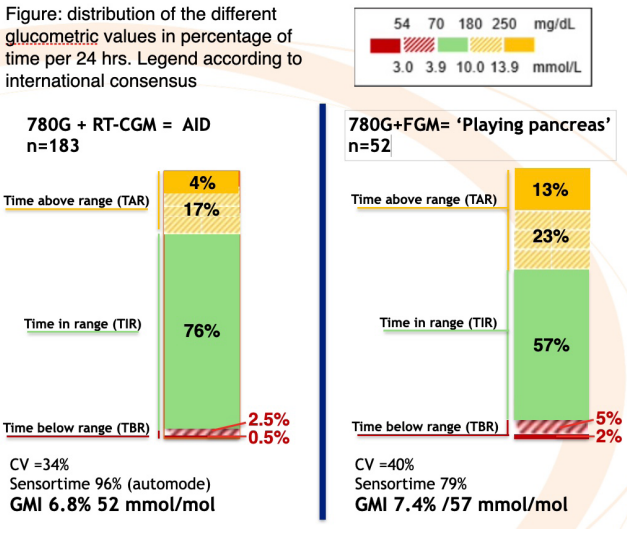

Figure 8. distribution of the different glucometric values in percentages of time per 24 hrs. Legend accoring to international consesus

Medtronic 780G insulin pump in 2021 (expiration warranty previous pump), which, with RT-CGM, works as AID. Due to our value-based outcome contracting, we were able to continue or start AID treatment (780G + RT-CGM) in most patients (n = 183). However, some insurance companies applied strict national reimbursement rules for RT-CGM use and did not allow their patients to combine their 780G with RT-CGM. They used Freestyle Libre FGM (780G+FGM; n = 52). We compared the glucometrics outcome of the 780G + RT-CGM group with the 780G + FGM group in a cross-sectional analysis (first quarter 2022). All patients used their devices for at least 3 month.

RESULTS

The use of the 780G as an AID (780G + RT-CGM) gave better glucometric outcomes, including more patients in HbA1c target (GMI), halving hypoglycaemias (even more for severe) and better coefficient of variation (CV) of glucose (see **figure 8** for data). Comparing patients in target, 79% in the 780G + RT-CGM versus 17% in the 780G + FGM group reached an HbA1c < 7.0 %/53 mmol/mol.

CONCLUSION

We conclude that in a real-world setting, switching to AID systems results in substantial improvement of glucoseregulation compared to non-automatic, manual handling of the T1D pump treatment.

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No effect of time on pregnancy outcomes in women with type 1 diabetes

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BACKGROUND

Women with type 1 diabetes mellitus (T1DM) are at risk for the development of foetal and maternal complications during pregnancy. Improvement of obstetrical care over the years might have improved the outcomes of pregnant women with T1DM. The aim of this meta-analysis is to give an overview of the risk of adverse pregnancy outcomes in women with T1DM compared with women without DM and assess the effect of time.

METHODS

A systematic search selecting studies reporting maternal/neonatal outcomes, in women with T1DM consisting of > 50 pregnancies was performed by two authors. Quality assessment was performed using the Newcastle-Ottawa scale. A meta-analysis was performed with Review Manager 5.4.

RESULTS

Analysis of studies from 1-7-2008 to 2020 was performed. This will be expanded to studies before 2008 and complete data will be presented during the meeting. A total of 2748 abstracts were retrieved, a total of 16 articles were included in the analysis. Women with T1DM had a higher risk of preterm delivery (OR 5.12, 95% CI 4.38-5.98), pre-eclampsia (OR 4.84, 95% CI 3.56-6.57) as well as caesarean section (CS) (OR 4.09, 95% CI 3.44-4.86) compared to women without diabetes. Neonatal outcomes included more large for gestational age infants (OR 4.75, 95% CI 2.96-7.63), still births (OR 4.05, 95% CI 3.00-5.48), and NICU admissions (OR 7.38, 95% CI 5.25-10.37). No effect of time was found on the abovementioned outcomes, except for a reduction in CS risk which can be explained by an absolute increase of CS over the years in the women without diabetes.

CONCLUSION

As expected, women with T1DM have a higher risk for adverse pregnancy outcomes compared to women without DM. We did not find a significant reduction in complication risk from 2008 to 2020.

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Pancreatic beta-cells express MT1 as stress defense mechanism compromising beta-cell identity and function

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BACKGROUND

Type 1 diabetes (T1D) is an inflammatory disease that is characterized by the autoreactive destruction of pancreatic beta-cells by immune cells. The goal of this study is to investigate the response of human pancreatic islets to inflammation, ultimately to unravel the molecular mechanisms driving loss of the functional beta-cell mass.

METHODS

Pancreatic islets from 3 donors were treated with pro-inflammatory cytokines (IL1b&IFNg) to mimic the physiopathology scenarios that occurs in diabetes. Human pluripotent stem cell derived islets (SC-islets) and EndoCBH1 cells were used as beta-cell models. Cells were processed for qPCR and single-cell RNA sequencing (scRNA-seq). Beta-cell function was assessed by dynamic glucose-stimulated insulin secretion test. Lentivirus-mediated knockdown (shRNA) vectors were used to silence the expression of target genes.

RESULTS

IL1b&IFNg treatment compromised the expression of the beta-cell canonical identity markers MAFA, IAPP, HADH, NPTX2 and PRSS23 (expression reduced by 41, 53, 27, 34, 28,%, respectively) and their functionality (stimulation index reduced by 40%, treated vs untreated). In contrast, beta-cells showed an up-regulation of the metallothionein 1 (MT1) gene family upon cytokine stress. In addition, we found that (immature) b SC-islets that present a lower MAFA expression as compared to adult beta-cells, express higher levels of MT1. Finally, silencing of MT1X in pancreatic islets and EndoCBH1 cells promoted the expression of MAFA (1.5 and 4x, respectively, $n = 4$, $p < 0.05$), and enhances glucose-stimulated insulin secretion (increase by 50%, $n = 2$).

CONCLUSION

Collectively these data indicate that the expression of MT1, that is part of the anti-oxidant defense mechanism of beta-cells, is negatively correlated with beta-cell identity and function. We propose that lowering MT1 expression is beneficial to enhance maturation of beta-cells from SC-islets.

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None of currently available diabetes data platforms meet the necessary functionality according to health care professionals and patients

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BACKGROUND

Continuous glucose monitoring (CGM) represents a tremendous advance in diabetes care. CGM data can be shared with health care providers by different diabetes data platforms. Unfortunately, almost every manufacturer comes with his/her own platform and often does not allow data incorporation from competitive manufacturers and cannot be directly imported into an electronic medical record (EMR). The needs from either patients or health care providers towards the functionality of diabetes data platforms are unknown.

METHODS

To assess these needs in more detail, we performed a nation-wide, qualitative study, using in depth interviews ($n = 10$) with patients and health care providers from different disciplines. We used priority setting by the MoSCoW method in five different priority domains. Based on these results, the currently available data platforms were reviewed for their functionality.

RESULTS

Overall, the preferences and priorities provided by the participants were quite consistent. Participants viewed availability of both glucose and insulin data in the same platform highly necessary and felt strongly for inclusion of data from different brands into the same platform. Direct connection between the data platform and EMR was highly

desirable. Opinions were split on whether data platforms should automatically alarm when data were out of range. Regarding privacy, all participants agreed that the data belong to the patient, who may provide permission to use the data for research purposes. These results were applied to the presently available diabetes data platforms, none completely matched the requirements. Most frequent "deficiencies" were inability to incorporate insulin data and interoperability.

CONCLUSION

People with diabetes and their health care providers agreed on most functionalities deemed necessary for diabetes data platforms and felt inclusion of both glucose and insulin data was mandatory. None of the currently available platforms provides the desired functionality. Further development and interoperability of diabetes data platforms is needed.

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Personalized Nutritional Advice To Improve Short-term Fitness and Long-term Health In Shift Workers

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BACKGROUND

Night work is associated with disturbances in sleep (shorter, less consolidated sleep) and alterations in glucose homeostasis (due to eating out of synchrony with the endogenous biological clock).

METHODS

We aim to assess the effects of a sleep and a nutritional intervention on measurements related to sleep and metabolic health in night shift workers. Primary objectives include sleep quality and quantity, and (continuous) glucose patterns. Secondary objectives include examination of clinical biomarkers and performance during night shifts. 25 male shift workers will be recruited in both intervention arms, working at least 4 night shifts/month, aged 18 to 60 years. The study is a non-blinded, controlled, intervention study of 3 months, preceded by a run-in period with baseline measurements, and a follow up after 12 months.

RESULTS

The sleep intervention consists of personalized advice on sleep hygiene/environment, sleep timing, naps, and exposure to light. The nutritional intervention consists of personalized advice on the daily distribution of calories and macronutrients, and on specific food products based on continuous glucose measurements (CGM). The control group will continue their normal sleep and nutritional habits.
During the intervention, sleep, physical activity, food intake and continuous blood glucose values will be measured. Sleep and physical activity will be measured using actigraphy and a sleep diary. Food intake will be monitored with short periods of food logging. Continuous blood glucose will be measured using a CGM three times for a period of 10 days. Short-term fitness during the night shifts will be assessed using psychovigilance tests.

Study outcomes will be compared using generalized linear mixed model, comparing within and between study groups.

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The effect of extended personalization to a combined lifestyle intervention program

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BACKGROUND

The combined dietary and physical activity lifestyle intervention (CLI) program "SLIMMER" is effective and is reimbursed by health care insurance in The Netherlands. However, achieving and maintaining healthier lifestyle behavior is difficult. Personalization may make it easier to achieve and maintain healthy lifestyle habits.

METHODS

In this study, we assessed the effects of extended personalization components to the SLIMMER program on metabolic health and low-grade inflammation. In this group-randomized intervention study, 60 intervention and 59 control participants, 18-70 years, with overweight or obesity, were included and followed during the first six months of their SLIMMER program. Body composition was measured at

baseline and end of study using bioimpedance (InBody 770). The PhenFlex test, a mixed-meal challenge, was used to examine changes in metabolic and inflammatory status due to the CLI and to determine prediabetic subtypes, which allowed for personalized dietary and exercise advice. Personalized feedback was achieved using a Fitbit activity watch and Fitbit weighing scale. Participants used a study app for goalsetting, goal evaluation, and motivation. Furthermore, participants had extra individual appointments with their lifestyle coach. Participants in the control group followed the regular SLIMMER program without extended personalization. Anthropometry was done and blood was drawn at the beginning and at six months of the intervention.

RESULTS

At six months, body weight (-4.5 kg ($p < 0.001$), body fat percentage, waist circumference, and fasting glucose significantly improved in the intervention group (n = 54). For fasting inflammatory markers, a significant decrease was seen in interleukin 6 (IL-6). A prevention of deterioration was seen in prediabetic subtypes.

CONCLUSION

While analyses, as well as the comparison to the control group, are still ongoing, the improvement in body weight in our intervention group was higher than reported in the regular SLIMMER program (-3.0 kg in 12 months). Therefore, these are promising results for the effects of this extended CLI on body composition, fasting glucose and inflammatory markers.

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The Apolipoprotein L family genes as markers of islet inflammation

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BACKGROUND

Type 2 diabetes (T2D) is a complex multifactorial disease characterized by β-cell failure, insulin resistance and abnormal lipid metabolism. Previous studies show that increased circulating Apolipoprotein L1 is associated with abnormal lipid metabolism in T2D patients, but whether Apolipoprotein L (ApoL) expression is altered or has a role in pancreatic β-cells is unknown.

METHODS

We analysed publicly available single-cell RNA-sequencing (scRNA-seq) datasets of islets from T2D (n = 12) and non-diabetic (ND) (n = 24) organ donors. We assessed ApoL protein levels by immunofluorescence in islets from T2D donors. In addition, we exposed human islets to various stress conditions (IL1β+IFNγ, IFNα, thapsigargin, high glucose, palmitate, H202) for 24h/72h and analyzed gene expression by scRNAseq. We knocked-down (KD) specific ApoL genes and inhibited the Jak/STAT pathway in the presence of pro-inflammatory cytokines in human islets and in the human β-cell line EndoC-βH1.

RESULTS

ScRNA-seq showed that ApoL2 and ApoL6 are upregulated in β-cells from T2D donors compared to non-diabetic subjects (Fold change, 2.4x and 2.6x respectively, $p < 0.01$), while a trend towards increased expression is found for ApoL1 (1.59x, p = ns). We confirmed at a protein level the increased expression of ApoL1/2/6 in β-cells of T2D donors. In vitro, human β-cells exposed to IL-1β+IFNγ displayed a significant upregulation of ApoL1/2/6 (Fold change, 1.49x, 2.02x and 1.45x, $p < 0.0001$), while Jak/STAT pathway inhibition significantly prevented cytokine-induced ApoL1/2/6 expression by > 95% ($p < 0.05$, n = 3). In turn, ApoL1/2 knock-down reduced the expression of Jak/STAT pathway transcription factors IRF1 (> 30%, $p < 0.01$), STAT1 (10-40%, $p < 0.05$) and STAT2 (> 25%, $p < 0.05$) in EndoC-βh1 cells (n = 5) and decreased IL8 and IL-1β gene expression in human islets (n = 3).

CONCLUSION

ApoL genes are novel regulators of islet inflammation and may play a role the development and progression of beta cell dysfunction in diabetes.

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Duration of Antibiotic Treatment Following Amputation: Two versus Fourteen Days of Postoperative Antibiotic Therapy Following Toe Amputation for Diabetic Foot Osteomyelitis

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BACKGROUND

In persons with diabetes, toe amputations for osteomyelitis are commonly performed interventions in Dutch hospitals. The optimal duration of antibiotic therapy for this indication is unknown and typically ranges from 2 days to 14 days. The main objective of this trial is to determine if a short duration of antibiotic therapy (2 days) is non-inferior to a long duration (14 days) of antibiotic therapy, in achieving remission of infection 6 weeks after trans-phalangeal or trans-metatarsal toe amputation for osteomyelitis in persons with diabetes.

METHODS

This is an open-label multicentre randomised controlled non-inferiority trial. Both groups receive postoperative antimicrobial therapy. The selection of appropriate antibiotic therapy is according to standard care, based on national guidelines (SWAB) or targeted at previous tissue cultures. Following surgical removal of the infected bone, one group will receive 2 days of antibiotic therapy and a second group will receive 14 days of antibiotic therapy.

RESULTS

Primary endpoint is remission of infection at 6 weeks after amputation. Remission is defined as no need for additional antibiotic therapy or surgery for infection at the original site of amputation. Secondary outcomes at 3 months after amputation are: re-operation for infection at the original amputation site, any additional antibiotic therapy for infection at the original amputation site, survival, amputation, wound healing, hospitalizations, adverse events of antimicrobial therapy and quality of life assessed with SF-12. We assume a remission rate of 90% in both treatment arms.

CONCLUSION

When we calculate Wald's confidence interval without correction for non-inferiority, 156 subjects in total are required to achieve 90% of power at a one-sided significance level of 0.05. With a drop-out rate of 10%, the total number of included subjects will be 174 (87 in each group).

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Gender differences in the prioritisation of health outcomes in diabetes: Informing gender-sensitive diabetes care

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BACKGROUND

Sex and gender can affect diabetes outcomes. Evidence suggests this is mediated by biological and sociocultural factors. However, little is known about associations between gender and patient-reported outcomes which reflect subjective perceptions of disease. This abstract presents such gender differences in results of a consensus process to define a person-centred outcome set for diabetes care in Europe.

METHODS

A three-round Delphi study was undertaken to reach consensus on the diabetes dataset. The importance of including an outcome in the dataset was rated on a 10-point-Likert scale with a consensus threshold of 70 %. In an exploratory analysis voting results were stratified according to the indicated gender of participating patients.

RESULTS

Sixty patients answered the third Delphi survey, of which 45 % were women and 55 % men. Consensus on inclusion in the dataset was achieved for most outcomes in both subgroups. Two outcomes reached consensus among women only and three among men only. The proportion of women

and men voting ≥ 7 differed significantly for two outcomes (Table 1). Yet, women were found younger and more likely to be living with type 1 diabetes. Subsequent analyses showed that Eating problems were rated significantly differently in importance depending on diabetes type (higher priority for type 1 diabetes). No age- or diabetes type-specific differences were found for the other outcomes.

Our results provide evidence that men and women prioritise diabetes outcomes differently: while feeling in control was a concern for men, women highlighted being mindful of side effects. Measuring outcomes in a personalized, gender-sensitive way to provide gender-specific diabetes care may support the achievement of personal treatment goals.

CONCLUSION

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Microbial 6-bromotryptophan ameliorates autoimmune type 1 diabetes by limiting inflammation and rewiring the immune and pancreatic beta-cell metabolism

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BACKGROUND

Gut microbial dysbiosis, associated with type 1 diabetes (T1D), may shape or underpin T1D pathogenesis, however the underlying mechanisms remain unclear.

METHODS

With non-targeted metabolomics, we discovered a novel serum metabolite, 6-bromotryptophan (6-BT), derivative of dietary tryptophan, that inversely correlates with key disease features (T cell activation and beta-cell loss) and is reduced in T1D. Strikingly, serum 6-BT levels are modulated by microbiota transplantations and vanish after antibiotic therapy in humans, underscoring its microbial origin.

RESULTS

To investigate the role of gut-derived 6-BT in T1D, we orally administered 6-BT to NOD mice, where 6-BT was found to ameliorate glucose metabolism, limit T cell activation and boost Treg expansion systemically and in inflamed pancreata. Mechanistically, 6-BT halts NF-κB signaling activation while endorsing mitochondrial oxidative metabolism in both immune and pancreatic beta-cells. The latter effects are linked to 6-BT anti-inflammatory and insulin secretagogue properties.

CONCLUSION

Thus, 6-BT is a novel microbially-produced metabolite that counteracts T1D pathogenesis.

Table 3. Proportion of women and men with diabetes that rated the importance of each outcome ≥ 7.
Achieved consensus is indicated in blue, lack of consensus is marked in yellow. Darker colours highlight disagreement between women and men. Outcomes that reached consensus among women or men only are highlighted in bold..

Outcome	%Women ≥ 7 (N = 27)	%Men ≥ 7 (N = 33)	p
Psychological well-being	78%	79%	.925
Depression	63%	61%	.852
Anxiety	59%	45%	.287
Eating problems	74%	48%	.044
Diabetes distress	85%	85%	1
Diabetes-specific quality of life	85%	88%	1
Health status	70%	91%	.051
Symptoms	81%	94%	.226
Side effects	74%	67%	.533
Altered glucose events	89%	70%	.073
Hypoglycemia unawareness	81%	70%	.294
Self-care performance (tracking)	81%	85%	.742
Capacity for self-care	81%	82%	1
Perceived importance of self-care	78%	91%	.276
Motivation for self-care	70%	91%	.051
Percieved control over diabetes	67%	88%	.047
Treatment satisfaction	81%	94%	.223
Social support	63%	70%	.582
Sleep quality	78%	76%	.854
Lifestyle	63%	82%	.100
Sexual health	63%	67%	.792
HbA1c	85%	88%	.722
Other lab values	74%	91%	.097
Blood pressure	70%	79%	.454
Height and weight	59%	70%	.399
Sensor data	81%	79%	.795
Complications	70%	79%	.454
Screenings	74%	85%	.299

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The strength of the social group in achieving behavior change in people with type 2 diabetes: a qualitative study on the working mechanisms of a group-based walking intervention

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BACKGROUND

Understanding motivations for participation in physical activity (PA) interventions is important to achieve behavior change in people with type 2 diabetes mellitus (T2DM). The present qualitative study aimed to gain more understanding on the working mechanisms of a group-based walking intervention in the Netherlands by examining: 1) initial motivation for participation, 2) perceived intervention benefits, and 3) facilitators and barriers in increasing and maintaining PA behavior.

METHODS

Seventeen people with T2DM (aged 48-79) who completed the intervention participated in semi-structured interviews. Interviews were transcribed verbatim and data were analyzed through thematic analysis.

RESULTS

Results indicated that the initial motivation for participation of most participants was more health-oriented and extrinsic, and that during the intervention this shifted to a more social-oriented and intrinsic motivation. Perceived intervention benefits included improved health outcomes (e.g. lower HbA1c), mental health outcomes (e.g. less stress) and social outcomes (e.g. social support). For participants, benefits were often greater than the outcome expectations they had beforehand, particularly regarding mental health and social benefits. Main facilitators PA identified were the involvement and support of healthcare providers, walking in a group, working towards and achieving a goal, and experiencing the positive effects of exercise. Identified barriers were related to the absence of facilitators: not having a clear goal, low outcome expectancies and self-efficacy as well as insufficient social support and connection.

CONCLUSION

This study highlights the impact of social-oriented motivation and perceived social benefits in increasing and maintaining PA in people with T2DM. A walking group facilitated by healthcare providers can be a vehicle to influence social motivation and benefits as well as behavior change. Future studies could further explore social and community influences on increasing and maintaining PA behavior.

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Physical activity, fructose from sugar-sweetened beverages and alcohol are mediators of the association between socioeconomic position and intrahepatic lipid content: The Maastricht Study

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BACKGROUND

It is well-known that an unhealthy lifestyle drives intrahepatic lipid (IHL) accumulation. More recently, a low socioeconomic position (SEP) has been associated with a higher IHL content. The aim of this study was to examine to what extent lifestyle factors mediate the relationship between SEP and IHL content.

METHODS

We used cross-sectional data from The Maastricht Study (n = 3,978). SEP indicators were education, income and occupation. The following lifestyle factors were assessed as potential mediators: physical activity (accelerometer), intakes of total energy, alcohol, saturated fat, protein, vitamin E, dietary fiber, and fructose from sugar-sweetened beverage (SSB) and fruit juice (food frequency questionnaires).

IHL content was quantified by MRI. Age, sex and type 2 diabetes were included as covariates.

RESULTS

Individuals with low education had a higher IHL content compared to high education (total effect: 0.78, 95% CI: 0.38; 1.18). Statistically significant mediators of this association were moderate-to-vigorous physical activity (indirect effect: 0.07, 95% CI: 0.03; 1.12, proportion mediated: 8.7%), fructose intake from SSB (indirect effect: 0.06, 95% CI: 0.01; 0.12, proportion mediated: 7.2%), and alcohol intake (indirect effect: -0.18, 95% CI: -0.27; -0.10, proportion mediated: -23.1%). Similar results were found when income and occupation were used.

CONCLUSION

These results illustrate the complex background of IHL accumulation and suggest that societal measures are warranted to alleviate the burden of non-alcoholic fatty liver disease. Moreover, the results show that there are other yet unknown factors besides lifestyle that mediate the association between SEP and IHL.

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Migraine And Diabetes: Is There Any Association?

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BACKGROUND

Migraine is a neurovascular disorder associated with metabolic disorders, including diabetes mellitus (DM). Both migraine and DM represent a major public health problem in all age groups and in both women and men. Moreover, it has been proposed that there is a direct and/or indirect relationship between both migraine and DM, nevertheless, the mechanisms involved in this possible association are not yet fully described.

METHODS

According to the existing literature so far, we can suggest that the link between migraine attacks and DM might be related to patient›s lifestyle and to central and peripheral mechanisms involved in the (patho)physiology of both migraine and DM, including: (i) biochemical biomarkers such as pro-inflammatory mediators, adipokines or neuropeptides (e.g. calcitonin gene-related peptide, CGRP, the main neuropeptide involved in migraine pathophysiology); (ii) the influence of socioeconomic, environmental, genetic and/or psychological factors; and (iii) the risk factor to develop cardiovascular complications, which also have a higher age- and gender-depending prevalence, and/or microvascular dysfunction.

RESULTS

Finally, due to the limitations that most of the clinical studies show when evaluating the possible association between migraine and DM, basic and clinical studies are required to identify the underlying mechanisms and to provide the exact link between migraine and DM considering different variables (e.g. sex hormones, reproductive age, and confounders factors).

CONCLUSION

This approach is needed to identify a potential therapeutic target to improve the quality of life of people with migraine and/or diabetes.

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Weight Loss Outcomes with Semaglutide 2.4 mg in Moderate or Severe Obesity in STEP 1 and 2

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Prof. Dr. Mireille Serlie, Department of Endocrinology and Metabolism, University of Amsterdam is presenting on behalf of the authors.

BACKGROUND

Conventional lifestyle and pharmacologic interventions alone result in only modest long-term weight loss in patients with moderate-to-severe obesity. We evaluated outcomes with semaglutide 2.4 mg in the STEP 1 and 2 trials for this specific population.

METHODS

In STEP 1 and 2, adults with overweight or obesity (with type 2 diabetes in STEP 2 only) were randomized to

once-weekly subcutaneous semaglutide 2.4 mg or placebo, both plus lifestyle intervention. This post-hoc analysis included participants with Class II obesity (BMI ≥ 35 - < 40 kg/m^2) with at least one obesity-related comorbidity (i.e. type 2 diabetes, hypertension, knee osteoarthritis, dyslipidemia, obstructive sleep apnea), or with Class III obesity (BMI ≥ 40 kg/m^2) irrespective of obesity-related comorbidities. We assessed changes in body weight and cardiometabolic risk factors from baseline to week 68.

RESULTS

1,356 participants were included: 969 from STEP 1 and 387 from STEP 2. Mean percentage body weight reductions with semaglutide 2.4 mg vs placebo were 13.9% vs 2.1% (ETD: –11.8% [95%CI: -13.1, -10.6]) among STEP 1 participants and 10.6% vs 4.2% (ETD: -6.4% [95% CI: -8.0, -4.8]) among STEP 2 participants. Compared with placebo, semaglutide 2.4 mg also resulted in significantly ($p < 0.05$) greater reductions in BMI (ETD, STEP 1: -4.9 kg/m^2; STEP 2: -2.7 kg/m^2) and waist circumference (ETD, STEP 1: -9.3 cm; STEP 2: -5.0 cm), and significant improvements in systolic blood pressure (ETD, STEP 1: -5.4 mmHg; STEP 2: -3.7 mmHg), HbA1c (ETD, STEP 1: -0.3 %-points; STEP 2: -1.3 % points), and C-reactive protein levels (estimated treatment ratio, STEP 1: 0.6; STEP 2, 0.5).

CONCLUSION

In adults with Class II obesity plus obesity-associated comorbidities, and Class III obesity, semaglutide 2.4 mg once weekly provided clinically significant weight loss and improvements in cardiometabolic risk factors.

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Know yoor clock!: Optimal exercise timing to maximise its benefits

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BACKGROUND

Shift work is deeply associated withe obesity and type 2 diabetes mellitus. Altered rhythms in the sleep-wake cycle, food intake and physical activities are considered the main contributor. These altered rhythms may result in disrupted synchrony between perihperal clocks and/or between the central clock and peripheral clocks.

METHODS

Our goal is to fix this desynchrony via timed exercise. We investigated in Wistar rats wether voluntary time-restricted running (TRR) during the natural sleep period (SP), as commonly experienced by people performing shift work, would be able to shift muscle clock. For acclimatisation, rats were first given 2 weeks of unlimited acces tot the running wheel. For the next 4 weeks, they could either run ad libitum (ALR) for 24/day, only during their nataural active period (dark runners: DR) or their usual inactive period (light runners: LR). LR did run during their SP. But the distance was significantly less than DR and ALR. LR also displayed significantly higher adiposity.

RESULTS

Comparing LR and DR runners that ran similar cumulative distances revealed that the higher adiposity in LR was due to both amount and timing of exercise. Food intake per body weight was highest in ALR and DR, lower in LR and lowest in animals without a wheel, i.e. non-runners. The timing of food intake was not affected bij TRR. To evaluate the impact of TRR on glucose metabolism, glucose intolerance tests were performed. No significant differences were observed at either ZT4 or ZT11. Insulin data are currently being analyzed. qPCR of clock genes in skeletal muscles and liver is ongoing. These results will be presented at the meeting

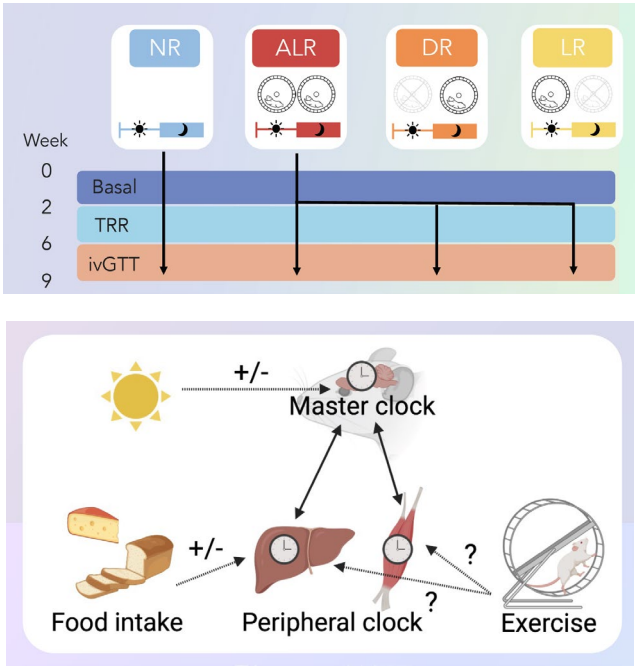

Figure 9. Voluntary time-restricted running (TRR) during the natural sleep period (SP) in rats.

CONCLUSION

Our results firmly support the idea that not only the amount but also the timing of exercise is important for an optimal effect on adiposity. Wheter this involves the muscle clocks and also holds for glucose tolerance is under investigation.

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Exploring immune cell metabolism to identify hallmarks of obesity

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BACKGROUND

Heterogeneity of obesity has resulted in the crude classification of healthy versus unhealthy obesity, the latter associated with a higher prevalence of metabolic complications, including insulin resistance. Obesity-associated inflammatory signals interfere with insulin signaling, causing tissue-specific and systemic insulin resistance. Since immune cells drive inflammation through alterations in intracellular metabolism, we explored immunometabolic phenotypes in overweight/obese individuals.

METHODS

We included n = 190 overweight/obese individuals (BMI > 25 kg/m^2). We measured the degree of systemic and tissue-specific specific insulin resistance together with functional and metabolic signatures of circulating monocytes using ELISA's and Seahorse-assays.

RESULTS

Metabolic signatures of monocytes, including glycolytic and oxidative metabolism rates, were highly variable among our population and significantly associated with cytokine production ($p < 0.04$). The rate of monocyte oxidative metabolism was positively associated with age ($p < 0.03$) and higher in males ($p < 0.02$). However, we did not find differences in monocyte metabolism or function between our participants with different types of insulin resistance. We observed four groups of monocytes presenting distinct glycolytic signatures. Linear models stratified by these groups revealed high variation in the direction of associations between insulin resistance and monocyte metabolism. For instance, the degree of muscle insulin resistance was positively associated with monocyte oxidative metabolism ($p < 0.04$) in only one of the four groups.

CONCLUSION

Our data show that monocyte metabolic features are associated with several clinical characteristics of overweight/obese individuals but are not different between individuals with varying types of insulin resistance. The four monocyte glycolytic signatures could reflect an extra layer in the complexity of the heterogeneity among overweight/obese individuals, shedding light on the hallmarks of obesity at the immunometabolic level.

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Modeling the effects of lifestyle on daily glucose profiles in individuals with type 2 diabetes using machine learning

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BACKGROUND

Normalizing blood glucose values in type 2 diabetes mellitus (T2DM) can be achieved with medication and lifestyle. However, daily life is complex and therefore it is difficult to compare and adjust to the individual effects of the various lifestyle factors. The Gluco-Insight study tries to address this by modeling the relation between lifestyle and glucose. In this abstract we focus on the question what (lifestyle) factors are most important for machine learning models and which model performs best.

METHODS

We measured sleep, exercise, food intake and continuous glucose values of 41 people with T2DM. A measurement period was 4 consecutive days. With 11 of those periods spread over half a year per person. Three oral glucose tol-

erance test were performed in that half year. Different machine learning models were used to predict glucose values 2 hours in the future or the incremental area under the curve (iAUC) of the glucose profile in response to food intake. Additional features (e.g. time lagged features) were generated and used to train the models.

RESULTS

Boosted regression tree models outperformed all other algorithms. When trained on the full feature set, historical glucose values explained the most variation. When historical glucose values were left out all models yielded poor prediction results. In both situations, with and without glucose data, including carbohydrate consumption increased the prediction accuracy. The models predicting meal response directly with an iAUC performed less accurately than predicting future 2h glucose and calculating the iAUC afterwards from the predictions.

CONCLUSION

A good performance has been reached in predicting glucose value over time. However, given the heavy reliance on historical glucose the next step would be to evaluate models with a strong autoregressive nature for instance long short-term memory neural networks.

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The high prevalence of gastrointestinal symptoms in type 1 diabetes shows no association with residual beta cell function

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BACKGROUND

Gastrointestinal (GI) symptoms, such as abdominal pain, reflux, diarrhoea, indigestion, and constipation are more prevalent in individuals with type 1 diabetes (T1D), the exact pathophysiology remains unclear. The aim of this cohort study is to determine if there is an association between GI symptoms and residual C-peptide function and other markers of glycemic control in individuals with T1D.

METHODS

500 individuals with T1D were included in this cross-sectional study (median age: 41.0, (interquartile range (IQR) 29.0-56.3 years), 63% female, HA1c: 53 ±12 mmol/mol, median duration: 14 years (IQR: 6-29 years)). A validated gastrointestinal symptoms rating scale (GSRS) was used to asses GI symptoms, grouped in abdominal pain, reflux, diarrhoea, indigestion, and constipation. As a marker of beta-cell function, postprandial urinary C-peptide/creatinine ratios (UCPCR) were measured. Data analyses performed in Rstudio using a Mann-Whitney-U test.

RESULTS

We found a prevalence of 41.9% for GI-symptoms in participants with T1D (vs. 28% reported in healthy individuals). Individuals with GI-symptoms were significantly younger ($p = 0.05$), leaner ($p = 0.03$) and more often female (73.6%, $p = 0.005$). Indigestion (24.2%) and constipation (30.2%) were the most prevalent abdominal syndromes. We found no relation with UCPCR, HbA1c, diet, celiac disease, irritable bowel disease and neuropathy in individuals with and without GI symptoms.

CONCLUSION

This study found a high prevalence of GI symptoms in T1D. Individuals with GI symptoms were significantly more often young lean females. Glycaemic control and neuropathy showed insufficient association with the high prevalence of GI symptoms. This suggests another aetiology of these symptoms and the increased prevalence in individuals with T1D.

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The Effect of Hormone Replacement Therapy on Glucose Regulation in Postmenopausal Women with Type 1 and Type 2 Diabetes: A Systematic Review and Meta-analysis

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BACKGROUND

It is observed that blood glucose regulation of women with type 1 and type 2 diabetes changes during and after menopause, which may be partly caused by estrogen deficiency. There is conflicting evidence about the impact of hormone replacement therapy (HRT) on blood glucose regulation. Therefore, we conducted a systematic review and meta-analysis to investigate the effect of HRT on glucose regulation in postmenopausal women with type 1 and type 2 diabetes.

METHODS

PubMed, Embase, Scopus, the Cochrane Library and the clinicaltrials.gov registry were searched to identify randomized-controlled trials (RCTs). We selected RCTs investigating the effect of HRT with at least estrogen monotherapy in postmenopausal women (final menstrual period > 6 months) with type 1 or type 2 diabetes. Outcomes were HbA1c (%), fasting glucose (mmol/l), postprandial glucose (mmol/l), and differences in use of glucose lowering drugs. The protocol was registered. (PROSPERO-ID: CRD42021258615)

RESULTS

2,592 records were identified. Nineteen RCTs were included (12 parallel-group trials and 7 crossover trials), with a total of 1,412 participants, of which 4.0% had type 1 diabetes. In parallel-group trials, HRT reduced HbA1c (mean difference -0.28 [95% CI -0.52, -0.04]) and fasting glucose (mean difference -0.79 [95% CI -1.18, -0.40]) with low heterogeneity. In crossover RCTs, HRT reduced HbA1c (mean difference -0.78 [95% CI -1.12, -0.43]) and fasting glucose (mean difference -1.51 [95% CI -2.93, -0.10]), with low and substantial heterogeneity, respectively. Subgroup analyses of the effect of transdermal HRT (3 studies) showed no differences in HbA1c or fasting glucose.

CONCLUSION

HRT reduces HbA1c and fasting glucose concentration in postmenopausal women with type 2 diabetes. The effect might be limited to oral HRT. Evidence for postmenopausal women with type 1 diabetes is lacking.

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Low SHBG is related to increased liver fat, which mediates a small part of the association between SHBG and T2D.

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BACKGROUND

Low levels of sex hormone binding globulin (SHBG) and fatty liver are related to an increased risk of type 2 diabetes (T2D). Our aim was to examine the relation between SHBG, liver fat content and T2D in middle aged women and men.

METHODS

In the Netherlands Epidemiology of Obesity study, SHBG was measured in 5722 middle-aged men and women (53%) without pre-existing diabetes. Liver fat content was assessed by proton-MR spectroscopy in a random subgroup (n=1834). Participants were followed for the occurrence of T2D. We examined sex-stratified associations between quartiles of SHBG and liver fat with linear regression, and with T2D using Cox regression, adjusted for age, total body fat, smoking, menopause, physical activity and hormone use. We included liver fat content in the adjusted Cox regression models and calculated the percentage mediation.

RESULTS

The median (IQR) SHBG was 47 nmol/L (34-64) in women and 34 nmol/L (26-43) in men. Median (IQR) liver fat was 3.4% (1.6-8.2) in women and 6.0% (2.9-13.3) in men. Compared with the first quartile of SHBG, in participants in quartile 4 liver fat was 66% (95% CI 71-59) lower in women and 37% (46-26) lower in men. During follow-up of 5.9 years (IQR 5.9-7.9), 128 women were diagnosed with T2D, and 154 men. Compared with the first quartile of SHBG, the hazard ratio (HR, 95% CI) of T2D in quartile 4

was 0.22 (0.11-0.44) in women and 0.55 (0.34-0.89) in men. After additional adjustment for liver fat content, the HRs were 0.29 (0.06-1.40) in women 0.62 (0.28-1.41) in men, reflecting a percentage mediation of 10% in women and 24% in men.

CONCLUSION

Low SHBG levels were associated with increased liver fat content and an increased risk of T2D. The amount of liver fat mediated a small part of the association between SHBG and T2D.

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Telemonitoring using a smart app for type 2 diabetes patients increases time in range

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BACKGROUND

The Freestyle Libre (FSL) provides rapid insight into glucose values and time in range (TIR). Recently, a home monitoring and telemonitoring app was designed and used at Canisius Wilhelmina Hospital (CWZ). The aim of this study was to gain insight into differences in TIR, above range (TAR) and below range (TBR) between type 2 diabetes (T2D) patients using FSL and the app, and patients using solely the FSL. Secondary outcome was number of contact moments.

METHODS

Data were collected between June 2021 and March 2022 from T2D using FSL and app (intervention group) versus patients solely on FSL (control group). Data regarding demographic, clinical and treatment characteristics as well as number of scans per day with the FSL were mapped and compared between groups. TIR, TAR and TBR were measured at inclusion, 2, 4 and 6 months. The number of telephone/video consultations, outpatient visits and within app messages were mapped. Relation between contact moments and TIR was investigated.

RESULTS

Forty-two patients were included in both groups. At 4 and 6 months, TIR was higher in the intervention group ($p = 0.01$). At 4 and 6 months, TAR was significantly lower in the intervention group ($p \leq 0.02$). No significant differences were present for TBR between the groups. At 6 months, more telephone/video consultations were executed in the intervention group compared to control group ($p = 0.03$). Total number of contact moments was also higher in the intervention group ($p < 0.01$). No significant correlation was present between the number of contact moments and time in range ($p = 0.14$; $r = 0.19$).

CONCLUSION

Telemonitoring by using the app contributes to better glucose regulation, as reflected by higher TIR and lower TAR. Number of contact moments is higher in the app group. No correlation in contact moments and TIR was seen.
Future in-depth analyses is recommended to detect total healthcare consumption, costs and user experience.

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Islet yield and function after total pancreatectomy with islet autotransplantation

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BACKGROUND

For patients with benign pancreatic disease and an indication for total pancreatectomy, pancreatic endocrine function may be preserved by means of autologous islet transplantation. Islets can be isolated from the resected pancreas and transplanted intrahepatically. This will lead to more stable glycemic control with fewer hypoglycemic events and lower risk of vascular complications. Here, we report on our experience with TPIAT in the LUMC.

METHODS

Patients were referred to the LUMC for TPIAT and screened for eligibility. After pancreatectomy, the pancreas was digested via combined mechanical and enzymatic digestion in our Good Manufacturing Practice (GMP) facility. An islet purification step was necessary if there was a large volume of the digest. The islet cell preparation was infused into the liver after percutaneous transhepatic portal catheterization. Mixed meal tolerance tests (MMTT) were administered at baseline, 3

months and 1 year postoperatively to assess beta cell function.

RESULTS

We screened 29 patients and 18 patients were eligible for TPIAT. The indications were chronic pancreatitis (CP) (n = 15), necrotic pancreatitis following ERCP-related duodenal perforation (n = 2) and malformation of the superior mesenteric artery (n = 1) The mean age was 45.9 ± 12.8 years and 4 patients were male. Fourteen patients received a median of 4144 (IQR 2903-5173) islet equivalents per kilogram bodyweight (IEQ/kg). Patients with CP (n = 11) received fewer islets (median 3221; IQR 2508-3550 IEQ/kg) compared to patients without CP (n = 3; median 5324; IQR 5122-8912 IEQ/kg; p = 0.04). Maximum C-peptide secretion during MMTT at baseline was 2.06 ± 1.18 nmol/L. This decreased at 3 months post-TPIAT (0.81 ± 0.54; p < 0.01) but remained stable at 1 year post-TPIAT (0.78 ± 0.63; p = ns). Infusion of islets was not performed in 4 cases due to low islet yield (n = 2), high endotoxin concentration in the islet product (n = 1) and perioperative death due to cardiac ischemia (n = 1).

CONCLUSION

TPIAT is a viable method to (partially) preserve partial pancreatic endocrine function in patients with a pancreatectomy. Long-term pancreatitis results in islet damage and complicates islet isolation leading to reduced islet yield. Due to islet loss during islet isolation and transplantation, some endocrine function is lost. Therefore, discussions are warranted on the best timing for TPIAT.

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The SCD enzyme and ghrelin mediate the associations of plasma cysteine with obesity and insulin resistance: The Maastricht Study

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BACKGROUND

High plasma total cysteine (tCys) relates to obesity and type 2 diabetes. We examined whether underlying mechanisms might involve the stearoyl-CoA desaturase (SCD) enzyme and appetite/satiety hormones.

METHODS

Cross-sectional data from a subset of The Maastricht Study enriched with (pre)diabetes individuals (n = 1130, 49.4% women, 60 ± 8 yrs) were analyzed. Outcomes included BMI, waist circumference, total and limb fat mass, subcutaneous and visceral adipose tissues (SAT and VAT), Matsuda index and HOMA-IR. SCD-activity indices were estimated as product/precursor ratios of fatty acids in total serum lipids with 16C and 18C. Serum appetite (ghrelin) and satiety (PYY, GIP, GLP-1, PP) hormones were measured by immunoassays. SCD-activity indices and satiety hormones were combined in standardized scores. Mediation by SCD-activity or appetite/satiety hormones was examined in models with z-standardized fasting plasma tCys and adiposity measures, adjusting for potential confounders. Models with SCD-activity were further adjusted for serum triglycerides, which might affect serum SCD-activity indices; these analyses might however be overadjusted.

RESULTS

tCys associated with all outcomes (e.g., BMI [β = 0.27; 95% CI: 0.21,0.32], limb fat [0.27; 0.22, 0.33], VAT [0.14; 0.09, 0.19], Matsuda index [-0.19; -0.25, -0.13] and HOMA-IR [0.19; 0.13, 0.25]). SCD-activity partly explained all associations, with mediated effects (ME) ranging from 5.9% for limb fat to 19.7% for VAT. ME for ghrelin ranged from 2.4% for limb fat to 5.6% for VAT. No mediation by satiety hormones was found. After adjustment for triglycerides, mediation by SCD-activity became non-significant.

CONCLUSION

SCD-activity and ghrelin may represent two pathways by which plasma tCys relates to obesity and insulin resistance.

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Digital biomarkers to support personalized lifestyle and disease management in diabetes type 2

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BACKGROUND

Digital health technologies may support the management and the prevention of disease through personalized lifestyle interventions. Wearables and smartphones are increasingly used to derive digital biomarkers for continuous, non-invasive monitoring of lifestyle and diabetes in everyday life. The challenge is to come to meaningful, reliable digital biomarkers that can be combined to actually support diabetes management and prevention. Here we present three examples of digital biomarkers based on multimodal wearable tracking.

METHODS

First of all, a healthy volunteer study with 24 participants was performed to continuously monitor glucose, food, activity and sleep over a period of 14 days. Gradient boosting machine was applied to derive two digital biomarkers from this study. A first digital biomarker was developed for eating moment detection from continuous glucose monitor and activity data. A second digital biomarker was developed to predict continuous glucose data from macronutrient intake, activity, sleep, and cardiometabolic features collected from a wearable. Explainable AI was applied to derive personalized insights into factors driving glucose peaks. Additionally, a subset of data from the GlucoInsight study was used to develop another type of digital biomarkers.

RESULTS

Forty people with diabetes type 2 underwent a personalized nutrition intervention. An oral glucose tolerance test was performed at three visits, while continuous glucose monitoring was applied around the visits (after intervention stopped). Fasting glucose, 2 hour glucose and insulin resistance indices were derived from the oral glucose tolerance test. Gradient boosting machine was applied to predict these metrics from the multi-day continuous glucose monitoring data.

CONCLUSION

Pending further validation and combination of these digital biomarkers in ehealth solutions, they show promise in supporting the prevention and management of type 2 diabetes through personalized lifestyle recommendations.

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The inflammatory response to hypoglycaemia occurs largely independent of prior exposure to hypoglycaemia in humans

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BACKGROUND

Prior exposure to hypoglycaemia attenuates the adrenaline response to subsequent hypoglycaemia. To what extent this affects the pro-inflammatory response induced by hypoglycaemia is unclear. We investigated the effect of antecedent hypoglycaemia on inflammatory responses to a subsequent hypoglycaemic event.

METHODS

Healthy participants (n = 32) were recruited and randomized to two 2-hour episodes of hypoglycaemia (HYPO-group) or normoglycaemia (NORMO-group) on day 1. All participants underwent a hyperinsulinaemic-hypoglycaemic (2.8 ± 0.1 mmol/l) glucose clamp on day 2. At the end of normoglycaemia, during hypoglycaemia and after 1, 3 and 7 days, blood was drawn to determine immune cell composition and 93 inflammatory proteins including hs-CRP.

RESULTS

In the HYPO-group, the adrenaline response to next-day hypoglycaemia was blunted. Granulocyte, lymphocyte and monocyte counts increased with $1.2x10^3$, $1.2x10^3$ and $0.3x10^3$ in the NORMO-group and with $0.4x10^3$/ml, $1.0x10^3$/ml and $0.2x10^3$/ml in the HYPO-group (all p <

0.05 compared to baseline), respectively, and remained elevated up to one week. The proportion of pro-inflammatory CD16^{+}-monocytes increased with 18.2% in the NORMO-group and 14.0% in the HYPO-group ($p < 0.001$ compared to baseline). Finally, hypoglycaemia increased the levels of 18 circulating inflammatory proteins after 1 day in both groups FDR < 0.05. After 7 days, 11 proteins were elevated in HYPO, whereas 36 proteins were elevated in the NORMO-group FDR < 0.05. In the NORMO-group, but not in the HYPO-group, hs-CRP increased from 1.09 to 1.49 ug/ml ($p < 0.001$) and remained elevated for one week. Although the direct inflammatory response to hypoglycaemia was similar, the persistent response including hs-CRP and circulating inflammatory proteins was blunted in the HYPO-group.

CONCLUSION

The acute response to hypoglycaemia occurs independent of prior exposure to hypoglycaemia and the release of adrenaline, whereas the persistent response to hypoglycaemia is partly blunted.

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IgG N-glycans are associated with prevalent and incident complications of type 2 diabetes

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BACKGROUND

Inflammation is important in development of type 2 diabetes (T2D) complications. The N-glycosylation of IgG influences its role in inflammation. Until now, the association of plasma IgG N-glycosylation with T2D complications has not been extensively investigated. We hypothesized that N-glycosylation of IgG is related to development of complications of T2D.

METHODS

In three independent T2D cohorts, plasma IgG N-glycosylation was measured by UPLC (DiaGene n = 1815, GenodiabMar n = 640) and mass spectrometry (DCS n = 1266). We investigated the associations of IgG N-glycosylation (fucosylation, galactosylation, sialylation and bisection) with incident and prevalent nephropathy, retinopathy and macrovascular disease using Cox- and logistic regression, followed by meta-analyses. Models were adjusted for age, sex and additionally for clinical risk factors.

RESULTS

IgG galactosylation negatively associated with prevalent and incident nephropathy after adjustment for clinical risk factors. Sialylation was negatively associated with incident diabetic nephropathy. For retinopathy, similar associations were found for galactosylation in the basic model. For macrovascular complications, negative associations with galactosylation and sialylation were confined prevalent cases.

CONCLUSION

We showed that IgG N-glycosylation traits associate with prevalence and future development of nephropathy, after correction for clinical risk factors. For other complications, IgG N-glycosylation associated with prevalence only, possibly reflecting ongoing vascular inflammation. This fuels future studies to look further into the underlying mechanisms and predictive potential of IgG N-glycosylation for diabetes complications.

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Using a complex carbohydrate mixture and a high-protein DIet to STeer fermentation and improve metabolic, gut and brain heALth: the DISTAL-study design

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BACKGROUND

Our gut microbiome plays an important role in the etiology of obesity and obesity-related disorders. The colonic microbiota ferments indigestible dietary fibers and proteins, yielding saccharolytic products (e.g. short-chain fatty acids (SCFA)) or proteolytic products (branched-chain fatty acids, BCFA) that, respectively, positively or negatively affect human metabolic, gut and brain health. We previously demonstrated that acute SCFA infusion to the distal, but not the proximal, colon, has positive effects on human substrate and energy metabolism. Here, we hypothesize that a fibre mixture that increases distal saccharolytic fermentation, thereby inhibiting distal proteolytic fermentation, increases distal SCFA production and improves metabolic, immune and brain health.

METHODS

The aim of this project is, firstly, to define a complex fiber mixture that increases saccharolytic and reduces proteolytic fermentation throughout the colon and, secondly, to study the impact of this microbial substrate switch on metabolic, immune and brain health.
First, we carried out in vitro experiments using the TIM-2 model, a computer-controlled dynamic model simulating colonic fermentation, using a standardized pooled microbiota from individuals with overweight/obesity and insulin resistance (resembling the target population of the clinical trial). Potato fiber, chicory inulin and sugar beet pectin were tested separately and in different combinations against a high protein background. The combination of potato fiber and sugar beet pectin showed the highest distal SCFA to BCFA production ratio.

RESULTS

This fiber combination will be tested in vivo in a double-blind, randomized, placebo-controlled trial in 44 humans with overweight (BMI 28-40 kg/m^2) and insulin resistance (Fasting glucose 5.6-6.9mmol/l; HbA1c 42-47mmol/mol; HOMA-IR > 2.2). This 12-week intervention consists of fiber (15 g) or maltodextrin placebo ingestion against a high-protein background (25E%, 45% plant-based). Primary outcome will be the change in peripheral insulin sensitivity. Furthermore, hepatic and adipose tissue insulin sensitivity, inflammatory profile, microbiome composition and functionality, and neurocognitive functioning will be analyzed.

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Comparison of measures of adherence and wearing time of prescribed footwear among people at risk of diabetes-related foot ulcers

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BACKGROUND

Adherence to wearing prescribed footwear is essential to prevent the development of diabetes-related foot ulcers. However, studies have used different measures of adherence, which makes the results difficult to compare. The purpose of this study was to compare different measures of adherence of prescribed footwear among people at high risk of diabetes-related foot ulcers.

METHODS

Forty participants (9 women, mean 63.9 years) were followed for seven consecutive days. A temperature sensor measured wearing time of prescribed footwear and an accelerometer assessed daily weight-bearing activities. The reference measure of adherence was proportion of weight-bearing time prescribed footwear was worn. Subjective wearing time was rated on a 5-level scale. We calcu-

lated Spearman's correlation coefficients, Kappa coefficients with quadratic weights (where adherence and wearing time measures were split into 5 categories) and areas under the curve (AUC) for the association between the reference measure of adherence and the other measures of adherence and wearing time. When calculating the AUC, the reference adherence measure was dichotomized into high and low adherence, using 60%, 70%, 80% and 90% as cut-offs.

RESULTS

Proportion of steps that the prescribed footwear was worn had a very strong association (r = 0.96; K = 0.911; AUC = 0.968-0.997), objective wearing time had a strong association (r = 0.80; K = 0.809; AUC = 0.848-0.952) and subjective wearing time had a weak association (r = 0.28; K = 0.373; AUC = 0.572-0.769) with the reference measure of adherence. This pattern was consistent for correlation coefficients, kappa values and AUC.

CONCLUSIONS

Objectively measured proportion of daily steps with prescribed footwear is a valid measure of footwear adherence. Objectively measured wearing time is reasonably valid, and may be used in clinical practice and for long-term measurements as wearing time monitors typically can record and store data for longer times than accelerometers. Subjective wearing time is not recommended to be used.

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Healthcare needs of adults with type 1 diabetes considering, in transfer to, using or formerly building/using open-source artificial pancreas systems

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BACKGROUND

This qualitative study examined the healthcare needs of adults with type 1 diabetes (T1D) in the context of open-source Artificial Pancreas Systems (open-source APS).Methods: Topics of the semi structured interviews were: barriers/facilitators, (previous) interaction with healthcare professionals (HCPs), (ideal) image of future diabetes care. Individual and thematic content analyses were conducted (open, axial, selective coding). Inclusion ended when data saturation was attained.

METHODS

In total, 24 adults with T1D (n = 10 female, n = 1 non-binary) participated. Five considered, five transferred to, 10 used and four formerly built/used open-source APS. Twenty participants used pumps, all used sensors: 11 intermittently scanned Continuous Glucose Monitoring (CGM), 13 real-time CGM. Age and diabetes duration (M ± SD) were 37 ± 13 and 20 ± 13 years. HbA1c was 6.5 ± 0.7% (47.9 ± 7.2 mmol/mol).

RESULTS

Peer support and instruction clarity were common facilitators towards open-source APS, absence of professional guidance and information overload were barriers. Those considering or transferring mostly preferred close monitoring by HCPs while (former) users tended to prefer independence. Overall, need for personalized diabetes care and freedom of choice was expressed. Given the advantages of open-source systems over commercial systems, open-source APS were predominantly perceived as superior. Therefore, participants believed their usage would continue in the future. As for the orientation and starting phases, participants hoped for more technological assistance and support by HCPs. Participants acknowledged several practical and legal barriers to the integration of open-source APS in diabetes care, such as limited reimbursement, lack of manufacturer support, technical complexity and HCP liability.

CONCLUSION

Healthcare needs differed according to the previous experience of the person with diabetes and their HCPs. Further examination of HCP views on (collaboration in diabetes care with) individuals involved in open-source APS is recommended.

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Two-year Effect of Semaglutide 2.4 mg on Control of Eating in Adults with Overweight/Obesity: STEP 5

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Prof. dr. Mireille Serlie, Department of Endocrinology and Metabolism, University of Amsterdam, is presenting on behalf of the authors.

BACKGROUND

The STEP 5 trial investigated once-weekly subcutaneous semaglutide 2.4 mg vs placebo for the treatment of overweight/obesity in adults over 2 years.

METHODS

Adults with BMI ≥ 30 kg/m2, or ≥ 27 kg/m2 and ≥ 1 weight-related
comorbidity, without diabetes, were randomized 1:1 to semaglutide 2.4 mg once-weekly or placebo for 104 weeks. Co-primary endpoints related to body weight (BW) changes. Control of eating questionnaire (CoEQ) was assessed in a Canada/USA subgroup, with scores from 19 individual items grouped into 4 domains: craving control, craving for savory, craving for sweet, or positive mood. P-values for exploratory CoEQ data are unadjusted for multiplicity.

RESULTS

304 adults were randomized (78% female, mean age 47 years, BW 106.0 kg, BMI 38.5 kg/m^2). Semaglutide significantly reduced BW from baseline to week 104 vs placebo (ETD: −12.6% [95% CI: -15.3, -9.8]; $p < 0.0001$). In participants completing CoEQ with semaglutide (n = 88) vs placebo (n = 86), all 4 domain scores significantly improved at week 20 and 52 (all $p < 0.05$). At week 104, craving control and craving for savoury domains remained significantly improved with semaglutide vs placebo ($p < 0.01$); positive mood and craving for sweet were not statistically significant. Scores for the following individual craving-related items were significantly reduced from baseline with semaglutide vs placebo at week 104: desire to eat salty and spicy food, craving for dairy food, craving for starchy food, difficulty in resisting cravings, and difficulty in control of eating (all $p < 0.05$). Scores for hunger and fullness improved with semaglutide vs placebo at week 20, 52 and 104, but differences were only significant at week 20 ($p < 0.001$ for both).

CONCLUSION

In adults with overweight/obesity, substantial weight loss with semaglutide 2.4 mg was accompanied by short- and long-term improvements in control of eating vs placebo, with greatest effect on craving control and craving for savoury foods.

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Accelerometer-derived physical activity and sedentary time and cardiac biomarkers: The Maastricht Study

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BACKGROUND

Cardiac troponins and NT-proBNP are biomarkers of cardiac injury that are used clinically in the diagnosis of myocardial infarction and heart failure. It is not known whether the amount, types and patterns of physical activity and sedentary time are associated with levels of cardiac biomarkers.

METHODS

In the population-based Maastricht Study (n = 2370, 51.3% male, 28.3% T2D) we determined cardiac biomarkers hs-cTnI, hs-cTnT, and NT-proBNP. Physical activity and sedentary time were measured by activPAL and divided into quartiles (quartile1 (Q1) served as reference). The weekly pattern of moderate-to-vigorous physical activity (MVPA) (insufficiently active; regularly active; weekend warrior) and coefficient of variation (CV) was calculated. Linear regression analyses were conducted with adjustment for demographic, lifestyle, and cardiovascular risk factors.

RESULTS

Higher amounts of total physical activity were associated with lower levels of hs-cTnI (Q2) and hs-cTnT (Q2). Higher levels of light intensity physical activity were associated with lower levels of hs-cTnI (Q2,Q3) and with higher levels of hs-cTnT (Q4). Those with the highest lev-

els of vigorous intensity physical activity had significantly higher levels of hs-cTnI and lower levels of NT-proBNP. Compared to the least sedentary, Q3 had significantly lower levels of hs-cTnI and, Q2 and Q3 had lower levels of hs-cTnT. With regard to physical activity patterns, weekend warriors and regularly actives had lower levels of NT-proBNP but not with hs-cTnI and hs-cTnT compared with insufficiently actives. A higher weekly MVPA CV (indicating more irregular activity) was associated with lower levels of hs-cTnI and higher levels of NT-proBNP, but not with hs-cTnT. Similar associations were found in those with and without T2D.

CONCLUSION

In general (for individuals with and without T2D), there is no association between physical activity and sedentary time and cardiac troponins. In contrast, vigorous and possibly MVPA, especially if done regularly, is associated with lower levels of NT-proBNP.

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Potential genetic determinants for impaired awareness of hypoglycaemia in people with diabetes: Genome-wide association meta-analyses

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BACKGROUND

We wanted to investigate potential genetic determinants of impaired awareness of hypoglycaemia (IAH) in individuals with diabetes mellitus.

METHODS

Genome-wide association meta-analyses were conducted for the presence of IAH, the clamp-validated Dutch modified Clarke questionnaire score, and the blood glucose before patients feel hypoglycaemia symptoms. Three independent cohorts were involved including the Radboud University Medical Center type 1 diabetes cohort, the Biomarkers of heterogeneity in type 1 diabetes cohort, and the type 2 diabetes Dutch Diabetes Pearl cohort. DNA samples were genotyped with the Illumina GSA v1 or v3 chip, imputed with HRC as reference, and meta-analysed using METAL.

RESULTS

A total of 1,087 patients with type 1 and 1,734 patients with type 2 diabetes were included. In individuals with type 1 diabetes a SNP on chromosome 5 coding for the gene CTC-546K23.1 reached genome-wide significance for the question "How low is your blood glucose before you feel hypoglycaemia symptoms?" ($p = 3.32e-8$). Although a function has yet to be described, GTEx (v8) expression data shows higher expression in brain-related tissue. In the meta-analyses for the presence of IAH and the Clarke score no genome-wide significant SNPs were found. However, SNPs of potential genome-wide interest ($p < 5e-6$) were identified, and lead SNPs mapped to protein-coding genes. Enrichment analysis of genes mapped with SNPs of genome-wide interest revealed some potentially enriched KEGG and Reactome pathways, as well as gene ontology (GO) terms. Amongst the enriched pathways were those involving neural regulation and development, and genes involved in the renin-angiotensin system. Similarly, enriched GO terms included processes of neural development and regulation, and regulation of systemic arterial blood pressure.

CONCLUSION

Genome-wide association meta-analyses of IAH show potential genetic determinants of IAH, particularly in people with type 1 diabetes. Pathways involved may include neural development and blood pressure regulation.

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Glucose-insulin responses following meal- and oral glucose tolerance tests during early and late pregnancy in overweight women

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**Shared first authorship*

BACKGROUND

During pregnancy, insulin sensitivity decreases to ensure a continuous supply of nutrients to the fetus. Higher pre-pregnancy BMI is linked to decreased insulin sensitivity and increases the risk of developing gestational diabetes (GDM). We investigated maternal glucose, insulin and C-peptide responses to meal tolerance tests (MTT) during pregnancy in overweight women. The aim of the study is to provide earlier prediction of changes in insulin sensitivity.

METHODS

Pregnant women with BMI ≥ 25 kg/m^2 were tested for postprandial responses between week 12-16 (MTT1), week 24-25 (MTT2) and week 26-27 of gestation (OGTT). Glucose, insulin and C-peptide were measured fasted (t = 0) and postprandial (T = 10, 20, 30, 45, 60, 90, 120 minutes) following an MTT (50 grams carbohydrate, protein, fats) or an OGTT (75 grams glucose).

RESULTS

The results of 25 tolerance tests from 10 participants were analyzed. One woman developed GDM based on 2h-OGTT, as well as the 1h-MTT2 value. Postprandial glucose, insulin and C-peptide responses were largely comparable between MTT1 and MTT2. Fasting glucose was equal at each test (4.6 mmol/l). Fasting insulin and C-peptide levels increased between MTT1 (6.3 ± 4.8 uU/mL and 481 ± 199 pmol/L) and MTT2 (9.6 ± 4.1 uU/ml and 608.4 ± 220.6 pmol/l), postprandial insulin responses remained unchanged. In contrast, C-peptide responses were equal between MTT1 and MTT2 (2790 ± 1012), but higher following the OGTT (3643 ± 1269, $p = 0.019$). Fasting glucose, insulin and C-peptide were highly correlated between early (MTT1) and late (OGTT) second trimester (glucose $r = 0.93$; insulin $p < 0.01$, $r = 0.98$; $p < 0.001$, C-peptide $r = 0.93$; $p < 0.01$) .

CONCLUSION

This exploratory analysis indicates that fasting insulin and C-peptide levels in early pregnancy may be superior to glucose in detecting decreased insulin sensitivity and the risk of developing pathological glucose responses in later pregnancy.

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Comparing a non-removable total contact cast with a non-removable softcast in diabetic foot ulcers: A retrospective study of a prospective database

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**presenting author*

BACKGROUND

Pressure offloading is an essential part of diabetic foot ulcer treatment, for which non-removable total contact casts are considered the gold standard. However, in clinical practice, these are rarely used due to negative effects on lifestyle and transportation. As an alternative, non-removable total contact softcast was introduced. This study was conducted to investigate treatment outcomes of non-removable total contact softcasts in comparison to conventional total contact casts.

METHODS

Retrospective analysis of prospectively collected data for 2010-2017. Included were patients with neuropathic diabetic forefoot ulcers. Patients with ischemic diabetic foot ulcers, non-plantar diabetic foot ulcers, Charcot arthropathy, and compliance issues were excluded. Patients treated with total contact softcasts were compared to patients treated with conventional total contact casts. Primary and secondary outcomes were ulcer healing ratio and ulcer healing time.

RESULTS

50 patients with 61 cast periods were included. Mean age was 63.7 ± 10.1 years. Overall ulcer healing was 71% (43/61). Except for depth of the diabetic foot ulcers, between-group patient characteristics were comparable; deeper diabetic foot ulcers were reported in the conventional total contact cast group. This group reported 65% healed diabetic foot ulcers (22/34), and the total contact softcast group reported 74% healed diabetic foot ulcers (20/27). Mean healing time was 8.4 weeks (95% CI 5.9-10.8) for conventional total contact casts and 5.5 weeks (95% CI 4.2-6.9) for total contact softcasts (p = 0.052). Ulcer depth was a confounder.

CONCLUSION

Total contact softcast offloading had a similar healing ratio and a potentially clinically relevant effect (Hazard ratio 1.47, 95% CI 0.64-3.38) on healing time (ns). Ulcer depth is important for time to ulcer healing. A randomized study is recommended.

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Metabolic effects of acute circadian desynchronization

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BACKGROUND

Shift workers have an increased risk to develop type 2 diabetes. Recently, a human study showed that an acute 12 hour phase shift has acute negative effects on muscle insulin sensitivity at the onset of the active period. To disentangle the underlying neuroendocrinological and metabolic mechanisms we subjected rats to acute circadian desynchronization.

METHODS

First, male Wistar rats were placed in metabolic cages for 3 days in a 12 hour light: 12 hour dark (LD) cycle with standard chow available ad libitum. Then a complete LD reversal (12 hour: 12 hour DL cycle) was DONE from day 4 in three different feeding time groups. Food and water intake, locomotor activity and RER were measured continuously. In a second experiment with food available ad libitum, jugular vein cannulation surgery was performed in rats, and 7-10 days later an intravenous glucose tolerance test (ivGTT) was performed at Zeitgeber Time 2 (ZT2) and ZT14. After 7-10 days rats underwent a complete 12 hour phase LD reversal, and after 3 days the ivGTTs were repeated.

RESULTS

The inverted LD cycle leads to an expected gradual adaptation of the daily rhythms in rats. Rats adapt their rhythm of locomotor activity faster to the inverted LD cycle compared to their rhythms of food and water intake. Food-restriction to the light period reduces the adaptation speed of the daily rhythm in locomotor activity. Nonetheless, the glucose tolerance test showed that the daily rhythm of glucose tolerance had returned to normal in three days after the LD reversal.

CONCLUSION

Our results indicate that locomotor activity in itself is not a sufficient marker of internal time after a phase shift, since the rhythms of food intake and energy expenditure take longer to adapt to the new schedule. In contrast, the daily rhythm of glucose tolerance has adapted within three days of inversed light exposure.

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Bone endocrine factor – Osteocalcin, Advanced glycation end products and type 2 diabetes mellitus – a low-profile step in the pathophysiology

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BACKGROUND

Advanced glycation end products (AGEs) have been implicated in the pathophysiology of type 2 diabetes mellitus (T2DM) and might potentiate the risk of T2DM also indirectly through affecting osteocalcin (OC) release from bone. However, no studies have been performed in this regard. We wanted to investigate whether there is an association between OC and AGEs and whether low OC and higher AGEs are associated with a higher risk of T2DM than either alone.

METHODS

Serum total OC and soluble receptor for AGE (sRAGE - a decoy receptor for AGEs) were measured at baseline. Skin AGEs were measured on average 11.5 years later using an AGE reader as skin autofluorescence (SAF). 2388 community-dwelling participants with SAF and 731 with sRAGE measurements were included from the Rotterdam Study. Linear regression was used to explore the association between SAF/sRAGE (as AGEs marker) and OC. Logistic regression was performed to explore the association between subjects with prevalent T2DM and low OC, high SAF (based on median/mean values). All analyses were adjusted for age, sex, cohort effect, renal function, smoking, vitamin D and BMI.

RESULTS

Higher SAF was associated with lower OC [β = -0.041, p = 0.04] even after excluding baseline T2DM. Higher sRAGE was associated higher OC [β = 0.111, p = 0.004]. When we used subjects with low SAF and high OC as reference, subjects with low OC, high SAF showed highest odds ratios (OR) for T2DM prevalence [2.70 (1.87-3.91)] when compared with high OC, high SAF [OR = 1.70 (1.14-2.54)] and low OC, low SAF [OR = 2.07 (1.41-3.03)], p-value for trend < 0.01.

CONCLUSION

AGE markers were associated with OC. Subjects with both low OC and high SAF have higher T2DM prevalence than other categories. Future studies should focus on the synergistic effect of OC and AGEs in better understanding their role in the pathophysiology of T2DM.

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Digital Acceleration Time (DAT), a novel method to detect ischemia in lower extremity arterial disease

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BACKGROUND

Calcification of the digital arteries is present in a majority of patients with diabetic foot syndrome, causing a false-high toe pressure value, impeding vascular diagnostics. Furthermore, measurement of toe pressure may be hampered by wounds or minor amputations. Acceleration time is a new parameter measured in an arterial pulse-wave curve, timing from the start of systole to the point of maximum flow. We investigated the prognostic value of the Digital Acceleration Time (DAT) from the photoplethysmographic pulse waveforms available in standard toe pressure measurements.

METHODS

This is a single center retrospective study of patients with toe pressure measurements in the years 2017-2018. DAT were measured from pulse waves in the toe pressure report. Threshold values for DAT were based on 90% sensitivity and 90% specificity in predicting 1 year major adverse limb events (MALE). Kaplan Meier survival analysis was performed for MALE-free-survival. Subgroup analysis of patients with an inability for toe pressure measurement was also performed.

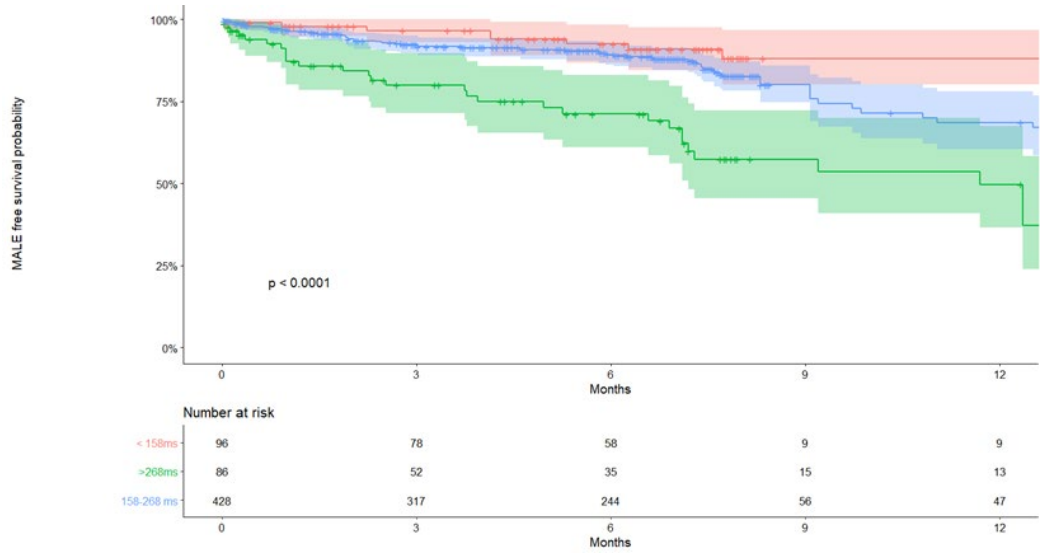

Figure 10.
MALE-free survival differed significantly with 88.2%, 68.6% and 49.7% for short, medium and long acceleration times.

Table 4. Measurements in 400 patients were analyzed.

	<158 ms (n=96) (90% spec)	158-268 ms (n=428)	>268 ms (n=86) (90% sens)	P-value
Leeftijd	66.1 (13.7)	71.8 (11.8)	76.5 (10.9)	< 0.001
Man (%)	67.7%	68.7%	57.0%	NS
Teendruk	123.5 (39.4)	101.5 (40.0)	90.3 (40.0)	< 0.001
Gecalcificeerde vaten (%)	23.3%	23.2%	26.0%	NS
GermanVasc score	7.9 (6.5)	10.2 (6.6)	12.6 (5.8)	< 0.001
WIFI				0.002
1	69.8%	68.5%	46.5%	
2	9.4%	15.9%	25.6%	
3	11.5%	9.6%	14.0%	
4	9.4%	6.1%	14.0%	
GLASS (n=125)	N=17	N=30	N=78	0.016
0	58.8%	46.2%	20.0%	
1	23.5%	30.8%	23.3%	
2	5.9%	12.8%	36.7%	
3	11.8%	10.3%	20.0%	
1 year Major Adverse Limb Event –free survival	88.2%	68.6%	49.7%	< 0.001

RESULTS

Six-hundred-thirteen measurements in 400 patients were analyzed in 3 groups based on DAT < 158 ms (n = 96, 90% sensitivity MALE), 158-268 ms (n = 428) and > 268 ms (n = 86, 90% specificity MALE). Patient characteristics differed significantly for age, absolute toe pressure, GermanVasc-, WIfI- and GLASS-score, all being worse in the longer acceleration time groups (table 1). MALE-free survival differed significantly with 88.2%, 68.6% and 49.7% for short, medium and long acceleration times respectively (p < 0.001, **Figure 10**). In 46 patients (8%) no toe pressure measurement were possible. A DAT of > 268 ms was again a significant predictor of 1-year MALE-free survival (30% vs 80%, p = 0.014)

CONCLUSION

Digital Acceleration Time accurately predicts 1-year major adverse limb events. Future prospective studies should define optimal threshold values.

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Effects of Short-Term Potassium Chloride Supplementation in Patients with Chronic Kidney Disease

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Keywords: Acidosis; Albuminuria; Blood pressure; Clinical trial; Hyperkalemia

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BACKGROUND

Observational studies suggest that adequate dietary potassium intake (90-120 mmol/day) may be renoprotective, but the effects of increasing dietary potassium and the risk of hyperkalemia are unknown.

METHODS

This is a prespecified analysis of the run-in phase of a clin-

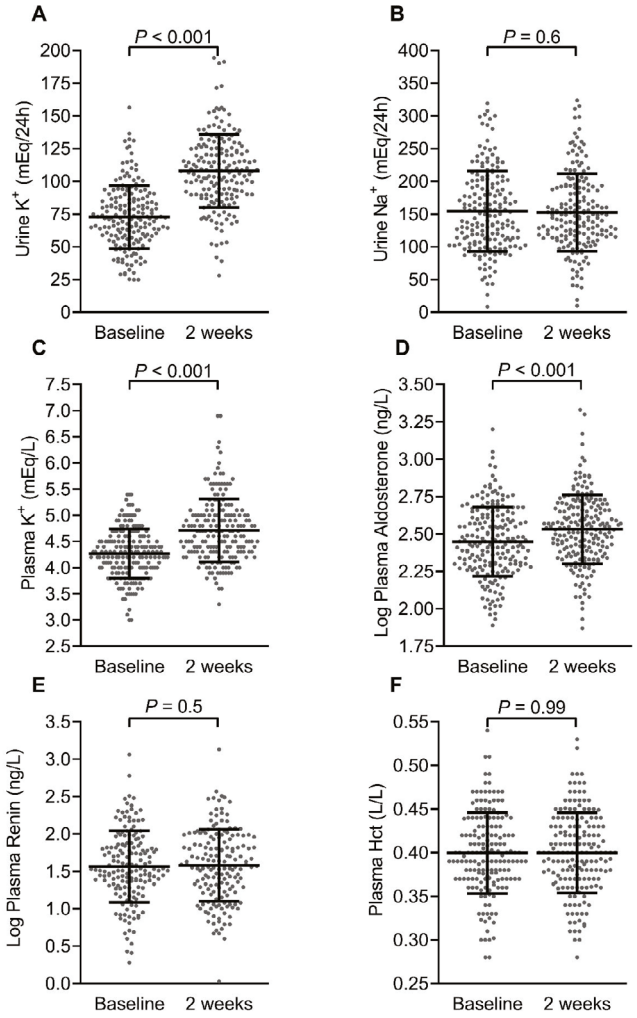
Table 5. Baseline characteristics associated with a change in plasma potassium after KCl supplementation.

Variable	Univariable regression		Multivariable regression	
	β (95% CI)	*P*-value	β (95% CI)	*P*-value
Female sex	0.1 (-0.02, 0.2)	0.1	0.08 (-0.05, 0.2)	0.2
Age, years	0.007 (0.001, 0.012)	0.01	0.006 (0.001, 0.01)	0.03
Diabetes mellitus	0.1 (-0.003, 0.2)	0.06	0.06 (-0.05, 0.2)	0.3
Renin-angiotensin inhibitor use	0.1 (-0.05, 0.3)	0.2	0.2 (0.08, 0.4)	0.004
Beta blocker use	0.1 (0.02, 0.3)	0.02	0.1 (-0.02, 0.2)	0.03
Diuretic use	-0.1, (-0.2, 0.008)	0.07	-0.2 (-0.3, -0.05)	0.004
Plasma potassium, mmol/L	-0.07 (-0.2, 0.05)	0.3	-0.3 (-0.4, -0.1)	<0.001
Plasma bicarbonate, mmol/L	-0.02 (-0.04, -0.005)	0.01	-0.02 (-0.04, -0.001)	0.04
eGFR, mL/min/1.73 m2	-0.009 (-0.02, -0.003)	0.01	-0.009 (-0.02, -0.002)	0.01
Urine potassium, mmol/day	-0.004 (-0.006, -0.001)	0.004	-0.002 (-0.005, 0.001)	0.08

Table 6. Comparison between patients who remained normokalemic and who developed hyperkalemia after KCl supplementation.

Characteristic	Normokalemia (n = 170)	Hyperkalemia (n = 21)	P-value
Female sex, n (%)	44 (26)	6 (29)	0.8
Age, years	67 ± 11	74 ± 8	0.01
Diabetes mellitus, n (%)	61 (36)	11 (52)	0.1
Renin-angiotensin inhibitor use, n (%)	138 (82)	20 (95)	0.1
Beta blocker use, n (%)	65 (38)	11 (52)	0.2
Diuretic use, n (%)	78 (46)	4 (19)	0.02
Baseline plasma potassium, mmol/L	4.2 ± 0.4	4.9 ± 0.4	< 0.001
Baseline plasma bicarbonate, mmol/L	24.7 ± 3.4	22.5 ± 3.5	0.01
Baseline eGFR, mL/min/1.73 m2	33 ± 9	24 ±8	< 0.001
Baseline urine potassium excretion, mmol/day	74 ± 25	66 ± 16	0.05

Figure 11. Effects of KCl supplementation on plasma and urine electrolytes, the renin-angiotensin system, and hematocrit



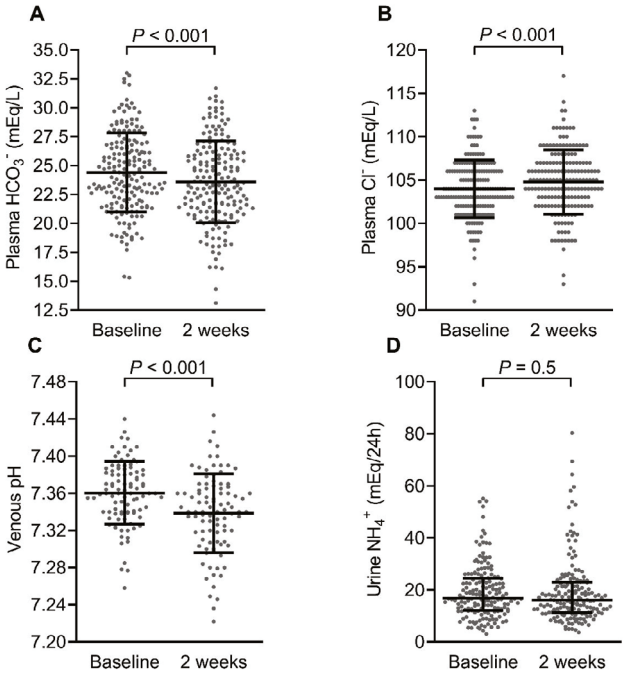
Effects of 40 mmol KCl supplementation for two weeks on (A) urine potassium (K+) excretion, (B) urine sodium (Na+) excretion, (C) plasma potassium (K+), (D) plasma aldosterone, (E) plasma renin, and (F) hematocrit (Hct). Data before and after KCl supplementation are shown in 191 patients. Data were analyzed by paired T-test.

ical trial in which 191 patients (age68 +/-11 years, 74% males, 86% European ancestry, eGFR 3169 ml/min per 1.73 m^2, 83% renin-angiotensin system inhibitors, 38% diabetes) were treated with 40 mmol potassium chloride (KCl) per day for 2 weeks.

RESULTS

KCl supplementation significantly increased urinary potassium excretion (72 +/- 24 to 107 +/- 29 mmol/day), plasma potassium (4.3 +/- 0.5 to 4.7 +/- 0.6 mmol/L), and plasma aldosterone (281 [198-431] to 351 [241-494] ng/L), but had no significant effect on urinary sodium excretion, plasma renin, BP, eGFR, or albuminuria. Furthermore, KCl supplementation increased plasma chloride (104 +/- 3 to 105 +/- 4 mmol/L) and reduced plasma bicarbonate (24.5 +/- 3.4 to 23.7 + /- 3.5 mmol/L) and urine pH (all p < 0.001), but did not change urinary ammonium excretion. In total, 21 participants (11%)

Figure 12. Effects of KCl supplementation on acid-base parameters.



Effects of 40 mmol KCl supplementation for two weeks on (A) plasma bicarbonate (HCO3-), (B) plasma chloride (Cl-), (C) venous pH, and (D) urine ammonium (NH4+) excretion. Data before and after KCl supplementation are shown in 191 patients (A, B, D) and 94 patients. Data were analyzed by paired T-test.

Table 7. Baseline characteristics associated with the development of hyperkalemia after KCl supplementation

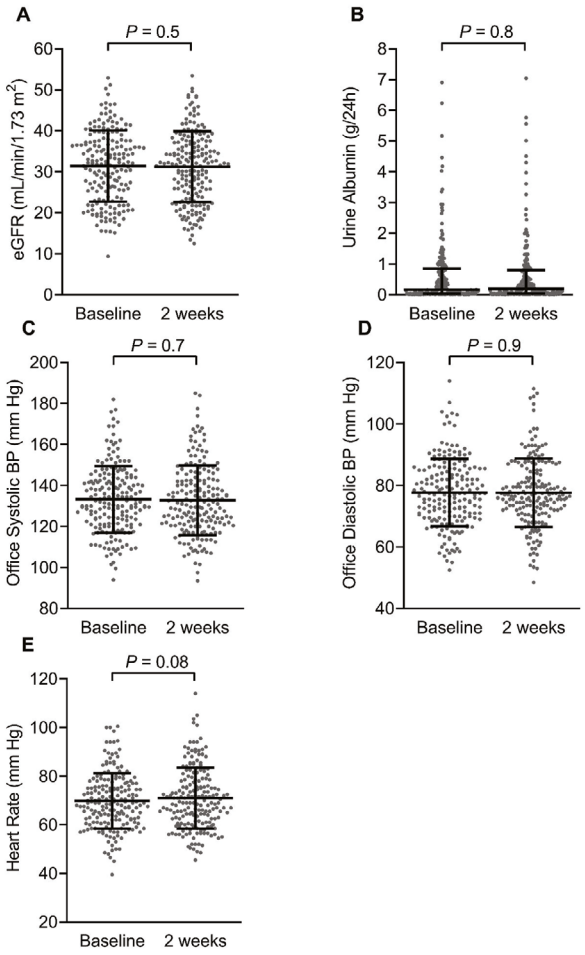
Variable	Univariable regression		Multivariable regression	
	β (95% CI)	P -value	β (95% CI)	P-value
Age, years	1.1 (1.0, 1.1)	0.01	1.1 (1.0, 1.2)	0.03
Baseline plasma potassium, mmol/L	51.0 (11.1, 232,9)	< 0.001	45.1 (6.8, 300.2)	< 0.001
Baseline plasma bicarbonate, mmol/L	0.8 (0.7, 1.0)	0.01	1.0 (0.8, 1.2)	1.0
Baseline eGFR, mL/min/1.73 m2	0.9 (0.8, 0.9)	< 0.001	0.9 (0.9, 1.0)	1.0
Beta blocker use, n (%)	65 (38)	11 (52)	0.2	
Diuretic use, n (%)	78 (46)	4 (19)	0.02	
Baseline plasma potassium, mmol/L	4.2 ± 0.4	4.9 ± 0.4	< 0.001	
Baseline plasma bicarbonate, mmol/L	24.7 ± 3.4	22.5 ± 3.5	0.01	
Baseline eGFR, mL/min/1.73 m2	33 ± 9	24 ±8	< 0.001	
Baseline urine potassium excretion, mmol/day	74 ± 25	66 ± 16	0.05	

developed hyperkalemia (plasma potassium 5.960.4 mmol/L). They were older and had higher baseline plasma potassium.

CONCLUSION

In patients with CKD stage G3b-4, increasing dietary potassium intake to recommended levels with potassi-

Figure 13. Effects of KCl supplementation on kidney function and blood pressure.



Effects of 40 mmol KCl supplementation for two weeks on (A) estimated glomerular filtration rate (eGFR), (B) urine albumin excretion, (C) office systolic blood pressure, (D) office diastolic blood pressure, and (E) heart rate. Data before and after KCl supplementation are shown in 191 patients. Data were analyzed by paired T-test.

um chloride supplementation raises plasma potassium by 0.4 mmol/L. This may result in hyperkalemia in older patients or those with higher baseline plasma potassium. Longer-term studies should address whether cardiorenal protection outweighs the risk of hyperkalemia.

Clinical trial number: NCT03253172

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Increased methylglyoxal formation in plasma and tissues during a glucose tolerance test originates from exogenous glucose and is enhanced in diabetes

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BACKGROUND

The dicarbonyl compound methylglyoxal (MGO) is the major precursor of advanced glycation endproducts and linked to diabetes and its vascular complications. We have previously shown that plasma MGO is increased postprandially and that this is enhanced in individuals with type 2 diabetes (T2D). We now investigated whether postprandial MGO formation in plasma and tissues originates from exogenous glucose, and whether these changes are affected by T2D.

METHODS

In humans, we performed an oral glucose tolerance test

(OGTT) with universally labelled D(+)^{13}C glucose in 12 healthy males. Analysis of labelled and unlabelled plasma MGO and glucose levels at eleven time-points during the OGTT revealed that the newly formed MGO during OGTT is completely derived from exogenous glucose. In C57BL/6J and db/db mice, we performed an intraperitoneal GTT (IPGTT) with universally labelled D(+)^{13}C glucose. Blood, pancreas, liver, spleen, kidney, visceral adipose tissue (VAT), and subcutaneous adipose tissue (SAT) were collected at time 0, 30 min, 60 min, and 120 min of IPGTT.

RESULTS

The fasting levels of MGO in plasma and in tissues were 2 to 4.5-fold higher in db/db mice than control mice. The IPGTT led to a fast increase of plasma ^{13}C3 MGO concentrations and reached a peak at 30 min in control mice and with higher levels in db/db mice (189.7 ± 23.5 vs 397.8 ± 64.4 nmol/L; $p < 0.001$). In tissues, ^{13}C3 MGO also increased in control mice during IPGTT and this was further increased in db/db mice (pancreas: 3.33 ± 0.38 vs 7.58 ± 0.64; liver: 8.58 ± 0.93 vs 18.10 ± 2.97; spleen: 10.57 ± 1.27 vs 69.98 ± 3.03; kidney: 3.33 ± 0.23 vs 18.32 ± 3.13; VAT: 4.55 ± 0.61 vs 75.42 ± 10.29; SAT: 6.67 ± 1.07 vs 52.40 ± 14.37 nmol per gram protein, $p < 0.05$, at 120 min of the IPGTT).

CONCLUSION

Exogenous glucose contributes to MGO formation both in plasma and in tissues during a glucose tolerance test and this was further increased in type 2 diabetes.