Personalized lifestyle interventions for the prevention and treatment of type 2 diabetes

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DIFFERENTIAL EFFECTS OF LIFESTYLE INTERVENTIONS ON CONTINUOUS GLUCOSE MONITORING METRICS IN PERSONS WITH TYPE 2 DIABETES: POTENTIAL FOR PERSONALIZED TREATMENT

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Submitted

ABSTRACT

Objective: The effects of lifestyle on glucose metabolism significantly differ between individuals. Hyperglycemia in type 2 diabetes is driven by tissue-specific insulin resistance and reduced beta-cell capacity, whose relative contribution varies between persons, potentially affecting the impact of lifestyle interventions. We quantified effects of lifestyle on continuously measured glucose (CGM) metrics and evaluated how these differ between type 2 diabetes phenotypes.

Research Design and Methods: Forty persons with type 2 diabetes wore a CGM for 11 periods of 4 days, of which 3 control and 4 duplicated intervention periods (2x low carbohydrate diet, 2x Mediterranean diet, 2x walking after each meal and 2x 'active day' (hourly 5-minute exercise bouts)). Tissue-specific insulin resistance and beta-cell function were quantified using an OGTT. A linear mixed effects model quantified lifestyle impact on CGM metrics.

Results: On overage, low carbohydrate diet, walking after meal and active day, but not the Mediterranean diet, resulted in lower mean glucose (7.74, 8.37, 8.40 and 8.70 mmol/L, respectively) as compared to control (8.66 mmol/L) in participants who did not restrict carbohydrate intake at baseline. Notably, the magnitude and direction of effects varied between individuals. For instance, the low carbohydrate diet had more beneficial effects for persons who had liver- or combined insulin resistance with poor beta-cell function than for individuals who only had poor beta-cell function.

Conclusions: On average, traditional lifestyle interventions improved CGM metrics within 4 days. Importantly, the effects appear to vary depending on the diabetes phenotype, thus pointing to the need for personalized lifestyle treatment.

1. INTRODUCTION

Type 2 Diabetes is a chronic metabolic disorder characterized by insulin resistance and dysglycemia. Lifestyle modifications, including adopting a healthy diet, increasing physical activity and losing weight, can improve glycemic control and insulin sensitivity, thereby mitigating diabetes-related complications [1–3]. The Look AHEAD trial has demonstrated that adopting a healthier lifestyle can delay progression of type 2 diabetes [4]. However, the impact of lifestyle interventions varies greatly between individuals, with high interindividual variability in the postprandial glucose response to identical foods [5,6], and differential responses to dietary interventions between normoglycemic and (pre-)diabetic people [7]. In view of the inherent heterogeneity of the disease [8], it seems quite conceivable that the efficacy of lifestyle interventions is not uniform across individuals with type 2 diabetes, and that personalization of dietary advice or physical activity regime may be required for optimal glycemic control [9].

Most lifestyle intervention studies so far were medium to long-term, group-based, and focus predominantly on HbA1c as measure of glycemic control. HbA1c, however, does not reflect acute glycemic excursions and events such as hypoglycemia or postprandial hyperglycemia [10]. Since the introduction of continuous glucose monitoring (CGM), it has been established that CGM-derived measures of glycemic control are clinically relevant [10,11] and linked to all-cause mortality and risk of macro- and microvascular complications [12,13]. A CGM system provides real-time (interstitial) glucose concentrations and can be used to calculate widely accepted metrics that reflect not only mean glucose, but also measures of glycemic variability as well as time in, below and above target ranges [10,11]. CGM can thus provide insight in short term effects of lifestyle on glycemic control.

Short term glycemic variations may differ between diabetic phenotypes, as the severity of insulin resistance may differ between various insulin-sensitive tissues [14]. It has been suggested that the diabetic phenotype or “diabetype”, based on the predominant location of insulin resistance (i.e., muscle, liver, or both) and the remaining capacity of beta-cells to produce insulin, may affect the response to different dietary interventions [15–17]. Also, physical exercise may be especially effective in improving glycemic control in people who are predominantly affected by muscle insulin resistance [18]. Insight in the differential effects of lifestyle interventions on glucose management among individuals with distinct diabetypes may contribute to more personalized lifestyle recommendations. Here, we aimed to explore the (sub)acute effects of distinct lifestyle interventions on CGM metrics in people with T2D, and the impact of their “diabetype” in this context.

2. RESEARCH DESIGN AND METHODS

2.1. Study Population

41 men and women with type 2 diabetes, as diagnosed by a physician, using either lifestyle and/or metformin for managing glycemic control were recruited via general practitioners (GPs), social media and newspaper advertisements. Participants were eligible if they met the following inclusion criteria: Body Mass Index (BMI) 25 – 40 kg/m2, preferably < 35 kg/m2, insulin-naive, able and willing to provide informed consent, and willing to comply with all study procedures. The main exclusion criteria were history of or planned (bariatric) surgery or MRI in the next six months, chronic medical conditions, medication use interfering with glucose metabolism, and Coeliac or Crohn's disease. A complete list of exclusion criteria can be found on https://www.onderzoekmetmensen.nl/en/trial/24321. Baseline characteristics are shown in **Table 1.**

Table 2. *Baseline characteristics of 41 participants with type 2 Diabetes Mellitus*

	n	**Mean**	**SD**
Sex (male/female)	22 / 19		
Education (lower / higher)	15 / 26		
Treatment (yes / no metformin)	25 / 16		
Age (y)		62.3	7.2
Diabetes duration (y)		9.7	6.5
BMI (kg/m2)		29.2	3.8
HbA1c (% (mmol/mol))		7.1 (54.5)	3.5 (14.8)
Insulin fasting (mU/L)		12.05	8.90
C-peptide fasting (nmol/L)		0.87	0.42
Hepatic Insulin Resistance Index (HIRI)		1812	1362
Muscle Insulin Sensitivity Index (MISI)		-3.60	4.23
Disposition Index (DI)		0.72	0.53
Total cholesterol (mmol/L)		4.67	1.13
LDL-cholesterol (mmol/L)		2.91	1.00
Triglycerides (mmol/L)		1.46	0.72
C-Reactive Protein (CRP) (mg/L)		2.27	2.49
Systolic blood pressure (mmHg)		160.4	17.9
Diastolic blood pressure (mmHg)		91.2	14.4

2.2. Study procedures

At the start of the study, a clinical visit was planned during which anthropometry (height (first visit only), bodyweight, waist- and hip circumference) and blood pressure were measured according to standard operating procedures, and online questionnaires were completed.

Hereafter, participants followed 11 four-day monitoring periods in a randomized crossover design (**Figure 1**). During three control periods, glucose was monitored in daily life, while the impact of two dietary- (low carbohydrate diet and Mediterranean diet) and two exercise-based interventions (walk after meal and active day) on CGM metrics was measured during eight intervention periods. During all periods, participants were instructed to use a continuous glucose monitor (CGM) monitor physical activity and sleep, and register food intake, medication use and wellbeing via a custom smartphone application. Participants were asked to calibrate their CGM system every morning using a finger-prick and manual blood glucose measurement device (Accu-Chek Instant, Roche, Basel, Switzerland).

Figure 1. *study design*

At the end of or just before each control period (week 2, 13 and 24), participants came to the clinic for an Oral Glucose Tolerance Test (OGTT). After the first control period (week 2), each participant underwent four lifestyle interventions in a randomized order. The second control period was planned after the first series of intervention periods (week 13), after which all four interventions were repeated in a randomized order. Subsequently, the last control period and OGTT were performed (week 24). All control and intervention periods were separated by at least one week wash-out period. The study ended with a clinical visit during which anthropometric and blood pressure measurements were repeated (week 27). Helpdesk support was available throughout the study. The study protocol was approved by the Medical Ethics Committee Brabant (NL70771.028.19). The study was performed in accordance with the Declaration of Helsinki and good clinical practice and registered at the Dutch Trial Register: NL7848. All participants provided written informed consent.

2.3. Interventions

During the "Active day" (AD) intervention, participants were asked to perform moderate to intense physical exercise (e.g., brisk walking, climbing the stairs or knee bends) for 5 minutes every hour between 09:00 and 17:00 hour to reduce sedentary time. During the "Walk after

meal" (WaM) intervention, participants were asked to walk for 15 minutes after each breakfast, lunch, and dinner to reduce postprandial glucose levels. During the "Low carbohydrate diet" (LC) intervention, participants were instructed not to exceed a maximum intake of 100 grams of carbohydrates a day. During the "Mediterranean diet" (Med) intervention, participants were instructed to eat a diet high in fruits, vegetables, nuts, fish, whole grain, and olive oil. During both dietary interventions, for breakfast, lunch and snacks participants received fitting recipes, and for dinner participants received meal boxes with unprocessed food and recipes for cooking at home from Ekomenu (Amsterdam, the Netherlands).

2.4. Measurements

2.4.1. Self-monitoring devices

The Dexcom G6 Continuous Glucose Monitoring (CGM) System (Dexcom Inc, San Diego, USA) was worn during all monitoring periods and measured the interstitial glucose concentration every 5 minutes. Values were transformed into estimated blood glucose levels by a proprietary algorithm and wirelessly send to participants' smartphone via attached transmitter. Participants applied the Dexcom G6 sensor on the upper arm one day before the start of each monitoring period, to allow for stabilization of the sensor.

Participants used the HowAmI app (TNO, Leiden, The Netherlands) [19], for collecting food intake data. The HowAmI app used the FatSecret food database (Secret Industries Pty Ltd., Victoria, Australia) to access detailed food and nutrition data and connected to a custom, parallel back-end database to record food intake and the time stamp for each meal.

The Fitbit Charge 3 activity tracker (Fitbit, San Francisco, CA, USA) was used to measure daily physical activity in Metabolic Equivalent of Tasks (METs) and sleep in hours. Data was collected and stored using Fitabase (Small Steps Labs, San Diego, CA, USA) prior to analysis.

2.4.2. Oral glucose tolerance test and diabetyping

An OGTT was performed to assess plasma glucose and insulin response to a standardized glucose solution (75 g of glucose dissolved in water) for subsequent calculation of indices of the level of insulin resistance (IR) in different organs and beta-cell function (BCF). To measure plasma glucose and insulin levels, venous blood samples were taken before as well as 30, 60, 90 and 120 minutes after consumption of the sugar water. Blood glucose and insulin concentrations were used to calculate the following three indices used for "diabetyping": (1) the hepatic insulin resistance index (HIRI); (2) the muscle insulin sensitivity index (MISI); and (3) the disposition index (DI) as a measure of pancreatic beta-cell function [14,20–22]. A combination of liver and/or muscle IR with or without impaired BCF resulted in a total of eight possible subgroups ("diabetypes") [23].

2.4.3. Questionnaires

Questionnaires were completed via an online portal, and included questions on demographics, lifestyle, diabetes duration and treatment. Regular dietary intake before study participation was assessed using the online 183-item Food Frequency Questionnaire (FFQ) developed by Wageningen University and Research [24,25]. Sleep was assessed using the Pittsburgh Sleep Quality Index, a questionnaire which assesses self-rated sleep quality and disturbances in the past month [26,27].

2.5. Statistical Analysis

Statistical analyses were performed using R software [28]. To check compliance with the lifestyle interventions, compliance scores for the LC, AD and WaM intervention were calculated. For the Med intervention no compliance score was calculated as adherence to the Mediterranean diet is not easily quantifiable. For the LC intervention compliance was defined as days during which carbohydrates (CHO) contributed < 26% to total caloric intake [29,30]. For the WaM intervention compliance was defined as days with ≥ 4 periods of physical activity for ≥ 10 minutes. For the AD intervention compliance was defined as days with ≤ 4 sedentary periods of ≥ 2 hours of inactivity; four consecutive sedentary periods of two hours or more were interpreted as sleep.

CGM metrics were calculated per person, per 4-day measurement period. Mean glucose, coefficient of variation (CV), time in range (TIR; > 3.9 & < 10.0 mmol/L), time above range level 1 (TAR-L1; >= 10.0 & < 13.9 mmol/L), time above range level 2 (TAR-L2; >= 13.9 mmol/L), time below range level 1 (TBR-L1; > 3.0 & <= 3.9 mmol/L), time below range level 2 (TBR-L2; <= 3.0 mmol/L), and mean amplitude of glucose excursions (MAGE) were calculated according to an international consensus statement [31].

A random effects multilevel model was used to quantify the effects of the four lifestyle interventions on CGM metrics with participant as random effect (null models). Time was tested as a covariate, but this showed no effect on CGM metrics nor model improvement. This indicates that our assumption that 4-day interventions followed by at least a week of wash-out indeed avoided longer term effects of and carry-over effects between interventions. Subsequently, a binary variable reflecting CHO consumption prior to the study, as assessed by FFQ, was added to the null model. Specifically, the study population was split into two groups, a “normal carb” group consuming more than 26% of calories as CHO at baseline, and a “low carb” group eating less than 26% of calories as CHO [29,30]. Adding this variable improved the performance of all models for CGM metrics (intermediate models). Lastly, the impact of further adding diabetype and interaction-effects on model performance was assessed (final models). Only diabetypes assigned to at least 10 participants at any point in time during the study were included in the models to allow for sufficient power in the models. As for some individuals the diabetype changed during the study (supposedly affected by lifestyle interventions), the diabetype defined by the most recent OGTT was used for the next

monitoring period in the model. Diabetypes assigned to at least 10 participants were 1) isolated impaired BCF (PB; n=16); 2) hepatic IR and impaired BCF (PB-HIR; n=30); and 3) both hepatic and muscle IR and impaired BCF (PB-HMIR; n=11), where 17 persons had two distinct phenotypes over time. Model performance for all CGM metrics but TAR-L2 improved significantly when the three most common diabetypes, PB, PB-HIR and PB-HMIR were added (Supplementary Table 1). Therefore, separate models were made for each diabetype assigned to at least 10 participants during the entire study to assess which lifestyle interventions sorted the most beneficial effects for each of the three diabetypes. The amount of CHO consumed at baseline (as measured using the FFQ) interacted with intervention effects on CGM metrics and was therefore also included in the models for the PB-group and PB-HIR group. In the PB-HMIR group there was only one participant with a low CHO intake at baseline, who was therefore excluded from the analysis. The final models included intercept, intervention, and for two subgroups (PB and PB-HIR) also CHO consumption at baseline as well as its interaction with intervention as fixed factors, and participant as random effect.

2.6. Data and Resource Availability

The datasets generated during and/or analyzed during the current study are not publicly available due to the data being generated as part of a public private partnership and shared intellectual property with partners but are available from the corresponding author upon reasonable request.

3. RESULTS

3.1. Compliance with lifestyle instructions

Subjects were 100% compliant with AD instructions, while compliance with WaM and LC instructions was 79% on average.

3.2. Control periods

For the total study population, glucose levels were in range for an average of 82.4% of time and above range for 17.4% of time during the control conditions. Time below range was less than 1% for all study periods and was therefore excluded from analyses. Nine participants were accustomed to consuming less than 26% of calories as CHO on average (as measured by FFQ) to control glycemia even before study participation. In control conditions, their CGM metrics were clearly different from those of participants who consumed more CHO (n=29) (Figure 2). According to the model, TIR was 12% higher, although non-significant, and CV and MAGE were significantly lower (-3.86% and -1.47 mmol/L respectively) in participants consuming <26% of calories as CHO (supplementary Table 2).

3.3. Effects of lifestyle interventions on average CGM metrics

Quite conceivably, the effects of interventions on CGM metrics were different in persons who deliberately restricted carbohydrate intake at baseline from those in participants who did not (figure 2, Supplementary Table 2). Indeed, LC clearly reduced Mean, TAR-L1/L2 and MAGE in participants consuming more than 26% of calories as CHO at baseline. However, in participants consuming less than 26% of calories as CHO at baseline, this effect was significantly lower for Mean, TIR, TAR-L1 and MAGE. In contrast, AD and WaM similarly benefitted several CGM metrics in both groups, while Med deteriorated various metrics, particularly in participants restricting CHO at baseline (although it also induced a slight increase of TAR-L2 and CV in those who did not).

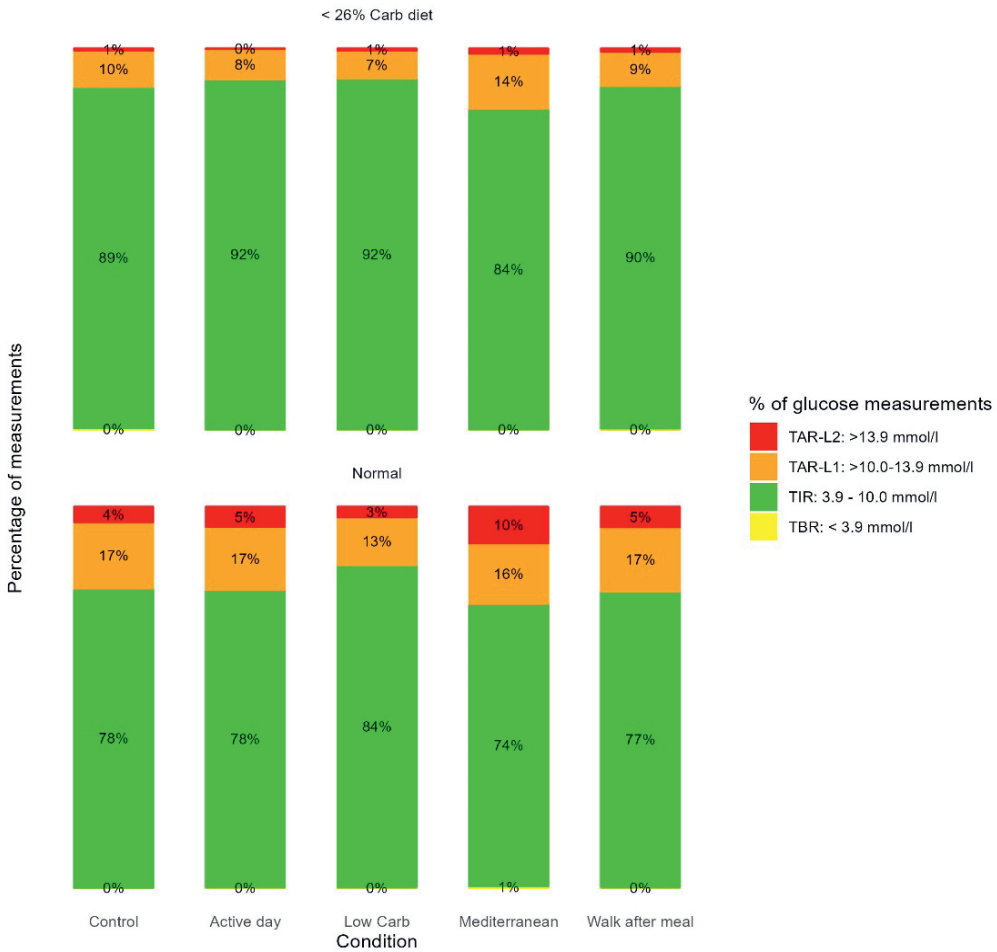

Figure 2*. TIR, TBR and TAR expressed as an average percentage of total time spent in this range for participants consuming >26% of calories from carbohydrates at baseline (upper bars) and for participants consuming <26% of calories from carbohydrates at baseline (lower bars).*

3.4. Interindividual differences in effects of lifestyle interventions on CGM metrics

Inspection of individual glucose profiles revealed apparent differences between individuals in terms of response to lifestyle intervention (Figure 3). For example, in subject 10, the mean glucose appears to improve in response to the LC, WaM and AD interventions, while TAR seems to decline during LC and AD interventions. Glucose variability seems to be lowest during LC intervention. In contrast, in subject 14, mean glucose, TIR and glucose variability seem to improve in response to all but the AD intervention. In subject 71, CGM metrics appear to remain unaffected by any of the interventions.

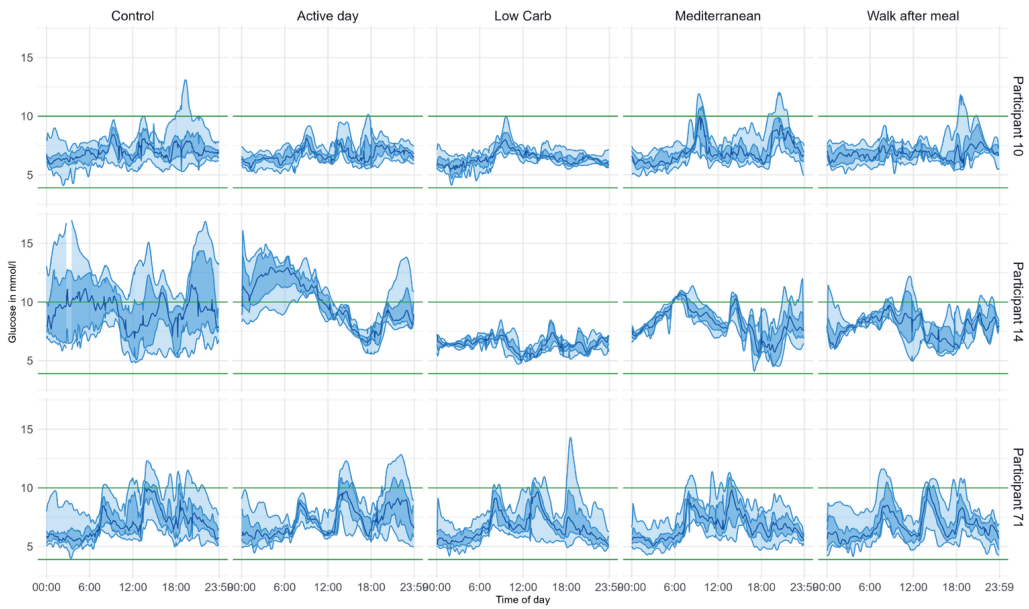

Figure 3. *Ambulatory glucose profiles during the control periods and the four intervention phases for three participants. The target glucose range (3.9-10.0 mmol/l) is shown as two parallel lines. The dark line is the median line, which is based on a rolling mean glucose, and shows whether the average glucose is within the target glucose range and how much it oscillates during the day. The darker shaded band represents the 25th–75th percentile and shows the 50% of all glucose values that are closest to the median line and their variability from day to day. The lighter shaded band represents 90% of all glucose values that are closes to the median line.*

3.5. Impact of diabetes phenotype on effects of lifestyle intervention

Further analysis was done to examine if interindividual differences could be explained by differences in diabetes phenotype or ‘diabetype’. Figure 4 shows the differences in TIR and TAR-L1/2 between the control and intervention periods per diabetype. During control periods, the PB-HMIR group had a lower TIR and higher TAR-L1/L2 than the PB group and PB-HIR group. Coefficients of the final models including either one of these diabetypes are listed in Supplementary Table 3. The data provides clues as to which lifestyle intervention improved CGM metrics most in each diabetype.

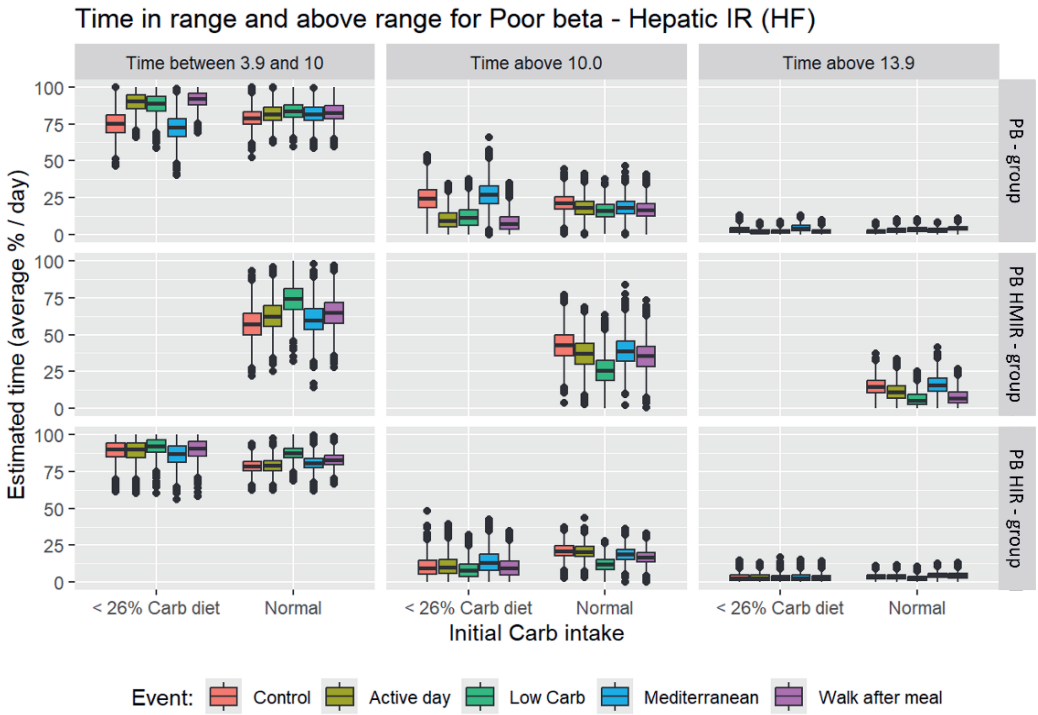

Figure 4. *Boxplots showing TIR and TAR level 1 and 2 in average percentage per day for control and intervention periods, per diabetype: PB, PB-HIR, PB-HMIR. In figure A and B results are presented separately for participants consuming > 26% of calories as carbohydrates, and participants consuming < 26% of calories as carbohydrate at baseline.*

In people with isolated impaired BCF, AD and WaM increased TIR (and reduced TAR-L1 and TAR-L2) only in those who restricted CHO intake at baseline (n=5). LC had no significant effects in this group. For participants in the PB-group with normal CHO intake at baseline, LC intervention resulted in a significantly lower mean glucose and MAGE. The Med intervention resulted in a higher CV and MAGE in those who restricted CHO at baseline and had no impact on participants with normal CHO intake at baseline.

In people with impaired BCF and hepatic IR (PB-HIR), LC, and to a lesser extent WaM, increased TIR and reduced TAR-L1 (and TAR-L2 for LC), especially in those with normal CHO intake at baseline. Additionally, LC decreased mean, CV and MAGE. For those who restricted CHO intake at baseline (n=6) beneficial effects of LC on mean and MAGE were significantly lower as compared to those with normal CHO intake at baseline. Med resulted in a significant increase in mean, MAGE and TAR-L1 and decrease in TIR only in those who restricted CHO intake at baseline and increase in TIR-L2 for those with normal CHO intake.

In people with impaired BCF and combined IR (PB-HMIR), largest improvements were seen with LC and WaM, which significantly improved all CGM metrics, but CV. AD resulted in a

small but significant decrease in mean and MAGE, and an insignificant increase in TIR and decrease in TAR L1/L2.

4. DISCUSSION

Within 4 days, various lifestyle interventions improved CGM metrics in patients with type 2 diabetes. The low carbohydrate intervention (LC) had the most pronounced effects, followed by the walk after meal (WaM) and active day (AD; hourly 5-minute exercise bouts) interventions. The Mediterranean diet (Med) did result in a small negative effect on TAR-L2 and CV. In the group with isolated poor BCF, LC intervention only had a modest effect on mean and MAGE. WaM and AD decreased TAR-L1 and increased TIR, but only in those with restricted CHO intake at baseline. In people with hepatic IR and poor BCF, especially LC and to some extent WaM had favorable effects on CGM metrics. The Mediterranean diet had a minor negative effect only in this group, which was more pronounced in the subgroup consuming a low carbohydrate diet at baseline. In people with combined IR and poor BCF, LC and WaM, and to a lesser extent AD, resulted in favorable effects on CGM metrics. These different effects of lifestyle interventions point towards the potential of personalized lifestyle advice based on diabetype and habitual carbohydrate intake.

The low carbohydrate intervention lowered both glucose variability and mean glucose levels in persons with hepatic or combined IR and poor BCF. As expected, the positive effects of the LC intervention were less pronounced in the subgroup already consuming a low carbohydrate diet at baseline. A previous paper reports that a low carbohydrate energy-deficient diet ameliorates liver insulin resistance and blunts basal glucose production more than a high carbohydrate energy-deficient diet in obese subjects without type 2 diabetes [32]. Also, the study by Kirk et al. shows that a short-term intervention including a low carbohydrate diet is more effective in altering hepatic IR as compared to muscle IR. In our study the effects of LC on CGM metrics were largest in the PB-HIR and PB-HMIR groups. The LC intervention was least beneficial in the group with isolated BCF, which is in line with previous research showing that the effectiveness of lifestyle interventions is dependent on the remaining capacity of the pancreas to produce insulin [33].

In a post-hoc analysis of the CORDIOPREV-DIAB study, the Mediterranean diet appeared to improve glycemic control more in type 2 diabetes individuals with muscle- or combined IR than in individuals with isolated liver IR [15]. In our study, the Med intervention had virtually no effects on CGM metrics, except for a (almost across the board) *deterioration* in PB-HIR individuals who restricted their carbohydrate intake at baseline. However, our study investigated the (sub)acute effects of lifestyle interventions on metrics of glucose profiles, whereas the CORDIOPREV-DIAB study evaluated more traditional markers of glucose metabolism, such as HbA1c and the glucose disposition index, over a period of 2 years. Nevertheless, the lack of effect of Med on CGM metrics in our study was unexpected. Indeed, a previous meta-analysis shows that the Mediterranean diet improves glycemic control to a

similar or even larger extent than low-carbohydrate-, low glycemic index- or high protein diets in people with type 2 diabetes [34]. Moreover, in the long term, Mediterranean diets are associated with a reduced risk of CVD in people with type 2 diabetes [35]. We envision several possible explanations for the lack of effect of the Med intervention in our study, including the short duration of the intervention period, the excellent glycemic control at baseline, and the fact that a significant part of the study population took dietary measures to manage their disease even before the study. Indeed, dietary intake during control periods may have been quite like the Mediterranean diet. The Med intervention increased mean glucose, TAR and MAGE, in particular in people with the PB-HIR diabetype who consumed <26% of calories as carbohydrate at baseline, probably because the Med intervention contained more carbohydrate than their usual diet.

A meta-analysis has shown that physical exercise can reduce mean glucose and time above range, but not fasting glucose in people with type 2 diabetes [36]. Accordingly, in our study both the AD and WaM interventions had beneficial effects on mean glucose, TAR-L1, and MAGE. The walking after each meal intervention sorted beneficial effects in people with impaired BCF and combined IR, and to a lesser extent in people with impaired BCF and hepatic IR as compared to control periods. These observations are in line with the expectation that physical activity most effectively improves glycemic control in people with muscle IR [18]. In people with isolated poor BCF, both physical activity interventions resulted in minor negative effects on CGM metrics in persons with a normal carbohydrate intake at baseline, with a higher CV during the AD intervention and a higher TAR-L1 during the WaM intervention as compared to control periods. Interestingly, when only looking at the subgroup already consuming a low carbohydrate diet at baseline, positive effects of the AD and WaM intervention on CGM metrics were observed. So, it seems that a combination of a low carb diet with WaM or AD could help persons with isolated BCF to improve CGM metrics.

Although the interventions in this study were short term, lasting only 4 days, they do provide some indication of long-term effects. Indeed, (sub)acute measures of glycemic control are associated with long-term health outcomes in people with type 2 diabetes. For example, time in range over a couple of days CGM trace is strongly associated with risk of macro- and microvascular complications, such as retinopathy and microalbuminuria [37]. Measures of glucose variability are associated with peripheral neuropathy and all-cause mortality, the latter especially in people with well-controlled glucose status [38]. More acute markers of glycemic control, such as time in range, also allow for personalized treatment plans and tracking of personal goals [39].

It should be noted that baseline glycemia was very well controlled in our study population. Indeed, average time in range was 82% during the control periods, while the American Diabetes Association recommends a time in range (3.9-10 mmol/L or 70-180 mg/dL) of at least 70% [11]. Part of the study population consumed a low carbohydrate diet before the start of the study. These baseline characteristics may well have affected our results, as benefits

of any intervention require room for improvement at baseline. This was also shown by the interaction effects between carbohydrate intake at baseline and some of the interventions. We nevertheless observed significant effects of various interventions, which probably would be even larger in a less well-controlled population. Another limitation is that the continuous glucose monitor was used in unblinded mode. Previous research has shown that the use of a continuous glucose monitor *per se* can drive behavior change in people with type 2 diabetes and thereby contribute to better glycemic control [40]. However, this was not apparent in our study, as there were no changes in CGM metrics over time when comparing the control periods.

In conclusion, lifestyle interventions differentially impacted continuous glucose monitoring metrics in people with type 2 diabetes on short term. The carbohydrate intake at baseline was an important determinant of the impact of any of the lifestyle interventions on CGM metrics. Furthermore, our data suggest that the type of tissue affected by insulin resistance (i.e., liver and/or muscle) as well as the remaining beta-cell capacity are important determinants of the direction and size of the effects of distinct lifestyle interventions. This latter finding suggests that further characterization of the disease phenotype may be of critical importance for optimal lifestyle advice and personalized treatment of type 2 diabetes mellitus.

Acknowledgements

The authors of this study would like to thank the research participants for their hard work and dedication.

Funding and Assistance. The GlucoInsight collaboration project is co-funded by a PPP Allowance made available by Health~Holland, Top Sector Life Sciences & Health, to stimulate public-private partnerships.

Conflict of Interest. I.M.H., R.J.M.K., T.K., A.A.G. and H.P. declare no conflicts of interest. T.S has a paid position at Roche Diabetes Care Nederland B.V. that markets tools related to diabetes self-management.

Author Contributions and Guarantor Statement. I.M.H. conducted the clinical study, researched data, and contributed to discussion. I.M.H and H.P. wrote the first draft of the manuscript. T.S. and R.J.M.K. conducted the clinical study. T.K conducted the statistical analyses. A.A.G, R.J.M.K., T.K. and H.P. contributed to discussion, reviewed and edited the manuscript. All authors approved the final version of the manuscript. I.M.H. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. An abstract on this data has been submitted for presentation at the 17th International Conference on Advanced Technologies & Treatments for Diabetes (March 2024, Florence, Italy).

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