Low glycaemic index diet and disposition index in type 2 diabetes (the Canadian trial of Carbohydrates in Diabetes): a randomised controlled trial

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Abstract

Aims/hypothesis We recently found that oral glucose tolerance over 1 year in type 2 diabetic patients declined to a significantly lesser degree on a low-glycaemic-index than on a reduced-carbohydrate diet. Here, we examined whether that finding was associated with an improvement in disposition index, an index of beta cell function defined as the product of insulin sensitivity and insulin secretion. Since this is a report of secondary analysis on a previously published trial, the results should be considered as hypothesis-generating.

Methods Type 2 diabetic patients treated by diet alone ($n=162$) were randomised by computer to high-carbohydrate/high-glycaemic index (High-GI, $n=52$), high-carbohydrate/low-glycaemic index (Low-GI, $n=56$) or low-carbohydrate/high-monounsaturated-fat (Low-CHO, $n=54$) diets for 1 year in a multi-centre, parallel-design clinical trial conducted at University teaching hospitals. At baseline and at 3, 6 and 12 months participants underwent 75 g OGTTs; 27 participants dropped out or were excluded. Indices of insulin sensitivity, insulin secretion and disposition index, derived from the OGTT, were compared among diets. Those assessing the outcomes were blinded to group assignment.

Results Neither muscle insulin sensitivity index nor insulinogenic index differed significantly among diets. However, a significant time×diet interaction existed for disposition index (muscle insulin sensitivity index×insulinogenic index) ($p=0.036$). After 3 months, disposition index tended to be higher on Low-CHO than on Low-GI diets, namely by 0.07 h^{-1} (95% CI −0.04, 0.18). However, by 12 months this reversed and disposition index became higher on Low-GI than on Low-CHO, namely by 0.12 h^{-1} (0.01, 0.23; $p<0.05$, baseline disposition index 0.23 h^{-1}). There were no important adverse effects associated with the treatments.

Conclusions/interpretation These results suggest that, in patients with type 2 diabetes on diet alone, a Low-GI diet for 1 year increases disposition index, an index of beta cell function, compared with a Low-CHO diet.

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Abbreviations

CVD	cardiovascular disease
High-GI	high-carbohydrate/high-glycaemic-index diet
Low-CHO	low-carbohydrate/high-MUFA diet
Low-GI	high-carbohydrate/low-glycaemic-index diet
HIR	hepatic insulin resistance index
HOMA-b	homeostasis model assessment for beta cell function
HOMA-r	homeostasis model assessment for insulin resistance
2hPCG	plasma glucose concentration at 2 h after 75 g OGTT
MIS×II	disposition index
MUFA	monounsaturated fatty acid
NSAID	non-steroidal anti-inflammatory drug

Introduction

We recently compared the effects of altering the amount vs the glycaemic index of dietary carbohydrate for 1 year in type 2 diabetic patients being treated by diet-alone on overall glycaemic control and the plasma glucose concentration at 2 h after 75 g OGTT (2hPCG) [1]. Although HbA_{1c} did not differ among diets, the results showed a significant adaptation in the OGTT. At 3 months 2hPCG was significantly lower than baseline on the low-carbohydrate but not on the low-glycaemic-index diet. However, by 1 year 2hPCG had increased significantly more on the low-carbohydrate than on the low-glycaemic-index diet. Here, we report the results of secondary analyses of the OGTT results, conducted to investigate possible mechanisms of this long-term adaptation in 2hPCG.

Blood glucose homeostasis depends on a balance between insulin sensitivity and insulin secretion. In normal individuals, between- and within-individual variations in insulin sensitivity are compensated for by reciprocal changes in insulin secretion [2, 3]. The product of insulin sensitivity and insulin secretion is the disposition index [3], which is considered to be a measure of beta cell function. Type 2 diabetes occurs when reduced insulin sensitivity cannot be compensated for by increased insulin secretion, i.e. reduced disposition index [4, 5]. The relentless progression of type 2 diabetes is thought to be due to a progressive decline of disposition index [5, 6].

The dietary management of type 2 diabetes is controversial, particularly with respect to dietary carbohydrate. Ideally, dietary treatment would increase disposition index, either by improving insulin sensitivity or insulin secretion or both. Low-carbohydrate, high-monounsaturated-fatty-acids (MUFA) [7, 8], or low-glycaemic-index diets [9], may improve insulin sensitivity in individuals with type 2 diabetes, but little is known about the effects of such diets on beta cell function in type 2 diabetes. Furthermore, the studies cited were of short duration (2–5 weeks) and it is not known whether the short-term effects persist over a longer period of time. Since use of low-glycaemic-index carbohydrate foods for 4 months increased disposition index in participants with impaired glucose tolerance [10], we hypothesised that a low-glycaemic-index diet would increase disposition index in patients with type 2 diabetes. Thus, the purpose of this paper was to compare the effects of a high-carbohydrate/low-glycaemic-index diet (Low-GI) with those of low-carbohydrate/high-MUFA (Low-CHO) and high-carbohydrate/high-glycaemic-index (High-GI) diets for 1 year on indices of insulin sensitivity, insulin secretion and disposition index derived from fasting and postprandial plasma glucose and insulin concentrations during OGTT in participants with type 2 diabetes who were being treated by diet alone. Because this is a secondary analysis, the results should be considered to be hypothesis-generating.

Methods

Study centres The study was carried out on an outpatient basis at five university-affiliated teaching hospitals across Canada. The protocol was approved by the human ethics review committee at each participating institution and all participants consented to participate.

Participants Men or non-pregnant women who had type 2 diabetes (fasting glucose ≥7.0 mmol/l or 2hPCG≥ 11.1 mmol/l within 2 months of randomisation) managed by diet alone were recruited. Participants were aged 35 to 75 years, had HbA_{1c} ≤130% upper limit of normal, BMI 24 to 40 kg/m², were not using insulin or any hypoglycaemic or anti-hyperglycaemic medication and were otherwise generally healthy. Detailed inclusion and exclusion criteria and the rationale for the sample size are reported elsewhere [1].

Dietary intervention After being identified, participants handed in a 3-day food record and underwent a baseline OGTT. A dietitian provided dietary advice with the aim of attaining 55% of energy from carbohydrate, 15% from protein and 30% from fat, consisting of 8% to 9% saturated fatty acids, 8% to 10% polyunsaturated fatty acids and 15%

to 20% MUFA. Two weeks later participants ($n=162$) were randomly assigned as previously described [1] to one of three diets: High-GI, Low-GI or Low-CHO. Blocks of various sizes were used to enhance allocation concealment. Treatment assignments were sealed in sequentially numbered opaque envelopes kept by a person not involved with the study. Further OGTTs were performed at 3, 6 and 12 months after randomisation, during which participants drank 75 g glucose solution (Ratiopharm, Mississauga, ON, Canada) within 5 min, with blood samples obtained in the fasting state and at 30, 60 and 120 min after starting the drink.

The dietary intervention was effected by instructing participants to consume an individually prescribed amount of key foods each day, chosen from a list of 16 to 21 key foods per diet and provided free of charge. A dietitian advised participants how to incorporate the key foods into their diets to avoid weight gain. The High-GI and Low-GI diet key foods were starchy foods whose glycaemic index we had determined and prescribed such that their carbohydrate provided 20% to 25% of energy. The Low-CHO diet key foods consisted of oils, spreads, nuts and other foods low in saturated fatty acids and high in MUFA and reported to reduce diabetes and cardiovascular disease (CVD) risk and/or to reduce blood lipids. They were prescribed to replace carbohydrate normally consumed with a view to increasing total fat intake by about 10%. Details about the amounts and types of key foods consumed are reported elsewhere [1]. Food records were made for a period of 3 days at 1, 3, 6, 9 and 12 months after randomisation.

Laboratory measurements and calculations Blood samples were analysed and the data managed centrally by individuals who were unaware of the treatment allocations of the participants. HbA$_{1c}$ was analysed by HPLC (Diamat HPLC; Bio-Rad Laboratories Canada, Mississauga, ON, Canada), plasma glucose by a hexokinase method and insulin by electrochemiluminescence immunoassay (Roche Diagnostics, Mannheim, Germany). The nutrient composition of the diets was assessed using an in-house programme as previously described [1]. As used here, the term 'carbohydrate' refers to available carbohydrate, defined as total carbohydrate minus dietary fibre.

Several models have been described for estimating insulin sensitivity and secretion from plasma glucose and insulin concentrations during the OGTT. We used the homeostasis model assessment for insulin resistance (HOMA-r) [11], ($[G_0 \times I_0]/135$, where G_0 is fasting glucose in mmol/l and I_0 is fasting insulin in pmol/l) and the hepatic insulin resistance index (HIR) and muscle insulin sensitivity index [12]. HIR is G_{0-30}(AUC)$\times I_{0-30}$(AUC) where G_{0-30}(AUC) and I_{0-30}(AUC) are the total glucose and insulin response AUCs respectively between 0 and 30 min. Muscle insulin sensitivity index is the rate of decay of plasma glucose from its peak to its nadir during the OGTT divided by mean plasma insulin during the OGTT. If glucose continued to rise throughout the 2 h period of the OGTT, the slope was taken to be zero.

For basal insulin secretion, we used HOMA for beta cell function (HOMA-b) [11]. The Stumvoll first-phase measure of insulin secretion [13] was not used because ∼50% of the values were negative. Instead we used insulinogenic index [14], defined as the rise in insulin divided by the rise in glucose from 0 to 30 min ($\Delta I_{0-30}/\Delta G_{0-30}$). Any negative values obtained were taken to be zero. The disposition index was calculated as muscle insulin sensitivity index $\times$ insulinogenic index (MIS$\times$II).

Endpoints The results for the primary endpoint of the study (HbA$_{1c}$) and for the secondary endpoints of plasma glucose and insulin concentrations in the fasting state and 2 h after the OGTT have been published elsewhere [1]. The results for plasma glucose and insulin concentrations at 30 and 60 min after the OGTT, as well as indices of insulin sensitivity and secretion derived from the OGTT, have not been published before. Insulinogenic index was declared as a secondary endpoint when the study was registered, but HOMA-r, HIR, muscle insulin sensitivity index, HOMA-b and MIS$\times$II were calculated post hoc as secondary analyses.

Statistics Data were analysed on an intent-to-treat basis for participants with OGTT results available at 6 and/or 12 months. Results are presented as mean±SEM or mean (95% CI). Plasma glucose and insulin concentrations were subjected to ANOVA examining for the main effects of diet, time (0–120 min) and visit (0–12 months) and their interactions [15]. HOMA-r, HOMA-b, HIR, muscle insulin sensitivity index, insulinogenic index and MIS$\times$II at 3, 6 and 12 months were adjusted for sex and baseline value and the residuals analysed by ANOVA for the main effects of diet and time (3–12 months) and the diet$\times$time interaction, with the error degrees of freedom being reduced by the number of imputed values. When significant interactions were found, the differences between individual means were tested using Tukey's test to adjust for multiple comparisons; the criterion of significance was two-tailed $p < 0.05$. The primary endpoint of the study was HbA$_{1c}$. Since all of the results reported here represent secondary endpoints or secondary analyses, we did not adjust the p values for the multiple endpoints. For this reason, the findings should be considered to be hypothesis-generating and requiring further confirmation.

Results

The flow chart for the study was published in the primary paper [1]. Participants ($n=162$) were randomised from

January 2002 to the end of October, 2003; for this paper, 25 participants were excluded because of insufficient data as follows: (1) OGTT at baseline ($n=11$) or baseline and 3 months ($n=10$) only; and (2) indices not calculable because blood samples were only available for fasting and 2 h ($n=4$). This left 137 participants with an OGTT at 6 and/or 12 months. Two participants were excluded because of outlying values for muscle insulin sensitivity index. One missing baseline OGTT was imputed as the mean of the three other values. Values missing at 3 or 6 months ($n=21$) were imputed as the mean of the values before and after. Values missing at 12 months ($n=25$) were replaced by the 6 month values (last value carried forward).

Baseline comparisons At baseline, there were no significant differences in glucose, insulin or indices of insulin sensitivity or secretion among diet groups; however, compared with women, men had significantly higher waist circumference, muscle insulin sensitivity index and MIS× II, and lower 2 h plasma insulin and insulinogenic index (Table 1). Records of concomitant medications used during the trial were available for 126 of the 135 participants included in this paper (93%). Since all participants had type 2 diabetes treated by diet alone, none were taking any oral hypoglycaemic or anti-hyperglycaemic drug or insulin at baseline or during the trial. There were no significant differences among diet groups in the number of participants taking medications at baseline nor in the number of participants who changed dose during the trial for any of the 18 categories of concomitant medications (Electronic supplementary material [ESM] Table 1). Steroids used during the trial were all short courses as follows: (1) cortisone

injection into a joint on one ($n=2$) or two ($n=1$) occasions; (2) topical prednisone for 2 to 3 weeks for dermatological conditions ($n=2$); (3) inhaled prednisone for bronchitis for 6 weeks ($n=1$); and (4) systemic prednisone for bronchitis for 6 ($n=1$) or 9 days ($n=1$). Participants taking aspirin had lower HOMA-r at baseline than those who did not, i.e. 2.5 (95% CI 2.1, 3.0) vs 3.6 (3.0, 4.1; $p=0.007$). Participants who took non-steroidal anti-inflammatory drugs (NSAIDs) had higher insulinogenic index, i.e. 33 (26, 40) vs 25 (21, 29; $p=0.044$) pmol/mmol, higher muscle insulin sensitivity index, 0.022 (0.010, 0.033) vs 0.010 (0.007, 0.013; $p=0.006$) mmol pmol^{-1} h^{-1} and higher disposition index, 0.34 (0.23, 0.45) vs 0.19 (0.14, 0.25; $p=0.009$) h^{-1} at baseline than those who did not. Participants taking nutritional supplements had higher insulinogenic index at baseline than those who did not, i.e. 31 (25, 36) vs 23 (19, 27; $p=0.041$) pmol/mmol. Participants on statins had higher insulinogenic index at baseline than those who did not, i.e. 31 (26, 36) vs 22 (18, 26; $p=0.009$) pmol/mmol.

Dietary composition Energy and protein intakes did not change significantly on the High-GI, Low-GI and Low-CHO diets (Table 2). Total fat intake decreased from baseline on the High-GI and Low-GI diets and increased on Low-CHO; about 66% of the increase in fat on Low-CHO was accounted for by MUFA and the remainder was accounted for by polyunsaturated fat. Intake of saturated fat fell slightly but significantly on all three diets. Carbohydrate intake increased from baseline on the High-GI and Low-GI diets and decreased on Low-CHO. Glycaemic index increased from baseline on High-GI, decreased on Low-GI and did not change on Low-CHO.

Table 1 Baseline variables at randomisation

Variable	High-GI	Low-GI	Low-CHO	Men	Women
n (men:women)	21:20	16:30	25:23	62:0	0:73
Age (years)	59.8±1.2	60.8±1.1	58.8±1.3	58.8±1.0	60.6±0.9
BMI (kg/m^2)	31.0±0.7	31.1±0.8	30.9±0.6	30.3±0.5	31.6±0.6
Waist circumference (cm)	103±2	99±2	102±2	105±1	98±1*
HbA$_{1c}$	0.061±0.001	0.062±0.001	0.062±0.001	0.061±0.001	0.062±0.001
Fasting glucose (mmol/l)	7.4±0.2	7.0±0.1	7.5±0.2	7.4±0.2	7.2±0.1
2hPCG (mmol/l)	13.4±0.5	13.5±0.5	14.1±0.4	13.3±0.4	14.0±0.4
Fasting insulin (pmol/l)	62±4	56±6	53±5	52±4	61±4
2 h plasma insulin (pmol/l)	391±36[a,b]	402±43[a]	285±26[b]	300±26	404±31*
HOMA-r	3.5±0.3	3.0±0.4	3.0±0.3	2.8±0.2	3.4±0.3
HOMA-b	57±5	55±5	48±4	47±4	58±4
HIR (mmol×pmol l^{-2} h^{-2})	339±29	305±36	270±23	274±24	328±25
Muscle insulin sensitivity index×100 (mmol pmol^{-1} h^{-1})	1.41±0.36	1.33±0.31	1.29±0.26	1.72±0.26	1.00±0.23*
Insulinogenic index (pmol/mmol)	28.5±3.0	28.9±3.6	22.4±2.0	21.6±2.2	30.6±2.5*
MIS×II (h^{-1})	0.25±0.04	0.25±0.05	0.22±0.04	0.29±0.04	0.19±0.03*

Values are means±SEM

[a,b] $p<0.05$ for difference between diet group means with different superscript letters

*$p<0.05$ for difference between men and women

Table 2 Composition of diets at baseline and on study diets

Variable	Baseline	High-GI	Low-GI	Low-CHO
Energy (kJ/d)	7,770±180	7,690±250	7,610±240	8,440±240
Protein (% energy)	20±0.3	20±0.5	21±0.5	19±0.4
Total fat (% energy)	33±0.5	30±0.7[a]*	27±0.8[b]*	40±0.6[c]*
Saturated fat (% energy)	11±0.3	10±0.4*	8±0.8*	11±0.3*
Monounsaturated fat (% energy)	14±0.3	12±0.4[a]*	11±0.4[b]*	18±0.3[c]*
Polyunsaturated fat (% energy)	6±0.1	6±0.2[a]*	5±0.2[a]*	8±0.2[b]*
Carbohydrate (% energy)	44±0.6	47±1[a]*	52±1[b]*	39±1[c]*
Dietary fibre (g/d)	22±0.6	21±0.8[a]	37±1.5[b]*	23±0.8[a]
Glycaemic index (%)	61±0.3	63±0.4[a]*	55±0.4[b]*	60±0.5[c]
Glycaemic load (g/d)	126±2	137±3[a]*	133±3[a]	110±2[b]*

Values are means±SEM

[a,b,c] $p<0.05$ for difference between means with different superscript letters

*$p<0.05$ for difference from baseline

Thus, glycaemic load increased on High-GI and decreased on Low-CHO, but did not change significantly on Low-GI. Dietary fibre intake did not change on High-GI or Low-CHO, but increased significantly on Low-GI.

Adverse events, body weight and HbA$_{1c}$ There were no important adverse effects associated with the treatments. As reported previously [1], body weight fell by ~0.5 kg over the first 8 weeks, then rose steadily to ~0.8 kg higher than at baseline by 12 months ($p=0.0005$). Mean weight on Low-GI was 0.4 kg less than that on High-GI and Low-CHO ($p=0.062$). The primary endpoint, HbA$_{1c}$, rose from ~0.061 at baseline to ~0.063 after 12 months ($p<0.0001$), but there was no significant difference among diets [1].

Glucose and insulin during OGTT There was a significant time×diet×visit interaction ($p=0.033$) for plasma glucose during the OGTT indicating that the pattern of responses to the different diets varied significantly over the course of the study. At 3 months unadjusted 2hPCG did not differ significantly from baseline on any diet, but the change on Low-CHO was significantly smaller than that on High-GI by 1.26 (0.22, 2.30) mmol/l ($p<0.05$) (ESM Fig. 1). However, by 12 months 2hPCG had risen significantly from baseline on both the High-GI and Low-CHO diets by 1.41 (0.37, 2.45) and 1.33 (0.29, 2.37) mmol/l, respectively ($p<0.05$). The increase in 2hPCG at 12 months on Low-GI, 0.37 (−0.63, 1.37) mmol/l, was not significant from baseline and was 1.06 (0.02, 2.10) mmol/l less than that
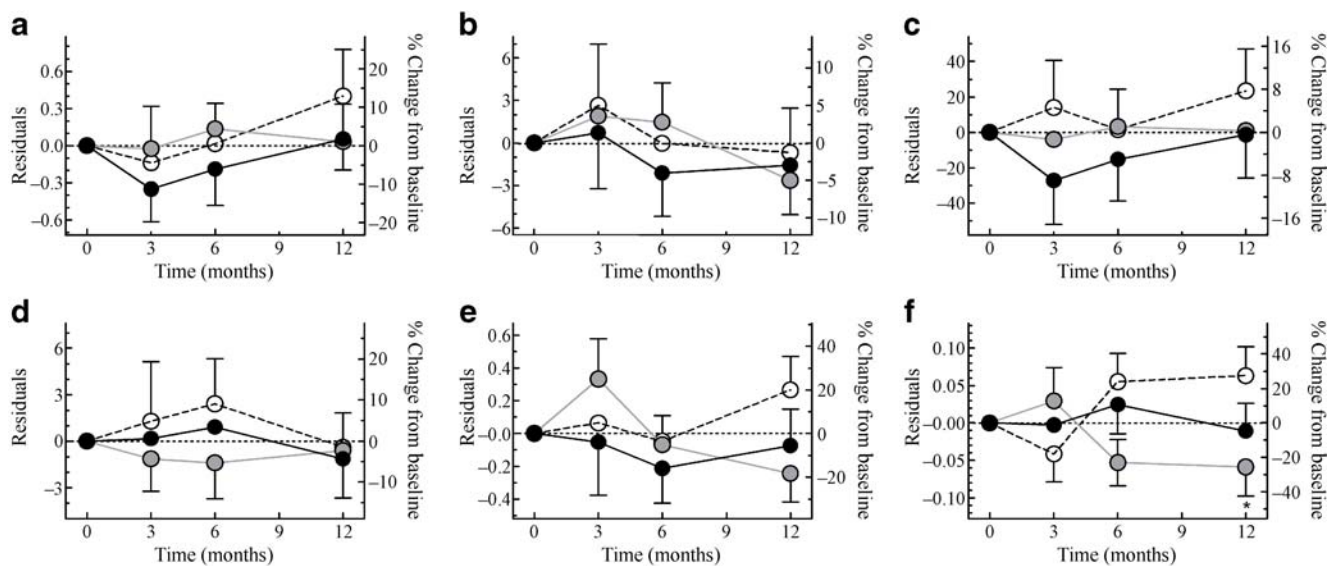

Fig. 1 Residuals of **a** HOMA-r, **b** HOMA-b, **c** HIR, **d** insulinogenic index, **e** muscle insulin sensitivity index and **f** disposition index, after adjustment for baseline value and sex in participants on High-GI (black circles, $n=41$), Low-GI (white circles, $n=46$) and Low-CHO (grey circles, $n=48$) diets. Values are means±SEM. (f) *$p<0.05$ for difference between Low-GI and Low-CHO; $p=0.036$ for time×treatment interaction

on High-GI ($p<0.05$) (ESM Fig. 1). There were no significant differences among diets for plasma insulin.

Insulin sensitivity, insulin secretion and disposition index There was no significant effect of time (3–12 months), diet, or time×diet interaction, respectively, for the residuals of HOMA-r ($p=0.25$, $p=0.72$, $p=0.83$), HOMA-b ($p=0.40$, $p=0.91$, $p=0.96$), HIR ($p=0.71$, $p=0.59$, $p=0.95$), insulinogenic index ($p=0.78$, $p=0.77$, $p=0.94$) or muscle insulin sensitivity index ($p=0.37$, $p=0.67$, $p=0.38$) (Fig. 1). However, a time×diet interaction was seen for MIS×II ($p=0.036$). Initially, the overall mean for MIS×II tended to be higher on Low-CHO than on Low-GI by 0.07 (−0.04, 0.18) h^{-1}, but by the end of the study, the reverse was seen and MIS×II was 0.12 (0.01, 0.23) h^{-1} higher on Low-GI than on Low-CHO ($p<0.05$, pooled baseline value 0.23 h^{-1}), with the value for High-GI being intermediate (Fig. 1).

The use of aspirin, NSAIDs, nutritional supplements or statins did not significantly affect the response of MIS×II to the Low-GI compared with the Low-CHO diet. In the 126 participants for whom data on drug use was available, the significance of the time×diet interaction for MIS×II, adjusted for baseline and sex, was $p=0.013$; this p value was unchanged after additional adjustment for use of aspirin, NSAID, nutritional supplements or statins during the trial. Regardless of whether participants were taking these drugs or not, the residuals for MIS×II after 12 months on Low-GI always tended to be greater than those on Low-CHO (ESM Table 2).

Changes (Δ) in 2hPCG were not significantly related to ΔHOMA-r, ΔHOMA-b or ΔHIR at any time. Δ2hPCG was related to Δmuscle insulin sensitivity index at 3, 6 and 12 months ($r=-0.463$, −0.466 and −0.502 respectively, $p<0.0001$ for all). Δ2hPCG was significantly related to

Δinsulinogenic index at 6 ($r=-0.204$, $p=0.017$) and 12 months ($r=-0.194$, $p=0.024$), but not at 3 months ($r=-0.092$). Δ2hPCG was related to ΔMIS×II at 3, 6 and 12 months ($r=-0.577$, −0.592 and −0.579 respectively, $p<0.0001$). The correlations between Δ2hPCG and ΔMIS×II were greater than those between Δ2hPCG and Δinsulinogenic index ($p<0.05$), and were non-significantly greater than those between Δ2hPCG and Δmuscle insulin sensitivity index (Fig. 2).

Discussion

Our results show that, in type 2 diabetic patients treated by diet alone, the short-term (3 months) changes in OGTT and disposition index resulting from changes in dietary carbohydrate intake did not reflect the longer term (1 year) results. In fact, the short-term effects were misleading, because the diet with the most beneficial effects on OGTT and disposition index after 3 months (Low-CHO) had the most deleterious effect after 12 months, whereas the diet with the most deleterious effect after 3 months (Low-GI) had the most beneficial effect after 12 months. The results also suggest that changes in OGTT are more closely related to changes in disposition index than to changes in insulin sensitivity or plasma insulin concentrations.

The overall goal of the treatment of diabetes is to prevent long-term micro- and macro-vascular complications. To this end, improving glycaemic control, as assessed by HbA$_{1c}$, is considered important [16, 17]. Thus, since we failed to show any significant difference in HbA$_{1c}$ among diets, the clinical relevance of the present study has been questioned [18]. However, it is becoming apparent that HbA$_{1c}$ is not the only relevant marker of risk for complications,
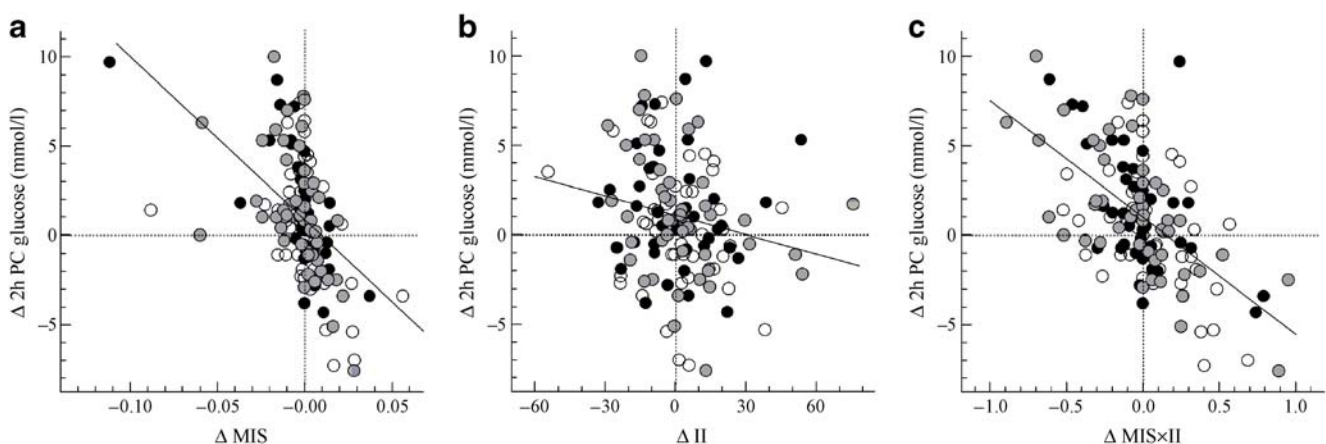

Fig. 2 Correlations between the changes (12 months–baseline) of 2hPCG and changes (12 months–baseline) in **a** muscle insulin sensitivity index (MIS) ($r=-0.504$, $p<0.0001$), **b** insulinogenic index (II) ($r=-0.194$, $p=0.024$) and (**c**) disposition index (MIS×II) ($r=-0.579$, $p<0.0001$) for individual participants on High-GI (black circles), Low-GI (white circles) and Low-CHO (grey circles) diets

particularly with respect to risk of CVD in type 2 diabetes. In the United Kingdom Prospective Diabetes Study, treating type 2 diabetes with insulin, sulfonylureas or metformin reduced HbA$_{1c}$ and microvascular complications to a similar extent, but only metformin reduced macrovascular complications [19, 20]. Repaglinide therapy was associated with greater regression of carotid artery atherosclerosis than glibenclamide (known as glyburide in the USA and Canada), despite no difference in HbA$_{1c}$ [21], while glibenclamide therapy for 4 years was associated with significantly fewer cardiovascular events than rosiglitazone, despite higher HbA$_{1c}$ at the end of the study (~0.076 vs ~0.070) [22]. More recently, the intensive-treatment arm in the Action to Control Cardiovascular Risk in Diabetes study, which aimed to reduce HbA$_{1c}$ to less than 0.06, was stopped because of increased mortality [23]. While these studies question the value of aggressive pharmacological therapy to reduce HbA$_{1c}$ in type 2 diabetes, their results may not be relevant to dietary management. Nevertheless, there is evidence that postprandial glucose, and not necessarily the level of HbA$_{1c}$ achieved, is associated with increased risk of cardiovascular complications [24] and mortality [25], and with increased oxidative stress [26] in patients with type 2 diabetes. The latter finding is consistent with the significant reductions in postprandial glucose and C-reactive protein that we found in the present study in participants on the Low-GI, but not in those on the Low-CHO diet [1]. Thus, the reduction in 2hPCG observed by us on the low-glycaemic-index diet could be clinically important as marking reduced CVD risk even in the absence of a difference in HbA$_{1c}$.

Our results suggest that the changes observed by us in 2hPCG may be due to changes in disposition index, as a measure of beta cell function. Deterioration of disposition index appears to be the pathophysiological mechanism responsible for the development [3–5] and progression [5, 6] of type 2 diabetes; treatments which improve disposition index may, therefore, prevent type 2 diabetes or slow its progression. It is less clear whether poor beta cell function predisposes to the development of CVD, at least in part, because published reports from studies that have the relevant information have focused mainly on the relationship between insulin sensitivity and CVD without reporting the effects of beta cell function [27]. However, some studies suggest that impaired beta cell function, assessed as HOMA-b [28], insulinogenic index [29] or increased plasma proinsulin concentrations [30], is associated, independently, with increased CVD risk and/or mortality rate.

We used muscle insulin sensitivity index and insulinogenic index as indirect indices, estimated from OGTT, of insulin sensitivity and insulin secretion to calculate disposition index (here MIS×II). Our results need to be interpreted with caution for a number of reasons. Muscle insulin sensitivity index and insulinogenic index were validated against the euglycaemic clamp and intravenous glucose infusion, respectively, in individuals with normal or impaired glucose tolerance but not diabetes [12, 14]. Therefore, we cannot be sure they are valid in patients with type 2 diabetes. Nevertheless, the relationship between insulinogenic index and muscle insulin sensitivity index values at baseline in our participants, plotted by quartile of MIS×II, were, as expected, hyperbolic curves which became closer to the origin as the disposition index became smaller (ESM Fig. 2). Muscle insulin sensitivity index and insulinogenic index are indirect measures that rely on a number of assumptions, such as the rate and amount of glucose absorbed from the gut, which may not hold in our population. In addition, we did not take as many blood samples at baseline and during the OGTT as did Abdul-Ghani et al. [12], so our estimates may be less accurate or precise. Nevertheless, we did detect a significant time× treatment interaction for MIS×II. Also, our results are consistent with those of several previous studies showing that low-glycaemic-index starchy foods improve beta cell function or insulin secretion in persons without diabetes [10, 31].

On Low-GI it took 6 to 12 months for the increase in disposition index to become evident. We speculate this may be due to increased glucagon-like peptide-1 secretion stimulated by the short-chain fatty acids produced by fermentation of the increased load of starch entering the colon after low-glycaemic-index compared with high-glycaemic-index foods [32]. Because of the complexity of the colonic ecosystem, short-chain fatty acid production may take 4 to 6 months to rise to a steady-state level after increased intake of resistant starch or fibre [33, 34] or acarbose therapy [35]. In animals, a high-fibre diet was shown to increase glucagon-like peptide-1 secretion [36], which, in turn, may increase beta cell mass or improve glucose sensing [37].

The reduction in 2hPCG and trend toward increased muscle insulin sensitivity index on Low-CHO at 3 months is consistent with short-term studies suggesting that Low-CHO diets improve insulin sensitivity in type 2 diabetes [7, 8]. Since exchanging saturated fat for MUFA does not improve insulin sensitivity if total fat intake is >37% energy [38], the short-term effect of low-carbohydrate/high-MUFA diets on insulin sensitivity may be due to reduced glucose toxicity resulting from lower postprandial glucose. However, our results suggest that Low-CHO meals did not continue to elicit low glycaemic responses in the long term [1]; the reason for this finding is unknown, but it is consistent with the progressive deterioration of disposition index on the Low-CHO diet between 3 and 12 months (Fig. 1). By contrast, the low glycaemic impact of Low-GI meals was sustained and even after 1 year was exactly predicted by the difference in meal glycaemic load [1].

Common drugs may affect glucose tolerance [39–43] or be used for conditions associated with insulin resistance, such as hypertension [44]; thus, the effect of diet on glucose metabolism may be modified by the use of drugs. In our population, use of aspirin, NSAIDs, nutritional supplements and statins was associated with differences in indices of carbohydrate metabolism at baseline. Nevertheless, the relative effects of the diets on disposition index did not appear to be influenced significantly by the use of these drugs. However, the study was not powered to investigate the interaction between diet and drugs, and because of the small number of participants in each diet/drug group, the 95% CIs were large and the power to detect such effects was small.

In conclusion, our results suggest that, in patients with type 2 diabetes on diet alone, use of a Low-GI diet for 1 year increases disposition index, an index of beta cell function, compared with a low-carbohydrate/high-MUFA diet. This hypothesis will require further testing before it can be accepted as proven.

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