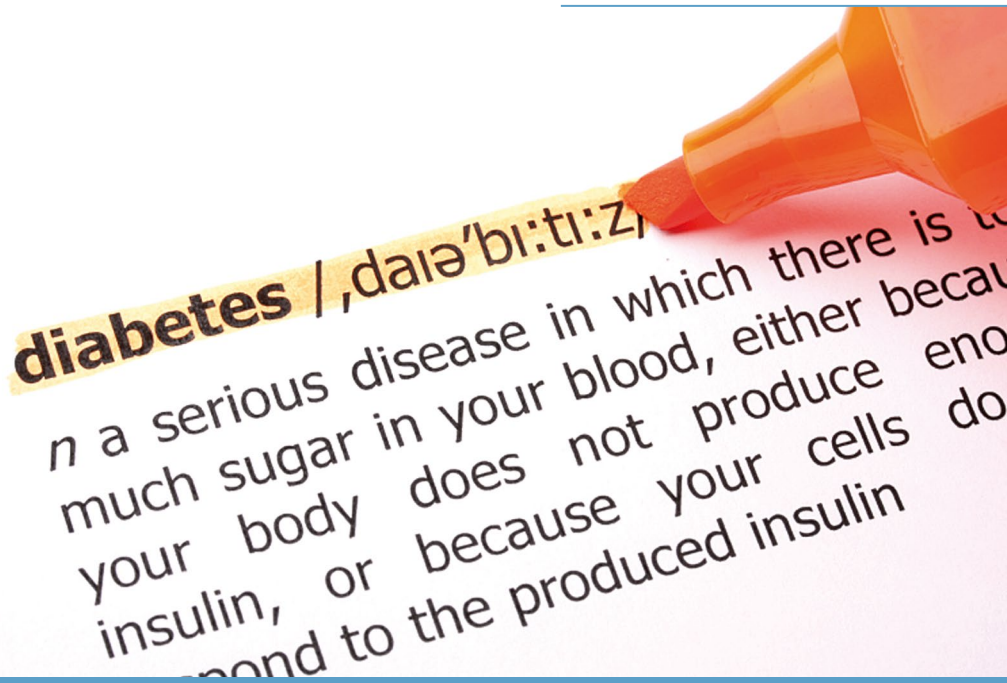
JAARGANG 21 / OKTOBER 2023

NTD

4

Nederlands Tijdschrift voor Diabetologie

Annual Dutch Diabetes Research Meeting 2023
2 & 3 november



WETENSCHAPPELIJK TIJDSCHRIFT VOOR PROFESSIONALS IN DE DIABETESZORG

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Beste lezer,

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

Op donderdag 2 november en vrijdag 3 november 2023 vindt de 49e ADDRM plaats in het WICC 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).

Het wetenschappelijke programma heeft een herkenbare ADDRM-identiteit, met de traditionele highlights, zoals een sterk klinisch programma, de *best meeting abstracts* en *keynote lectures* van (inter)nationaal gerenommeerde sprekers. Daarnaast zullen de Terpstra en Gerritzen Awards worden uitgereikt tijdens de ADDRM.

Dit jaar komen er verschillende aspecten aan bod in het klinische programma, waaronder aandacht voor stigmatisatie rondom diabetes, de rol van hormonen bij migraine en diabetes en de laatste stand van zaken met betrekking tot eilandjestransplantatie. Ook worden ervaringen gedeeld van het gebruik van CGM in ons omringende landen.

Verder zijn er meerdere parallelsessies, met een keur aan verschillende onderwerpen, die een goed beeld schetsen van de breedte van het diabetesonderzoeksveld in Nederland.

Verderop in dit nummer vindt u het plenaire programma en een overzicht van alle abstracts die zijn geaccepteerd voor de 49e editie van de ADDRM.

Graag tot ziens in Wageningen!

Dr. Rinke Stienstra
Voorzitter Nederlandse Vereniging
voor Diabetes Onderzoek

Zustervereinigingen
PSAD, NDESG, NVCD en NASO

NVD

2 & 3 november 2023

ANNUAL DUTCH DIABETES RESEARCH MEETING

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Abstracts ADDRM 2023

1

Magnesium supplementation attenuates T-cell function in people with type 2 diabetes with low serum magnesium levels

*Linda C.A. Drenthen[1], *Mandala Ajie[1], Jeroen H.F. de Baaij[2], Cees J. Tack[1], Bastiaan E. de Galan[1,3], Rinke Stienstra[1,4]
*Shared first authorship

1 Department of Internal Medicine, Radboudumc, Nijmegen, The Netherlands
2 Department of Medical Biosciences, Radboudumc, Nijmegen, The Netherlands
3 Department of Internal Medicine, Maastricht UMC+, Maastricht, The Netherlands
4 Division of Human Nutrition and Health, Wageningen University, Wageningen, The Netherlands

BACKGROUND

Low magnesium levels, which commonly occurs in people with type 2 diabetes, are associated with pro-inflammatory response. In this study, we investigated whether magnesium supplementation in people with type 2 diabetes and low magnesium levels would benefit their immune system.

METHODS

In this double-blind, placebo-controlled, two-period cross-over study, 12 people with type 2 diabetes and low serum magnesium levels were recruited to assess the effect of magnesium supplementation (15 mmol/day) on immune function. Blood was drawn at the end of each treatment period to measure the levels of circulating inflammatory proteins, circulating immune cell numbers, and *ex vivo* immune cell functionality. Circulating inflammatory protein levels were measured using Olink inflammation panel. Flow cytometry was used to determine the whole blood immune cell composition, as well as *ex vivo* functionality of peripheral blood mononuclear cells.

RESULTS

Magnesium supplementation increased the levels of circulating magnesium as compared to placebo (0.69 ± 0.02 and 0.76 ± 0.02, respectively). We found no change in circulating inflammatory protein levels post-magnesium supplementation. The number of circulating immune cells were also not affected by magnesium supplementation. However, we observed lower *ex vivo* production of IFNy and IL4/IL5/13 from CD4+ T-cells ($p = 0.011$ & $p = 0.015$), and IFNy production from CD8+ T-cells ($p = 0.008$) after PMA+ionomycin supplementation. The effect of magnesium supplementation exclusively affected lymphocytes, as we observed no change in *ex vivo* monocyte functionality post-supplementation.

CONCLUSION

Magnesium supplementation attenuates pro-inflammatory response in CD4+ and CD8+ T-cells in people with type 2 diabetes and low serum magnesium levels.

2

Less is more: A process analysis of the optimalisation of medication in older patients with type 2 diabetes mellitus (OMED2) intervention pilot study

C. Andriessen[1,2], M.T. Blom, B.A.C.E. Van Hoek, A.W. De Boer, R.C. Vos, K.M.A. Swart, P.J.M. Elders[1,2]

1 Amsterdam UMC, location Vrije Universiteit, Department of General Practice, Amsterdam, The Netherlands
2 Amsterdam Public Health, Health Behaviors & Chronic Diseases, Amsterdam, The Netherlands

BACKGROUND

Older patients with type 2 diabetes (T2D) are regularly prescribed too many glucose lowering medication (GLM), which puts them at risk of hypoglycemic episodes. Therefore, a GLM deprescription program for patients aged >= 70 years was developed, consisting of i) a selection tool used in the electronic medical record (EMR) system identifying eligible patients, ii) a training program for general practitioners (GPs) and practice nurses (PNs), iii) supporting practice visits by research assistants and iv) the option to consult experts. Here, we evaluate barriers and facilitators for implementing the deprescription program in a pilot study preceding the full program.

METHODS

Notes from training meetings and interviews with GPs (n = 6), PNs (n = 7) and patients (n = 5) were analysed by at least two researchers (BvH, LV, PE), for a qualitative analysis based on the Extended Normalisation Process Theory (ENPT), identifying barriers and facilitators for deprescription.

RESULTS

Nine GP-practices participated in the pilot study. Using the EMR-selection tool, 71 patients were found eligible for reduction of GLM. Barriers to implementation were: 1) time investment for meetings and monitoring; 2) study-related tasks performed by the PNs that are not part of the primary care process; 3) inexperience with deprescribing and fear of adverse consequences; 4) inexperience with the EMR-selection tool; 5) inexperience in performing deprescribing consultations.
Enabling factors were: 1) practical on-site help by research assistants; 2) case studies in the education material; 3) role-play to rehearse the deprescribing consultation; 4) the option to consult the expert team.

CONCLUSION

The deprescription program is feasible in general practice. Results of this pilot are used to adapt the final program: deprescribing steps are decreased to reduce anxiety and to be better adjusted to routine care, practical help of research assistants is maintained, and complete separation of study-related and healthcare-related processes is ensured.

3

DPARD five years later, assessing mortality in diabetes outpatients

Jessica C.G. Bak[1,2], Silvia A.G. de Vries[1,2], Erik H. Serné[1], Rolf H.H. Groenwold[3], Harold W. de Valk[4], Dick Mul[5], Theo C.J. Sas[5,6], M. Bizino[7], Max Nieuwdorp[1], Mark H.H. Kramer[1], Carianne L. Verheugt[1]

1 Amsterdam University Medical Centers, Amsterdam, The Netherlands
2 Dutch Institute for Clinical Auditing, Leiden, The Netherlands

BACKGROUND

Diabetes mellitus is ranked in the top ten causes of death worldwide. To improve quality of diabetes care and prevent mortality, the nationwide Dutch Pediatric and Adult Registry of Diabetes (DPARD) was founded in 2017. We aim to provide an overview of the developments of DPARD and of mortality among diabetes outpatients.

METHODS

All patients in DPARD who visited the diabetes outpatient clinic from 2016 up to 2021 were linked to Statistics Netherlands (CBS). All-cause and cardiovascular mortality rates were estimated using Cox proportional hazard regression models, rendering hazard ratios (HR) to identify clinical patient variables associated with mortality.

RESULTS

After five years, 64 (88%) of all medical centers participate in DPARD, and 71,168 patients have been included from 44 centers across the Netherlands. Linkage to CBS rendered 12,992 patients a median follow-up of 3.1 years. Mortality rates in type 1 diabetes was 67.7 deaths per 10,000 person-years (PY) and 324.2 deaths per 10,000 PY in type 2. Malignancy was the major cause of non-cardiovascular mortality. During the years of the influenza (2018) and COVID pandemic (2020), mortality rates were up to 32.9 deaths per 10.000 PY higher in patients with type 1 and 129.6 deaths per 10,000 PY higher in type 2. Smoking and an eGFR < 60 ml/min were associated with all-cause mortality in both types. In type 2, additional mortality-linked factors were male sex, BMI < 20 kg/m^2, diabetes duration < 1 year and hypertension.

CONCLUSION

DPARD is nearing national coverage, and provides feedback to healthcare professionals and valuable insight into the quality of diabetes care delivered. Mortality among Dutch diabetes outpatients is high. Malignancy is the major cause of non-cardiovascular mortality. Smoking and renal failure were associated with all-cause mortality. Further focus on prevention, early detection and treatment of mortality-associated factors may improve clinical outcomes.

4

Endoscopic sutured Gastroplasty in Type 2 diabetic, obese patients using the Endomina device – the GATE trial study design

F.M.M. Beeren[1], M.J.M. Groenen[1], A.C. van Bon[1], P.D. Siersema[2]

1 Rijnstate, Arnhem, The Netherlands
2 Erasmus MC, Rotterdam, The Netherlands

BACKGROUND

Approximately 70% of patients with type 2 diabetes mellitus (DM2) is overweight or obese. Weight loss benefits several aspects in DM2, such as improved glycemic control and insulin sensitivity. Achieving substantial weight loss is difficult. Lifestyle interventions are responsible for 3-5% of total weight loss (TWL) and GLP1 analogues for 7-15% of TWL. Bariatric surgery usually leads to an average TWL of 28%, but is invasive and has the risk of complications during follow-up. Endoscopic bariatric techniques can also be used as therapeutic option to achieve weight loss. One of them is endoscopic sutured gastroplasty (ESG). ESG mimics a laparoscopic sleeve gastrectomy by placing transoral full thickness sutures alongside the great curvature. This decreases the stomach size with approximately 70%. After 12 months, the average TWL has been found to be up to 21%. There is however a paucity of data showing the effect of ESG on metabolic comorbidities including DM2.

METHODS

The GATE trial is a single center, randomized controlled trial (NCT05711043) that will evaluate the efficacy of ESG with the Endomina device on glycemic control. In addition, it will evaluate whether ESG can also be performed under procedural sedation.
In total, 58 patients will be randomized 1:1 to the intervention group (ESG in addition to standard diabetic care) or control group (standard diabetic care). Patients with insulin-dependent DM2 with a BMI of 30-40kg/m^2 are eligible for inclusion. ESG will be performed under general anesthesia or procedural sedation with propofol. The primary endpoint is the proportion of patients with a clinically relevant dose reduction of insulin (defined as a 50% decrease) after 12 months. Secondary endpoints include decrease in HbA1c, remission of DM2, weight loss, quality of life and (serious) adverse events.

CONCLUSION

The GATE trial will provide insights into the effect of ESG on glycemic outcomes, quality of life and safety. Moreover, the feasibility of performing ESG under procedural sedation will be evaluated.

5

Differences in inflammatory pathways between Dutch South Asians vs Dutch Europids with type 2 diabetes

Maaike E. Straat[1], Borja Martinez-Tellez[1], Huub J. van Eyk[1], Maurice B. Bizino[1], Suzanne van Veen[1], Eleonora Vianello[1], Rinke Stienstra[2], Tom H.M. Ottenhoff[1], Hildo J. Lamb[1], Johannes W.A. Smit[3], Ingrid M. Jazet[1], Patrick C.N. Rensen[1], Mariëtte R. Boon[1]

1 Leiden University Medical Center, Leiden, The Netherlands
2 Wageningen University, Wageningen, The Netherlands
3 Radboud University Medical Center, Nijmegen, The Netherlands

BACKGROUND

South Asians are more prone to develop type 2 diabetes (T2D), coinciding with earlier complications than Europids. While inflammation plays a central role in the development and progression of T2D, this factor is still underexplored in South Asians. In the current study, we assessed whether circulating mRNA transcripts of immune genes are different between South Asian versus Europid patients with T2D.

METHODS

We performed a secondary analysis of two randomized controlled trials. We included participants with T2D of Dutch South Asian (n = 45; age: 55 ± 10 years, BMI: 29 ± 4 kg/m^2) and Dutch Europid (n = 44; age: 60 ± 7 years, BMI: 32 ± 4 kg/m^2) descent. We assessed mRNA transcripts of 182 immune genes (microfluidic qPCR; Fluidigm Inc., USA) in fasted whole blood, ingenuity pathway analyses (Qiagen, USA).

RESULTS

South Asians, compared to Europids, had higher mRNA levels of B cell markers [CD19, CD79A, CD79B, CR2, CXCR5, IGHD, MS4A1, PAX5; all FC > 1.3, FDR < 0.008] and IFN signaling genes [CD274, GBP1, GBP2, GBP5,

FCGR1A/B/CP, IFI16, IFIT3, IFITM1, IFITM3, TAP1; all FC > 1.2, FDR < 0.05]. In South Asians, the IFN signaling pathway was the top canonical pathway (z-score 2.6, $p < 0.001$) and this was accompanied by higher plasma IFN-γ levels (FC = 1.5, FDR = 0.01). Notably, the ethnic difference in gene expression was larger for females [20/182 (11%)] than males [2/182 (1%)].

CONCLUSION

South Asian patients with T2D show a more activated IFN signaling pathway compared to Europid patients with T2D, which is more pronounced in females than males. We speculate that a more activated IFN signaling pathway may contribute to the more rapid progression of T2D in South Asians compared with Europids.

6

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], Jodie A. Schildkraut[2], Rinke Stienstra[1,3], Cees J. Tack[1], Jakko van Ingen[4], Reinout van Crevel[1]

1 Department of Internal Medicine, Radboud University Medical Center, Nijmegen, The Netherlands
2 Department of Pulmonology, Radboud University Medical Centre, Nijmegen, The Netherlands
3 Nutrition, Metabolism and Genomics Group, Wageningen University, Wageningen, The Netherlands
4 Department of Medical Microbiology, Radboud University Medical Centre, Nijmegen, The Netherlands

BACKGROUND

Tuberculosis (TB) and diabetes mellitus (DM) are two co-emerging diseases that are increasingly prevalent worldwide. People with DM have a tripled risk of developing active TB and are twice as likely to succumb to the disease. We hypothesize that macrophage function in DM is altered, creating a preferred niche for *Mycobacterium tuberculosis* (Mtb).
Previous research primarily focused on either the host‘s response or the pathogen‘s response during infection, but not both. Simultaneous profiling of both host and pathogen mRNA, known as dual RNAseq, is necessary to uncover the crosstalk between macrophage and Mtb. However, performing dual RNAseq to mycobacterial infections is challenging due to the low levels of mycobacterial mRNA within infected macrophages.

METHODS

This study conducted a dual RNAseq approach, which overcomes the hurdles of low mycobacterial transcript numbers by applying a unique enrichment protocol. Human monocyte-derived macrophages from individuals with DM (n = 4) and age-/sex-matched healthy controls (n = 4) were infected with Mtb H37Rv strain, followed by gene expression profiling of both the host and the pathogen.

CONCLUSION

Results show that sufficient read counts and high read quality derived from the unique enrichment approach, which allows for transcriptional profiling of host and pathogen. Additionally, the production of cytokines in response to infection and the mycobacterial load within the macrophages were assessed. By integrating the data on transcriptional changes, cytokine production and mycobacterial growth, this study gains new insights into the interaction between macrophages and Mtb in the context of DM.

7

Gut bacterium *Intestinimonas* improves the host metabolism evidenced via cohort studies and animal intervention

Elena Rampanelli[1#], Nadia Romp[1#], Antonio Dario Troise[2], Jakshana Ananthasabesan[1], Hao Wu[3], Vincenzo Fogliano[4], Max Nieuwdorp[1], Thi Phuong Nam Bui[1]
 # equal contribution

1 Department of Experimental Vascular Medicine, Amsterdam UMC, The Netherlands
2 Proteomics & Mass Spectrometry Laboratory, ISPAAM, National Research Council, Portici, NA, Italy
3 The Wallenberg Laboratory, Department of Molecular and Clinical Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
4 Food Quality & Design Group Wageningen University, Wageningen, The Netherlands

BACKGROUND

Diet, the human microbiome and host genetics are deter minants of metabolic status, partially via production of metabolites via fermentation of dietary components by the gut microbiota. Understanding the metabolism of dietary ingredients by the microbiome is key to mediate the effects of the human microbiome on host metabolism.

METHODS

Fructoselysine is among one of the most abundant Amadori products formed in food via the non-enzymatic reaction between a reducing sugar and amino acids during cooking process. We discovered that a commensal *Intestinimonas butyriciproducens* is capable of metabolizing fructoselysine to butyrate which is a microbial metabolite with proven health benefits. While the accumulation of fructoselysine is undesired due to its further conversion to advanced glycation end products (AGEs), which have been associated with aging, atherosclerosis and diabetes, fructoselysine conversion to butyrate is highly desired.

RESULTS

In our study, we observed the reverse associations of butyrogenic *Intestinimonas butyriciproducens* and fructoselysine pathway genes in subjects with poor metabolic performances compared to heathy subjects in a Swedish prediabetic cohort. We further isolated 3 different *Intestinimonas* strains from stool of healthy volunteers. Administration of the *Intestinimonas* isolate with optimal metabolic features reduced weight gain and improved insulin sensitivity in DIO mouse model as compared to the control group.

CONCLUSION

These findings foster novel efficacious approaches to modulate gut bacteria with desired function, using bacteria combined with dietary components to improve human metabolic health.

8

Hepatic glucokinase regulatory protein and carbohydrate response element binding protein do not explain the fatty liver phenotype in aldolase B deficiency

A.M. Buziau, M.H. Oosterveer, K. Wouters, D.R. Tolan, C.D.A. Stehouwer, C.G. Schalkwijk, M.C.G.J. Brouwers

Maastricht University, Maastricht, The Netherlands
University of Groningen, Groningen, The Netherlands
Boston University, Boston, USA
Maastricht University Medical Center+, Maastricht, The Netherlands
E-mail: amee.buziau@maastrichtuniversity.nl

BACKGROUND

Evidence is accumulating that intrahepatic lipid (IHL) accumulation *per se* is a risk factor for type 2 diabetes. Furthermore, recent studies have shown that fructose 1-phosphate (F1P) has a signalling function in the pathogenesis of IHL accumulation. However, the underlying mechanism by which F1P causes hepatosteatosis remains unknown. Therefore, the aim was to determine the role of putative mediators in the pathogenesis of F1P-mediated IHL accumulation.

METHODS

We used a mouse model with global knockout of aldolase B (AldoB$^{-/-}$ mice), that is characterized by both hepatocellular F1P and IHL accumulation. First, to study the role of glucokinase regulatory protein (GKRP) in the pathogenesis of IHL accumulation, we crossbred the AldoB$^{-/-}$ mice with mice deficient for GKRP. Second, to study the role of the lipogenic transcription factor carbohydrate response element binding protein (ChREBP) in the pathogenesis of IHL accumulation, we treated AldoB$^{-/-}$ mice with adeno-associated virus short hairpin RNAs directed against hepatic ChREBP.

RESULTS

First, we found that AldoB$^{-/-}$ mice and AldoB$^{-/-}$/GKRP$^{-/-}$ mice had a higher relative liver weight when compared to wildtype mice ($p = 0.003$ and $p = 0.029$, respectively). In addition, AldoB$^{-/-}$ mice had a higher IHL content when compared to wildtype mice ($p = 0.011$), consistent with previous reports. However, GKRP knockout did not protect AldoB$^{-/-}$ mice from IHL accumulation ($p = 0.503$). In the second experiment, in contrast to our expectation, we found that hepatic ChREBP knockdown markedly increased the relative liver weight and tended to cause a higher IHL content in shChREBP-treated AldoB$^{-/-}$ mice when compared to shSCR-treated AldoB$^{-/-}$ mice ($p < 0.001$ and $p = 0.195$, respectively).

CONCLUSION

GKRP and ChREBP do not appear to contribute to the pathogenesis of IHL accumulation in AldoB$^{-/-}$ mice. Future studies are warranted to elucidate the mechanisms by which fructose participates as a signalling molecule in the pathogenesis of IHL accumulation, e.g. by exploring the role of beta-oxidation and VLDL-triglyceride secretion.

9

The RepEAT study – a controlled dietary intervention to examine the variation in glucose responses

M. Daanje, A.E. Siebelink, A.H. Kersten, D. Esser, L.A. Afman

Wageningen University & Research, Wageningen, The Netherlands

BACKGROUND

General dietary guidelines aim to promote health and reduce the risk of chronic metabolic diseases such as diabetes, yet a 'one-size-fits-all' strategy fails to take into account inter-individual differences in glucose responses. Existing research recognises the presence of inter-individual variation in postprandial glucose responses to the same meal or food product. However, the role of other consumed meals and timing of meals in postprandial glucose responses is unclear, and the robustness of glucose responses is still unknown. The RepEAT study was designed to determine to what extent glucose responses are variable between and within individuals. In addition, within the RepEAT study we aimed to examine how this variation in glucose responses is related to the diet, the time of consumption, and to an individual's phenotype.

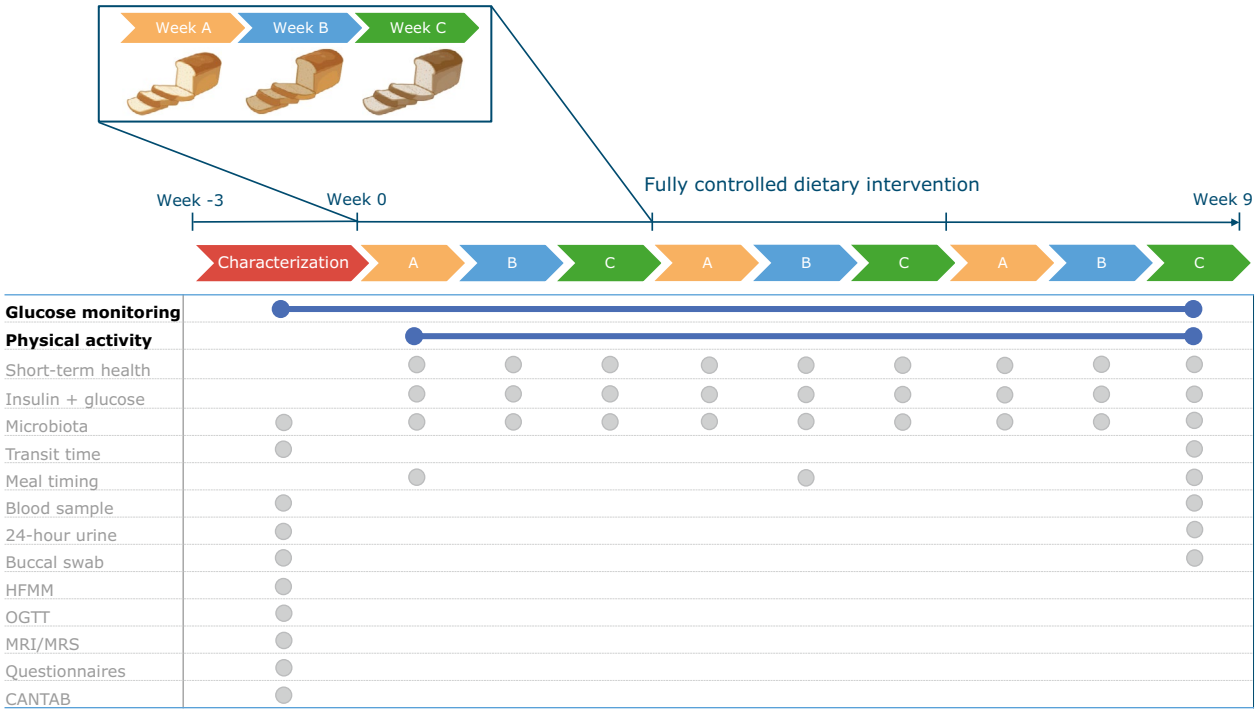
METHODS

63 apparently healthy men and women with a BMI of 25-40 kg/m^2 and aged 45-75 years were enrolled in the RepEAT study. The RepEAT study comprised a fully controlled dietary intervention of nine weeks. The 9-week dietary intervention consisted of three repetitive periods of three weeks. Within these three weeks, intervention products and meals were tested that were of the same food category, but varied in composition. Due to the repetitive design, the robustness of glucose responses within individuals was measured. To measure postprandial glucose responses to all meals and to assess physical activity patterns, glucose and physical activity were continuously monitored throughout the dietary intervention (**figure 1**). To measure associations between glucose responses and an individual's phenotype, participants were comprehensively characterized before the start of the dietary intervention. Due to the fully controlled dietary setting, this study will provide essential information on the variation in postprandial glucose responses between and within individuals.

CONCLUSION

The RepEAT study has completed in December 2022. During the ADDRM 2023 we aim to share our first results on the variability in glucose responses within and between individuals to identical meals/products.

Figure 1. 9-week fully controlled dietary intervention.



10

Using multilevel modelling to predict acute glucose responses to contextual factors in people with type 2 diabetes

I.M. de Hoogh[1,2], T. Snel, R.J.M. Kamstra, T. Krone, H. Pijl, A.A. de Graaf[1]

1 Netherlands Organization for Applied Scientific research (TNO), The Netherlands
2 Leiden University Medical Center (LUMC), Leiden, The Netherlands

BACKGROUND

Although the effects of interventions on glucose levels are well-studied in a controlled setting, little is known about acute effects of lifestyle in real-life and at an individual level. We aimed to quantify acute effects of lifestyle factors on glucose values 2-hours later in people with type 2 diabetes, and how these differ between individuals.

METHODS

38 participants with type 2 diabetes wore a continuous glucose monitor, activity and sleep tracker, and logged food intake and wellbeing for 11 periods of 4 days. A linear mixed effect model was used to quantify the effect of sleep, stress, current glucose, carbohydrate intake and exercise on glucose levels two hours later. We started out with a full model, after which we took out effects in a stepwise fashion. For fixed effects, variables were considered significant at $p < 0.05$. For both random and fixed effects we compared measures of model fit to select the best fitting model.

RESULTS

Fixed effects included in the final model influenced the glucose values 2-hours (mmol/l) later by (estimates ± SE): intercept 6.15 ± 1.62, current glucose 0.34 ± 0.01, sleep -0.01 ± 0.00, exercise past 12h -0.31 ± 0.02, carbohydrates last 5 minutes 0.02 ± 0.01, carbohydrates last 30 minutes 0.02 ± 0.01 per unit change in the predictor. Random or individualized effects were intercept (SD 1.62), exercise in the past (SD 0.20) and future 30 minutes (SD 0.16), and carbs eaten in the past 5 (SD 0.03) and 30 minutes (0.04).

CONCLUSION

The multilevel model allowed quantifying effects of lifestyle factors. Effects were small, but can add up considerably, e.g., two slices of bread with 35 grams of carbohydrates would increase 2-hour glucose with 0.7 mmol/L on average. Beneficial effects of exercise before and after a meal on glucose control seem individually determined with non-significant fixed effects. These insights allow for real-time personalized recommendations, for instance targeted at avoiding high glucose peaks.

11

Different classes of circulating small non-coding RNAs are associated with future diabetic kidney disease

J.A. de Klerk[1,2], R.C. Slieker[1,3,4], J.W.J. Beulens[3,4,5], A.J. van Zonneveld[2], P.J.M. Elders[3,6], J.H.D. Peerlings[1], R. Bijkerk[2], L.M. 't Hart[1,3,4,7]

1 Department of Cell and Chemical Biology, Leiden University Medical Center, Leiden, The Netherlands
2 Department of Internal Medicine (Nephrology) and the Einthoven Laboratory for Vascular and Regenerative Medicine, Leiden University Medical Center, Leiden, The Netherlands
3 Amsterdam Public Health Institute, Amsterdam UMC, Amsterdam, The Netherlands
4 Department of Epidemiology and Data Science, Amsterdam UMC, location Vrije Universiteit, Amsterdam, The Netherlands
5 Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands
6 Department of General Practice and Elderly Care Medicine, Amsterdam Public Health Research Institute, Amsterdam UMC, location VUmc, Amsterdam, The Netherlands
7 Department of Biomedical Data Sciences, Section Molecular Epidemiology, Leiden University Medical Center, Leiden, The Netherlands

BACKGROUND

Chronic kidney disease (CKD) is a heterogenous disorder affecting kidney structure and function. It is one of the most common complications in type 2 diabetes (T2D) and characterized by high albuminuria (albumin > 3 mg/mmol) and reduced glomerular filtration rate (< 60 ml/min eGFR). Nonetheless, while some individuals develop complications like CKD early in the disease trajectory, others will not. Increasing evidence shows that circulating small non-coding RNAs (sRNAs), like miRNAs, associate with disease progression. However, very little is known about the association of other sRNA classes with future diabetic CKD.

METHODS

The plasma sRNA transcriptome was measured in participants from the Hoorn DCS study (n = 260). They were

eligible for the current study if they are CKD stage 0 at the time of their first biobank sample and at least the year before. Cases where those that developed CKD during on average nine years follow-up (risk stage ≥ 2) in at least two consecutive years whereas controls where sex and diabetes-duration matched persons who remained stable in stage 0 during at least three yearly follow-up visits. We aimed to elucidate if circulating sRNAs are associated with incident CKD in diabetes during follow-up with a negative binomial generalized log-linear model.

RESULTS

We found that eleven small RNAs, including the small nucleolar RNAs *SNORD12C* (logFC = -1.6, p-value = $1{\cdot}10^{-6}$) and *SNORD105B* (logFC = −1.4, p-value = $2{\cdot}10^{-6}$) as the strongest signals, are associated with future CKD. In addition, we found that miR-581 is associated with eGFR lower than 60 ml/min (logFC = -0.3, p-value = $2{\cdot}10^{-3}$).

CONCLUSION

Together, our results show that different classes of small non-coding RNAs are associated with future development of diabetic CKD, including small nucleolar RNAs (snoRNAs). This provides a starting point for our future functional studies to investigate the role of the identified sRNAs during the development of diabetic CKD.

12

The DiaGame Study: Free-Living Data Collection in Patients with Diabetes Using Wearable Devices

Ryan de Vries[1*], Edouard Reinders[2*], Danilo Ferreira de Carvalho[1], Elma Cruts[2], Pleun van Poppel[2], Pieter Van Gorp[1], Uzay Kaymak[1], Peter Hilbers[1], Harm Haak[2], Natal van Riel[1]

***Shared first authors**
1 Eindhoven University of Technology, Eindhoven, The Netherlands
2 Máxima Medical Center, Eindhoven, The Netherlands
Correspondence: r.d.vries@tue.nl

BACKGROUND

Self-management of Diabetes Mellitus is a multi-faceted and persistent process, for which an adequate understanding is required of factors influencing blood glucose levels at an individual level. The collection of data in free-living conditions can aid in gaining insight into patient-specific effects of lifestyle and daily decision-making (e.g., dietary intake, physical activity) on blood glucose dynamics.

METHODS

To alleviate associated burdensome tasks of data digitization and information inference, we designed and executed an observational study leveraging merely wearable devices for scalable and patient-centered data collection. Furthermore, the feasibility of this study was evaluated.
Free-living data was collected over 14 days from 60 patients (type 1 and 2, predominantly elderly) utilizing a CGM, smartwatch and smartphone, as well as anthropometric and fasting laboratory measurements (**figure 2** gives a workflow overview). Patient-reported dietary intake and physical activity were collected through a smartphone application, while insulin medication and mood were reported using our smartwatch application supplemented with measurements from integrated sensors (accelerometer, pedometer, heart rate).

RESULTS

The study demonstrated inter- and intra-patient variability in blood glucose dynamics. Furthermore, the feasibility analysis indicated successful compliance and overall sufficient data quality. Additionally, preliminary results showed participants were susceptible to nudging via the smartwatch to promote mood reports. Nonetheless, while the reported data were generally in line with expected values, the quantity and quality of information differed between individuals.

CONCLUSION

Ultimately, the aim is to develop a personalized educational interactive serious game using the acquired data, to empower patients and stimulate adequate self-management in a playful manner.

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Does size matter? Hospital volume and resource utilization in pediatric diabetes care

Silvia A.G. de Vries[1,2], Jessica C.G. Bak[1,2], Dick Mul[3], Vincent A. Stangenberger[4], Michel W.J.M. Wouters[2,5], Max Nieuwdorp[1], Carianne L. Verheugt[1], Theo C.J. Sas[3,6]

1 Amsterdam University Medical Centers, Amsterdam, The Netherlands
2 Dutch Institute for Clinical Auditing, Leiden, The Netherlands
3 Diabeter, Rotterdam, The Netherlands
4 Institute of Epidemiology and Medical Biometry, ZIBMT, University Ulm, Ulm, Germany
5 German Center for Diabetes Research (Dz), Neuherberg, Germany
6 Erasmus MC, Sophia Children's Hospital, Rotterdam, The Netherlands

BACKGROUND

Pediatric diabetes care has become increasingly specialized due to the multidisciplinary approach and technological developments. Guidelines recommend sufficient experience of treatment teams. This study evaluates the associations between hospital volume and resource use and hospital expenditure in Dutch children with diabetes mellitus.

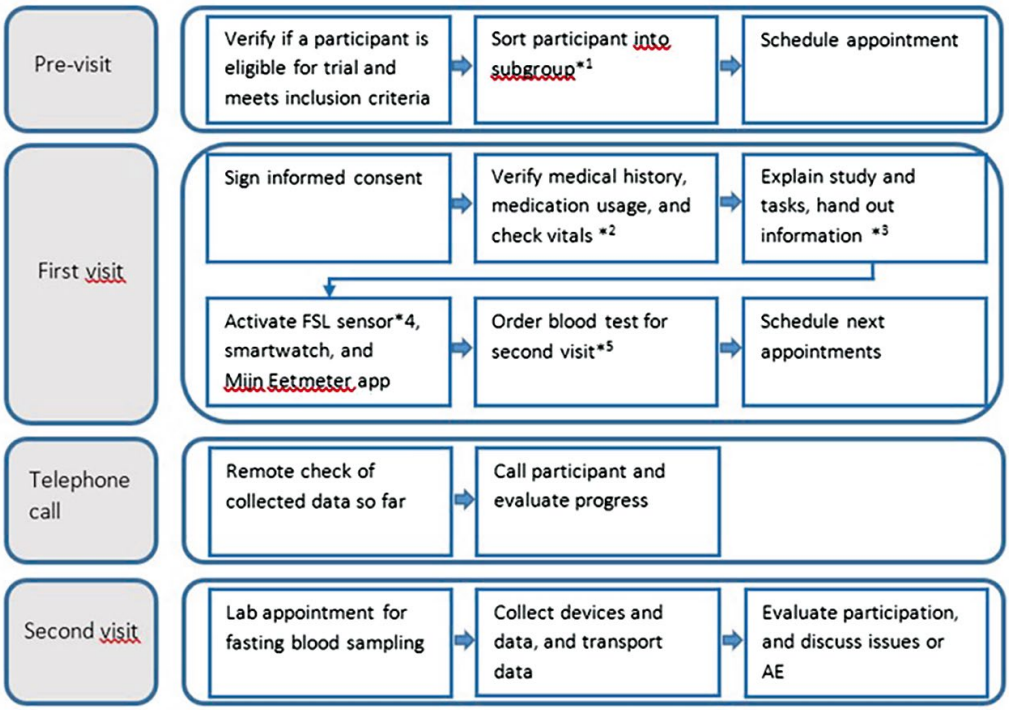
METHODS

Observational retrospective cohort study using hospital claims data of 5,082 children treated across 44 Dutch hospitals in 2019-2020. Hospitals were categorized into three size categories; small (≥ 20-100 patients), medium (≥ 100-200 patients) and large (≥ 200 patients). All-cause hospitalizations, consultations, technology use and hospital expenditure were analysed per volume category and adjusted for age, sex, and socio-economic status (SES).

RESULTS

Large hospitals had lowest hospitalization rates, with their patients being hospitalized less often compared to small hospitals (adjusted OR 0.49; [95% CI 0.40-0.59]; $p < 0.001$). The median number of outpatient pediatrician visits in one year was 7 in large hospitals and 6 in small hospitals. Patients in large hospitals more often had ≥ 7 yearly consultations (adjusted OR 1.63; [95% CI 1.41-1.89]; $p < 0.001$) compared to other hospital sizes. Real-time continuous

Figure 2. Workflow overview of the DiaGame Study.



1: type of diabetes, insulin usage, BMI. 2: Blood pressure, heart rate, weight, length, BMI.
3: Instruction manual of devices and FAQ page. 4: FreeStyle Libre pro iQ sensor.
5: Fasting glucose, Hba1c, insulin, C-peptide.

glucose monitoring (rtCGM) use was highest in medium-sized hospitals (adjusted OR 1.30; [95% CI 1.12-1.53]; p < 0.001) compared to small and large hospitals, whereas no difference in pump usage was observed. Mean diabetes care expenditure per patient was the highest in medium-sized centers (€ 5,642, IQR € 1,947-6,944); the difference in diabetes care costs with small hospitals was attenuated after adjustment for age, sex, and SES.

CONCLUSION

Care provision patterns vary by hospital size. Large hospitals had the lowest hospitalization rate, yet the highest number of consultations, whereas medium-sized hospitals showed highest rtCGM use and expenditure. Diabetes care costs were similar across hospital volumes after adjustment for patient characteristics.

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A 3'UTR eQTL regulates PTEN expression via miRNA binding specifically in beta cells

Twan de Winter[1,2,3], Miha Sovrovic[2,3], Françoise Carlotti[1,3], Anna Alemany[2,3], Eelco de Koning[1,3]

1 Department of Internal Medicine, LUMC, Leiden, The Netherlands
2 Department of Anatomy and Embryology, LUMC, Leiden, The Netherlands
3 The Novo Nordisk Foundation Center for Stem Cell Medicine (reNEW), LUMC, The Netherlands
E-mail: t.j.j.de_winter@lumc.nl

BACKGROUND

The 3' untranslated region (UTR) of mRNAs is involved in mRNA regulation. Some genetic variants can change mRNA levels by disruption or creation of binding sites of for example miRNAs. The effect of these so-called expression quantitative trait loci (eQTLs) has been shown to be highly specific to cell state. Here we set out to investigate human pancreas cell type-specific eQTLs of non-diabetic (ND) and type 2 diabetes (T2D) donors.

METHODS

We developed a computational pipeline to identify 3'UTR eQTLs by correlating gene expression with donor-specific genetic variants directly from scRNA-seq datasets. We utilized four published datasets of pancreatic islets (ND = 24, T2D = 12). In addition, we combined the database miRNASNP v3 and small RNA-seq datasets of islets to predict loss of miRNA binding site. A luciferase miRNA-3'UTR assay in HEK293 cells was performed for experimental validation.

RESULTS

We identified around 1.2E6 3'UTR genetic variants directly from scRNA-seq data. In total we found 6.9E4 (ND = 5.0E4, T2D = 3.7E4) significant eQTLs. Interestingly, 50% (ND) and 55% (T2D) of eQTLs have an effect only in one cell type. In ND beta cells specifically, the expression level of PTEN is regulated by the rs701848 SNP (p = 0.01). PTEN expression was increased in carriers of the C-allele compared to the T-allele. Noteworthy, rs701848 had no effect on T2D beta cells, with upregulated expression in all genotypes. We hypothesize that the C-allele causes loss of miRNA binding site miR-127-5p. Expression of miR-127-5p is enriched in islets and primarily restricted to beta cells (3.4-fold beta vs islets). In a luciferase assay miR-127-5p more strongly down-regulates the T-allele compared to C-allele.

CONCLUSION

Our data indicate that the 3'UTR eQTL landscape of pancreatic cells is highly cell type-specific. In ND beta cells miR-127-5p binding may cause the downregulation of PTEN expression mainly in rs701848 T-allele carriers.

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The association between food intake and time in euglycaemic range in individuals with Type 1 Diabetes

Douwe F. de Wit[1], Coco M. Fuhri Snethlage[1], Elena Rampanelli[1], Daniël van Raalte[2], Max Nieuwdorp[1], Maarten Soeters[3*], Nordin M.J. Hanssen[1*]
Equal contribution

1 Department of vascular medicine, Amsterdam UMC, location AMC, Amsterdam, The Netherlands
2 Department of Endocrinology, Amsterdam UMC, location VUmc, Amsterdam, The Netherlands
3 Department of Endocrinology Amsterdam UMC, location AMC, Amsterdam, The Netherlands
E-mail: d.f.dewit@amsterdamumc.nl

BACKGROUND

Little consensus exists on optimal dietary strategies in Type 1 Diabetes (T1D). Therefore, we investigated the link between macronutrient intake and time in euglycemia or hypoglycemia in individuals with T1D.

METHODS

In a subset of 219 individuals of the GUTDM1 cohort (65% female, mean age 41,0 ± 15,1 years, median diabetes duration 15,0 [IQR 6,3-28,0] years), we used logistic regression to establish associations between food intake, using online dietary questionnaires, and time in euglycemic range (TIR, set at ≥ 70%) and time below range (TBR, set at < 4%,). Outcomes were expressed per 1 SD intake of nutrient, and adjusted for age, sex, duration of T1D, BMI and alcohol intake.

RESULTS

The median TIR was 69% (IQR 53-81%], median TBR 2% (IQR 1-4%), mean energy intake 1751 ± 536 kcal, fat intake 77 ± 32g, carbohydrate intake 167 ± 63g, fiber intake 20 ± 9g and protein intake 70 ± 24g. Higher fat intake was associated with a higher odds of a TIR ≥ 70% (OR 1,45 (95% CI 1,07-1,96)). This was similar for protein- (OR 1,41 (95%CI 1,04-1,92)) and fiber intake (OR 1,41 (95% CI 1,04-1,91)). In contrast, carbohydrate intake was not associated with TIR ≥ 70% (OR 0,83 (95% CI 0,61-1,12)). Of the macronutrients, solely a higher carbohydrate intake strongly trended towards an association with a higher odds of having a TBR < 4% (OR 1,36 (95% CI 0,98-1,89)).

CONCLUSION

Higher fat , fiber and protein, but not carbohydrate intake were associated with favorable TIR (≥ 70%) in T1D. In contrast, a higher carbohydrate intake trended towards a lower risk of TBR. This may suggest that carbohydrate reduction does not improve TIR, while increasing risk of hypoglycemia. Therefore, these findings warrant confirmatory (interventional) investigations and may impact current nutritional guidelines for T1D.

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Explaining the effects of GLP-1 in humans: Visualizing GLP-1 receptor expression *in vivo* by radiolabeled exendin PET/CT

Laura N. Deden, Martin Gotthardt, Edo O. Aarts, Hans de Boer, Cees J. Tack, Mijke Buitinga, Ignace M.C. Janssen, Eric J. Hazebroek, Bastiaan E. de Galan, Marti Boss

BACKGROUND

Introduction Glucagon-like peptide-1 (GLP-1) is a strong incretin hormone, which actions are mediated via the GLP-1 receptor (GLP-1R). Although knowledge about actions of GLP-1 in humans is increasing, our understanding of GLP-1R expression and its relation with GLP-1 signaling remains incomplete, since studying GLP-1R expression is challenging. We propose that ^{68}Ga-NODAGA-exendin-4 (EX4) PET/CT is a valuable tool to assess GLP-1R expression in vivo. In this study we have assessed accumulation of EX4 by PET/CT, aiming to non-invasively detect relevant organ-specific GLP-1R expression in humans for the first time.

METHODS

Sixty-two participants were included from ongoing studies into insulinoma detection, type 1 diabetes, obesity and type 2 diabetes and post-bariatric outcomes. All participants received 75-100 MBq EX4 (4-7 µg peptide) and underwent PET/CT. Radiotracer distribution was assessed visually and quantitatively in abdominal (all participants), chest (n = 57), head (n = 41) and pelvic (n = 8) imaging.

RESULTS

Apparent radiotracer uptake was observed in pancreas and duodenum in all participants. In addition, the majority of

participants showed uptake in salivary glands (95%) and pituitary gland (78%). Uptake in cardiac tissue was observed in four participants (7%). Of the female participants, half showed uptake in glandular breast tissue (47%), uterus and ovary (4 out of 8). No accumulation higher than blood pool was observed in liver, adipose tissue and skeletal muscles.

CONCLUSION

Our data confirm accumulation of EX4 in organs with well-known GLP-1R expression, such as the pancreas and duodenum. In addition, accumulation was observed in organs in which the physiological role of GLP-1 and GLP-1R expression is still somewhat elusive, like the pituitary gland, salivary glands, glandular breast tissue and myocardium. In the majority of these tissues, EX4 accumulation corresponds with GLP-1R expression as described in previous reports. These findings suggest that EX4 PET/CT is a promising tool to target and visualize GLP-1R expression *in vivo* and may elucidate pathophysiological mechanisms underlying (variable) treatment responses of GLP-1R agonists.

Conflict of interest: none

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Enhanced BMP5 signaling is associated with type 2 diabetes and affects insulin secretion in pancreatic β -cells.

Esmée Dekker, Amadeo Muñoz, Twan de Winter, Eelco de Koning, Françoise Carlotti

Department of Internal Medicine, LUMC, Leiden, The Netherlands
E-mail: e.dekker@lumc.nl

BACKGROUND

Type 2 diabetes (T2D) is a complex multifactorial disease defined by β-cell failure and insulin resistance. Considering the increasing global prevalence of this disease, unravelling common underlying mechanism that can lead to β-cell failure is of pronounced importance. We hypothesized that BMP5 signaling plays a role in the onset and progression of type 2 diabetes.

METHODS

Single-cell transcriptomic analysis was performed on primary human islet cells isolated from donor pancreas (n = 3 donors without diabetes). Previously published scRNA-seq datasets of human pancreatic islets were used to compare gene expression in islet cells from donors with and without type 2 diabetes. In addition, we performed lentivirus-mediated knockdown using shRNAs targeting BMP5 in human islets. These islets were analysed for gene expression and glucose-stimulated insulin secretion. INS-1E β-cells treated with recombinant BMP5 (50 ng/ml) were assessed for glucose-stimulated insulin secretion.

RESULTS

ScRNAseq data revealed that BMP5 is highly and specifically expressed in islet β-cells compared to other pancreatic cell types. ScRNAseq data from donors with type 2 diabetes showed a 2.0-fold upregulation of BMP5, and 3.4-fold upregulation of the BMP target gene ID3 in β-cells ($p < 0.05$ and $p < 0.01$, respectively) compared to beta cells from donors without diabetes. Downregulation of BMP5 in primary human islets induced a 1.5-fold upregulation of the beta-cell maturity marker MAFA compared to the non-target control ($n = 3$, $p < 0.05$). This was associated with increased insulin secretion (Stimulation index (SI) 11.04 vs 7.02 in non-target control, $p < 0.001$; $n = 3$). In contrast, treatment of INS-1E β-cells with recombinant BMP5 induced impaired glucose-stimulated insulin secretion (SI 2.02 vs 3.63 in untreated control, n = 3, ns).

CONCLUSION

The upregulation of BMP5 in beta cells from subjects with type 2 diabetes and negative association with beta-cell identity and secretion points towards a role of BMP5 in beta cell health and disease.

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The effect of bolus advisors on glycaemic parameters in adults with diabetes on intensive insulin therapy: a systematic review with meta-analysis

Elisabeth J. den Brok[1], Cecilie H. Svensson, Maria Panagiotou, Stephan Proennecke, Peter Mertens, Stravoula Mougikakou, Ulrik Pedersen-Bjergaard, Bastiaan E. de Galan[1,2] on behalf of the MELISSA consortium

1 CARIM School for Cardiovascular Diseases, Maastricht University, Maastricht, The Netherlands
2 Department of Internal Medicine, MUMC+, Maastricht, The Netherlands
E-mail: lisa.denbrok@maastrichtuniversity.nl

BACKGROUND

The effect of bolus advisors (BAs) on glycaemic control in adults with diabetes on intensive insulin therapy remains unclear. This systematic review with meta-analysis aimed to provide a comprehensive synthesis of randomised controlled trials investigating the effects of currently available BAs on glycaemic parameters in adults with diabetes.

METHODS

An electronic search of MEDLINE, Embase, CINAHL, Cochrane Library, and ClinicalTrials.gov was performed. The (standardised) mean difference was selected to determine the difference in continuous outcomes between the intervention groups. A random-effect model meta-analysis with meta-regression was performed.

RESULTS

A total of eighteen randomised controlled trials involving 1641 participants (50.74% females) with a median HbA1c of 8.45% (IQR 7.95-9.30) and diabetes duration of 18 years (16-21) were included in the systematic review. Most participants had Type 1 diabetes (n = 1506, 91.8%) and were on multiple daily injections (n = 1176, 70%). The median follow-up was 15 weeks (16-31). Fourteen articles investigated a standard BA, and four articles assessed an adaptive BA. In the meta-analysis of ten studies, the use of BAs did not significantly reduce HbA1c compared to standard treatment (-0.13, 95% CI: -0.32 to 0.07, I^2 = 42.6%). There was substantial heterogeneity in the effect estimate, largely attributable to the variations in the risk of bias assessment. The use of BAs was associated with a modest decrease in Low Blood Glucose Index (LBGI) and improvement in treatment satisfaction, but not with reduction in hypoglycaemic events or significant effects on other secondary outcomes.

CONCLUSION

The use of a BA does not lead to better glycaemic control, except for a modest reduction in LBGI and modest improvement in treatment satisfaction. These data do not support standard use of bolus advisors for people with diabetes on intensive insulin treatment.

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Early time-restricted eating in diabetes type 2: preliminary results of the e-TIMED trial

Carmen A.W. Dietvorst, Kirsten A.C. Berk

Department of Internal Medicine, Division of Dietetics, Erasmus MC, Rotterdam, The Netherlands
E-mail: c.dietvorst@erasmusmc.nl

BACKGROUND

Early Time-Restricted Eating (eTRE), a form of intermittent fasting, has shown great potential in improving glycaemic regulation in patients with prediabetes. However, long-term metabolic effects and feasibility of eTRE have not yet been studied in people with type 2 diabetes (T2D) and obesity in a randomized controlled manner. The aim of this study is to determine the difference in effectiveness in glycemic regulation of eTRE, compared to continues caloric restriction, after one year in overweight adults with T2D.

METHODS

172 patients with T2D and overweight or obesity aged 18-75 years will be randomized to receive a low carbohydrate Mediterranean diet, where the intervention group must also adhere with a ten-hour eating time restriction. During the 1-year program, glucose levels, cardiovascular risk factors, food intake and quality of life are monitored and all participants receive four group meetings and access to a nutrition app. Preliminary results between baseline (n = 20) and 6 months (n = 8) were analyzed using paired samples t-test.

RESULTS

Twenty patients (32-73 years) are currently included in the trial. After following 6 months eTRE diet a reduction was shown in weight (109.3 ± 19.4 vs 99.8 ± 18.5; p = 0.002), HbA1c (50.4 ± 5.9 vs 45.1 ± 5.8; p = 0.010) and fasting

glucose (8.1 ± 2.5 vs 6.4 ± 1.4; p = 0.035) compared to baseline. During the program, both fat mass (41.4 ± 16.3 vs 39.6 ± 17.6; p = 0.005) and lean mass (65.9 ± 11.4 vs 60.1 ± 10.0; p = 0.007) decreased. No significant difference is found between calorie (1398 ± 406 vs 1228 ± 243; p = 0.913) and carbohydrate (120 ± 46 vs 107 ± 42; p = 0.861) intake at baseline and after 6 months.

CONCLUSION

Preliminary results show that eTRE is a promising intervention to improve glycaemic regulation and to stimulate weight loss. In the coming year, more participants will be included, allowing for comparison with continuous fasting.

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Daily unstructured physical activity affects mean glucose, occurrence of hypoglycaemia and glucose variability in people with type 1 diabetes

L.C.A. Drenthen[1], M. Ajie[1], E.A. Bakker[2,3], E.J. Abbink[1], D.H.J. Thijssen[2,4], C.J. Tack[1], B.E. de Galan[1,5]

1 Department of Internal Medicine, Radboudumc, Nijmegen, The Netherlands
2 Department of Physiology, Radboudumc, Nijmegen, The Netherlands
3 Department of Physical Education and Sports, University of Granada, Granada, Spain
4 Research Institute for Sport and Exercise Sciences, John Moores University, Liverpool, UK
5 Department of Internal Medicine, MUMC+, Maastricht, The Netherlands
E-mail: linda.drenthen@radboudumc.nl

BACKGROUND

People with type 1 diabetes are advised to follow a healthy lifestyle with sufficient physical activity, including activity that is 'unstructured'. Little is known about glycaemic responses to such unstructured physical activities.

METHODS

This is a post-hoc analysis of a clinical trial, wherein participants wore a blinded continuous glucose monitoring device and thigh accelerometer for 18 days. We assessed effects of unstructured physical activity on glucose variability (i.e. coefficient of variation (CV)), mean glucose concentration, and occurrence of hypoglycaemia on the same day, subsequent night and next day. Data are expressed as coefficient (B) or OR with [95% CI].

RESULTS

18 adults with type 1 diabetes participated in the study (12 males, mean ± SD age 38 ± 13 years, HbA1c 56 ± 8 mmol/mol). More active time was associated with a higher CV during the same day (B 1.14 [0.02, 2.26], p = 0.045) and next day (B 1.22 [0.09, 2.35], p = 0.034), a lower mean glucose concentration the same day (B -0.35 [-0.56, -0.14], p=0.001) and subsequent night (B -0.45 [-0.78, -0.12], p = 0.008), and higher hypoglycaemia risk the same day (OR 1.56 [1.11, 2.21], p = 0.011), subsequent night (OR 2.40 [1.46, 3.96], p = 0.001) and next day (OR 1.59 [1.12-2.24], p = 0.009). More active time before 3PM was associated with a lower mean glucose concentration during the subsequent night (B -0.60 [-0.96, -0.24], p = 0.001) and higher risk for nocturnal hypoglycaemia (OR 2.08 [1.30, 3.35], p = 0.002).

CONCLUSION

Unstructured, daily life physical activity is associated with increased glucose variability and, even when performed before 3PM, with a lower mean glucose and higher risk for (nocturnal) hypoglycaemia in people with type 1 diabetes. These results highlight the difficulties of incorporating physical activity into overall glycaemic management.

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The effect of including eHealth in dietary interventions in patients with type 2 diabetes with overweight or obesity: a systematic review

Karlijn A.M Geurts[1], Sandra Woodcock-Nekeman, Mitchell Hummel, Elisabeth F.C. van Rossum, Kirsten A.C Berk[1]

1 Department of Internal Medicine, Division of Dietetics, Erasmus MC, University Medical Centre Rotterdam, Rotterdam, The Netherlands
E-mail: k.geurts@erasmusmc.nl

BACKGROUND

EHealth has a growing impact on the delivery of health care, making health systems more efficient. This systematic review examines the (cost) effectiveness of dietary interventions using eHealth alone or combining eHealth with face-to-face contact, in patients with (pre)diabetes and obesity, compared with a face-to-face control group.

METHODS

Literature databases were searched up to 17 November 2022 with the following search terms: diabetes mellitus, obesity, weight loss program, diet therapy, overweight and telehealth. Inclusion criteria: randomized controlled trial, < 6 months in duration, involving a dietary intervention, performed in adults with type 2 diabetes or prediabetes and overweight or obesity, using eHealth alone or combining eHealth with face-to-face contact, compared to face-to-face contact alone, and report an outcome on weight loss, glycaemic regulation and/or cost-effectiveness. Selection of articles was done manually and with ASReview Lab. The Cochrane Risk of Bias 2 tool was used to assess the risk of bias.

RESULTS

Fifteen studies were included, investigating a wide variety of eHealth interventions. Seven of fourteen studies reporting on weight (change) showed a significant between-group difference in weight loss, ranging from −1.18 to −5.5 kg, and five studies showed a trend in favour of the eHealth programs (alone or combined). Eleven studies reported HbA1c, three found a significant between-group difference with a decrease of −0.23 to −0.70 %, and six studies showed non-significant changes in favour of the eHealth programs. EHealth alone, without interaction with a health care provider, was less effective. Two studies reported incomplete data on cost-effectiveness.

CONCLUSION

This review indicates that eHealth leads to better results of dietary interventions for patients with (pre)diabetes, especially when combined with face-to-face contact or interaction with a healthcare professional. Insufficient data was available on cost-effectiveness to draw conclusions.
ADDRM 2023 abstract.

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Evaluating the relationship between glycemic control and bone fragility within the UK biobank: observational and Mendelian randomization analyses

Samuel Ghatan[1], Fjorda Koromani[1], Carolina Medina-Gomez[1], Maryam Kavousi[2], Fernando Rivadeneira[1], Ling Oei[1]

1 Department of Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands
2 Department of Epidemiology, Erasmus Medical Center, Rotterdam, The Netherlands

BACKGROUND

Individuals with diabetes have an increased risk of fractures. The observational and potential causal effects of glycemic control on bone fragility have not been explored in a large population-based setting. This study aimed to (1) examine the relationship between glycemic control and fracture risk in individuals with T1D and T2D, (2) assess changes in BMD in these populations, and (3) utilize non-linear Mendelian randomization to explore potential causal associations between glycemic control, BMD, and fractures.

METHODS

This study comprised 452,131 individuals from the UK Biobank. At baseline, 23,682 individuals had type 2 diabetes (T2D), and 4,078 had type 1 diabetes (T1D). Individuals with diabetes were stratified by glycated hemoglobin levels (HbA1C) into two groups: Adequately Controlled Diabetes (ACD; n = 17,078; HbA1c < 7.0%) and Inadequately Controlled Diabetes (ICD; n = 10,682; HbA1c ≥ 7.0%). Linear and Cox regression models, controlling for covariates, were used to estimate associations with eBMD/fractures across groups. HbA1c was also assessed continuously in both T1D and T2D. Mendelian randomization (MR) was used to obtain linear and non-linear causal inferences on the relationship between HbA1c levels, fracture risk, and eBMD.

RESULTS

In individuals with T1D, a 1% unit increase in HbA1C levels was associated with a 12% increase in fracture risk (95% CI [1.05-1.19]). Fracture risk was also higher in individuals with ICD. In T2D stratified analyses, significant evidence for a non-linear association with fracture risk was observed (ANOVA p-value = 0.002), with risk being increased at both low and high levels of HbA1c. Concordantly, fracture risk between the ACD and ICD groups was similar. Despite increased eBMD in those with ICD (beta = 0.12 SD, 95% CI [0.10, 0.14]), genetically predicted HbA1c levels were not significantly associated with increased fracture risk. However, we did observe both linear and non-linear causal associations with eBMD, indicating that low to moderate levels of HbA1c are associated with decreasing eBMD, and high levels are associated with increasing eBMD.

CONCLUSION

Aiming to reduce HbA1c levels will effectively reduce fracture risk in patients with T1D, but not T2D. We infer no evidence for a causal relationship between increasing HbA1c levels and fracture risk, but do for eBMD.

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Free flap reconstruction of the diabetic foot: a case-report and research proposal

S.C. Ghijsen, O.J. Bakker
St. Antonius Ziekenhuis, Nieuwegein, The Netherlands
E-mail: s.ghijsen@antoniusziekenhuis.nl and o.bakker@antoniusziekenhuis.nl

BACKGROUND

Amputations are associated with reduced quality of life and a high 5-year mortality risk, making the prevention of amputations in the treatment of diabetic foot (DF) essential. Tissue coverage of DF defects holds promise in improving healing rates and reducing the risk of major amputation. Currently, free tissue transfer (FTT) does not have a standardized role in the operative treatment of DF, being reserved for extensive cases, even though flap survival rates in literature are as high as 92%. We present three recent cases of DF patients treated with FTT, along with our research proposal.

METHODS

We retrospectively reviewed all patients with DF and exposed bone that were treated with FTT in our institution. Early postoperative results were assessed at 30 days after FTT.

RESULTS

A total of three patients underwent FTT for DF with exposed bone. The first patient presented with a heel defect, treated with a gracilis flap following extensive endovascular revascularization. The muscle flap showed full viability, but 11 days after the FTT, a new split skin graft (SSG) was required due to partial SSG loss. At 30-days post-FTT the SSG showed 100% viability.
Two patients with foot phlegmon due to a DF ulcer initially underwent debridement and minor amputation. Subsequently, one received a gracilis muscle flap, and the other an anterolateral thigh (ALT) flap. The gracilis muscle fully integrated, but at 20 days postoperative, treatment with fusidic acid cream was initiated due to superficial infection. Immediately postoperative, the anastomosis of the ALT was dehiscence due to ankle joint mobilization, necessitating operative restoration. At 10 days postoperative, the wound showed superficial dehiscence at the proximal site. At day 20, the flap exhibited necrosis distally.

CONCLUSION

FTT in DF reconstruction is a complex and delicate procedure. Nevertheless, literature reports 92% flap survival rates and its potential in limb salvage. Further research is needed to optimize patient selection.

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Natural daylight through windows as opposed to artificial lighting during office hours improves glucose control and 24h substrate metabolism in type 2 diabetes patients

Ivo Habets[1], Jan-Frieder Harmsen[1], Marit Kotte[1], Dzhansel Hashim[1], Soraya de Kam[1], Merel Timmermans[1], Gert Schaart[1], Anne Gemmink[1], Tineke van de Weijer[1], Patrick Schrauwen[1], Charna Dibner[2], Joris Hoeks[1]

1 Department of Nutrition and Movement Sciences, NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University Medical Center, Maastricht, The Netherlands
2 Thoracic and Endocrine Surgery Division, Department of Surgery/Department of Cell Physiology and Metabolism, Faculty of Medicine, University of Geneva, Geneva, Switzerland

BACKGROUND

Misalignment between the internal circadian clock and external rhythms imposed by our current 24/7 society is associated with an increased incidence of metabolic diseases, including type 2 diabetes (T2D). Although natural daylight is the strongest *zeitgeber* for the circadian clock, most people spend daytime in indoor environments under constant artificial lighting. Here, we investigated the potential benefit of increased daytime exposure to natural light compared to constant artificial lighting on 24h glucose control and substrate metabolism in T2D patients.

METHODS

Thirteen T2D patients (70 ± 6 years, BMI: 30.1 ± 2.3 kg/m^2, HbA1c: 6.1 ± 1.0 %, Fasting plasma glucose: 8.1 ± 1.5 mmol/L) were exposed to two lighting interventions of 4.5 days in a randomized cross-over fashion: natural daylight facilitated through windows versus constant artificial LED lighting during office hours (8:00-17:00). Between interventions there was a washout of at least 4 weeks. Light spectra were obtained from the natural daylight room on multiple occasions each day. Evenings were spent in dim light (< 5 lux) and the sleeping period in darkness (23:00-7:00). Volunteers were provided with standardized meals and wore continuous glucose monitors (Abbott, Freestyle

Libre Pro iQ) on their upper arm. On day 4, indirect calorimetry was performed around the clock (every 5h) to assess 24h substrate metabolism and energy expenditure together with frequent blood draws to assess circulating metabolites. Core body temperature was measured for 24h using a telemetric pill. On day 5, a fasted muscle biopsy was taken to assess clock gene expression after which a mixed meal test (MMT) was executed, with frequent blood samplings in conjunction with indirect calorimetry.

RESULTS

The highest light intensity upon natural daylight was usually reached at 12:30 PM with on average 2.453 lux (range: 1.000-10.000 lux) versus a constant 300 lux in the artificial light condition. Volunteers spent more time ($p = 0.01$) in the normal glucose range (4.4-7.8 mmol/L) over the 4.5 days upon natural daylight, accompanied by a lower respiratory exchange ratio throughout the 24h cycle (condition effect: $p = 0.028$). Particularly at 1PM the respiratory exchange ratio was lower ($p = 0.04$), indicating a shift towards fat metabolism in the natural versus the artificial light condition. At all times of day resting energy expenditure was similar between light conditions. Core body temperature was significantly higher upon natural daylight during exposure hours (8:00–15:00) on day 4 ($p = 0.025$). mRNA levels of *Per1* and *Cry1* in skeletal muscle were higher upon natural daylight ($p < 0.05$). During the MMT, whole-body energy expenditure and the respiratory exchange ratio were not different between both light conditions. Additional data, such as plasma metabolites from the 24h assessment and the MMT will be available at the time of the conference.

CONCLUSION

Our findings suggest that exposure to natural daylight positively impacts metabolism and could support the treatment and prevention of metabolic diseases.

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A microfluidic platform to study single islet insulin secretion

Esmay Hammink, Françoise Carlotti, Marten Engelse, Eelco de Koning

Department of Internal Medicine, LUMC, Leiden, The Netherlands
E-mail: e.j.hammink@lumc.nl

BACKGROUND

Pancreatic islets are heterogeneous, where the heterogeneity in composition has been extensively studied. However, little is known about the heterogeneity in the insulin secretion pattern among individual islets. Physiological insulin secretion from islets in response to elevated glucose levels is a dynamic, biphasic and oscillatory process. Traditional glucose-stimulated insulin secretion (GSIS) assays require pooling of islets, masking the individual islet response. Here, we introduce a microfluidic system that enables the detection of dynamic insulin secretion patterns from individual islets to study functional heterogeneity.

METHODS

Single human pancreatic islets were placed in parallel on the µ-slide spheroid perfusion microfluidic chip from Ibidi and connected to the Biorep V5 for glucose perfusion and automated sample collection. Insulin content in the perfusate was quantified using insulin ELISA. Insulin concentrations were normalized to the islet size in islet equivalents (IEQs), estimated by measuring the diameter of islets using microscopy. FDA/PI staining was performed after the assay to assess islet viability.

RESULTS

Placement inside the microfluidic chip for 4 hours did not significantly affect islet viability, confirmed by FDA/PI staining (viability > 90%). Single pancreatic islets showed heterogeneous responses to elevated glucose levels, both in quantity and secretion pattern. Within one donor, baseline secretion ranged from 0.008 to 0.08 fmol/min/IEQ, total insulin secreted from 35.9 to 370.4 fmol/IEQ and stimulation index from 2.3 to 15.4 ($n = 5$). Heterogeneity in insulin secretion patterns was observed between two islets tested at a higher temporal resolution (every minute), with only one of the two islets exhibiting a rapid first phase in addition to the sustained second phase.

CONCLUSION

These preliminary data indicate that this microfluidic platform may offer a valuable tool for studying secretory patterns in single pancreatic islets, allowing to test various hypotheses of which factors contribute to the heterogeneity in islet insulin secretion.

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Modelling MODY1 using human pluripotent stem cells

Roxanna D. Hauck, Siebe Spijker, Natasja de Jong, Françoise Carlotti, Eelco de Koning

Department of Internal Medicine, LUMC, Leiden, The Netherlands
E-mail: r.d.hauck@lumc.nl

BACKGROUND

MODY1 is a monogenetic form of diabetes characterized by a mutation in the HNF4A gene, which encodes for the transcription factor HNF4α. Patients with MODY1 experience transient hyperinsulinaemia at birth, but paradoxically develop hyperglycaemia in early adulthood. To date, the exact role of HNF4α in the development and function of beta cells is unclear. In vivo models are either incompatible with life or do not show a diabetic phenotype. We hypothesize that HNF4α is required for proper beta cell development, and that insulin secretion is affected by reduced HNF4α expression.

METHODS

Patient-specific (HNF4A+/-), gene-corrected, and knock out (KO)-cell lines were generated and used in our 3D, multistage, 30 day beta cell differentiation protocol, in which differentiation stages are verified using FACS, qPCR, and immunocytochemistry. Additionally, immunohistochemistry of fetal and adult human pancreatic tissue was assessed to determine HNF4α protein expression in islet cells.

RESULTS

Immunohistochemistry of adult human pancreatic tissue showed that pancreatic islets express HNF4α. Intriguingly, HNF4A colocalized with glucagon in adult human pancreatic islets, rather than with C-peptide ($p < 0.05$, $n = 3$). For new HNF4A-KO lines, 96 clones were generated, of which 3 were selected for further testing. The remaining clones were frozen. At present, all three cell lines could be successfully differentiated to the definitive endoderm stage (> 95% expression of stage-specific markers in all cell lines).

CONCLUSION

Alpha cells, rather than beta cells, are the main source of HNF4α expression in human adult pancreatic islets. These observations raise questions about the role of HNF4α in insulin secretion and beta cell development, as well as alpha cell development. This will be investigated further using our novel HNF4A-iPSC lines.

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Development and validation of a lifetime prediction model of cardiovascular disease in individuals with type 1 diabetes

Marga A.G. Helmink[1], Frank L.J. Visseren[1], Steven H.J. Hageman[1], Jan Westerink[2]

1 Department of Vascular Medicine, University Medical Center Utrecht, Utrecht, The Netherlands
2 Department of Internal Medicine, Isala Clinics, Zwolle, The Netherlands
E-mail: M.A.G.Helmink@umcutrecht.nl

BACKGROUND

Individuals with type 1 diabetes (T1D) have an increased risk of developing cardiovascular disease (CVD) compared to the general population. The aim of this study was to develop and externally validate a sex-specific and competing-risk adjusted prediction model for the estimation of 10-year and lifetime risk of CVD in individuals with T1D.

METHODS

Cox proportional hazards models were developed in 39,756 individuals with T1D without established CVD from the Swedish National Diabetes Register (SNDR), using age as follow-up variable. Predictors included onset age of diabetes, smoking status, body mass index, systolic blood pressure, HbA1c, eGFR, non-HDL-cholesterol, albuminuria and retinopathy and the model was externally validated in 1,022 individuals from the UK Biobank.

RESULTS

During a median follow-up of 11.8 years (interquartile range 6.1-17.1), 4,608 CVD events were observed. The competing endpoint non-CVD mortality was observed 1,316 times. C-statistics for prediction of 10-year risk of CVD were 0.86 (95% confidence interval [CI] 0.85-0.86) for internal validation and 0.74 (95%CI 0.70-0.78) for external validation (**figure 3**). Calibration plots showed good agreement between expected and observed 10-year CVD risks for both internal and external validation.

CONCLUSION

This model can be used to estimate the 10-year and lifetime risk of CVD in individuals with T1D without established CVD, using readily available clinical characteristics. The model may aid in communication of CVD risks towards patients and support shared decision making.

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Proteome and transcriptome analyses reveal a role for the liver in hypoglycemia-induced inflammation in diabetes

Marijn S. Hendriksz[1], Julia I.P. van Heck[1], Clementine E.M. Verhulst[1], Judit Castillo-Armengol[2,3], Bernard Thorens[2], Rinke Stienstra[1,4], Cees J. Tack[1]

1 Department of Internal Medicine, Radboud University Medical Center, Nijmegen, The Netherlands
2 Center for Integrative Genomics, University of Lausanne, Lausanne, Switzerland
3 Novo Nordisk A/S, Måløv, Denmark
4 Division of Human Nutrition and Health, Wageningen University, Wageningen, The Netherlands
E-mail: marijn.hendriksz@radboudumc.nl

BACKGROUND

People with diabetes who require insulin treatment experience hypoglycemia on a regular basis. Previously we have shown that a single experimental hypoglycemic episode induces a systemic pro-inflammatory response. However, underlying mechanisms are still largely unknown. Therefore, we aim to uncover mechanisms and tissue-specific contributions that promote hypoglycemia-induced inflammation by studies in humans and mice.

METHODS

Twenty-five participants with type 1 diabetes underwent a hyperinsulinemic euglycemic-hypoglycemic clamp. Plasma was collected at euglycaemia and 24h after the hypoglycemic event to analyze 368 inflammatory and cardiovascular markers using the Olink proteomics platform. In addition, tissues from diabetic C57BL6/N male mice were collected 2h post insulin-induced hypoglycemia or alternative saline injection and compared using bulk RNA sequencing analysis.

RESULTS

Twenty-four hours after the experimental hypoglycemic episode, 43 proteins were significantly upregulated ($p < 0.05$) compared to baseline. To elucidate the origin of these proteins, analysis on tissue specificity was performed, revealing proteins predominantly from adipose and lymphoid tissue, and the liver. Initially, we studied the contribution of the liver in hypoglycemia-induced inflammation using bulk RNA sequencing. Data analyses revealed 205 significantly upregulated and 176 downregulated genes (FDR < 0.05) in the insulin-induced hypoglycemia group when compared to the saline-control group. To identify groups of genes with a common biological function, gene set enrichment analysis was performed. In the insulin-induced hypoglycemia group,

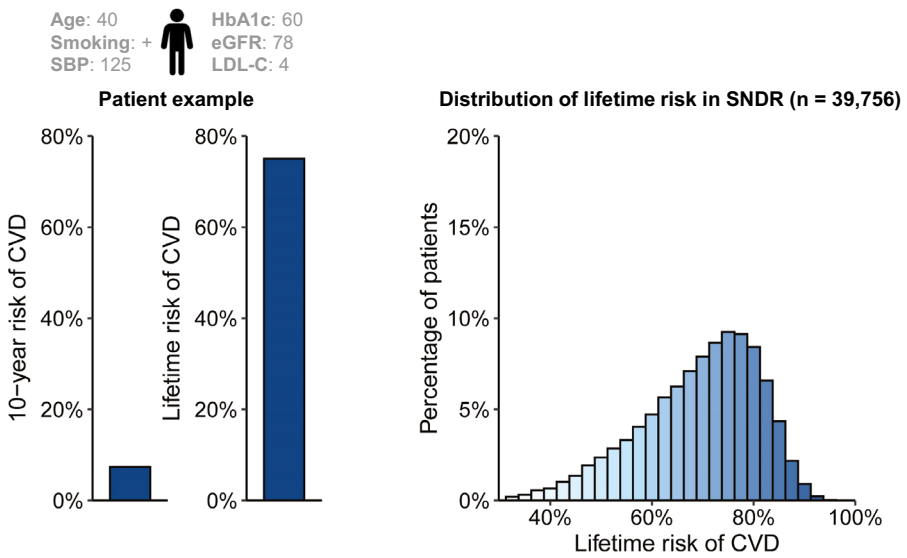

Figure 3. Risk of CVD.

significantly upregulated genes were associated with TNF-α signaling via the NF-κB signaling pathway (Normalized Enrichment Score = 2.278, adjusted p value = 2.26e-07).

CONCLUSION

An experimental hypoglycemic episode led to systemic inflammation evidenced by increased inflammatory and cardiovascular markers. These proteins appear to originate from adipose and lymphoid tissue and the liver. Hepatic changes induced by hypoglycemia involved genes associated with the TNF-α signaling via the NF-κB pathway. Together, these findings suggest that systemic inflammation induced by hypoglycemia is at least partly from the liver.

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Developing Lifestyle Support Tools for People with Type 2 Diabetes and Low Health Literacy: A Participatory Design Approach

Eclaire Hietbrink[1,2], Floor Lieverse[1], Marlin Meulman[3], Anouk Logtenberg[3], Lara Schemkes[3], Manou Hijink[3], Petra Welmers[3], Eline Droppers[3], Dorthe Brands[3], Arie Koster[3], Anouk Middelweerd[1]

1 Department of Biomedical Signals and Systems, University of Twente, Enschede, The Netherlands
2 Department of Internal Medicine/Nephrology, Ziekenhuisgroep Twente, Almelo, The Netherlands
3 Smart Solution Semester, Saxion University of Applied Sciences, Enschede, The Netherlands
E-mail: e.a.g.hietbrink@utwente.nl

BACKGROUND

Type 2 diabetes (T2D) management requires a healthy lifestyle, which is extra challenging for individuals with low health literacy (LHL). Existing lifestyle interventions often fail to meet the specific needs of this group. This study aimed to develop a lifestyle support tool to support individuals with T2D and LHL.

METHODS

A participatory design approach was employed in three phases. The first phase involved reviewing literature and conducting semi-structured interviews to identify design principles for individuals with LHL. Fourteen interviews were conducted with individuals with LHL, healthcare professionals, and a language expert. The second phase focused on developing an initial version of the tool based on the identified requirements. The final phase consisted of evaluating the tool through think-aloud sessions.

RESULTS

The first phase revealed design principles and needs related to delivery modes, comprehensibility, and applicability. Individuals with LHL expressed a desire for choice between digital and non-digital tools to cater to their preferences. Design considerations included choice of words, structure, colour indications, and inclusion of images. Step-by-step plans are necessary for actionable lifestyle advice. The development phase resulted in an app and a magazine, both incorporating design principles for enhanced comprehensibility and applicability. These features included concise sentences with key words in bold, supporting illustrations/videos, a text reading function, and clear instructions for action. Feedback from evaluations highlighted positive aspects such as the reading function, font size, and illustrations. Improvements were made to the app's chat function and recipe complexities based on feedback.

CONCLUSION

The participatory design approach facilitated the translation of needs into the tools and provided valuable improvement points. Further work should focus on further development with the target group and implementation strategies.

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Novel in vivo zebrafish model and beta cell reporters to address whether exocrine malfunction leads to beta cell stress

Willem M. H. Hoogaars[1], Noura Faraj[1] , Mette C. Dekkers[2], Anouk H.G. Wolters[1], B.H. Peter Duinkerken[1], Arnaud Zaldumbide[2], Ben N.G. Giepmans[1]

1 Department of Biomedical Sciences of Cells and Systems, UMCG, Groningen, The Netherlands
2 Department of Cell and Chemical Biology, Leiden University Medical Center, Leiden, The Netherlands

BACKGROUND

Autoimmune-mediated destruction of pancreatic beta cells and subsequent insulin insufficiency causes type 1 diabetes (T1D). Importantly, multiple studies showed that beta cells show signs of chronic ER stress and activation of apoptotic and inflammatory pathways before the onset of T1D. However, the trigger of this pre-symptomatic beta cell stress is unknown. Recent studies also suggest a possible involvement of exocrine tissue in the onset of T1D pathology based on a decrease in total pancreatic weight in T1D patients and pre-symptomatic donors, the presence of inflammatory cells in the exocrine pancreas and the presence of aberrant exocrine/endocrine cells. We hypothesize that exocrine dysfunction may induce beta cell ER stress and/or apoptosis, thereby contributing to beta cell dysfunction and T1D pathology. This possible cause-consequence relationship cannot directly be assessed in human pancreas and therefore we use zebrafish larvae to test this hypothesis in vivo.

METHODS

To determine the effect of exocrine dysfunction on beta cells, we generated transgenic zebrafish to specifically ablate exocrine cells using the nitroreductase/nifurpirinol system. To develop a functional readout in zebrafish beta cells for live cell imaging in vivo, we generated beta cell specific fluorescent ER stress and apoptosis reporters.

RESULTS

We show proof of principle of exocrine ablation/apoptosis by demonstrating caspase-dependent translocation of the fluorescent reporter mScarlet from the membrane to the cytosol. The function of ER stress and apoptosis reporters was validated in vitro in HEK293T cells, after which we generated transgenic reporter fish that specifically express the ER stress and apoptosis reporters in islet beta cells. These reporter fish are currently crossbred with the exocrine ablation fish to assess beta cell stress after exocrine ablation.

CONCLUSION

Our model will be a crucial in vivo tool to answer if exocrine malfunction can induce beta cell stress and thus ultimately may be involved in T1D pathology.

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PIONEER REAL: A multi-centre, prospective, non-interventional single-arm study investigating clinical parameters associated with the use of once-daily oral semaglutide in a real-world adult population with type 2 diabetes in the Netherlands

W.H. van Houtum, P. Schrombges, A. van Bon, H. Herrings

BACKGROUND

Oral semaglutide, a novel GLP-1RA in a tablet for once-daily oral administration, is anticipated to improve glycaemic control in adults with type 2 diabetes (T2D) in a real-world setting. The PIONEER REAL Netherlands study aimed to complement the findings from the clinical development programme by investigating the glycaemic control as mean change in HbA1c, in bodyweight and treatment satisfaction in 34 to 44 weeks in adult patients with T2D according to local clinical practice.

METHODS

This was a 34 to 44 weeks, multi-centre, prospective, open-label, non-interventional, single-armed study. Data was obtained through primary data collection. The study was non-interventional as the decision to initiate treatment with oral semaglutide was at the treating physician's discretion and clearly separated from the decision to include the patient in the study. This study was conducted in a real-world setting among 187 adult people with T2D at 27 sites in the Netherlands.

RESULTS

Patients treated with oral semaglutide during the study experienced reductions in HbA1c values. The estimated mean change (SE) in HbA1c value from baseline to week 38 was statistically significant (p-value: < 0.0001). In MMRM adjusted model, the observed mean (standard deviation [SD]) baseline HbA1c was 8.5% (1.28) and estimated mean at week 38 was 7.3% showing the estimated mean change (SE) of -1.2% (0.16). The estimated mean

change in body weight was statistically significant (p-value: < 0.0001) the baseline observed mean (SD) body weight was 102.6 kg (17.71) and the estimated mean at week 38 was 96.7 kg showing a statistically significant estimated mean (SE) change of 5.8 kg (0.53).

CONCLUSION

Patients treated with oral semaglutide during the study showed improvement in body weight reduction, HbA1c levels, and diabetes treatment satisfaction.

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Postpartum development of non-alcoholic fatty liver disease in a lean mouse model of gestational diabetes mellitus

K. Hribar[1], D. Eichhorn[2], N.J. Kloosterhuis[1], J.K. Kruit[1], M.H. Oosterveer[1], E.M. van der Beek[1,3]

1 Department of Pediatrics, University Medical Center Groningen, Groningen, The Netherlands
2 The Central Animal Facility, University Medical Center Groningen, Groningen, The Netherlands
3 Nestlé Institute of Health Sciences, Switzerland

BACKGROUND

Human studies indicate that gestational diabetes mellitus (GDM) is associated with an increased risk for non-alcoholic fatty liver disease (NAFLD) development in mothers. As NAFLD predisposes to the development of advanced liver disease, a better understanding of the course and mechanisms underlying NAFLD development in GDM mothers and offspring is warranted. In this preclinical study, we evaluated the development of NAFLD postpartum in a mouse model for lean GDM.

METHODS

Lean GDM was induced by short-term high-fat diet (HF) and low-dose streptozotocin (STZ) injections before mating in female C57BL/6N mice. Control dams received high-fat (HF) or low-fat (LF) diets only. Livers from GDM dams were collected postpartum at postnatal day 30 (PN30).

RESULTS

At PN30 hepatic triglyceride (TG) content was increased in GDM dams as compared to HF and LF controls (TG: 65,9 vs 33,6 and 32,8 umol/g, $p < 0.05$). Hepatic cholesterol ester (CE) levels were markedly lower in HF animals compared to GDM and LF (CE: 3,0 vs 6,2 and 9,2 umol/g, $p < 0.05$). Moreover, the PL/TG ratio was significantly increased in GDM dams compared to HF and LF dams (1,9 vs 0,9 and 1,0, $p < 0.05$), indicative of higher lipid droplet size. Plasma TGs were, however, comparable between groups. Plasma Cholesterol and NEFA levels were increased in GDM and HF dams compared to LF controls (Chol: 2,8 and 2,9 vs 2,5 nM, $p < 0.05$; NEFA: 0,7 and 0,7 vs 0,4; $p < 0.05$). Plasma liver disease markers were increased in GDM dams compared to HF and LF controls (ALT: 81,9 vs 26,7 and 24,0 U/L, $p < 0.05$; AST: 155,0 vs 63,7 and 71,5 U/L, $p < 0.05$). Finally, the histopathological analysis showed increased NAFLD activity scores in livers from GDM dams (3,4 vs 1,0 and 1,5 $p < 0.05$) as well as higher energy accumulation (lipid and glycogen), inflammation, and cell turnover indices.

CONCLUSION

We confirmed that GDM dams develop NAFLD over a relatively short period after giving birth. Our findings indicate that the double-hit model of lean GDM can be used to further study the effects of pregnancy hyperglycemia in absence of obesity and its role in the development of postpartum NAFLD.

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Walking on eggshells: incidence of diabetes-related foot ulcer recurrence and its association with demographic and physical activity data

C.M. Hulshof, J.J. van Netten, T.E. Busch-Westbroek, L.W.E. Sabelis, R.S. Lagrand, M. Nieuwdorp, E.J.G. Peters, S.A. Bus

Department of Rehabilitation Medicine, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands
Amsterdam Movement Sciences, Ageing & Vitality and Rehabilitation & Development, Amsterdam The Netherlands
E-mail: c.m.hulshof@amsterdamumc.nl

BACKGROUND

The number of people with diabetes-related foot ulcers is growing. Our aim was to gain insight into the incidence of foot ulcers during 12-months, and to associate demographic and physical activity data with foot ulcer development in people with diabetes at high risk of foot ulceration.

METHODS

In an observational prospective cohort study conducted in a tertiary referral center, we longitudinally followed 60 participants for 12 months. At baseline, we examined participants' feet, screened their medical and ulcer history, and assessed their physical activity. The primary outcome was the development of foot ulcers. We used Student's t-tests and Chi-square to select demographic and physical activity data ($p < 0.05$) for multivariate, backward, logistic regression analysis.

RESULTS

In total, 32 (53%) participants developed a total 90 foot ulcers during 12-months follow-up, of which 47 plantar and 43 non-plantar foot ulcers. Median time to ulceration was 5 months after study start. Among participants who developed a foot ulcer, 11 developed them only plantar, 10 only non-plantar and 11 plantar and non-plantar. Plantar ulcers were located at the hallux (43%), digits (11%), metatarsals (26%), and midfoot (2%). In multivariate analysis, a more recent history of foot ulceration (ulcer-group: 5.5 (SD 8.5); no ulcer-group: 21.5 (SD 41.8) months), an amputation (ulcer-group: 53%; no ulcer-group: 21%), unemployed (ulcer-group: 69%; no ulcer-group: 43%), and a slower walking speed (ulcer-group: 1.0 (SD 0.3); no ulcer-group: 1.2 (SD 0.2) m/s) were independently associated with foot ulceration.

CONCLUSION

The foot ulcer recurrence rate in this study is rather high, likely due to the high-risk population investigated. More generic health-condition related markers indicating patient fragility seem factors in diabetes-related foot ulcer recurrence. These factors could help identify those at highest risk and implement preventive care to prevent skin breakdown in them.

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Clinical translation and implementation of a bio-artificial pancreas: A qualitative study exploring the perspectives of patients with Type 1 Diabetes

Dide de Jongh[1,2], Eline M. Bunnik[2], Emma K. Massey[1]

1 Department of Nephrology and Transplantation, Erasmus MC, University Medical Centre Rotterdam, Rotterdam, The Netherlands
2 Department of Medical Ethics, Philosophy and History of Medicine, Erasmus MC, University Medical Centre Rotterdam, Rotterdam, The Netherlands
E-mail: d.dejongh.1@erasmusmc.nl

BACKGROUND

In preclinical research settings the bio-artificial pancreas is being developed that can be implanted in patients with Type 1 Diabetes to produce and secrete insulin. First-in-human clinical trials are expected in a few years. In this interview study, the perspectives of patients with Type 1 Diabetes on the clinical translation and implementation of the bio-artificial pancreas were explored to elucidate their perspectives, needs, and concerns.

METHODS

Semi-structured interviews were carried out with 20 adult patients with Type 1 Diabetes treated at Erasmus MC, University Medical Centre Rotterdam. Inclusion was stopped once data saturation was reached. The interviews were audio-taped, and transcribed verbatim. A qualitative content analysis with an inductive approach was conducted to categorize the data, and develop themes within a coding frame.

RESULTS

Patients reported a range of hoped-for benefits of the bio-artificial pancreas as a potential treatment that could be divided into four themes: psychological (e.g. more headspace, more flexibility in their daily lives and the invisibility of the treatment to others, thus avoiding stigmatization), social (e.g. more participation in society and a relief for loved ones), health-related (e.g. fewer diabetes-related complications) and societal (e.g. less dependency on third parties and the suitability of the therapy for patients lacking self-management skills required for current device-based treatments). Further, patient needs were identified regarding the informed consent procedure, implantation site and follow-up care. Patients also shared their perspectives on rescinding control of their disease and/or treatment, and their concerns regarding the irreversibility of the surgical procedure, cell sources used and accessibility of the therapy.

CONCLUSION

Insights from this interview study allow researchers, policy makers and clinicians to align the clinical translation and implementation of the bio-artificial pancreas with patients' needs. Alignment is likely to improve the chances of successful implementation.

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Muscle and liver insulin resistance have distinct plasma protein profiles; a proteomics analysis using the Diogenes cohort

Esther J. Kemper[1], Ellen E. Blaak[1], Michiel Adriaens[2], Ruth C.R. Meex[1]

1 Department of Human Biology, NUTRIM, School of Nutrition and Translational Research in Metabolism, Maastricht University, Maastricht, The Netherlands
2 Maastricht Centre for Systems Biology (MaCSBio), Maastricht University, Maastricht, The Netherlands
E-mail: esther.kemper@maastrichtuniversity.nl

BACKGROUND

Insulin resistance is a hallmark of type 2 diabetes, and used to be considered as a uniform systemic alteration. However, previous studies showed that insulin resistance can manifest in a tissue-specific manner in adipose tissue, skeletal muscle and/or liver. Previous research from our lab has shown that different tissue-specific insulin resistant phenotypes display different metabolic, lipidome and adipose tissue transcriptome profiles. Hence, this study aimed to determine if different tissue-specific insulin resistant phenotypes also have distinct plasma protein profiles.

METHODS

We analyzed SomaLogic plasma proteomic profiles from participants with overweight or obesity that previously participated in the Diet, Obesity and Genes (DiOGenes) study (n = 594). A linear regression analysis in R (package 'Limma') was applied to identify the proteins associated with muscle or liver insulin resistance (p-value < 0.05). Subsequently, we used these differentially expressed proteins in a pathway enrichment analysis, utilizing the KEGG and WikiPathways databases.

RESULTS

In total, we identified 1129 proteins in plasma. Of these, 111 were associated with muscle IR and 109 were associated with liver IR. Pathway enrichment analysis showed that both in muscle and liver insulin resistance there was an overlap in the enrichment of several pathways, including 'Complement system', 'Focal adhesion' and 'PI3K-Akt signaling pathway'. Interestingly however, the enrichment of these pathways is driven by different differentially expressed proteins.

CONCLUSION

This study shows that similar pathways are enriched in the plasma of individuals with muscle and liver insulin resistance. The enrichment of these pathways, however, is caused by different proteins. A better understanding of the processes involved in these distinct IR phenotypes may provide insights for possible personalized prevention or treatment strategies.

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12 weeks of HIIT modify the skeletal muscle clock and mitochondrial respiration in males at risk for developing type 2 diabetes

Jan-Frieder Harmsen, Marit Kotte, Ivo Habets, Soraya S. de Kam, Johanna Jorgensen, Frederieke Bosschee, Koen Frenken, Jochem F. Cissen, Tineke van de Weijer, Mijke Buitinga, Joris Hoeks, Patrick Schrauwen

Maastricht University, Maastricht, The Netherlands

BACKGROUND

We previously reported that young healthy lean males display 24h rhythmicity in substrate metabolism and skeletal muscle mitochondrial function. This rhythmicity was blunted in older males at risk for developing type 2 diabetes. Here, we investigated whether 12 weeks of HIIT could restore 24h rhythmicity in substrate metabolism, plasma substrate levels and skeletal muscle mitochondrial function in males at risk for developing type 2 diabetes.

METHODS

We included 10 males at risk for developing type 2 diabetes (40-75 years, BMI > 25 kg/m^2). Indirect calorimetry was performed at 8 AM, 1 PM, 6 PM, 11 PM and 4 AM, blood draws were taken two-hourly and muscle biopsies were obtained at 8:30 AM, 1:30 PM and 11:30 PM prior to and following 12 weeks of HIIT. Body composition was measured using air displacement plethysmography and exercise capacity was measured by an incremental cycling test.

RESULTS

12 weeks of HIIT significantly decreased fat mass ($p < 0,05$), improved exercise capacity($p < 0,05$), enhanced mitochondrial respiration ($p < 0,05$), and slightly reduced 24h plasma glucose levels as well as improved insulin sen-

sitivity based on HOMA-IR ($p < 0,05$). However, no changes in day-night rhythmicity of whole-body substrate metabolism, plasma triglycerides and free fatty acid levels or skeletal muscle mitochondrial function were observed. A significant interaction effect between time and our intervention was found for expression of core clock genes Per1 ($p = 0,013$) and Per3 ($p = 0,006$) in skeletal muscle.

CONCLUSION

We show that 12 weeks of HIIT improved body composition, exercise capacity and insulin sensitivity, but did not influence day-night rhythmicity in substrate metabolism and skeletal muscle mitochondrial function. However, our HIIT intervention modified core clock gene expression in skeletal muscle. Future studies could investigate whether different exercise models can restore 24h metabolic rhythmicity in individuals at risk for developing type 2 diabetes.

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Cortisol and Food Cravings: The Association of Long-term Biological Stress with Long-term Hedonic Eating Tendencies in Patients with Obesity

Susanne Kuckuck[1,2], Eline S. van der Valk[1], Jenny A. Visser[1], Sjoerd A.A. van den Berg[3], Mariëtte R. Boon[1], Elisabeth F.C. van Rossum[1]

1 Obesity Center CGG, Department of Internal Medicine, Division of Endocrinology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands
2 Department of Epidemiology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands
3 Department of Clinical Chemistry, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands

BACKGROUND

Obesity (BMI ≥ 30.0 kg/m^2) is associated with increased levels of the stress hormone cortisol as well as uncontrolled hedonic overeating. Overexposure to glucocorticoids such as cortisol has adverse cardiometabolic effects, but may also pose a disposition for decreased eating control. The latter is mainly suggested by studies using experimental short-term stress exposure, subjective self-reports or exposure to supraphysiological levels of glucocorticoids due to medication or disease.

METHODS

Data was collected of n = 104 adults with obesity (89 women, median BMI = 40, 9.2 IQR). In our primary analysis, we investigated cross-sectional associations of endogenous long-term glucocorticoid levels (cortisol and cortisone measured in the first 3 cm of hair most proximal to the scalp) with self-reported long-term emotional and external eating tendencies (assessed using the Dutch Eating Behavior Questionnaire (DEBQ)) and trait food cravings (assessed using the Food Craving Questionnaire (FCQ-T)). In secondary analyses, we also investigated how emotional eating, external eating, food craving and hair glucocorticoid levels relate to self-reported psychological stress (measured using the Perceived Stress Scale).

RESULTS

In the full group, we did not see significant associations of hair glucocorticoid levels with eating behavior (all $p > 0.5$). Only among n = 44 patients who scored high on food craving, there was a positive association between food cravings and levels of hair cortisone ($p = 0.017$), as well as, in trend, hair cortisol ($p = 0.065$). Hair glucocorticoid levels did not correlate with psychological stress ($p > 0.05$). Psychological stress was highly associated with higher food craving and emotional eating ($p < 0.001$), as well as with external eating ($p = 0.40$).

CONCLUSION

Patients with obesity who experience stronger food cravings may be more susceptible to craving-inducing effects of high hair glucocorticoid levels, representing long-term biological stress. Psychological stress is strongly associated with hedonic eating tendencies, confirming earlier results. Long-term biological and psychological stress may play different roles in appetite regulation among patients with obesity.

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The novel plant-based active principle Totum-448 decreases hepatic steatosis and inflammation in diet-induced NAFLD mice

Joost M. Lambooij[1,2], Vivien Chavanelle[3], Hendrik J.P. van der Zande[1], Yolanda F. Otero[3], Marie Vallier[3], Frank Otto[1], Robbie Schuurman[1], Arnaud Zaldumbide[2], Sebastien L. Peltier[3], Pascal Sirvent[3], Bruno Guigas[1]

1 Department of Parasitology, Leiden University Medical Center, Leiden, The Netherlands
2 Department of Cell & Chemical Biology, Leiden University Medical Center, Leiden, The Netherlands
3 Valbiotis SA, La Rochelle, France
E-mail: j.m.lambooij@lumc.nl

BACKGROUND

The increasing prevalence of obesity-associated non-alcoholic fatty liver disease (NAFLD) urges the development of new therapeutic strategies. Totum-448 is a unique patented blend of plant extracts designed to reduce hepatic steatosis, a risk factor for NAFLD and type 2 diabetes. Here, we investigated the effects of Totum-448 on steatohepatitis and metabolic homeostasis in dietary-induced obese mice.

METHODS

Male C57Bl6/J mice were fed a high-fat diet (HFD, 45% kcal from fat) in addition to sucrose-containing drinking water (10% w/v) for 12 weeks, after which the diet was supplemented with or without Totum-448 (1.5, 2, 2.5% w/w) for 4 weeks. Body weight/composition and calorie intake were monitored and whole-body metabolic homeostasis was assessed by glucose/insulin tolerance tests. Hepatic steatosis and tissue-specific immune cell composition were determined by histology/biochemical assays and flow cytometry, respectively.

RESULTS

We found that Totum-448, except at the highest concentration, did not significantly affect body weight, fat mass, food/calorie intake and feces production in obese mice. However, Totum-448 induced a significant, dose-dependent decrease in liver steatosis, hepatocyte ballooning, and lobular inflammation (all $p \leq 0.05$). Hepatic triglycerides and cholesterol levels were also reduced by Totum-448 ($p \leq 0.05$). Furthermore, Totum-448 strongly reduced HFD-induced tissue-resident Kupffer cell activation and death, infiltration of newly-recruited monocytes and hepatic accumulation of monocyte-derived pro-inflammatory $CD11c^+$ macrophages (all $p \leq 0.05$). This effect was associated with a potent decrease in the hepatic expression of inflammatory (*Ccl2, Tnf, Lcn2*) and fibrotic (*Col1a1, Acta2, Timp1*) gene markers (all $p \leq 0.05$). Finally, Totum-448 reduced circulating pro-inflammatory monocytes, fasting plasma alanine aminotransferase, glucose and insulin levels, and improved insulin sensitivity and glucose tolerance (all $p \leq 0.05$).

CONCLUSION

Totum-448 decreases hepatic steatosis and inflammation in obese mice, a dual effect likely contributing to improved whole-body metabolic homeostasis. Altogether, supplementation with Totum-448 may constitute a promising novel nutritional approach for preventing/treating NAFLD.

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Increased Glucocorticoid Receptor Sensitivity is associated with Higher Weight in Patients with Obesity

Robin Lengton, Anand M. Iyer, Mostafa Mohseni, Eline S. van der Valk, Mariëtte R. Boon, Elisabeth F.C. van Rossum

Obesity Center CGG, Department of Internal Medicine, Division of Endocrinology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands
E-mail: r.lengton@erasmusmc.nl

BACKGROUND

Mounting evidence points to an association between increased glucocorticoid (GC) action and weight gain. However, the response to GCs is not only determined by GC serum concentrations, but also by individual differences in tissue-specific sensitivity, influenced by genetic and acquired (e.g. disease-related) factors. The extent to which differences in GC sensitivity may influence development of obesity, or vice versa, is poorly understood. In this study we investigate the relation between GC sensitivity and obesity.

METHODS

Data were collected from 57 patients with obesity (48 women, average BMI = 39.7 kg/m^2), who either underwent bariatric surgery or a combined lifestyle intervention. Anthropometric data and peripheral blood mononuclear cells

(PBMCs) were obtained at baseline and after 10 weeks of treatment. The half maximal effective concentration of dexamethasone (DEX), mediating the transactivation (EC50) or transrepression (IC50) of responsive genes GC-induced leucine zipper (GILZ) and FK506 binding protein 5 (FKBP5) or interleukin (IL)-2 and IL-6 respectively in PBMCs, was used as a measure of GC sensitivity. The associations of EC50 and IC50 with BMI, weight and waist circumference were analysed using linear regressions corrected for age and sex.

RESULTS

A lower EC50 of DEX-mediated transactivation of FKBP5 at baseline (higher sensitivity) was associated with higher weight (β = −1.15, 95%CI = −2.02 to −0.27). Similar, but non-significant, associations were observed with BMI and waist circumference. There were no associations between EC50 of DEX-mediated transactivation of GILZ or IC50, and any of the above-mentioned anthropometric variables. Also no associations were found between GC sensitivity and weight loss after treatment.

CONCLUSION

This study suggests that increased GC sensitivity is associated with higher weight in patients with obesity. Further analysis of the data is in progress to determine whether this association might be related to changes in GC levels, e.g. cortisol, as a compensation for increased GC sensitivity.
Conflicts of interest: All authors declare that they have no conflict of interest.
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The Natural Metabolite 6-halo-tryptophan Ameliorates Adiposity in vivo and Promotes Lipid Catabolism

Moyan Liu[1,3,5], Stefan R. Havik[1], M.J. Nordin Hanssen[2,3,4], Max Nieuwdorp[2,3,4], Elena Rampanelli[1,3,5]

1 Department of Experimental Vascular Medicine, Amsterdam UMC, location Academic Medical Center, Amsterdam, The Netherlands
2 Department of Vascular Medicine, Amsterdam UMC, location Academic Medical Center, Amsterdam, The Netherlands
3 Amsterdam Cardiovascular Science Research Institute, Amsterdam, The Netherlands
4 Amsterdam Gastroenterology Endocrinology Metabolism Research Institute, Amsterdam, The Netherlands
5 Amsterdam institute for Infection and Immunity, Amsterdam, The Netherlands

BACKGROUND

The prevalence of obesity and associated type 2 diabetes (T2D) is consistently increasing worldwide. Yet the complex interaction among multiple genetic and environmental factors that can influence the development of obesity remains enigmatic. Growing evidence underscores a role of dietary derivatives and plasma metabolites in the etiology of metabolic diseases.

METHODS

Through metabolome profiling, we found that the plasma levels of an halogenated form of dietary tryptophan (6-bromotryptohan, 6-BT) are inversely associated with plasma lipid profile and body mass index in obese individuals.
Prompted by these clinical observations, we further investigated the functions of this metabolite in vivo, using a severe model of obesity and diabetes (db/db mice). For this, db/db mice were treated with intraperitoneal injections of placebo or 20 mg/kg 6-BT at 8 weeks of age, when obesity and hyperglycemia are already present.

RESULTS

After a 4-week intervention, 6-BT administration was found to counteract adiposity, as evidenced by the reduced proportion of white adipose tissue (WAT), adipocyte hypertrophy, and macrophage infiltration in WAT. Mechanistically, we found that 6-BT exposure in vitro boosts the mitochondrial oxidative metabolism of adipocytes. This effect was accompanied by the upregulation of genes involved in mitochondrial beta-oxidation and a reduction in intracellular lipid accumulation.

CONCLUSION

Collectively, our findings highlight the potential of 6-BT as a natural therapeutic agent to counteract adiposity and promote lipolysis. Further studies are warranted to fully unravel its underpinning molecular mechanisms, and to assess its long-term efficacy.

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Fetuin B in white adipose tissue induces inflammation and is associated with peripheral insulin resistance in mice and humans

K. Pasmans[1], G.H. Goossens[1], E. Groenhuijzen[1], E.J. Kemper[1], D. Reijnders[1], J. Most[1,2], E.E. Blaak[1], M.J. Watt[3,4] and R.C.R. Meex[1,4]

1 Department of Human Biology, Maastricht University Medical Centre+, Maastricht, The Netherlands
2 Department of Orthopedics, Zuyderland Medical Center, Sittard-Geleen, The Netherlands
3 Department of Anatomy and Physiology, School of Biomedical Sciences, Faculty of Medicine, Dentistry & Health Sciences, The University of Melbourne, Melbourne, Australia
4 Department of Physiology, Monash University, Clayton, Australia
E-mail: Ruth.meex@maastrichtuniversity.nl

BACKGROUND

The liver plays a major role in maintaining whole-body glucose homeostasis. This is in part via the synthesis and secretion of hepatokines; proteins that have the potential to regulate metabolism in local or distant organs. Fetuin B (FetB) is a steatosis-responsive hepatokine that causes glucose intolerance in mice, but the underlying mechanisms remain incompletely described. We aimed to elucidate the mechanisms of action of FetB by investigating its putative effects on white adipose tissue (WAT) metabolism.

METHODS

First, FetB gene and protein expression were measured in multiple organs in C57BL/6J mice, and in 3T3-L1 adipocytes treated with or without FetB to investigate whether FetB is taken up by adipocytes. Next, we performed a two-step hyperinsulinemic-euglycemic clamp in C57BL/6J mice treated with FetB, and in insulin resistant individuals, to examine the link between WAT FetB content and indices of insulin sensitivity. Finally, the effects of FetB on inflammation was investigated in 3T3-L1 adipocytes by qPCR and full RNA-sequencing.

RESULTS

FetB gene expression in C57BL/6J mice was high in liver, but nearly absent in other organs, while FetB protein expression was low in liver, but ~34-fold higher in WAT. FetB treatment increased intracellular FetB levels in 3T3-L1 adipocytes (3.2-fold, $p < 0.05$). Similarly, injection of FetB in mice increased FetB protein content in WAT (4.2-fold, $p < 0.05$). These findings suggest that FetB is produced and secreted by the liver and taken up by WAT. Intriguingly, we found a strong negative correlation between FetB content in WAT and glucose disposal rate in mice ($r^2 = 0.95$, $p < 0.001$) as well as in humans ($r^2 = 0.37$, $p < 0.01$). Furthermore, RNA-sequencing and PCR analysis revealed that FetB induced a pro-inflammatory response in 3T3-L1 adipocytes.

CONCLUSION

FetB content in WAT strongly associates with peripheral insulin resistance in mice and humans. Furthermore, FetB induced a pro-inflammatory response in adipocytes, which might drive peripheral insulin resistance.

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Blended lifestyle coaching for people with diabetes type 2 in secondary care: A feasibility study of the Diameter + CooL

Anouk Middelweerd[1], Eclaire Hietbrink[1,2], Carine Gotink[1], Annemieke Konijnendijk[1,3], Goos Laverman[1,2]

1 Biomedical Signals and Systems, Twente University, Enschede, The Netherlands
2 Interne Geneeskunde/Nefrologie, ZGT, Almelo, The Netherlands
3 ZGT Academie, ZGT, Almelo, The Netherlands
E-mail: a.middelweerd@utwente.nl

BACKGROUND

The CooL+Diameter intervention, combining face-to-face coaching and a mobile app, aimed to promote lifestyle changes in individuals with type 2 diabetes mellitus (T2DM). The Diameter app facilitates continuous monitoring of nutrition, physical activity, and glucose levels and provides tailored feedback, i.e. guided goal setting, daily informative and motivating coaching messages, and weekly exercises aimed at learning to cope with barriers that arise in daily life to maintain a healthy lifestyle. The aim was to evaluate the feasibility of the combined intervention secondary care from the perspectives of patients and healthcare professionals.

METHODS

Five patients have successfully completed the study, while

the remaining five are currently participating. Measurements on glycemic regulation, body composition, PA, and nutritional intake were performed at baseline and at the three-month follow-up. Post-intervention semi-structured interviews were conducted with five patients and eight healthcare professionals (HCs).

RESULTS

Initial findings indicate positive perceptions from both patients and healthcare professionals, emphasizing the value of the Diameter app for glucose and lifestyle monitoring. Suggestions have been made to customize the coaching content to better align with the CooL program and individual needs. Limited efficacy testing demonstrated significant improvements in HbA1C (ΔHbA1c = 11 mmol/mol, 95% CI = 0.35-21.65) and BMI (Δ BMI = 0.78 kg/m^2, 95% CI = 0.28-1.28), along with promising results for hip (Δ Hip = 1 cm, 95% CI= -0.24-2.24) and waist circumference (Δ Waist = 2.6 cm, 95% CI = -1.38-6.58).

CONCLUSION

In conclusion, the CooL+Diameter intervention demonstrated feasibility in T2DM patients receiving secondary care. Both patients and healthcare professionals viewed the Diameter app as beneficial, though they emphasized the need for customized coaching content aligned with the CooL program. These findings highlight the potential of the CooL+Diameter intervention for promoting lifestyle changes in T2DM patients, while further research is needed to optimize the program's effectiveness.

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Metabolic and functional improvements 3 months after total knee replacement surgery

Jasper Most, Henriette Eijking, Isobel Dorling, Martijn Schotanus, Bert Boonen

Department of Orthopedic Surgery, Zuyderland Medical Center, Sittard-Geleen, The Netherlands
E-mail: j.most@zuyderland.nl

BACKGROUND

In an ageing population, metabolic and functional impairments are increasingly common. Patients with arthrosis are disproportionally affected by metabolic diseases, likely due to low physical activity caused by pain in activity. Moreover, first-line treatment for metabolic deterioration, i.e. lifestyle interventions, are difficult to adhere to due to functional limitations. The present study was designed to assess the efficacy of total knee arthroplasty on functional capacity, physical activity and ultimately metabolic parameters.

METHODS

Within an ongoing randomized controlled trial testing the clinical efficacy or robot-assistance in total knee arthroplasty, metabolic, functional and activity parameters are assessed to investigate the effect of knee replacements on metabolic health and its determinants. In 23 patients, data was collected on vitals, fasting plasma concentrations, body composition using bioimpedance, patient-reported outcome measures on arthrosis symptoms, mobility, function and strength by clinical testing (De Morton-mobility-index, stand-up-and-go, 2-minute-walking, sit-to-stand, handgrip strength) and physical activity using hip-worn accelerometry for 7 days. Pre- and postoperative data was compared by paired t-tests using SPSS.

RESULTS

The present cohort consists of 23 patients (57% female, 69 ± 9 years, 32 ± 6 kg/m^2) with pre-operative and 3-month-postoperative data. Three months after surgery, symptoms have improved mildly (Oxford Knee Score [0 worst, 48 best], 25 ± 7 to 29 ± 7, $p = 0.007$) and mobility and daily activities are more frequently reported to be unproblematic (+40%, $p < 0.05$). Fasting glucose concentrations decreased significantly (6.5 ± 1.9 to 5.8 ± 1.1 mmol/l, $p = 0.01$), whereas medication use and HbA1c, fasting triglycerides and HDL-cholesterol were unchanged ($p > 0.2$). Physical activity and leg strength significantly increased (5729 ± 2232 to 10017 ± 4430 steps/day, $p < 0.001$, and 8.3 ± 3.1 to 10.0 ± 3.5 sit-to-stand transfers during 30, $p = 0.007$), while endurance remained unchanged (two-minute walking distance, 135 ± 45 to 132 ± 24m, $p = 0.66$). On average, patients lost 1.7 ± 2.7 kg body mass ($p = 0.007$), at unchanged body composition (40 ± 10% body fat, data of only 11 patients available).

CONCLUSION

The present study demonstrates clinically meaningful improvements in metabolic and lifestyle parameters three months after knee replacement, demonstrating the potential of arthroplasty in the prevention of metabolic diseases.

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Single-cell RNA sequencing of human pancreatic islets reveals a role of pancreatic duct cells as mediator of inflammation

Amadeo Muñoz García, Juri Juksar, Nathalie Groen, Arnaud Zaldumbide, Eelco de Koning, Françoise Carlotti

Department of Internal Medicine, LUMC, Leiden, The Netherlands
E-mail: a.munoz_garcia@lumc.nl

BACKGROUND

In diabetes, the pro-inflammatory niche that is generated in the pancreatic islet affects initially the function and, ultimately, the viability of insulin producing pancreatic beta cells. The goal of this study is to investigate the response of the main pancreatic cell types to pro-inflammatory conditions.

METHODS

Primary human islets from 3 non-diabetic donors were treated with pro-inflammatory cytokines (IL1β&IFNγ and IFNa) for 24 and 72h, and subsequently processed for single-cell RNA sequencing. In addition, islets from 2 T1D donors, 3 non-diabetic controls, 1 donor with Wolfram syndrome and (islet-depleted) exocrine tissue of 4 non-diabetic controls were processed for single-cell RNA-seq. Finally, validation experiments were performed with human islets and EndoCBH1 cells treated with human recombinant IL8 or blocking IL8 antibody.

RESULTS

Pathway analysis revealed that common processes are promoted in endocrine and exocrine pancreatic cells by cytokine stress such as antigen processing and presentation. In contrast, we identified a duct subpopulation presenting a unique proinflammatory signature (IL8, CXCL1,2,3,6,9,10 and 11 and complement system related genes) among all pancreatic cell types in both inflammation conditions, Wolfram syndrome and T1D pancreatic islets. These cells express HES1, SOX9 and ion transporter genes such as KCNJ15-16 and AQP1, characteristic of centro-acinar cells. Finally, treatment of primary human islets with recombinant IL8 induces beta-cell dysfunction, while blocking IL8 prevents cytokine-induced beta-cell failure.

CONCLUSION

Our data reveal a potential role of the duct cell compartment in the amplification of islet inflammation that is detrimental for beta cell health.

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Dietary methylglyoxal improves insulin sensitivity and vascular function in high-fat diet-induced type 2 diabetic mice

Stefanie I.J. Nass[1], Philippe Vangrieken[1], Paul M.H. Schiffers[2], Jean L.J.M. Scheijen[1], Casper G. Schalkwijk[1]

1 Department of Internal Medicine, School for Cardiovascular Diseases (CARIM), Maastricht University Medical Center+, Maastricht, The Netherlands
2 Department of Pharmacology and Toxicology, School for Cardiovascular Diseases (CARIM), Maastricht University Medical Center+, Maastricht, The Netherlands
E-mail: stefanie.nass@maastrichtuniversity.nl

BACKGROUND

Type 2 diabetes is a chronic disease, characterized by insulin resistance and hyperglycemia, with an increased risk for the development of vascular complications. Plasma levels of the dicarbonyl methylglyoxal, formed during glycolysis, are increased in diabetes and associated with endothelial dysfunction and microvascular complications. Besides endogenous formation of methylglyoxal, methylglyoxal is also present in our diet. Surprisingly, and in contrast to endogenously formed methylglyoxal, recent observational cohort studies from our group showed that dietary methylglyoxal is associated with greater insulin sensitivity and less low-grade inflammation. Therefore, the potential of dietary methylglyoxal as an intervention for insulin resistance and vascular dysfunction was investigated in an animal model of type 2 diabetes.

METHODS

Healthy C57BL/6 mice were divided into a control group (n = 16), a high-fat diet group (n = 16), and a group on high-fat diet with 1 mM methylglyoxal in the drinking water (n = 16). The study period was 13 weeks after which insulin tolerance and blood pressure was measured. After sacrifice, saphenous arteries were isolated to test vascular reactivity by myography and soluble E-selectin was measured in plasma as a biomarker for endothelial dysfunction by ELISA.

RESULTS

Dietary methylglyoxal improves insulin sensitivity (+23%) ($p = 0.005$), and lowered both diastolic (-9%, $p = 0.07$) and systolic (-8%, $p = 0.03$) blood pressure compa-

red to the high-fat diet group. In saphenous arteries, acetylcholine-induced relaxation was impaired by the high-fat diet (p = 0.04), which was not observed in the high-fat diet group supplemented with methylglyoxal. Besides, plasma soluble E-selectin was elevated (+23%) in the high-fat diet group (p = 0.04) compared to the control group and lowered (−28%) (p = 0.001) by dietary methylglyoxal.

CONCLUSION

Dietary methylglyoxal prevents insulin resistance, reduces blood pressure and improves endothelial function in high-fat diet-induced type 2 diabetes. Those findings set the arena for investigating the therapeutic potential of dietary methylglyoxal to prevent and/or treat type 2 diabetes and its complications.

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Metformin Immediate Release Pellets in Capsule 500 mg (Fasting and Fed)

O.W.F. Natan[1], A.A.M. Franken, K.P. Bouter

1 Hubrecht Institute, Utrecht, The Netherlands
E-mail: o.natan@hubrecht.eu

BACKGROUND

Metformin pellets is a new formulation with the potential of less side effects and presumable insignificant changes in pharmacokinetic properties.

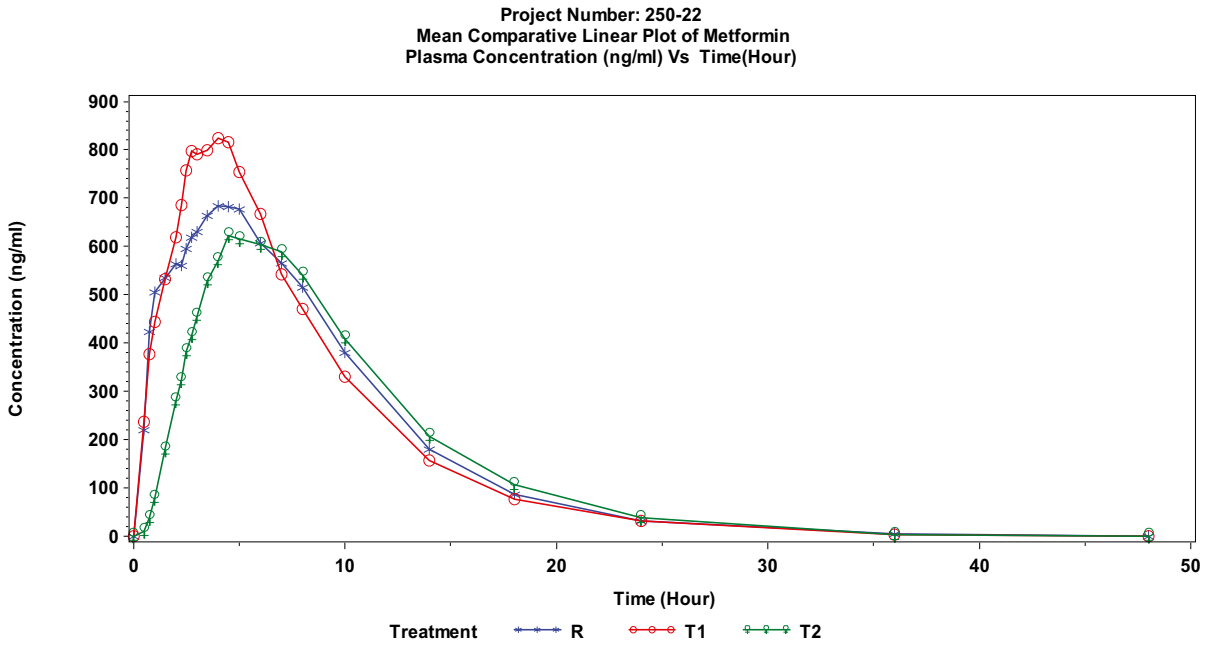
METHODS

An open-label, balanced, randomized, single-dose, three-treatment, three-sequence, three-period, crossover, relative bioavailability study of Metformin immediate release

Table 1. Statistics of reference and test in fed conditions.

ABE - T2 vs R								
Parameters	GLSM T2	CLSM R	Ratio	90% lower	90% upper	Intra cv	Power	Bioequivalence
LCmax	654.314	779.257	83.97	74.91	94.12	17.75	94.23	NO
LAUCt	6.681.741	7.325.772	91.21	82.42	100.92	15.73	97.46	YES

Figure 4. R (Reference fed), T1 (Test fast) and T2 (Test fed).



pellets in capsule 500 mg (T1 and T2) with Metformin immediate release tablets 500 mg (R) of Merck Healthcare Germany GmbH, in adult, human healthy volunteers under fasting and fed conditions. We compared the rate and extent of absorption, evaluated the effect of food on pharmacokinetics and monitored the safety and tolerability of a single dose of Metformin from Metformin immediate release pellets in capsule 500 mg and Metformin immediate release tablets 500 mg in 15 healthy volunteers under fasting and fed conditions (**figure 4**).

RESULTS

The ratios of geometric least squares mean & 90% confidence intervals of the test product (T2) and reference product (R) for the Ln-transformed pharmacokinetic parameters LCmax and LAUC-t of Metformin were found to be 83.97 (74.91-94.12) and 91.21 (82.42-100.94) respectively (**table 1**). The 90% confidence intervals (T2 vs R) of the ratio of geometric least squares means for the Ln-transformed pharmacokinetic parameters Cmax of Metformin is not within the bioequivalence acceptance limits of 80.00 - 125.00%. However, the Ln-transformed pharmacokinetic parameters AUC0-t of Metformin is within the bioequivalence acceptance limits of 80.00-125.00%.

CONCLUSION

Hence, it is concluded that the test product (T2) Metformin immediate release pellets in capsule 500 mg and reference product (R) Metformin immediate release tablets 500 mg are not bioequivalent with respect to rate and extent of absorption. Intrasubject variability observed in the study suggests that there is high variability of the product under fasting conditions and variability reduce significantly under fed conditions (food effect has been observed which can be confirmed from the published literature of Metformin IR Tablets). No severe, serious or life-threatening adverse events were reported during the course of the study. Further research will be performed to evaluate the effects on metformin intolerant patients.

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Blended lifestyle coaching for people with diabetes type 2 in secondary care: A feasibility study of the Diameter + CooL

Anouk Middelweerd[1], Eclaire Hietbrink[1,2], Carine Gotink[1], Annemieke Konijnendijk[1,3], Goos Laverman[1,2]

1 Biomedical Signals and Systems, Twente University, Enschede, The Netherlands
2 Interne Geneeskunde/Nefrologie, ZGT, Almelo, The Netherlands
3 ZGT Academie, ZGT, Almelo, The Netherlands
E-mail: a.middelweerd@utwente.nl

BACKGROUND

The CooL+Diameter intervention, combining face-to-face coaching and a mobile app, aimed to promote lifestyle changes in individuals with type 2 diabetes mellitus (T2DM). The Diameter app facilitates continuous monitoring of nutrition, physical activity, and glucose levels and provides tailored feedback, i.e. guided goal setting, daily informative and motivating coaching messages, and weekly exercises aimed at learning to cope with barriers that arise in daily life to maintain a healthy lifestyle. The aim was to evaluate the feasibility of the combined intervention secondary care from the perspectives of patients and healthcare professionals.

METHODS

Five patients have successfully completed the study, while the remaining five are currently participating. Measurements on glycemic regulation, body composition, PA, and nutritional intake were performed at baseline and at the three-month follow-up. Post-intervention semi-structured interviews were conducted with five patients and eight healthcare professionals (HCs).

RESULTS

Initial findings indicate positive perceptions from both patients and healthcare professionals, emphasizing the value of the Diameter app for glucose and lifestyle monitoring. Suggestions have been made to customize the coaching content to better align with the CooL program and individual needs. Limited efficacy testing demonstrated significant improvements in HbA1C (Δ HbA1c = 11 mmol/mol, 95% CI = 0.35-21.65) and BMI (Δ BMI = 0.78 kg/m^2, 95% CI = 0.28-1.28), along with promising results for hip (Δ Hip = 1 cm, 95% CI = −0.24-2.24) and waist circumference (Δ Waist = 2.6 cm, 95% CI = −1.38-6.58).

CONCLUSION

In conclusion, the CooL+Diameter intervention demonstrated feasibility in T2DM patients receiving secondary care. Both patients and healthcare professionals viewed the Diameter app as beneficial, though they emphasized the need for customized coaching content aligned with the CooL program. These findings highlight the potential of the CooL+Diameter intervention for promoting lifestyle changes in T2DM patients, while further research is needed to optimize the program's effectiveness.

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The effect of sweeteners and sweetness enhancers on adipose tissue function in individuals with overweight or obesity – A SWEET sub-study.

Michelle Pang[1], Jacco Bastings[1], Johan Jocken[1], Jason Halford[2,3], Anne Raben[4,5], Gijs Goossens[1], Ellen Blaak[1]

1 Department of Human Biology, School of Nutrition and Translational Research in Metabolism (NUTRIM), Maastricht University Medical Centre+, Maastricht, The Netherlands
2 Department of Psychology, Institute of Population Health, University of Liverpool, Liverpool, United Kingdom
3 School of Psychology, University of Leeds, Leeds, United Kingdom
4 Department of Nutrition, Exercise and Sports, Faculty of Science, University of Copenhagen, Frederiksberg, Denmark
5 Clinical Research, Copenhagen University Hospital – Steno Diabetes Center Copenhagen, Herlev, Denmark
E-mail: m.pang@maastrichtuniversity.nl

BACKGROUND

Studies investigating the role of sweeteners and sweetness enhancers (S&SEs) on adipose tissue (AT) function are scarce and previous in vitro and in vivo studies yielded inconsistent findings. We aimed to investigate the effect of S&SEs in replacement of sugar on AT morphology and gene expression in adults with overweight

or obesity that participated in the European SWEET project.

METHODS

In this randomized controlled trial, 63 adults (age 18-65 yrs) with overweight or obesity that participated in the study in Maastricht underwent a dietary intervention consisting of a 2-months weight loss (WL)-period (low-energy diet, 800-1000 kcal/day) and a 10-months weight-maintenance (WM)-period during which individuals followed a healthy diet (< 10 energy -% added sugar) with or without the inclusion of S&SEs (S&SEs group vs. sugar group, respectively). Abdominal subcutaneous AT biopsies were collected at baseline, after WL and at the end of the WM-period to determine fat cell size and gene expression.

RESULTS

After the WL-period, AT gene expression of leptin was decreased (0.58 ± 0.06 fold change (FC), $p < 0.001$), which was accompanied by reduced expression of genes involved in fatty acid (FA) uptake (LPL, 0.068 ± 0.06 FC; SREBF1, 0.64 ± 0.07 FC; both $p < 0.001$), FA synthesis (FASN, 0.60 ± 0.14 FC; SCD, 0.25 ± 0.06 FC; both $p < 0.001$), intracellular lipolysis (ATGL, 0.79 ± 0.07 FC, $p < 0.001$; HSL, 0.79 ± 0.06 FC, $p = 0.001$), adipogenesis (CEBPα, 0.80 ± 0.06 FC; $p = 0.004$), and oxidative phosphorylation (CS, 0.88 ± 0.06 FC; $p = 0.048$). During the WM-period, the increase in gene expression of LPL and PLINA was less pronounced in the S&SEs compared to the sugar group (1.41 ± 0.14 vs. 1.79 ± 0.25 FC, $p = 0.018$; 0.85 ± 0.21 vs. 1.53 ± 0.75 FC, $p = 0.031$, respectively). Analyses on adipocyte size are currently ongoing.

CONCLUSION

The intake of S&SEs during a 10-month WM-period following WL alters AT gene expression of extra- and intracellular lipolytic markers in individuals with overweight or obesity.

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Whole-body insulin sensitivity decreases after 4-week high fructose compared to 4-week high saturated fat consumption in overweight individuals

K.H.M. Roumans[1], P.M.G. van Lier[1], E. Phielix[1], B. Havekes[3], P. Schrauwen[1], V.B. Schrauwen-Hinderling[1,2]

1 Department of Nutrition and Movement Sciences, Maastricht University, Maastricht, The Netherlands
2 Department of Radiology and Nuclear Medicine, Maastricht University Medical Center, Maastricht, The Netherlands
3 Department of Internal Medicine, Division of Endocrinology, Maastricht University Medical Center, Maastricht, The Netherlands
E-mail: k.roumans@maastrichtuniversity.nl

BACKGROUND

Diets high in fructose as well as diets high in saturated fatty acids (SFA) have been suggested to impair insulin sensitivity. The underlying mechanisms for the negative effects of both diets are however unknown, but may involve hepatic lipid accumulation, albeit via different pathways. Recent evidence suggests that next to intrahepatic lipid content (IHL) also its composition (IHLC), i.e. the percentage of hepatic saturated and unsaturated fatty acids, might play a role in determining insulin sensitivity. The primary aim was to investigate the effect of a 4-week high SFA diet compared to a 4-week high fructose diet on insulin sensitivity. Secondary endpoints included IHL and IHLC, and substrate oxidation.

METHODS

Eleven individuals (males/females n = 4/n = 7; BMI 31.8 ± 3.2 kg/m^2; age 65 ± 6 year) consumed a 4-week eucaloric high SFA diet (SFA 20 En%) and a 4-week eucaloric high fructose diet (fructose 20 En%) in randomized order, with a 6-week washout in between. Insulin sensitivity was measured by a two-step hyperinsulinemic-euglycemic clamp, IHL and IHLC were determined using proton magnetic resonance spectroscopy, and substrate oxidation by indirect calorimetry.

RESULTS

Insulin sensitivity (M-value) was significantly lower upon high fructose (4.21 ± 0.53 µmol/kg/min), compared to high SFA (4.63 ± 0.45 µmol/kg/min, $p = 0.048$). As expected, fasting respiratory exchange ratio was higher upon high fructose (0.82 ± 0.01) compared to high SFA (0.78 ± 0.01, $p < 0.001$). IHL and IHLC did not change upon diets, nor were they different between diets.

CONCLUSION

This study shows that under eucaloric conditions a diet high in fructose is more detrimental for insulin sensitivity than a diet high in SFA. Differences cannot be explained by changes in IHL or IHLC. Further analyses will reveal whether de novo lipogenesis differs between diets and could underly the differences in insulin sensitivity independent of changes in intrahepatic fat.

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Non-invasive fibrosis scores as prognostic biomarkers of liver events, CV events and all-cause mortality in people with obesity and T2D in the UK: a longitudinal cohort study

Q. Anstee[1,2], T. Landsvig Berentzen, L. Nitze, M. Jara, M. Kjaer, K.K. Magla, J.M. Tarp, K. Khunti[3]

1 Translational & Clinical Research Institute, Newcastle University, Newcastle, United Kingdom
2 Newcastle NIHR Biomedical Research center, Newcastle University, Newcastle, United Kingdom
3 Diabetes Research Centre, University of Leicester, Leicester, United Kingdom

BACKGROUND

Progression of non-alcoholic steatohepatitis may lead to life-threatening liver-related complications, cardiovascular (CV) disease and all-cause mortality. An important predictor of severe outcomes is biopsy-confirmed liver fibrosis, but biopsies are not scalable outside of specialist practice. This real-world study investigated the prognostic utility of a.o. fibrosis-4 Index (FIB4) on clinical outcomes in patients with obesity and/or type 2 diabetes (T2D) in routine general practice.

METHODS

In a longitudinal cohort, patients ≥ 18 years were followed from inclusion date until time of first clinical outcome (liver event, CV event and all-cause death), 10 years' follow-up or 1 January 2020, whichever came first. FIB4 was categorized as low (< 1.30), indeterminate (1.30-2.67) or high (> 2.67) risk and cumulative incidence functions were calculated, and hazard ratios (HRs) estimated using Cox proportional hazards models with calendar time as underlying timescale.

RESULTS

44 481 eligible patients (46% male, median age 58.8 years) had FIB4 calculation. The incidences of a liver event, CV event and all-cause death were 15%, 33% and 61% in the high group, 3%, 27% and 37% in the indeterminate and 1%, 11% and 13% and in the low group, respectively. Patients in the indeterminate and high FIB4 groups were at greater risk of liver events vs the low-risk group (HR 2.81 [95% confidence interval 2.43, 3.26] and 18.42 [15.67, 21.65], respectively). An increased risk was also seen for CV events and all-cause mortality in these groups.

CONCLUSION

In this real-world population of patients with obesity and/or T2D, and no other clinically recognized liver disease, the risk of a clinical event was significantly higher in patients with high vs low FIB4 score, highlighting the prognostic potential of FIB4 in this population.

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The Effect of Preprandial versus Postprandial Physical Activity on Glycaemia: Meta-Analysis of Human Intervention Studies

R. Slebe[1,2], E. Wenker[1], L.J. Schoonmade[3], E.J. Bouman[1,2], D.P. Blondin[4,5], D.J.T. Campbell[6], A.C. Carpentier[4,7], J. Hoeks[8], P. Raina[9,10], P. Schrauwen[8], M.J. Serlie[11,12], D. Stenvers[11,12], R. de Mutsert[13], J.W.J. Beulens[1,14], F. Rutters[1,2]

1 Department of Epidemiology and Data Sciences, Amsterdam UMC, location Vrije Universiteit Amsterdam, Amsterdam, The Netherlands
2 Amsterdam Public Health, Health Behaviours & Chronic Diseases, Amsterdam, The Netherlands
3 University Library, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands
4 Centre de recherche du Centre hospitalier universitaire de Sherbrooke, Sherbrooke, QC, Canada
5 Department of Medicine, Division of Neurology, Université de Sherbrooke, Sherbrooke, QC, Canada
6 Department of Medicine, Department of Community Health Sciences and Department of Cardiac Sciences, University of Calgary Cumming School of Medicine, Calgary, AB, Canada
7 Department of Medicine, Division of Endocrinology, Université de Sherbrooke, Sherbrooke, QC, Canada
8 Department of Nutrition and Movement Sciences, Maastricht University, Maastricht, The Netherlands
9 Health Research Methods, Evidence and Impact, McMaster University, Hamilton, ON, Canada
10 McMaster Institute for Research on Aging, McMaster University, Hamilton, ON, Canada
11 Department Endocrinology and Metabolism, Amsterdam UMC, location Vrije Universiteit Amsterdam, Amsterdam, The Netherlands
12 Amsterdam Gastroenterology Endocrinology Metabolism, Amsterdam, The Netherlands
13 Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands
14 Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht, The Netherlands
E-mail: r.slebe@amsterdamumc.nl

BACKGROUND

The timing of physical activity (PA) relative to meal intake

seems to influence glycaemia. However, no meta-analysis has examined the acute and long term effect on different glycaemic measures. Therefore, the TIMED consortium performed this systematic review and meta-analysis to assess the effect of preprandial PA versus postprandial PA on glycaemia in human intervention studies.

METHODS

MEDLINE and Embase.com were searched till September 2021 for intervention studies in the general adult population, directly comparing preprandial PA versus postprandial PA on glycaemic measures, using relevant search terms. Studies were screened using ASReview (23,308) and full texts were read by two independent reviewers (37 full text, 25 included). Methodological quality was assessed by two independent reviewers and results were meta-analyzed using pooled mean differences in a random-effects analysis or qualitatively described.

RESULTS

Included studies were either acute response studies (n = 18) or Randomized Controlled Trials (RCTs) over multiple weeks (n = 7). Methodological quality was strong (n = 10), moderate (n = 11) or weak (n = 4). In acute response studies, postprandial outcomes followed the expected physiological patterns (e.g. following meal intake), while outcomes measured over 24h showed no significant associations. For the RCTs over multiple weeks, glucose AUC during an OGTT was slightly, but not significantly lower in preprandial PA vs postprandial PA (-0.29 mmol/L [95% CI -0.66; 0.08] I^2 = 64.36%). Sensitivity analyses did not significantly change the outcomes.

CONCLUSION

This study showed no differences between preprandial PA versus postprandial PA on glycaemia both acute and long term, showing contradictive results and low to moderate quality of evidence. More homogeneous RCTs with large populations and long follow-up periods (≥ 12 weeks) are needed.

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The impact of obesity and insulin resistance on circulating immune markers and monocyte metabolic signatures

Lisa Smeehuijzen[1], Anouk Gijbels[1,2], Joline P. Boogaard[1], Frank Vrieling[1], Mehdi Boutagoug[1] Boudjadja[4], Inez Trouwborst[2,3], Kelly M. Jardon[2,3], Gabby B. Hul[3], Edith J.M. Feskens[1], Ellen E. Blaak[3], Gijs H. Goossens[3], Lydia A. Afman[1], Rinke Stienstra[1]

1 Division of Human Nutrition and Health, Wageningen University, Wageningen, The Netherlands
2 TiFN, Wageningen, The Netherlands
3 Department of Human Biology, NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University Medical Center+, Maastricht, The Netherlands
4 Metofico Scientific, London, United Kingdom

BACKGROUND

Obesity-associated inflammatory signals interfere with insulin signaling, contributing to tissue-specific and systemic insulin resistance. The etiology of IR can be highly variable among individuals, which might be explained by differences in the degree of inflammation. Since immune cells drive inflammation through alterations in intracellular metabolism, we aimed to explore the impact of IR on monocyte metabolic signatures combined with measurements of circulating inflammatory proteins in overweight/obese individuals.

METHODS

We performed a cross-sectional study including n = 185 individuals (BMI > 25kg/m^2). We measured the degree of systemic insulin resistance, together with circulating inflammatory markers using Olink, monocyte metabolic signatures based on glycolysis and oxidative metabolism using Seahorse assays, and cytokine production using ELISA. We applied linear models to study the impact of obesity and IR on monocytes.

RESULTS

Our results showed that monocyte metabolic and functional responses are highly variable between individuals. Whereas monocyte metabolism was strongly associated with cytokine production of the cells (FDR < 0.02), no association with age, sex, or BMI was found. However, monocyte metabolism was associated with IR, illustrated by a reduced metabolic dependency on glycolysis ($p < 0.02$, FDR < 0.16). Furthermore, we found that monocyte metabolism and systemic IR were associated with circulating inflammatory markers, particularly CXCL11 (FDR < 0.02; FDR < 0.05, respectively). More precisely, elevated levels of IR were accompanied by reduced circulating CXCL11 levels and a shift in monocyte metabolic dependency from glycolysis to oxidative metabolism

CONCLUSION

Our study is the first to describe metabolic signatures of circulating monocytes from a large sample size of 185 individuals. The strong association between monocyte metabolism and cytokine production supports the tight relationship between immune cell metabolism and functionality, as often described in the literature. Obesity is a risk factor for developing metabolic complications and is associated with impaired immune responses. Our data show that obesity may lead to altered plasma cytokine profiles and monocyte metabolic signatures, which associate with the level of systemic IR. Hence, the shift in monocyte metabolism may result from a change in circulating inflammatory markers, involving CXCL11. Therefore, we conclude that obesity and IR impact monocyte metabolism, which may contribute to the progression of obesity-related metabolic disease.

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The gut microbiome is associated with residual β-cell function and glycemic control in type 1 diabetes

Coco M. Fuhri Snethlage[1], Mark Davids[1], Elena Rampanelli[1], Pleun de Groen[1], Xanthe Verdoes[1], Hilde J. Herrema[1], Daniël H. van Raalte[2], Bart O. Roep[3], Max Nieuwdorp[1], Nordin M.J. Hanssen[1]

1 Department of Experimental Vascular Medicine, Amsterdam Cardiovascular Science Institute, Amsterdam University Medical Center, location AMC, Amsterdam, The Netherlands
2 Department of Endocrinology and Metabolism, Amsterdam University Medical Center, location VUMC, Amsterdam, The Netherlands
3 Department of Internal Medicine, Leids Universitair Medisch Centrum, Leiden, The Netherlands

BACKGROUND

Perturbations of the gut microbiome play a role in the development of type 1 diabetes (T1D). A recent trial in new-onset T1D individuals showed that fecal microbiota transplantation can preserve residual β-cell function. Therefore, in this study, we investigated the association between the microbiome and residual β-cell function and/or time in range in T1D.

METHODS

In this cross-sectional cohort, 477 participants with established T1D were included, 37.7% was male, mean age was 40.0 ± 14.0 years, T1D duration was 15.0 years [IQR 6.0-28.3] and HbA1c was 55.6 ± 12.2. To assess time in range (defined as 3.9-10.0 mmol/L), 14-day CGM data was collected. Metagenomic sequencing was performed to measure fecal microbiota diversity and composition. Postprandial urine c-peptide to creatinine ratios (UCPCR) were assessed to determine residual β-cell function. Ordination plots and PERMANOVA were used to calculate beta diversity and linear models were used to calculate the difference in microbiome taxonomy.

RESULTS

Participants with detectable residual β-cell function had significantly higher alpha and beta diversity ($r^2 = 0.002$, $p = < 0.05$). Additionally, more time in range was significantly associated with higher alpha and beta diversity ($r^2 = 0.003$, $p = < 0.05$). At the genus levels, Ruminococcus ($p_{adjusted} = < 0.05$, effect = 0.05) and Roseburia ($p_{adjusted} = < 0.05$, effect = 0.005) associated with residual β-cell function, whereas Prevotella ($p_{adjusted} = < 0.05$, effect = −4.05) was negatively correlated with time in range.

CONCLUSION

The microbiome differs significantly between individuals with and without residual β-cell function. Further studies are warranted to assess a role of the differential intestinal microbial genera in preserving versus deteriorating residual β-cell function.

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Methylglyoxal is a mediator of the association between 2-hour plasma glucose, HbA1c and inflammation: The Maastricht Study

Dijia Sun, Marleen M.J. van Greevenbroek, Jean L.J.M. Scheijen, Simone J.M.P. Eussen, Coen D.A. Stehouwer, Kristiaan Wouters, Casper G. Schalkwijk

Department of Internal Medicine, Maastricht University Medical Center and CARIM School for Cardiovascular Disease, Maastricht, The Netherlands
E-mail: d.sun@maastrichtuniversity.nl

BACKGROUND

Dysregulated glucose metabolism in diabetes drives chronic low-grade inflammation. The reactive dicarbonyl methylglyoxal (MGO) is a potent glycating agent that is linked with increased inflammation. MGO is formed from glucose, is increased in diabetes, and is further increased after a glucose load. We hypothesized that glucose, and particularly post-load glucose excursions are associated with chronic low-grade inflammation and that this association is mediated by MGO.

METHODS

We investigated this hypothesis in The Maastricht Study (population-based n = 3017, 59.9 ± 8.2 yrs, 49.5% women, by design 26.5% with type 2 diabetes) Independent variables were fasting plasma glucose (FPG), 2-hour plasma glucose (2-h PG) after a glucose tolerance test, and HbA1c. The dependent outcome was low-grade inflammation (Z-score of plasma C-reactive protein, serum amyloid A, interleukin-6, interleukin-8, tumor necrosis factor, soluble intercellular adhesion molecule-1). MGO was measured with ultra-performance liquid chromatography tandem mass spectrometry. Linear regression analyses adjusted for potential confounders (age, sex, lifestyle factors, medication use and body mass index) were done to evaluate the associations between FPG, 2-h PG and HbA1c and the low-grade inflammation score and results are presented as standardized regression coefficients and 95% CIs. Mediation analyses assessed whether associations between glucose and inflammation were mediated by MGO.

RESULTS

In the fully adjusted models, 2-h PG (0.172 [0.110; 0.234]) and HbA1c (0.148 [0.101; 0.196]), but not FPG (0.049 [-0.002; 0.100]), were significantly associated with low-grade inflammation. Mediation analyses showed that MGO mediated 23% of the association between 2-hPG and inflammation, and 16% of the association between HbA1c and inflammation.

CONCLUSION

Post-load glucose excursions and HbA1c are associated with inflammation and this association is mediated, at least in part, by MGO. Mitigating glucose excursions and targeting MGO formation may thus be bona fide strategies to lower chronic low-grade inflammation in diabetes.

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Plasma indoles after broad-spectrum antibiotic use in individuals with impaired glucose metabolism

Charlotte Teunis, Stijn Meijnikman, Han Levels, Mark Davids, Hilde Herrema, Victor Gerdes, Max Nieuwdorp, Nordin Hanssen

Departments of Internal and Experimental Vascular Medicine, Amsterdam University Medical Centers, location AMC, Amsterdam, The Netherlands
Corresponding/presenting author: Charlotte Teunis

BACKGROUND

Tryptophan metabolism has emerged as a promising target in diabetic complications. Multiple studies have shown that metabolites from the kynurenine pathway are increased in cardiometabolic disease via indoleamine 2,3-dioxygenase (IDO) induction by pro-inflammatory molecules. This, in turn, potentially diverts tryptophan away from indole metabolism by the gut microbiome. This is of importance since indoles may exhibit immune-modulatory properties via the aryl hydrocarbon receptor (AhR) and pregnane X receptor (PXR). Our study aimed to verify the same pattern of metabolite disruption in NASH and to investigate which metabolites are dependent on the gut microbiome. By exploring these aspects, we aimed to deepen our understanding of tryptophan metabolism's relevance in NASH and its interplay with the gut microbiome.

METHODS

We enrolled 10 insulin-resistant patients with biopsy confirmed NASH, and 10 healthy controls. Blood samples were collected from all patients before and after a mix meal test (MMT). In nine NASH patients, we administered a two-week course of antibiotics (metronidazole, clindamycin, and ciprofloxacin) to completely deplete the gut bacteriome. After two weeks of antibiotics, new blood samples

were collected for untargeted metabolomics before and after a MMT.

RESULTS

The MMT confirmed impaired glucose tolerance in the NASH participants (glucose levels 7.6 vs 5.1 mM, $p < 0.001$). There were no differences in metabolites concentrations in fasting and post-prandial state in healthy controls and NASH patients. However indole-3-propionate (IPA) and 3-indoxyl sulfate (IS) were significantly lower in patient with NASH after antibiotic treatment. We observed no differences in tryptophan concentrations or metabolites from the kynurenine pathway before and after antibiotic treatment.

CONCLUSION

The administration of antibiotics demonstrated that indole metabolism, particularly IPA and IS, is entirely dependent on the gut microbiota. These results provide valuable insights into the tryptophan-associated metabolic alterations in NASH and highlight the essential role of the gut microbiome in indole metabolism. Understanding these dynamics could pave the way for novel therapeutic interventions targeting tryptophan metabolism and its impact on NASH pathogenesis.

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The role of the hypothalamus-pituitary-adrenal axis in the difference in treatment response to GLP-1 receptor agonists in type 2 diabetes

S. Tokgöz[1], T.J.P Jansen[1], R. Meijer[2], C. Frielink[1], C.J. Tack[2], B.E. de Galan[2,3], M. Gotthardt[1], M. Boss[1]

1 Department of Medical Imaging, Radboud University Medical Center, Nijmegen, The Netherlands
2 Department of Internal Medicine, Radboud University Medical Center, Nijmegen, The Netherlands
3 Department of Internal Medicine, Maastricht University Medical Center, CARIM School for cardiovascular diseases, Maastricht university, Maastricht, The Netherlands
E-mail: Sevilay.Tokgoz@radboudumc.nl

BACKGROUND

About 20% of individuals with T2D are partly/completely unresponsive to treatment with glucagon-like peptide-1 receptor agonists (GLP-1RAs). Besides the insulinotropic effects on beta-cells, GLP-1RAs can stimulate the hypothalamic-pituitary-adrenal (HPA) axis inducing cortisol secretion, which is associated with weight gain and insulin resistance. We hypothesized that this effect could be at the root of unresponsiveness to GLP-1RA treatment. To investigate this, we used PET/CT imaging with a radiolabeled GLP-1 analogue ([^{68}Ga]Ga-NODAGA-exendin-4) to quantify GLP-1R expression in the pituitary of individuals with T2D with and without an adequate response to GLP-1RA treatment and assessed the downstream effects on the HPA-axis.

METHODS

Responders (n = 10) and non-responders (n = 9) were defined based on HbA1c and weight loss after a maximum of one year of GLP-1RA treatment. Both groups underwent an OGTT, HPA-axis stimulation test and a PET/CT scan of the brain after infusion with 101 ± 7.2 MBq of [^{68}Ga]Ga-NODAGA-exendin-4.

RESULTS

Our data showed tracer uptake in the pituitary of all individuals with T2D, which did not significantly differ between responders and non-responders (SUVmax 2.7 ± 1.0 vs 3.2 ± 1.3, $p = 0.41$). However, we found significant interindividual differences in pituitary GLP-1R expression in the entire population (25th-vs-75th percentile: 1.8 ± 0.19 vs 4.5 ± 0.75, $p < 0.001$). No significant differences were observed in beta-cell function ($AUC_{C\text{-}peptide}$:$AUC_{glucose}$ $p = 0.26$) and HPA hormones upon HPA-axis stimulation (AUC_{ACTH} $p = 0.47$; $AUC_{cortisol}$ $p = 0.18$) between responders and non-responders. Pituitary tracer uptake did not correlate to BMI ($r^2 = 0.00053$, $p = 0.93$), beta-cell function ($AUC_{C\text{-}peptide}$:$AUC_{glucose}$ $r^2 = 0.051$, $p = 0.42$) and HPA hormones (AUC_{ACTH} $r^2 = 0.10$, $p = 0.23$; $AUC_{cortisol}$ $r^2 = 0.010$, $p = 0.71$).

CONCLUSION

Our data do not indicate a role of pituitary GLP-1R expression and HPA-axis stimulation in the difference in treatment response to GLP-1RA among individuals with T2D. The origin of this heterogeneity in treatment response remains thus unclear. The substantial tracer uptake with significant interindividual differences does point to a potential role of GLP-1Rs in the pituitary, which requires further elucidation.

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Incidence of pancreatic injury and post traumatic pancreatic resections in the Netherlands; is there a role for autologous islet transplantation?

Maarten Tol[1,2], Samantha Scharringa[2], Sven Mieog[2], Eelco de Koning[1], Pieta Krijnen[2], Volkert Huurman[2], Inger Schipper[2]

1 Department of Internal Medicine, Leiden University Medical Center, Leiden, The Netherlands
2 Department of Surgery, Leiden University Medical Center, Leiden, The Netherlands

BACKGROUND

Traumatic pancreatic injuries occur seldomly and little is known about the incidence and (surgical) treatment in the Netherlands. Diabetes can develop depending on the degree of resection of the pancreas. It is possible to isolate pancreatic islets from the resected pancreas and give them back to the patient by means of an intraportal infusion. This autologous islet transplantation (AIT) may prevent diabetes or reduce glucose dysregulation. In this study, we assessed the incidence of pancreas injury and pancreatic resection after trauma and the eligibility for AIT in The Netherlands.

METHODS

A multicenter, retrospective cohort study was conducted in level 1 trauma centers in the Netherlands. Data of trauma patients that were acutely admitted with pancreatic injuries between 01-01-2012 and 31-12-2021 were obtained from the national trauma registratry. Data on injury, treatment and (relative) contra-indications for AIT (such as pre-existing diabetes and liver injury) were collected from patient records.

RESULTS

On average, 48 patients presented with pancreatic injury per year. Until now, 115 patients were included. The mean (SD) age was 33.7 (18) years, 66% was male and 4 patients had type 2 diabetes. Blunt trauma was the cause in 82%. High-grade (OIS III-V) pancreas injuries were present in 35.1% of patients. Fourteen patients (12.2%), all grade III-V underwent pancreatic resection. The median time to resection was 2.1 hours (IQR: 0.8-60.3). Seven of the 14 patients with a pancreas resection had (relative) contraindications for AIT.

CONCLUSION

Pancreatic injury after trauma is rare and is usually treated conservatively. In 12% of the patients, a resection was performed, only in patients with grade III or higher. A majority of these patients is likely to be eligible for autologous islet transplantation.

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Developing a vascularized islet-on-a-chip model

Maarten van Agen[1], Ulgu Arslan[2], Valeria Orlova[2], Eelco de Koning[1], Françoise Carlotti[1]

1 Department of Internal Medicine, LUMC, Leiden, The Netherlands
2 Department of Anatomy and Embryology, LUMC, Leiden, The Netherlands

BACKGROUND

The interaction between endocrine cells and vasculature in pancreatic islets is of major importance for islet development, identity, function and interaction with circulating cells and factors. Isolated pancreatic islets lose their vasculature. Organ-on-a-chip platforms and iPSC (induced pluripotent stem cell) technology represent an opportunity to create a next generation islet culture system, which would also allow high throughput screening. Here we propose to setup a vascularized islet on a chip model with pre-vascularized islets.

METHODS

The first step consisted in 'pre-vascularizing' the islets: Primary human islets were individually cultured in microwells in the presence of 0, 625, 1250 or 1875 mCherry labeled hiPSC derived endothelial cells (hiPSC-EC) in different culture media (CMRL, EBM-2, or a 50/50 combination) during 5 days, to establish optimal conditions for hiPSC-EC to migrate into the islet. Islet viability was assessed by FDA/PI staining. Next, hiPSC-EC islet-clusters or control islets were mixed in a fibrin gel with additional 100,000 hiPSC-ECs and 20,000 human pericytes and subsequently loaded in a lab-on-a-chip (AIM biotech). Monitoring of the islet-on-a chip was done by confocal microscopy.

RESULTS

Islet viability in the microwells was stable and > 90% in all coculture conditions during 5 days. From day 3 onward, we observed hiPSC-ECs migrating into the islet in all culture media, forming an accumulation of cells within. The 1250 hiPSC-ECs and 50/50 medium coculture

condition was chosen in subsequent experiments, containing medium beneficial for each cell type and an abundance of hiPSC-ECs for migration to occur. Next, control islets and 1250 hiPSC-EC islet-clusters were loaded into the chip, with additional hiPSC-ECs and human pericytes, forming a structure resembling a vascular network. A direct connection between the vascular network and the islet was found in case of hiPSC-EC islet-clusters, but not in the case of control islets.

CONCLUSION

These preliminary data show that a pre-vascularization strategy of primary human islets with endothelial cells in vitro is feasible. When cultured in a lab-on-a-chip platform, these islets appear to form a better connection to the surrounding vasculature. This platform of vascularized islets can be used for drug screening, disease modeling, islet function and interactions between islet cells and other cell types (e.g., immune cells)

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Integration of a periodic fasting-mimicking diet program in primary care for type 2 diabetes

Elske van den Burg[1], Marjolein Schoonakker, Petra van Peet, Elske van den Akker–van Marle, Hildo Lamb, Valter Longo, Mattijs Numans, Hanno Pijl[2]

1 Department of Public Health and Primary Care, Leiden University Medical Centre, Leiden, The Netherlands
2 Department of Internal Medicine, Leiden University Medical Centre, Leiden, The Netherlands
E-mail: e.l.van_den_burg@lumc.nl

BACKGROUND

Current effective lifestyle interventions as treatment for type 2 diabetes (T2D) can be difficult to sustain. A periodic fasting-mimicking diet (FMD) has been developed that allows the intake of small amounts of food while mimicking the physiological effects of water-only fasting. Our aim was to evaluate the impact of periodic use of an FMD as an adjunct to usual care on glycemic management in patients with T2D under regular primary care surveillance.

METHODS

In this randomized controlled, assessor-blinded trial, one hundred patients with T2D using only metformin and/or diet alone for glycemic control were included. Participants were randomized to receive an FMD for 5 consecutive days every month as an adjunct to usual care (n = 51) or usual care only (n = 49) for a period of one year. The primary outcomes were glucose-lowering medication use and HbA1c levels. Changes in HbA1c and the use of glucose-lowering medication in individual patients were combined to yield a clinically relevant primary outcome measure to indicate glycemic management, categorized as improved, stable, or deteriorated.

RESULTS

Regarding glucose-lowering medication, the mean medication effect score declined in patients receiving FMD as compared to controls (FMD -0.2 ± 0.3 vs controls +0.2 ± 0.4, $p < 0.0001$) in the face of similar changes of HbA1c (FMD -2.4 ± 8.0 vs controls 0.0 ± 9.6 mmol/mol, $p = 0.22$). Glycemic management was improved in 53% (n = 23) of individual participants of the FMD group compared to 8% (n = 3) of controls, while 23% (n = 10) of patients receiving FMD and 33% (n = 13) of controls remained stable, and 23% (n = 10) using FMD and 59% (n = 23) of controls deteriorated ($p < 0.0001$).

CONCLUSION

Integration of an FMD program in primary care for persons with T2D improves glycemic management, and can be a valuable treatment option for patients with T2D using metformin only or no medication.

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Prospective relation between long-term glucocorticoid exposure and incident cardiovascular diseases in a large population based cohort: results from the Lifelines cohort study.

Eline S. van der Valk[1,2], Mostafa Mohseni[1,2], Anand M. Iyer[1,2], Maartje van den Hurk[1,2], Robin Lengton[1,2], Susanne Kuckuck[1,2], Vincent L. Wester[2], Jenny A. Visser[1,2], Mina Mirzaian[3], Sjoerd A.A. van den Berg[1,3], Elisabeth .F.C. van Rossum[1,2]

1 Obesity Centre CGG, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands
2 Department of Internal Medicine, division of Endocrinology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands
3 Department of Clinical Chemistry, University Medical Center Rotterdam, Rotterdam, The Netherlands

BACKGROUND

Long-term glucocorticoid levels measured in scalp hair (HairGCs), including hair cortisol and the inactive form hair cortisone, have become frequently used biomarkers that represent the cumulative exposure to glucocorticoids over the last months. HairGCs, have repeatedly shown promising associations with cardiometabolic parameters, but longitudinal data are lacking.

METHODS

We investigated 6341 hair samples of participants from the Lifelines cohort study for cortisol and cortisone levels, and associated these to incident cardiovascular diseases (CVD) during the 5-7 years of follow-up. We computed the odds ratio (OR) of HairGC levels for incident CVD via logistic regression, and adjusted these for age, sex, waist circumference, corticosteroid use, current smoking, systolic blood pressure, and type 2 diabetes mellitus. Next, we performed a sensitivity analysis in subcohorts based on age (median split, age < = 57 years and age > 57 years).

RESULTS

Hair cortisone levels (available in n = 4701) were associated with incident CVD ($p < 0.001$), even in the adjusted analyses (OR 1.95, 95% confidence interval (CI) 1.05-3.56 per point increase in 10-log cortisone concentration (pg/mg), $p = 0.032$). Hair cortisone had the highest odds ratio within younger cases (OR 3.25, 95% CI 1.40-7.21, $p = 0.005$); in elder cases it was not significant. Hair cortisol measurements had more technical difficulties (results available in n = 2776), and were not associated with incident CVD.

CONCLUSION

In this large, prospective cohort study, we found that long-term cortisone levels, measured in scalp hair, represent a relevant and significant predictor for future cardiovascular diseases, even after correction for established cardiovascular risk factors and particularly in younger individuals. These results highlight glucocorticoid action as possible treatment target for CVD, and suggest that hair glucocorticoid measurements could help identify that may benefit from such treatments.

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Associations between chronotype and total body fat, visceral fat, liver fat, and incidence of type 2 diabetes

Jeroen H.P.M. van der Velde[1], Frits R. Rosendaal[1], Hildo J. Lamb[2], Andries Kalsbeek[3], Femke Rutters[4], Renée de Mutsert[1]

1 Department of Clinical Epidemiology, LUMC, Leiden, The Netherlands
2 Department of Radiology, LUMC, Leiden, The Netherlands
3 Department of Endocrinology and Metabolism, Amsterdam University Medical Centers, Amsterdam, The Netherlands
4 Department of Epidemiology and Biostatistics, Amsterdam University Medical Centers, location VU Medical Center, Amsterdam, The Netherlands
E-mail: jeroen.vandervelde@lumc.nl

BACKGROUND

Late chronotype, i.e., someone's preference for eveningness, has been associated with an increased risk of type 2 diabetes (T2D). Studies have reported associations between late chronotype and obesity, but relations with ectopic fat remain unclear. Therefore, we aimed to examine associations between chronotype and BMI, total body fat, visceral fat, liver fat, and the risk of T2D in a middle-aged population.

METHODS

In the Netherlands Epidemiology of Obesity study, we calculated mid-point of sleep (MPS) from the Pittsburgh Sleep Questionnaire, and defined late chronotype as MPS ≥ 4 hours and intermediate chronotype (reference category) as MPS between 3-4 hours. We measured total body fat via bioimpedance, visceral fat using magnetic resonance imaging (MRI), and liver fat using MR spectroscopy in n = 1628. Incidence of T2D was collected via electronic health records. We performed linear regression analyses to examine cross-

sectional associations between late chronotype and BMI, total body fat, visceral fat and liver fat. We calculated hazard ratios with 95% confidence intervals (HR, [95% CI]) of T2D using Cox regression. All analyses were adjusted for age, sex, education, physical activity, and diet quality.

RESULTS

After exclusion on lost-to-follow-up, prevalent T2D, missing MPS, and missing covariates, 5048 participants (54% women) were analysed, with a mean (SD) age of 56(6) years, BMI of 30(5) kg/m^2, 19% with late chronotype. During median follow-up of 6.6 years, 225 participants were diagnosed with T2D. Compared with intermediate chronotype, participants with late chronotype had a higher BMI (0.6 kg/m^2 [95% CI 0.2, 0.9]) and more liver fat (1.79%; [0.47, 3.12]). These differences were 0.4% [-0.1, 0.8] for total body fat and 7 cm^2 [-0.4, 13.6] for visceral fat. Further, those with late chronotype had an increased risk of T2D; HR 1.46 [1.03, 2.06].

CONCLUSION

Late chronotype was associated with increased BMI and liver fat content and with an increased risk of T2D, and is an emerging risk factor for metabolic diseases.

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Weight cycling modifies the visceral adipose tissue and liver immune landscape without impacting whole-body insulin resistance in mice

Hendrik J.P. van der Zande[1], Frank Vrieling[1], Lisa Smeehuijzen[1], Brecht Attema[1], Jenny Jansen[1], Sander Kersten[1], Rinke Stienstra[1,2]

1 Division of Human Nutrition & Health, Wageningen University, Wageningen, The Netherlands
2 Department of Internal Medicine, RadboudUMC, Nijmegen, The Netherlands
E-mail: patrick.vanderzande@wur.nl

BACKGROUND

Although weight loss mitigates obesity-associated metabolic complications such as insulin resistance, the majority of individuals will regain lost weight through the mechanistically incompletely resolved phenomenon of weight cycling. Obesity-associated insulin resistance is driven by inflammation of metabolic tissues such as white adipose tissue (WAT) and the liver. Here, we investigated the immunometabolic impact of weight cycling in mice.

METHODS

Male C57BL/6J mice were subjected to weight cycling by alternating between a low fat diet (LFD) and high fat diet (HFD) upon reaching the weight of the LFD-fed lean or HFD-fed obese control groups. Mice were sacrificed when weight-cycled mice completed two cycles and reached the weight of the obese control group, and the impact of weight cycling on WAT and liver immune cell composition was tested via flow cytometry.

RESULTS

Body weight and composition were unchanged by weight cycling as compared to the obese control group. Principal component analysis on the abundances of 37 WAT and liver immune cell subsets revealed distinct clustering of all groups, where the obese and weight-cycled group were significantly separated on PC2 (23.43% variance explained; obese: 2.629 ± 3.033 vs weight-cycled: -2.578 ± 1.738; $p = 0.0247$). Top loadings on PC2 contained WAT macrophages (WAT-Mφ), and WAT and liver cytotoxic and T helper cell subsets. Indeed, weight cycling increased WAT-Mφ abundance (+40%, $p = 0.0329$). Although neutral lipid content and expression of lipid-associated macrophage markers was unaffected, WAT-Mφ from weight-cycled mice displayed increased protein synthesis (+100%, $p = 0.016$), indicative of increased anabolic/inflammatory activation. Yet, HOMA-IR as proxy for whole-body insulin resistance was similar between weight-cycled and obese mice.

CONCLUSION

Although weight cycling impacts WAT and liver immune cell composition and WAT-Mφ activation, these changes do not culminate in aggravated whole-body insulin resistance. In-depth phenotyping of metabolic tissues via western blot and immunohistochemistry may uncover tissue-specific weight cycling-induced changes.

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Inflammatory markers are elevated in type 1 and type 2 diabetes and linked to long-term complications

Julia I.P. van Heck[1], Rinke Stienstra[1,2], Leo A.B. Joosten[1,3], Cees J. Tack[1]

1 Department of Internal Medicine, Radboud University Medical Centre, Nijmegen, The Netherlands.
2 Division of Human Nutrition and Health, Wageningen University & Research, Wageningen, The Netherlands.
3 Department of Medical Genetics, Iuliu Haţieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania
E-mail: julia.vanheck@radboudumc.nl

BACKGROUND

Inflammation is important in the development of diabetes related complications. Although the presence of low-grade inflammation is well-established, particularly in type 2 diabetes (T2D), the underlying mechanism remains largely unknown. We used a proteomics approach to compare the inflammatory profile of people with type 1 diabetes (T1D) and T2D with controls, and linked these markers to diabetes related characteristics and complications.

METHODS

This study included 239 participants with T1D, 388 participants with T2D and 150 age, sex and BMI matched healthy controls. Clinical information, including complications, was collected from all participants. Participants with T2D were followed for 10 years to determine the development of complications. Plasma was collected and used to determine C-reactive proteins (CRP) and 92 inflammatory markers using the Olink proteomics platform.

RESULTS

Hs-CRP was increased in both T1D and T2D but higher in T2D. 41 inflammatory markers were higher in T1D compared to healthy controls (FDR < 0.05), 64 inflammatory markers were higher in T2D compared to healthy controls (FDR < 0.05). 14 markers were positively associated with HbA1c in both cohorts (FDR < 0.05). A positive association was found between BMI and inflammation in T2D, not in T1D. Nephropathy was positively associated with several inflammatory markers in both cohorts including IL-10RB, IL15-RA and TNFRSF9 (FDR < 0.05). These markers are important in initiating responses from the innate and adaptive immune system. Using the follow up data, we found that EN-RAGE, Flt3L, and CD8A were associated with an increased risk of developing cardiovascular complications in T2D (p-value < 0.05).

CONCLUSION

Although inflammatory markers are higher in T2D, chronic low-grade inflammation is present in both T1D and T2D. In T1D this is mainly associated with glycaemic control, whereas BMI is an additional factor associated with inflammation in T2D. These results suggest that the drivers of inflammation might be different in T1D and T2D, while similar pathways may be involved in the development of diabetes associated complications.

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Falls in people with diabetes and peripheral neuropathy and their association with physical activity and gait quality

Jaap J. van Netten, Chantal M. Hulshof, Abe F. Funnekotter, Mirjam Pijnappels, Sicco A. Bus

Department of Rehabilitation Medicine, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands
Amsterdam Movement Sciences, Ageing & Vitality and Rehabilitation & Development, Amsterdam, The Netherlands
Department of Human Movement Sciences, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands
E-mail: j.j.vannetten@amsterdamumc.nl

BACKGROUND

Falls are a major clinical problem. In people with diabetes, peripheral neuropathy is a predictor of falls. However, within this population, it is unknown which characteristics are associated with falls. Our aim was to determine fall incidence and its association with physical activity and gait quality characteristics in people with diabetes and peripheral neuropathy.

METHODS

In a prospective longitudinal observational study, we included 43 participants with diabetes and neuropathy (9 females, mean age 64 years (SD: 8.9), BMI 30 kg/m^2 (SD: 5.7)) and followed them for 6 months. Falls were reported in a fall diary. Physical activity and gait quality were measured using a tri-axial accelerometer, worn for seven consecutive days. We tested associations between falls and independent

variables using forward multivariate logistic regression analysis.

RESULTS

During 6 months follow-up, 17 participants (40%) reported a total 23 falls. Fallers had a lower number of lying episodes per day than non-fallers (fallers: 8.8 (SD: 5.1), non-fallers: 12.8 (SD: 5.6)), significantly associated with falls in multivariate analysis ($p = 0.02$). Compared to non-fallers, fallers were more often female (fallers: 35%, non-fallers: 21%), had lower walking speed (fallers: 0.8 m/s (SD: 0.2), non-fallers: 0.9 m/s (SD: 0.2)) and more consistent gait pattern (power spectral density: fallers: 0.6 (SD: 0.2) vs. non-fallers: 0.5 (SD: 0.1)). However, none of these characteristics were significantly associated with falls in multivariate analysis.

CONCLUSION

40% of people with diabetes-related peripheral neuropathy had a fall incident during 6 months follow-up. Fewer daily lying episodes was the only characteristic statistically significantly associated with falls, suggesting limited rest or greater exposure to weight-bearing activity as underlying reasons. Gait quality characteristics did not discriminate within this high-risk population.

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Bacterial membrane vesicles derived from lean men and men with overweight/obesity elicit different *in vitro* immunogenic responses in adipocytes

Jari Verbunt*[1,2], Johan Jocken[2], Emanuel Canfora[2], Ellen Blaak[2], Paul Savelkoul[1,3], Frank Stassen[1]
***Presenting author**

1 Department of Medical Microbiology, infectious diseases & Infection prevention, Maastricht University Medical Center+, Maastricht, The Netherlands
2 Department of Human Biology, School of Nutrition and Translational Research in Metabolism (NUTRIM), Maastricht University, Maastricht, The Netherlands
3 Department of Medical Microbiology and Infection Control, Amsterdam University Medical Centers, Amsterdam, The Netherlands
E-mail: jari.verbunt@maastrichtuniversity.nl

BACKGROUND

The intestinal microbiota play a pivotal role in human health. In people with obesity and type 2 diabetes (T2D) the composition and functionality of the gut microbiota is often altered, with profound implications for host substrate and energy metabolism. Importantly, gut bacteria produce bacterial membrane vesicles (bMVs) containing bacterial metabolites, nucleic acids and toxins. These bMVs can contribute to the etiology of metabolic disease by interacting with insulin sensitive tissues such as adipose tissue (AT), skeletal muscle and the liver. The aim of this study was to investigate differences in bMV composition and their effects on human adipocytes *in vitro*.

METHODS

Fecal samples from participants (12 with a BMI < 25, 12 with a BMI ≥ 25) were collected and DNA was obtained from purified bMVs and bacteria. Purified DNA was subjected to 16S rRNA variable region amplification and Illumina sequencing. Subsequently, human adipose tissue-derived stem cells (ASCs) were differentiated and pretreated 24 hours with 10^9 bMVs followed by incubation with or without 5 µg of LPS for 24 hours to elicit an inflammatory response.

RESULTS

The bacterial composition is different from the bMV composition (Bray-Curtis dissimilarity, $p < 0.001$). However, no clear distinctiveness of bMV composition based on BMI or insulin sensitivity was observed. Nevertheless, preliminary data suggests that *in vitro* pretreatment of adipocytes with bMVs obtained from individuals with high BMI induces a significantly more pronounced pro-inflammatory response (IL-1β + 33%, IL6 + 23%, TNFα + 51%).

CONCLUSION

bMVs constitute an additional layer of complexity in host-microbe interactions given that their composition cannot be predicted solely from bacterial compositions. Their immunomodulatory potential suggests they might be relevant players in onset and progression of metabolic disease.

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The potential of the prebiotic 2'-Fucosyllactose to improve recovery of the gut microbiome after vancomycin antibiotic use

Lars M.M. Vliex[1], John Penders[2], Arjen Nauta[3], Erwin G. Zoetendal[4], Ellen E. Blaak[1]

1 Department of Human Biology, NUTRIM, School for Nutrition and Translational Research in Metabolism, Maastricht University Medical Center+, Maastricht, The Netherlands
2 Department of Medical Microbiology, Infectious Diseases and Infection Prevention, Maastricht University Medical Center+, Maastricht, The Netherlands
3 FrieslandCampina, Amersfoort, The Netherlands
4 Laboratory of Microbiology, Wageningen University & Research, Wageningen, The Netherlands
E-mail: l.vliex@maastrichtuniversity.nl

BACKGROUND

Antibiotics are widely used to treat bacterial infections. And while generally effective, they may also negatively impact host health. Antibiotic use not only affects pathogenic, but also commensal bacteria, resulting in disturbances in gut microbial composition. These perturbations can have detrimental effects on host metabolic health. Supplementation with prebiotics after antibiotic use could be a novel strategy to improve recovery of the microbiome and limit detrimental health effects. We aimed to investigate the potential of the prebiotic 2'-Fucossyllactose to restore gut microbiota composition and activity, as well as parameters of host metabolic health, after vancomycin antibiotic use.

METHODS

A double-blind placebo-controlled randomized intervention study was performed, in which 37 adults with overweight or obesity (Body Mass Index: 25-40 kg/m^2) and without impaired fasting glucose and impaired glucose tolerance received vancomycin for seven days to disrupt gut microbial composition. Participants were then randomized to daily supplementation of either 2'-Fucosyllactose or placebo for eight weeks. At baseline, after antibiotic use and after supplementation, microbial composition was analyzed. Whole-body and tissue-specific insulin sensitivity was assessed from plasma glucose, insulin and free fatty acid levels measured during a 7-point Oral Glucose Tolerance Test.

RESULTS

Preliminary analyses show that one-week vancomycin use decreased gut microbial alpha diversity (Shannon: 2.86 ± 0.06 vs. 1.71 ± 0.09; $p < 0.001$). Microbial community structure (b-diversity, illustrated by Jaccard Dissimilarity) did not return to baseline after supplementation, indicating long-lasting disruption. In contrast, oneweek vancomycin use did not significantly affect the Hepatic Insulin Resistance Index (HIRI) (491 ± 43 vs. 436 ± 36; $p = 0.106$), nor other indices of whole-body and tissuespecific insulin sensitivity.

CONCLUSION

The disrupting impact of vancomycin on the gut microbiome is clearly shown. Analyses currently underway will further elucidate the potential of 2'-Fucosyllactose supplementation in microbial recovery and metabolic health after vancomycin use. As antibiotics are widely prescribed, our findings could have immediate clinical impact.

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The effects of custom-made footwear on stability during walking in people with diabetes and peripheral neuropathy

L.E. Vossen[1,2], J.J. van Netten[1,2], S.A. Bus[1,2]

1 Department of Rehabilitation Medicine, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands
2 Amsterdam Movement Sciences, Rehabilitation & Development, Amsterdam, The Netherlands
E-mail: l.e.vossen@amsterdamumc.nl

BACKGROUND

Custom-made footwear for people with diabetes and neuropathy effectively reduces peak plantar pressures and helps reduce the risk of foot ulceration. However, this footwear might also introduce instability during walking, which could lead to a higher fall risk. Our aim was to explore the effects of custom-made footwear on stability during walking.

METHODS

In a cross-sectional design 46 participants (92 feet) with diabetic neuropathy at high risk of ulceration and in possession of custom-made footwear completed both barefoot and in-shoe pressure measurements during walking. The maximum velocity of the Center-of-Pressure (CoP) was calculated for four phases of stance, and compared for

shod vs barefoot walking. An increase in maximum velocity defined an increase in instability. In secondary analysis we compared feet with and without an amputation at any level of the foot. We used paired and indepentdent t-tests for statistical analyses.

RESULTS

The maximum velocity of the CoP for shod vs barefoot walking was lower during midstance ($t(91) = -8.107$, $p < 0.001$), but higher during preswing ($t(91)= 3.75$, $p < 0.001$) (**Figure 5**). The difference between both conditions increased during midstance for amputated vs non-amputated feet, but decreased during preswing.

CONCLUSION

Custom-made footwear can increase instability during the preswing phase of walking in people with diabetic neuropathy. Further research is needed into which footwear design aspects contribute to this change and its effect on biomechanical, clinical and patient-related outcomes such as falls.

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Personalized lifestyle to prevent, revert and remit type 2 diabetes in primary care practice

Suzan Wopereis, Iris M. de Hoogh, Johanneke E. Oosterman, Dagmar Smid, Regina J.M. Kamstra, Wilma Otten, Anne-Margreeth Krijger, Susanne Berbée-Zadelaar, Hanno Pijl, Andre Boorsma, Ben van Ommen, Wilrike J. Pasman

TNO, Microbiology & Systems Biology, Leiden, The Netherlands

BACKGROUND

The current treatment paradigm in type 2 diabetes (T2D) is focused on treatment of symptoms rather than on the underlying metabolic dysregulation. Therefore an extended oral glucose tolerance test was developed to determine the type of insulin resistance (liver or muscle) and degree of beta-cell function as starting point for personalized lifestyle treatment.

METHODS

To test this approach, three personalized lifestyle studies were performed in a real-life primary health-care setting to evaluate the effect on the prevention, reversal and remission of T2D. One study was performed in 118 persons newly diagnosed with T2D (58 control, 60 intervention) and followed for 2 years. Based on their sub-phenotype, participants received a personalized lifestyle treatment for 13 weeks. The intervention group achieved 75% T2D remission after 13 weeks with long-term health benefits especially in the subgroup with isolated hepatic insulin resistance. A second study was performed in 15 persons with an average T2D duration of 13.4 years. These persons received a personalized nutrition treatment for six months.

RESULTS

Three out of 15 participants were successful to revert or remit their T2D, but results showed that underlying pathology was minimally affected, possibly due to an impaired beta cell function. Together these two studies suggest that a personalized lifestyle modification based on the subtype of type 2 diabetes can be a successful strategy in primary care especially when intervening as early as possible. Therefore, a third personalized lifestyle study was performed in 100 persons at risk of developing T2D (54 intervention, 46 control). At six months, greater improvement in body weight and fasting glucose was observed in the intervention group. While analyses are still ongoing, these are promising effects for T2D prevention.

CONCLUSION

Personalized lifestyle in primary care practice is promising to achieve long-term health benefits, especially at an early stage of T2D.

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Evaluating the cardiometabolic and intestinal health impact of habitual plant-based meat analogue consumption via a randomized controlled crossover dietary intervention study

R.M. van 't Spijker[1,2], J.G. Kers[2], D. Esser[1], H. Smidt[2], L.A. Afman[1]

1 Division of Human Nutrition & Health, Wageningen University & Research, Wageningen, The Netherlands
2 Laboratory of Microbiology, Wageningen University & Research, Wageningen, The Netherlands

BACKGROUND

Plant-based diets with little to no meat are considered healthy and sustainable by the general public. The increasingly popular plant-based meat analogues (PBMAs) allow consumers to easily decrease meat intake while maintaining their dietary pattern. PBMAs are designed to mimic the sensory and textural properties of meat and to replace animal pro-

tein with plant protein. Processing of plant-based ingredients is needed to achieve this, which potentially compromises sustainability and health assets of PBMAs. However, scientific knowledge on the health impact of PBMAs on humans is currently very limited. Therefore, evaluating the health impact of PBMAs may contribute to a better understanding of how these products fit into a healthy diet. The objective is to evaluate the effect of replacing all meat products in an average Dutch diet with currently commercially available PBMAs on the systolic blood pressure of middle aged men and women and on other parameters related to human cardiometabolic and intestinal health.

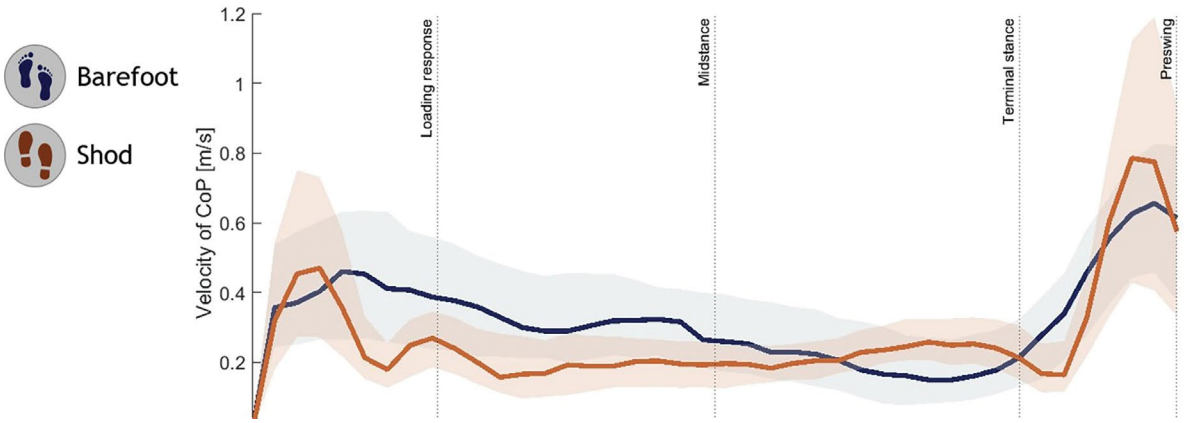
METHODS

114 middle aged men and women (age 45-75, BMI 24-40 kg/m^2) will participate in a randomized crossover controlled dietary intervention study at Wageningen University & Research. Participants will follow both a 8-week completely controlled diet in which all meats are of plant-based origin (PBMAs) and a 8-week diet in which all meats are of animal origin in randomized order with a 10-week washout period in between. Diets are fully controlled, which implies that all foods and meals are provided to participants and are based on their habitual energy needs to achieve weight stability througout the study. Except for meat/PBMAs all other foods will be the same in both interventions. The diets are based on the habitual diet as derived from the Dutch National Food Consumption Survey. Detailed measurements will be done before, during and after the interventions.

RESULTS

Primary outcomes are systolic and diastolic blood pressure (at-home measuments and in-clinic measurements). Secondary outcomes are cardiometabolic parameters, including 24-h glucose values (continuous glucose monitoring), metabolomics, transcriptomics and proteomics. Intestinal microbiome-related parameters include fecal and oral microbiota composition (shotgun metagenomics), microbial metabolites, microbiome functionality, stool consistency & frequency, transit time and gastro-intestinal symptoms. Other parameters include anthropometrics, well-being and satiety.

Figure 5. Median and standard deviation of the velocity of the Center of Pressure in m/s during the stance phase. Data is shown for barefoot (blue) and shod (orange) walking.



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Fasting and postprandial metabolite profiles differed in subjects with high and low liver fat

Yan Fang, Anouk Gijbels, Lydia A. Afman

Human Nutrition and Health, Wageningen University and Research, Wageningen, The Netherlands
E-mail: yan.fang@wur.nl

BACKGROUND

Excessive liver fat content is a known risk factor for some chronic metabolic diseases, such as cardiovascular disease, non-alcoholic fatty liver disease (NAFLD) and type II diabetes. Exposure to a high-fat and high-glucose challenge is a good way to measure metabolically resilient capacity.. We investigated the differences in fasting and postprandial metabolite profiles in people with different liver fat content.

METHODS

In this study, which is part of the Belly Fat Study, abdominal obese people received a high fat and high glucose mixed meal, plasma samples were taken before (T = 0) and after (T = 120, T = 240, T = 360) the mixed meal. Intrahepatic lipids values were determined using MRS. Intrahepatic lipid values were known for 66 of the 100 individuals who 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. At fasted and at T = 120, T = 240, T = 360 postprandially, 153 metabolites including lipoproteins, cholesterol, amino acids, ketone bodies, fatty acids, glycolysis-related metabolites and fluid balance were quantified using nuclear magnetic resonance spectroscopy.

RESULTS

The postprandial responses of plasma glucose, insulin as well as triglycerides are significantly stronger in the high liver fat group than in the low liver fat group. The high liver fat group was characterized by greater levels of fasting plasma VLDL particles and lower levels of fasting plasma ketone bodies, compared to the low liver fat group. And in the high liver fat group, there were greater increases in postprandial response of triglycerides (TG) in small IDL, very small VLDL and ketone bodies. Greater postprandial response of citrate was seen in the low liver fat group.

CONCLUSION

Fasting and postprandial metabolite profiles differed in subjects with high and low liver fat. Consumption of a mixed meal shake caused greater responses of dyslipidemic metabolites in the high liver fat group compared to the low liver fat group.

Coen D.A. Stehouwer[1], Erik H. Serné[2], Hilda J.I. de Jong[3], Jetty A. Overbeek[3], Jan Palmen[4]

Cardiorenale uitkomsten van diabetes mellitus type 2 tijdens behandeling met een sulfonureumderivaat in de Nederlandse praktijk

SAMENVATTING

Inleiding

Het is onbekend in hoeverre het risico op cardiovasculaire complicaties verhoogd is bij mensen met diabetes mellitus type 2 die niet voldoen aan de criteria voor een zeer hoog risico op hart- en vaatziekten, en die conventioneel behandeld worden met een sulfonureumderivaat (SU-derivaat).

Methode

De gegevens voor deze gematchte cohortstudie zijn verkregen uit het PHARMO Datanetwerk uit de eerste en tweede lijn in Nederland. De onderzoeksperiode liep van 1 januari 2013 tot en met 31 december 2019. Patiënten met diabetes mellitus type 2 die niet binnen de nieuwe richtlijn voor diabetes mellitus type 2 en een zeer hoog risico op hart- en vaatziekten vielen, werden ingedeeld in twee groepen: één groep met 'meerdere risicofactoren' (MRF) op basis van risicofactoren in de NHG CVRM Standaard, en één groep zonder aanvullende risicofactoren (non-RF). Het risico op verschillende cardiorenale complicaties afzonderlijk en een samengesteld eindpunt (hartfalen, myocardinfarct, beroerte, perifeer arterieel vaatlijden, niertransplantatie, dialyse, > 50% daling van de eGFR-waarde en overlijden) werd onderzocht vanaf de start van een SU-derivaat en vergeleken met een gematchte diabetesvrije populatie.

Resultaten

In de 6.148 patiënten in de MRF-groep was de incidentie van het samengestelde cardiorenale eindpunt 13 (95% CI, 9-18) per 1.000 patiëntjaren. Vergeleken met de diabetesvrije populatie was dit risico significant verhoogd (gecorrigeerde hazardratio 3,6; 95% CI, 2,1-6,3). Ook in de 3.219 patiënten in de non-RF-populatie was zowel de incidentie als de gecorrigeerde hazardratio voor het samengestelde cardiorenale eindpunt significant verhoogd.

Conclusie

Ondanks conventionele behandeling met SU-derivaten en CVRM-management hebben mensen met diabetes mellitus type 2 – zowel met als zonder aanvullende cardiovasculaire risicofactoren – een verhoogd risico op cardiorenale complicaties.

INLEIDING

Mensen met diabetes mellitus hebben een twee tot vier keer verhoogd risico op het ontwikkelen van hart- en vaatziekten in vergelijking met mensen zonder diabetes mellitus. Uiteindelijk zijn hart- en vaatziekten de meest voorkomende doodsoorzaak bij de diabetespopulatie.[1] Bij mensen met diabetes mellitus type 2 is naast hart- en vaatziekten ook chronische nierschade een veelvoorkomende complicatie, wat op zichzelf ook een onafhankelijke risicofactor is.[2]

Bij de diabetesbehandeling in Nederland spelen – voor wat de glykemische regulatie betreft – naast leefstijlinterventies metformine, sulfonureumderivaten (SU-derivaten) en insuline een belangrijke rol. Naast de diabetesrichtlijn vallen patiënten met diabetes mellitus type 2 bovendien onder de NHG-Standaard voor cardiovasculair risicomanagement (CVRM), waarbij wordt bepaald of deze mensen in aanmerking komen voor interventies zoals leefstijladviezen, bloeddrukcontrole en cholesterolverlagende therapie.[3] Ondanks de organisatie van de diabeteszorg in Nederland[4] hebben mensen met diabetes mellitus type 2 nog altijd een verhoogd risico op hart- en vaatziekten.[5] Dit heeft onlangs (november 2021) geleid tot een aanpassing van de richtlijn voor mensen met diabetes mellitus type 2 en een zeer hoog risico op hart- en vaatziekten. Hierin is naast leefstijladviezen en glykemische regulatie ook aandacht voor cardiorenale protectie met een *sodium-glucose transport protein 2* (SGLT2)-remmer of *glucagon-like peptide 1* (GLP1)-recep-

1 Afdeling Interne Geneeskunde, CARIM School for Cardiovascular diseases, Maastricht University Medical Centre, Maastricht
2 Amsterdam UMC, Amsterdam
3 Institute for Drug Outcomes Research, Utrecht
4 Aarveld Medisch Centrum, Heerlen

Correspondentie:
Coen DA Stehouwer, MD, PhD
Maastricht University Medical Centre
Afdeling Interne Geneeskunde
6202 AZ Maastricht, Nederland
Telefoonnummer: +3143-3877006
Email: cda.stehouwer@mumc.nl

toragonist.[6] Belangrijk is dat een zeer hoog risico op hart- en vaatziekten in deze richtlijn wordt gedefinieerd als eerder doorgemaakte hart- en vaatziekten, chronische nierschade met een matig tot sterk verhoogd cardiovasculair risico en/of hartfalen met een verminderde ejectiefractie. Mensen met diabetes mellitus type 2 die buiten deze definitie vallen, kunnen in de CVRM-standaard op basis van andere risicofactoren – zoals roken, ernstige verhoogde bloeddruk of hypercholesterolemie – eveneens worden aangemerkt als patiënten met een zeer hoog risico op hart- en vaatziekten[3], waarbij echter niet dezelfde behandeladviezen gelden. Afhankelijk van het bereiken van de HbA1c-streefwaarde, contra-indicaties en/of bijwerkingen komt deze groep na leefstijladviezen en metformine in aanmerking voor een SU-derivaat[7], naast het cardiovasculair risicomanagement.[3] Van SU-derivaten is echter het beschermende effect op cardiovasculaire en renale complicaties controversieel.[8-10] Bovendien is onbekend in hoeverre het risico op cardiovasculaire complicaties verhoogd is bij mensen met diabetes mellitus type 2 die weliswaar geen zeer hoog risico op hart- en vaatziekten hebben, maar wel andere CVRM-risicofactoren, en die behandeld worden met een SU-derivaat.

In deze studie onderzochten we het risico op cardiovasculaire en renale complicaties van mensen met diabetes mellitus type 2 zonder zeer hoog risico op hart- en vaatziekten zoals gedefinieerd in de nieuwe richtlijn diabetes mellitus type 2, maar wel met (andere) cardiovasculaire risicofactoren, die behandeld worden met een SU-derivaat, vergeleken met mensen zonder diabetes mellitus type 2, in de Nederlandse praktijk.

METHODE

Gegevensverzameling

De gegevens voor dit onderzoek zijn verkregen uit het PHARMO Datanetwerk. Dit populatiegebaseerde netwerk combineert gegevens uit verschillende primaire bronnen uit de eerste- en tweedelijnszorg, waaronder huisartsen en ziekenhuizen. Deze databronnen zijn op patiëntniveau gekoppeld via gevalideerde algoritmes. Gedetailleerde informatie over deze data, de methodologie en validatie van de koppelingen en representativiteit is eerder beschreven.[11,12] Voor dit onderzoek werden mensen geïncludeerd die ingeschreven waren in de huisartsenpraktijk en daarnaast tweedelijnsgegevens beschikbaar kónden hebben doordat ze in het verzorgingsgebied van de aangesloten ziekenhuizen woonden. De onderzoeksperiode liep van 1 januari 2013 tot eind 2019, vanwege de beschikbaarheid van de gegevens en om eventuele invloed van de COVID-19-pandemie op de resultaten uit te sluiten.

Studiepopulatie

Voor dit onderzoek werd uit het PHARMO Datanetwerk stapsgewijs een selectie gemaakt van de studiepopulatie. Allereerst werden mensen met diabetes mellitus type 2 geselecteerd en vervolgens werden hieruit nieuwe SU-derivaatgebruikers geselecteerd. Tot slot werd deze groep onderverdeeld in drie verschillende cardiovasculaire risicogroepen. Deze mensen werden vervolgens gematcht met mensen zonder diabetes, eveneens uit het PHARMO Datanetwerk.

Selectie van de type 2-diabetespopulatie

Voor de selectie van een eerstelijns type 2-diabetespopulatie werden alle personen met diabetes mellitus type 2 geselecteerd op basis van een vastgelegde diagnose diabetes mellitus type 2 (ICPC-code T90.02) en/of ≥ 2 voorschriften voor bloedglucoseverlagende medicatie binnen 6 maanden. Uitgesloten werden mensen met diabetes mellitus type 1 en zwangerschapsdiabetes, vastgesteld op basis van een gestelde diagnose bij de huisarts of ontslagdiagnose in het ziekenhuis, en in het geval van diabetes mellitus type 1 tevens op basis van leeftijd bij het eerste voorschrift voor insuline (< 30 jaar) of bloedglucoseverlagende middelen (< 15 jaar).

Selectie van SU-derivaatgebruikers

Uit deze populatie van mensen met diabetes mellitus type 2 werden de mensen geselecteerd die startten met een SU-derivaat tussen 1 januari 2013 (vanwege de toen ingevoerde aanbeveling in de richtlijn voor gliclazide als eerste keus SU-derivaat) en 30 september 2019 (vanwege het kunnen vaststellen van gecontinueerd gebruik tot het eind van de studieperiode (31 december 2019)). Mensen jonger dan 18 jaar of met minder dan 12 maanden historie in de database voorafgaand aan de startdatum van het SU-derivaat werden geëxcludeerd (om vast te kunnen stellen dat het om nieuwe gebruikers ging), evenals mensen die op de startdatum van het SU-derivaat een SGLT2-remmer of GLP1-receptoragonist gebruikten (gezien het bewezen effect van deze middelen op het cardiorenale risico).

Risicogroepen

Er werd in dit onderzoek onderscheid gemaakt tussen drie risicogroepen ten tijde van de start van het SU-derivaat:

1. Zeer hoog risico:
   Zeer hoog risico op hart- en vaatziekten vanwege ooit eerder doorgemaakte hart- en vaatziekten, chronische nierschade in de twee jaar voor startdatum van het SU-derivaat met daardoor een verhoogd cardiovasculair risico en/of hartfalen ooit voor startdatum van het SU-derivaat. Deze groep werd voor dit onderzoek verder buiten beschouwing gelaten, aangezien de richtlijn voor deze groep recent is aangepast.[6] Door het ontbreken van gegevens over de ejectiefractie bij de huisarts zijn in dit onderzoek zowel patiënten met als zonder verminderde ejectiefractie (HFpEF en HFrEF) buiten beschouwing gelaten.
2. Meerdere risicofactoren (MRF):
   Aanwezigheid van orgaanschade en/of belangrijke cardiovasculaire risicofactoren naast diabetes mellitus type 2 zoals beschreven in de NHG CVRM-standaard[3]: roken, ernstige hypercholesterolemie (totaal cholesterol (TC) > 8 mmol/l), ernstig verhoogde bloeddruk (≥ 180 mmHg), leeftijd (≥ 55 jaar voor mannen en ≥ 60 jaar voor vrouwen) gecombineerd met minimaal dyslipidemie of hypertensie, of chronische nierschade met een

mild verhoogd cardiovasculair risico[13] (een eGFR ≥ 60 mL/min/1.73 m^2 met een UACR 3-30 mg/mmol of een eGFR tussen 45-59 mL/min/1.73 m^2 met een UACR < 3 mg/mmol).

3. Geen risicofactoren (non-RF):
   Geen van bovengenoemde cardiovasculaire risicofactoren anders dan diabetes mellitus type 2.

Diabetesvrije populatie
Uit de eerstelijnspopulatie van het PHARMO Datanetwerk werden mensen zonder diabetes geselecteerd op basis van de afwezigheid van diabetes mellitus type 1 en 2 of zwangerschapsdiabetes, zoals hierboven beschreven. Voor deze populatie werden dezelfde definities voor de indeling in de risicogroepen gebruikt als voor de type 2-diabetespopulatie. Dit betekent dat de diabetesvrije populatie per definitie één risicofactor minder had dan de type 2-diabetespopulatie, namelijk het ontbreken van diabetes mellitus type 2.

Uitkomstvariabelen
Vanaf de startdatum van het SU-derivaat werden de volgende uitkomsten bepaald. Alleen mensen zonder de uitkomst in de voorgeschiedenis werden als *at risk* beschouwd voor die bepaalde uitkomst:

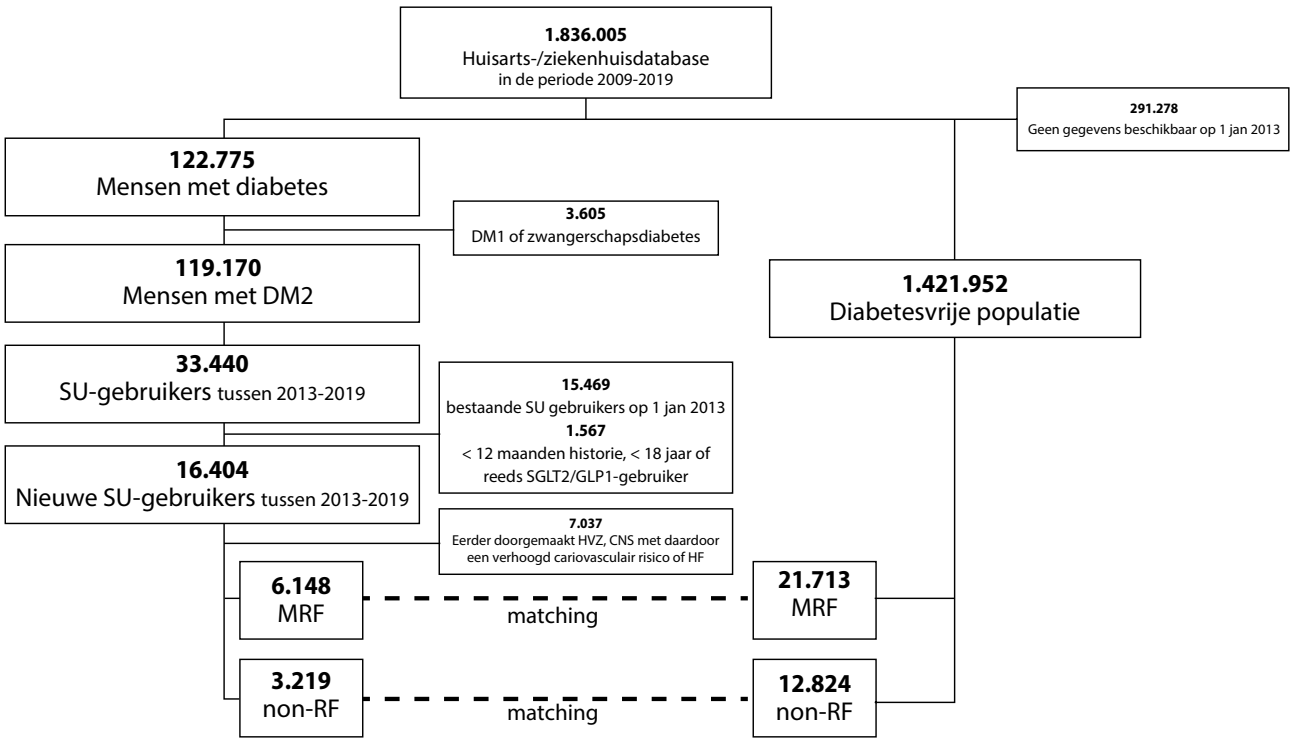
- Cardiorenale ziekte, gedefinieerd als het samengesteld eindpunt van hartfalen, > 50% daling van de eGFR-waarde, eindstadium nierfalen en/of overlijden.
- Atherosclerotische cardiovasculaire ziekte, gedefinieerd als het samengesteld eindpunt van myocardinfarct en/of beroerte.
- Overlijden vanwege alle oorzaken.
- Overlijden vanwege cardiovasculaire oorzaak.
- Overlijden vanwege renale oorzaak.
- eGFR-daling.
- Verslechtering van het stadium van chronische nierschade.
- Dialyse.
- Niertransplantatie.
- Perifeer arterieel vaatlijden.

Om het totale risico vast te stellen – vanwege deels overlappende uitkomsten – werd tevens het samengestelde klinische eindpunt van alle bovenstaande uitkomsten (met uitzondering van eGFR-daling en verslechtering van het stadium van chronische nierschade) onderzocht.

Statistiek
Dit is een gematchte cohortstudie. De analyses op de data werden uitgevoerd in SAS 9.4.

Matching
De SU-derivaatgebruikers werden één op maximaal vier gematcht met diabetesvrije controlepersonen, gebaseerd op de volgende criteria: leeftijd (± 2 jaar), geslacht, stadium van chronische nierschade en diagnose, risicogroep en huisartsenpraktijk of gemeente. Diabetesvrije controlepersonen kregen dezelfde startdatum toegewezen als hun eigen gematchte SU-derivaatgebruiker. De gematchte diabetesvrije controlepersonen moesten in leven zijn op deze datum en minimaal twaalf maanden databasehistorie hebben.

Figuur 1. Stroomschema van patiëntenselectie.



CNS = chronische nierschade; DM = diabetes mellitus; MRF = meerdere risicofactoren; RF = risicofactor; SU = sulfonylureumderivaat

Tabel 1. Baseline karakteristieken van de studiepopulaties na matching.

	MRF-groep		non-RF-groep	
	SU-derivaatgebruikers (n = 6.148)	**Gematchte diabetesvrije controlepersonen (n = 21.713)**	**SU-derivaatgebruikers (n = 3.219)**	**Gematchte diabetesvrije controlepersonen (n = 12.824)**
Leeftijd (jaar ± SD)	65 ± 10	65 ± 9	52 ± 10	52 ± 10
Geslacht				
Man (n, %)	3.380 (55%)	12.001 (55%)	1.698 (53%)	6.763 (53%)
Vrouw (n, %)	2.768 (45%)	9.712 (45%)	1.521 (47%)	6.061 (47%)
Gewicht (kg ± SD)*	89,6 ± 18,4	80,7 ± 15,9	94,5 ± 20,9	82,7 ± 18,6
Gewicht onbekend (n, %)	766 (12%)	14.530 (67%)	1.075 (33%)	12.187 (95%)
BMI (kg/m^2 ± SD)*	30,6 ± 5,5	27,6 ± 4,5	31,9 ± 6,3	28,4 ± 5,7
BMI onbekend (n, %)	787 (13%)	14.623 (67%)	1.082 (34%)	12.233 (95%)
Diabetesduur < 2 jaar (n, %)	1.497 (24%)	n.v.t.	1.514 (47%)	n.v.t.
Laboratoriumparameters*				
HbA1c (mmol/mol ± SD)	65,4 ± 17,0	38,6 ± 4,5	70,0 ± 19,8	37,0 ± 7,7
HbA1c onbekend (n, %)	492 (8%)	20.174 (93%)	745 (23%)	12.644 (99%)
LDL-C (mmol/l ± SD)	2,6 ± 0,9	3,3 ± 0,9	2,7 ± 0,9	3,3 ± 0,9
LDL-C onbekend (n, %)	575 (9%)	8.150 (38%)	918 (29%)	11.322 (88%)
TC (mmol/l ± SD)	4,7 ± 1,2	5,4 ± 1,0	4,8 ± 1,1	5,4 ± 1,0
TC onbekend (n, %)	868 (14%)	8.119 (37%)	988 (31%)	11.285 (88%)
eGFR (ml/min/1,73m^2 ± SD)	83,6 ± 16,2	79,4 ± 14,1	97,7 ± 14,7	91,6 ± 13,3
eGFR onbekend (n, %)	618 (10%)	7.198 (33%)	752 (23%)	10.558 (82%)
UACR				
< 3 mg/mmol (n, %)	4.083 (66%)	7.432 (34%)	1.747 (54%)	480 (4%)
3-30 mg/mmol (n, %)	615 (10%)	622 (3%)	39 (1%)	5 (< 0,5%)
30-300 mg/mmol (n, %)	n.v.t.	n.v.t.	n.v.t.	n.v.t.
Onbekend (n, %)	1.419 (23%)	13.640 (63%)	1.429 (44%)	12.339 (96%)
Bloeddruk*				
Systolisch (mmHg ± SD)	137,4 ± 16,4	137,5 ± 16,7	131,9 ± 14,1	131,0 ± 15,8
Diastolisch (mmHg ± SD)	80,2 ± 9,6	80,6 ± 9,6	82,4 ± 9,4	81,2 ± 9,6
Onbekend (n, %)	571 (9%)	8.445 (39%)	932 (29%)	10.967 (86%)
Comorbiditeiten				
Chronische nierschade	2.130 (35%)	6.135 (28%)	n.v.t.	n.v.t.
Dyslipidemie	4.613 (75%)	16.281 (75%)	1.589 (49%)	1.433 (11%)
Hypertensie	4.110 (67%)	10.163 (47%)	1.049 (33%)	690 (5%)
Metforminegebruik (n, %)	5.717 (93%)	n.v.t.	2.892 (90%)	n.v.t.
Metforminegebruik en start SU-derivaat				
Switch van metformine naar SU-derivaat (n, %)	452 (7%)	n.v.t.	219 (7%)	n.v.t.
SU-derivaat toegevoegd aan metformine (n, %)	4.178 (68%)	n.v.t.	1.901 (59%)	n.v.t.
Geen metformine voorafgaand aan start van SU-derivaat (n, %)	1.518 (25%)	n.v.t.	1.099 (34%)	n.v.t.
Duur van follow-up (jr ± IQR)	0,8 (0,2-2,1)	3,6 (1,9-5,1)	0,6 (0,1-1,6)	3,6 (1,9-5,2)
Reden voor einde follow-up				
Overlijden (n, %)	19 (<0,5%)	131 (1%)	2 (< 0,5%)	65 (1%)
Einde van studieperiode (n, %)	1.264 (21%)	18.638 (86%)	562 (17%)	11.004 (86%)
Einde van beschikbare data (n, %)	426 (7%)	2.944 (14%)	151 (5%)	1.755 (14%)
Stoppen van SU-derivaat (n, %)	4.274 (70%)	n.v.t.	2.380 (74%)	n.v.t.
Starten van SGLT2-remmer of GLP-1-receptoragonist (n, %)	165 (3%)	n.v.t.	124 (4%)	n.v.t.

* indien gegevens beschikbaar

BMI = body mass index; eGFR = estimated glomerular filtration rate; GLP-1 = glucagon-like peptide 1; IQR = interquartile range; LDL = low density lipoprotein; MRF = meerdere risicofactoren; RF = risicofactor; SD = standard deviation; SGLT2 = sodium-glucose transport protein 2; SU = sulfonylureum; TC = total cholesterol; UACR = urine albumin to creatinine ratio

Follow-upperiode

Om het risico te onderzoeken tijdens de blootstelling aan het SU-derivaat werd de type 2-diabetespopulatie gevolgd vanaf de startdatum van het SU-derivaat tot één van de volgende, eerst voorkomende gebeurtenissen: (i) einde registratie in de database, (ii) stop SU-behandeling, (iii) start behandeling met een SGLT2-remmer of GLP-1-receptoragonist, (iv) overlijden, of (v) einde van de studieperiode (31 december 2019).

Tabel 2. Medicamenteus cardiovasculair risicomanagement op baseline van de studiepopulaties na matching.

	MRF-groep		non-RF-groep	
	SU-derivaatgebruikers (n = 6.148)	Gematchte diabetesvrije controlepersonen (n = 21.713)	SU-derivaatgebruikers (n = 3.219)	Gematchte diabetesvrije controlepersonen (n = 12.824)
Medicamenteus cardiovasculair risicomanagement (n, %)	5.163 (84%)	11.150 (51%)	1.908 (59%)	898 (7%)
Lage dosering salicylaten (n, %)	718 (12%)	1.310 (6%)	154 (5%)	94 (1%)
Lipidenverlagende medicatie (n, %)	4.032 (66%)	5.439 (25%)	1.515 (47%)	265 (2%)
Statines (n, %)	3.899 (63%)	5.258 (24%)	1.482 (46%)	253 (2%)
Antihypertensiva (n, %)	3.473 (56%)	7.904 (36%)	902 (28%)	469 (4%)
ACE-remmers (n, %)	1.655 (27%)	3.180 (15%)	491 (15%)	199 (2%)
ARB's (n, %)	1.339 (22%)	3.057 (14%)	299 (9%)	167 (1%)
Dihydropyridinederivaten (n, %)	955 (16%)	2.220 (10%)	226 (7%)	100 (1%)
Thiaziden (n, %)	1.064 (17%)	2.444 (11%)	269 (8%)	137 (1%)
Bètablokkers (n, %)	1.711 (28%)	3.594 (17%)	450 (14%)	389 (3%)

ACE = angiotensin converting enzyme; ARB = angiotensine-II-blokker; MRF = meerdere risicofactoren; RF = risicofactor; SU = sulfonylureum

Diabetesvrije controlepersonen werden gevolgd vanaf de gematchte startdatum tot één van de volgende, eerst voorkomende gebeurtenissen: (i) einde registratie in de database, (ii) overlijden, of (iii) einde van de studieperiode (31 december 2019). SU-derivaatgebruikers werden vergeleken met diabetesvrije controlepersonen totdat de follow-up van één van beide groepen ten minste voor 50% was beëindigd, om differentiële uitval te voorkomen.

Eventanalyse
De incidentie (als *incidence rate*) van cardiovasculaire en renale complicaties gedurende de follow-up zijn berekend als aantallen events per 1.000 patiëntjaren en vergeleken tussen de SU-derivaatgebruikers en hun gematchte diabetesvrije controlepersonen. De risico's van de SU-derivaatgebruikers vergeleken met de diabetesvrije controlepersonen werden uitgedrukt met de hazardratio (HR). Een zogenoemd *competing-risk regression model* werd gebruikt om de onafhankelijkheid van de uitkomstvariabelen onderling vast te kunnen stellen. Een multivariaatanalyse werd uitgevoerd om de uitkomsten in de SU-derivaatgebruikersgroep en diabetesvrije populatie te vergelijken, waarbij *confounders* in het multivariaatmodel werden toegelaten als ze > 5% invloed hadden op de uitkomstvariabele in het bivariaatmodel (met daarin de potentiële *confounder* en de groep), met een maximum van één covariaat per tien events in het multivariate regressiemodel. De hierdoor gecorrigeerde HR werd gerapporteerd als '*adjusted*' HR (aHR). Om de specifieke invloed van een aantal bekende risicofactoren (LDL, UACR, eGFR, BMI en bloeddruk) te bepalen, werd de HR voor het samengestelde eindpunt gecorrigeerd voor deze variabelen separaat. Tot slot werd door middel van een interactieanalyse onderzocht of het risico voor mannen en vrouwen verschilde.

RESULTATEN

Van de 1.836.005 mensen met beschikbare gegevens hadden 119.170 mensen diabetes mellitus type 2. Hiervan gebruikten 33.440 patiënten een SU-derivaat, van wie 15.469 dit middel reeds gebruikten aan het begin van de onderzoeksperiode (1 januari 2013). Van de overgebleven nieuwe SU-derivaatgebruikers tussen 1 januari 2013 en 30 september 2019 voldeden 6.148 aan de definitie MRF en 3.219 aan de definitie non-RF. Deze groepen werden gematcht met respectievelijk 21.713 en 12.824 diabetesvrije mensen (**figuur 1**).

In **tabel 1** zijn de baseline karakteristieken weergegeven van de MRF en non-RF studiepopulaties, voor zowel de SU-derivaatgebruikers als hun gematchte diabetesvrije controlepersonen. Zoals verwacht ontbrak een aanzienlijk deel van de beschikbare gegevens van een aantal klinische en laboratoriumvariabelen van met name de laag-risico diabetesvrije populatie; bij deze groep worden deze variabelen niet per definitie gemeten in de huisartspraktijk.
In de meeste gevallen (59-68%) werd het SU-derivaat toegevoegd aan een reeds bestaande behandeling met metformine, conform de geldende richtlijn. De duur van de follow-up van de SU-derivaatgroepen was korter (mediaan 0,6-0,8 jaar) dan die van de diabetesvrije populaties (mediaan 3,6 jaar). Dit werd hoofdzakelijk veroorzaakt door het stoppen van het SU-derivaat als reden voor einde van de follow-up in de SU-derivaatgroepen.
In de MRF-groep werd door 84% van de SU-derivaatgebruikers ook enige vorm van medicamenteus cardiovasculair risicomanagement gebruikt, terwijl dit bij de diabetesvrije controlepersonen 51% was. Ook in de non-RF-groep gold dat SU-derivaatgebruikers vaker medicamenteus cardiovasculair risicomanagement kregen dan de diabetesvrije controlepersonen (**tabel 2**).
In zowel de MRF-groep als de non-RF-groep kwamen de verschillende onderzochte cardiorenale uitkomsten vaker voor bij de SU-derivaatgebruikers dan bij de diabetesvrije controlepersonen, ook wanneer deze werden gecorrigeerd in een multivariaat *competing hazards* regressiemodel (**tabel 3 en 4**). De afzonderlijke invloed van LDL, UACR, eGFR, BMI en bloeddruk op de aHR was beperkt (< 8%). De interactie met geslacht was niet significant (p = 0,66).

DISCUSSIE

Dit onderzoek beschrijft het optreden van cardiovasculaire en renale complicaties bij mensen met diabetes mellitus type 2 in Nederland die een behandeling startten met een SU-derivaat volgens de toentertijd geldende richtlijn voor de behandeling van diabetes mellitus type 2, vergeleken met een gematchte diabetesvrije populatie. Dit is een herkenbare groep patiënten voor behandelaars in zowel de eerste als tweede lijn.

In dit onderzoek is onderscheid gemaakt tussen mensen met diabetes mellitus type 2 en additionele risicofactoren (MRF-groep: aanwezigheid van orgaanschade en/of belangrijke cardiovasculaire risicofactoren zoals beschreven in de NHG CVRM Standaard[3]) en mensen met diabetes mellitus type 2 zonder aanvullende cardiovasculaire risicofactoren (non-RF-groep). Mensen met een zeer hoog risico op hart- en vaatziekten werden in dit onderzoek buiten beschouwing gelaten, omdat de behandelrichtlijn voor deze populatie recent is aangepast.[6]

In dit onderzoek is gebleken dat de MRF-groep een absoluut risico had voor het samengestelde eindpunt van cardiovasculaire en renale complicaties van 13 per 1.000 patientjaren, wat wordt beschouwd als een intermediair risico.[3] Bovendien was dit risico significant en relevant hoger vergeleken met gematchte mensen zonder diabetes met een aHR van 3,6. Voor de non-RF-groep was de incidentie lager (7,9 per 1.000 patiëntjaren), met ook een significant verhoogde aHR van 5,9. Voor beide groepen waren ook de risico's van vrijwel alle afzonderlijke cardiorenale uitkomsten verhoogd. Bovendien waren deze van een vergelijkbare orde van grootte als de risico's die recent gerapporteerd zijn voor het SU-derivaat glimepiride in de GRADE-studie in een deels vergelijkbare populatie van mensen met diabetes mellitus type 2.[14] Dat de risico's verhoogd zouden zijn was daarom weliswaar verwacht, maar de hoogte van de risico's in de Nederlandse populatie was onbekend, zowel in absolute als relatieve zin.

Hoewel het optreden van vrijwel alle cardiovasculaire en renale complicaties bij de SU-derivaatgebruikers hoger was dan bij de diabetesvrije controles (**tabel 3 en 4**) moeten de resultaten zorgvuldig worden geïnterpreteerd. Hoewel gebruik werd gemaakt van een grote en representatieve steekproef uit de Nederlandse eerste lijn, met aanvullende gegevens in de tweede lijn[12], konden de gegevens niet bij de bron worden geverifieerd op juistheid en volledigheid. Bovendien ontbrak voor een aantal parameters een deel van de gegevens (zoals klinische als laboratoriumgegevens op baseline), met name voor mensen die tot de groepen behoorden met een lager risico. Het ontbreken van deze gegevens is op zich geen verrassing, aangezien er geen aanleiding is geweest om deze gegevens in de praktijk te onderzoeken bij deze mensen. Omgekeerd betekent het wellicht ook dat de gevonden gegevens van va-

Tabel 3. Cardiorenale uitkomsten gedurende follow-up van de MRF-studiepopulatie.

	SU-derivaatgebruikers				Diabetesvrije controlepersonen				SU-derivaatgebruikers versus diabetesvrije controlepersonen	
	aantal 'at risk'	aantal events	patiëntjaren	incidentie per 1.000 patiëntjaren	aantal 'at risk'	aantal events	patiëntjaren	incidentie per 1.000 patiëntjaren	Ongecorrigeerde HR (95% CI)	Gecorrigeerde HR (95% CI)
Samengesteld eindpunt*	6.142	39	2.897	13 (9-18)	21.703	51	14.803	3,4 (2,5-4,5)	3.8 (2,5-5,8)	3,6 (2,1-6,3)
Cardiorenale ziekte	6.144	20	2.904	6,9 (4,2-10,3)	21.706	28	14.814	1,9 (1,2-2,7)	3,6 (2,0-6,5)	3,2 (1,78-5,9)
Atherosclerotisch cardiovasculaire ziekte	6.148	19	2.903	6,5 (3,9-9,9)	21.713	23	14.814	1,6 (1,0-2,3)	4,1 (2,3-7,6)	4,0 (2,0-8,1)
Overlijden vanwege alle oorzaken	6.148	8	2.909	2,7 (1,1-5,0)	21.713	16	14.822	1,1 (0,6-1,7)	2,5 (1,1-5,8)	2,5 (1,0-5,9)
Overlijden vanwege cardiovasculaire oorzaak	6.148	7	2.909	2,4 (0,9-4,6)	21.713	7	14.822	0,5 (0,2-0,9)	4,9 (1,7-13,9)	4,6 (1,6-13,3)
Overlijden vanwege renale oorzaak	6.148	2	2.909	0,7 (0,1-2,0)	21.713	2	14.822	0,1 (0,0-0,4)	5,2 (0,7-36,9)	5,2 (0,7-36,9)
≥ 50% daling van eGFR vergeleken met baseline	5.530	0	2.615	-	14.515	0	9.895	-	n.a.	n.a.
Verslechtering van het stadium van chronische nierschade	803	18	376	48 (28-73)	1.720	40	1.160	34 (24-46)	1,4 (0,8-2,4)	0,9 (0,5-1,6)
Dialyse	6.144	0	2.907	-	21.706	1	14.817	0,07 (0,0-0,27)	n.v.t.	n.v.t.
Niertransplantatie	6.145	0	2.908	-	21.710	0	14.820	-	n.v.t.	n.v.t.
Perifeer arterieel vaatlijden	6.148	2	2.909	0,7 (0,1-2,0)	21.713	2	14.821	0,1 (0,0-0,4)	4,9 (0,7-35,3)	4,9 (0,7-35,3)

* samengesteld eindpunt van cardiorenale ziekte, atherosclerotisch cardiovasculaire ziekte, overlijden vanwege alle oorzaken, overlijden vanwege cardiovasculaire oorzaak, overlijden vanwege renale oorzaak, dialyse, niertransplantatie en perifeer arterieel vaatlijden

CI = Confidence Interval; eGFR = estimated Glomerular Filtration Rate; HR = Hazard Ratio; MRF = meerdere risicofactoren; SU = sulfonylureum

Tabel 4. Cardiorenale uitkomsten gedurende follow-up van de non-RF-studiepopulatie.

	SU-derivaatgebruikers				Diabetesvrije controles				SU-derivaatgebruikers versus diabetesvrije controles	
	aantal 'at risk'	aantal events	patiëntjaren	incidentie per 1.000 patiëntjaren	aantal 'at risk'	aantal events	patiëntjaren	incidentie per 1.000 patiëntjaren	Ongecorrigeerde HR (95% CI)	Gecorrigeerde HR (95% CI)
Samengesteld eindpunt*	3.219	11	1.390	7,9 (3,9-13,4)	12.823	11	8.745	1,3 (0,6-2,1)	6,7 (2,9-15,5)	5,9 (2,5-13,9)
Cardiorenale ziekte	3.219	6	1.391	4,3 (1,5-8,6)	12.824	8	8.746	0,9 (0,4-1,7)	4,9 (1,7-14,3)	4,7 (1,6-13,6)
Atherosclerotisch cardiovasculaire ziekte	3.219	4	1.391	2,9 (0,7-6,5)	12.824	3	8.746	0,3 (0,1-0,9)	9,8 (2,2-43,8)	9,8 (2,2-43,8)
Overlijden vanwege alle oorzaken	3.219	2	1.392	1,4 (0,1-4,2)	12.824	6	8.747	0,7 (0,2-1,4)	2,4 (0,5-11,9)	2,4 (0,5-11,9)
Overlijden vanwege cardiovasculaire oorzaak	3.219	2	1.392	1,4 (0,1-4,2)	12.824	1	8.747	0,1 (0,0-0,5)	14,7 (1,3-162,0)	14,67 (1,3-162,0)
Overlijden vanwege renale oorzaak	3.219	0	1.392	-	12.824	0	8.747	-	n.v.t.	n.v.t.
≥ 50% daling van eGFR vergeleken met baseline	2.467	0	1.100	-	2.266	0	1.544	-	n.v.t.	n.v.t.
Verslechtering van het stadium van chronische nierschade	n.v.t.	-	-	-	n.v.t.	-	-	-	n.v.t.	n.v.t.
Dialyse	3.219	1	1.392	0,7 (0,0-2,9)	12.823	0	8.746	-	n.v.t.	n.v.t.
Niertransplantatie	3.219	0	1.392	-	12.824	0	8.747	-	n.v.t.	n.v.t.
Perifeer arterieel vaatlijden	3.219	1	1.391	0,7 (0,0-2,9)	12.824	0	8.747	-	n.v.t.	n.v.t.

* samengesteld eindpunt van cardiorenale ziekte, atherosclerotisch cardiovasculaire ziekte, overlijden vanwege alle oorzaken, overlijden vanwege cardiovasculaire oorzaak, overlijden vanwege renale oorzaak, dialyse, niertransplantatie en perifeer arterieel vaatlijden
CI = Confidence Interval; eGFR = estimated Glomerular Filtration Rate; HR = Hazard Ratio; MRF = meerdere risicofactoren; SU = sulfonylureum

riabelen met veel ontbrekende data niet altijd geheel representatief zijn. Echter, gegevens om de populatie in te delen in risicogroepen en uitkomstparameters zullen vanwege hun aard waarschijnlijk wel vollediger geregistreerd zijn in de databases.
De vergelijking tussen complicaties bij de SU-derivaatgebruikers en de diabetesvrije populatie werd zorgvuldig onderzocht door matching en correctie in multivariaatanalyses voor bekende risicofactoren. Het is echter niet geheel uit te sluiten dat het gevonden verhoogde risico veroorzaakt werd door een niet-onderzochte factor. Daarnaast is het van belang niet alleen de verhouding van de risico's (aHR) te interpreteren, maar ook de onderliggende absolute risico's (incidentie).
Opvallend was dat de mediane follow-upduur in de SU-derivaatgroep 0,6-0,8 jaar was, wat voornamelijk verklaard werd doordat de behandeling met het SU-derivaat gestopt werd. Door de risico's uit te drukken in incidentie per 1.000 patiëntjaren werd het verschil in follow-upduur echter gecorrigeerd. Medicamenteus cardiovasculair risicomanagement werd vaker ingezet bij de SU-derivaatgebruikers dan bij de mensen zonder diabetes. De reden voor dit verschil kon niet worden onderzocht, maar maakt de betrouwbaarheid van het desondanks gevonden gegeven dat het cardiorenale risico verhoogd was mogelijk wel groter. In dit licht is het belangrijk om op te merken dat het behalen van streefwaarden van bekende risicofactoren een verlaagd risico oplevert.[15]
In dit onderzoek hadden de SU-derivaatgebruikers door de studieopzet per definitie één risicofactor meer (namelijk diabetes mellitus type 2) dan hun gematchte diabetesvrije controlepersonen. Dat betekent voor de interpretatie van het gevonden hogere risico dat hierin waarschijnlijk het additionele risico te zien is dat diabetes mellitus type 2 met zich meebrengt. Hieruit kan geconcludeerd worden dat dit additionele risico niet verlaagd kon worden met conventionele behandeling tot het niveau van mensen zonder diabetes in deze populaties.
Het doel van de behandeling van mensen met diabetes mellitus type 2 is op korte termijn het behandelen van de hyperglykemie en op lange termijn het voorkomen van micro- en macrovasculaire (cardiorenale) complicaties, met als uiteindelijk doel een betere kwaliteit van leven en een langer leven. Ons onderzoek laat echter zien dat – ondanks conventionele behandeling met SU-derivaten en CVRM-management – mensen met diabetes mellitus type 2 en aanvullende cardiovasculaire risicofactoren een 3,6 maal hoger risico hebben op cardiorenale complicaties vergeleken met mensen zonder diabetes mellitus type 2. Omdat het risico in deze herkenbare groep niet laag is maar intermediair, zouden (nieuwe) richtlijnen hier apart aandacht aan moeten besteden.

Deze studie is gefinancierd door AstraZeneca BV, Nederland

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Multidisciplinaire NDF-nascholing 'Eerste hulp bij diabetisch voetulcus'

Dit artikel is gebaseerd op de NDF-nascholing en het artikel dat Jaap Kroon, stafarts diabetes PoZoB, Nicolaas Schaper, emeritus hoogleraar endocrinologie en (diabetes)podotherapeut Lian Stoeldraaijers hebben gepubliceerd in Huisarts en Wetenschap. De informatie is met hun toestemming overgenomen. Zie: Kroon J, Schaper N, Stoeldraaijers L., "Eerste hulp bij een diabetisch voetulcus", H&W 2021;64(3):53-8.

Een voetulcus is een gevreesde complicatie van diabetes. De kans dat een voet of been moet worden geamputeerd bij een voetulcus is 20%.[1] Van de diabetespatiënten met een voetulcus overlijdt 40% binnen 5 jaar. Dit loopt op tot meer dan 50% als er ook sprake is van perifeer arterieel vaatlijden (PAV).[2,3] Een deel van de amputaties zou voorkomen kunnen worden wanneer tijdig de juiste behandeling wordt ingezet of als de patiënt wordt doorverwezen naar een multidisciplinair voetenteam. Reden voor de NDF om een online nascholing te ontwikkelen over het voorkomen, vaststellen, beoordelen en behandelen van ulcera en over de multidisciplinaire benadering die daarvoor nodig is. De nascholing is te vinden in de NDF Toolkit in de rubriek Diabetische voetzorg. De expertgroep van deze rubriek heeft ook twee tools ontwikkeld die ondersteunen bij tijdige signalering en doorverwijzing; deze vormen de leidraad voor het maken van lokale/regionale samenwerkingsafspraken. Beide zijn als pdf en als interactieve webpagina beschikbaar. Doel is om als zorgverlener, team en netwerk – samen met de patiënt – amputaties en verlies van kwaliteit van leven te voorkomen.

OPTIMAAL CVRM VOORKOMT AMPUTATIES

Een voetulcus is een defect door alle lagen van de huid (dermis en epidermis) onder de enkel bij een patiënt met diabetes, ongeacht de bestaansduur van de wond.[4] Volgens Kroon is de aanwezigheid van een voetulcus een alarmsignaal: 85-90% van de amputaties zijn het gevolg van een voetulcus.[5] Ook het sterftecijfer is hoog. De mortaliteit van iemand met een voetulcus staat gelijk aan die van iemand met kanker.[6] De 5-jaarsmortaliteit na een voetulcus is 40% en wanneer sprake is van PAV neemt dit cijfer toe tot zelfs 50%.[3] Schrikbarende cijfers, maar met tijdige signalering en adequate behandeling kan een deel van de amputaties voorkomen worden. Meer dan de helft van de patiënten met een voetulcus overlijdt aan een cardiovasculaire oorzaak.[7] Optimaal cardiovasculair risicomanagement kan de kans om binnen vijf jaar te overlijden fors verminderen: van 48 naar 27%.[8] Daarbij blijven tijdige behandeling – en de juiste zorg op de juiste plek – van groot belang.

GOEDE BEOORDELING DIABETISCH VOETULCUS

De belangrijkste taak voor de huisarts bij 'eerste hulp bij een diabetisch voetulcus' is een goede beoordeling, die antwoord geeft op de vraag of de patiënt in de eerste lijn kan worden behandeld door de huisarts en podotherapeut samen. Er zijn er zeven belangrijke vragen die bij deze eerste beoordeling beantwoord moeten worden, legt Stoeldraaijers uit. Allereerst is het van groot belang direct gegevens te verzamelen om het verdere beleid te bepalen. Soms kunnen huisarts en podotherapeut zelf een behandeling starten, maar het kan ook noodzakelijk zijn om naar een multidisciplinair voetenteam te verwijzen, eventueel nog dezelfde dag. De belangrijkste vragen die bij deze eerste beoordeling beantwoord moeten worden, zijn de volgende:

1. Wat is de lokalisatie van het voetulcus?
2. Is er sprake van een oppervlakkig of van een diep voetulcus?
3. Zijn er aanwijzingen voor PAV?
4. Zijn er tekenen van een infectie?
5. Wat is de directe oorzaak?
6. Hoe is de glykemische instelling?
7. Gebruikt de patiënt een SGLT2-remmer?

PLANTAIR OF NIET-PLANTAIR?

Bij een plantair voetulcus (onder de voet, onder de tenen of op de teentop) is directe verwijzing naar een voetenteam geïndiceerd.[4,9] Lokale druk speelt vrijwel altijd een belangrijke rol bij deze voetulcera. Als deze druk niet wordt weggenomen, kan het voetulcus niet genezen. Met een onderbeengips zal een plantair voetulcus meestal binnen een paar weken genezen, maar het is essentieel dat de doorbloeding adequaat is en dat infectie is uitgesloten.

OPPERVLAKKIG OF DIEP VOETULCUS?

Ieder voetulcus dat dieper is dan de subcutis – dus met betrokkenheid van fascie, pees, spier, gewricht of bot – moet direct verwezen worden naar een voetenteam[10,11], aangezien het risico op infectie van het dieper gelegen weefsel en op amputatie sterk verhoogd is (OR 6,08; 95%-BI 4,10 tot 9,08).[12] Bij een diep ulcus is de kans op amputatie onder de enkel zes keer zo hoog, met PAV is dat risico twee keer zo hoog en met alleen een infectie anderhalf keer.[12] Stoeldraaijers benadrukt dat een kleine plek zeker ook diep kan zijn, waardoor onderschatting op de loer ligt. Zij geeft aan dat inspectie al onvoldoende is om de diepte te beoordelen, omdat het ulcus vaak bedekt is met eelt en necrotisch materiaal. Bij de eerste presentatie moet daarom het necrotische materiaal verwijderd worden, indien nodig met een scalpel. De diepte van het ulcus is meestal alleen in te schatten door vervolgens te sonderen met een steriele metalen sonde.

ONDERZOEK NAAR PERIFEER ARTERIEEL VAATLIJDEN

Zijn er aanwijzingen voor PAV, dan moet iemand doorverwezen worden naar het diabetisch voetenteam. Er is geen eenvoudige test die PAV kan uitsluiten. Daarom is het van belang te kijken naar de voorgeschiedenis, een anamnese te doen en lichamelijk onderzoek. Hiervoor kan de dopplermeting gebruikt worden of de EAI (enkelarmindex). Deze kunnen meer duidelijkheid geven over de diagnose PAV. Beide metingen vereisen voldoende training en ervaring. Het advies is dan ook ervoor te zorgen dat een beperkt aantal praktijkondersteuners of praktijkassistenten hierin goed getraind zijn. Inspectie en palpatie alleen zijn onvoldoende. Dan is er ook de teen-armindex (TAI), die de verhouding aangeeft tussen de systolische bloeddruk gemeten aan de teen en de systolische bloeddruk gemeten aan de bovenarm. Voor een TAI-bepaling zijn speciale apparatuur, expertise en ervaring nodig. Daarom wordt de TAI in het algemeen niet in de eerste lijn bepaald. Het advies is om zo betrouwbaar mogelijk onderzoek te doen. De diagnose vaatlijden is erg belangrijk, dus verwijs door bij twijfel.

Voor de diagnose PAV bij voetulcera bestaat een beslisregel gebaseerd op EAI, dopplermeting en TAI. Deze is te vinden in de NDF Toolkit Diabetische voetzorg.

INFECTIE

Tekenen van een infectie zijn: lokale zwelling en warmte, roodheid rondom het ulcus, pijn (deze kan echter verminderd of afwezig zijn door neuropathie) en purulente afscheiding. Een ernstige infectie betekent direct een spoedverwijzing naar het diabetisch voetenteam.

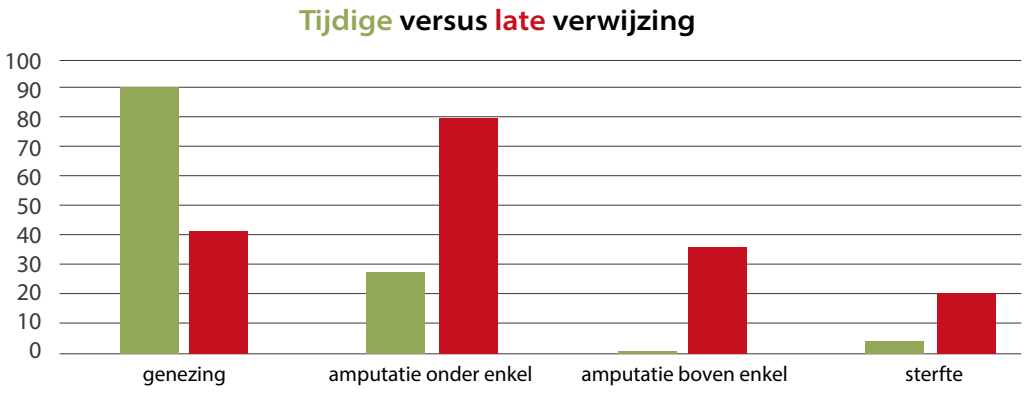
OORZAAK

Lokale druk speelt vrijwel altijd een rol bij het ontstaan van een voetulcus; het is van groot belang die druk weg te nemen. Als dat niet gebeurt, is de kans op verslechtering zeer groot. De podotherapeut kan het schoeisel aanpassen of vilt rondom het voetulcus aanbrengen. In het geval van een infectie kunnen huisarts en podotherapeut samen overleggen over het antibioticabeleid. Kroon en Stoeldraaijers benadrukken dat samenwerking tussen huisarts en podotherapeut van groot belang is. Signalering en behandeling is volgens hen teamwork. Hoe klein het wondje ook is, er is direct overleg nodig tussen huisarts en podotherapeut om er samen beleid op te maken dat past bij de individuele patiënt. Om een recidief te voorkomen, is het belangrijk de oorzaak van het ulcus vast te stellen. In veel gevallen blijkt schoeisel de boosdoener.

GLYKEMISCHE INSTELLING EN MEDICATIE

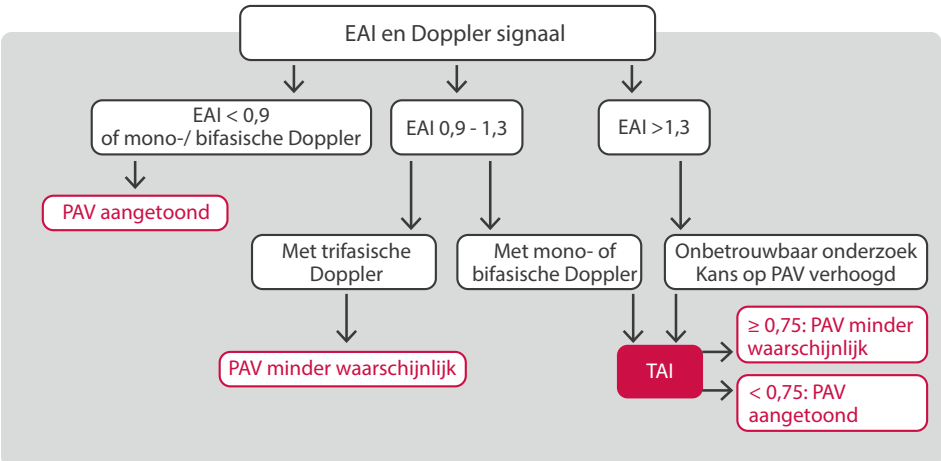
Tot slot zijn er nog de glykemische instelling en de medicatie. Een goede glykemische instelling verlaagt het amputatierisico met 35%, zo blijkt uit onderzoek.[13] Rond medicatiegebruik en specifiek het gebruik van SGLT2-remmers bestaat enige discussie. Er zou er een verhoogd risico zijn op amputatie, al zijn de onderzoeksresultaten niet consistent. Voor de zekerheid adviseren de NHG-Standaard *Diabetes mellitus type 2* en de NIV-richtlijn *Medicamenteuze behandeling zeerhoogrisicopatiënten met diabetes mellitus type 2* bij aanwezigheid van een voetulcus het gebruik van een SGLT2-remmer te staken.

Figuur 1. Tijdige versus late verwijzing.



Bron: Meloni, et al. Effectiveness of fast-track pathway for diabetic foot ulcerations. Acta Diabetologica 2021.

Figuur 2. Beslisregen voor de diagnose perifeer arterieel vaatlijden (PAV) bij patiënten met een voetulcus.



EAI = enkel-armindex, TAI = teen-armindex, PAV = perifeer arterieel vaatlijden.

TIJDIG DOORVERWIJZEN

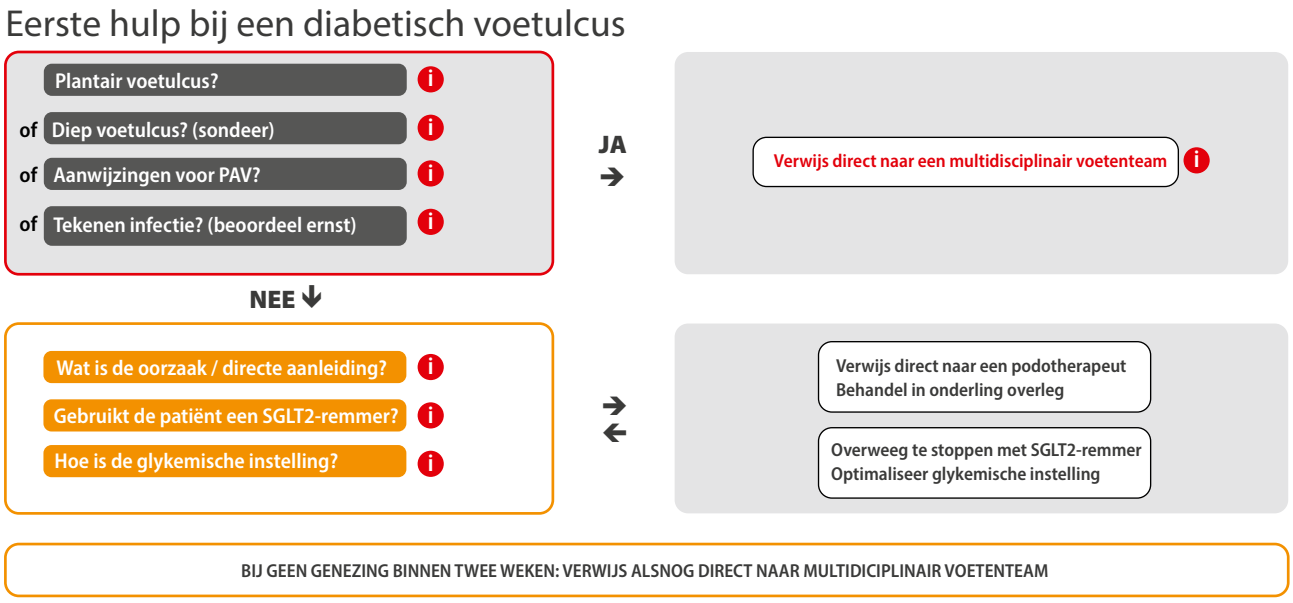
Samenvattend kan worden gesteld dat een plantair gelokaliseerd voetulcus, een diepliggend voetulcus, PAV of tekenen van systemische infectie redenen zijn om de patiënt door te verwijzen naar een diabetisch voetenteam. Hetzelfde geldt voor elk voetulcus dat niet binnen twee weken geneest. Snelle verwijzing is echt van belang, zo laat onderzoek zien.[14] In de helft van de gevallen is genezing mogelijk, het aantal amputaties onder de enkel daalt met zo'n 60 %, van amputaties boven de enkel is vrijwel geen sprake meer en het aantal sterfgevallen is een kwart van wat het was met late verwijzing.

Behandeling in de eerste lijn is uitsluitend mogelijk bij niet-plantaire, oppervlakkige voetulcera zonder aanwijzingen voor PAV. Zoals eerder gezegd, goede samenwerking tussen de huisarts en podotherapeut is essentieel. Ook opvolging is teamwork. Voetulcera hebben een hoog recidiefpercentage (40% in het eerste jaar, 65% na 5 jaar).[15] Daarom is ook na genezing goede follow-up bij alle patiënten noodzakelijk.

De belangrijke boodschap is: als de patiënt tijdig en op de juiste plek wordt behandeld, dan kan een deel van de amputaties voorkomen worden.

Alle informatie is terug te vinden in de NDF Toolkit-

Figuur 3. Flowchart *Eerste hulp bij een diabetisch voetulcus*. Deze is beschikbaar in pdf-vorm als spreekkamerkaart en als interactieve website, waarbij meer informatie volgt door op de het informatie-icoon te klikken.



rubriek Diabetische voetzorg. Zie hiervoor: https://diabetesfederatie.nl/ndf-toolkit-persoonsgerichte-diabeteszorg/diabetische-voetzorg

Ook de flowchart en de nascholing zijn hier te vinden. De nascholing duurt een uur, kost 49 euro en is goed voor 1 accreditatiepunt.

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Hoofdredacteur
Dr. E. Serné, internist-vasculair geneeskunde/diabetologie, Amsterdam UMC, locatie VUmc, Amsterdam

Redactie
Dr. T. van Bemmel, internist - vasculair geneeskundige, Gelre Ziekenhuizen, Apeldoorn
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Uitgever
Lucienne Bongers, Bohn Stafleu van Loghum, Postbus 246, 3990 GA Houten

Contact
Submissie artikelen en contact met de redactie via redactieNTD@bsl.nl

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