Dietary carbohydrate intake and cardio-metabolic risk factors in type 1 diabetes

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ABSTRACT

Aims: Low-carbohydrate diet (LCD) has gained interest among individuals with diabetes as a means to manage glycaemia. We investigated the adherence to LCD in the Finnish Diabetic Nephropathy Study and whether carbohydrate restriction is associated with cardio-metabolic risk factors.

Methods: Cross-sectional data were available from 902 individuals with type 1 diabetes (44% men, age 47 ± 13 years). Dietary data were collected twice with a 3-day diet record. Mean of the measurements was used. Carbohydrate intake <130 g/day or <26 E% was used as indication of LCD. Individuals reporting LCD were compared to sex-, diabetes duration- and eGFR-matched controls with higher carbohydrate intakes (>253 g/day or >48 E%). In the whole population, carbohydrate-to-fat ratio was calculated and its association with health variables was investigated.

Results: Higher carbohydrate-to-fat ratio was associated with higher blood glucose variability, higher blood pressure, lower HDL cholesterol concentration, and in men with lower waist-to-hip ratio. LCD adherence (n = 69) was associated with lower BMI (25.6 vs. 27.8 kg/m^2, p = 0.030), lower variability of blood glucose measurements (0.38 vs. 0.45 mmol/l, p = 0.030), and lower diastolic blood pressure (74 vs. 79 mmHg, p = 0.048). Men reporting LCD had higher total (5.1 vs. 4.0 mmol/l, p = 0.007) and non-HDL cholesterol (3.4 vs. 2.7 mmol/l, p = 0.021). Women with LCD had higher HDL-cholesterol concentration (1.9 vs. 1.5 mmol/l, p = 0.014).

Conclusions: Reduced blood glucose variability, related to LCD, could have clinical relevance to individuals with type 1 diabetes.

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1. Introduction

Prior to the discovery of insulin, dietary carbohydrate restriction was used as a method to manage blood glucose levels in type 1 diabetes [1]. After the exogenous insulin became available, however, diets with carbohydrates as the predominant macronutrient, became the standard of nutritional management. While today, recommending a particular macronutrient distribution is no longer officially enforced [2], carbohydrates persistently continue to provide the majority of dietary energy in the diets of individuals with type 1 diabetes [3,4]. Importantly, dietary carbohydrates contribute to postprandial glycaemia, which is a major determinant of, not only long-term glycaemia [5], but also of macrovascular complications and mortality [6].

Carbohydrate counting and subsequent dosing of bolus insulin, as taught in various education programmes such as the Dose adjustment for normal eating (DAFNE) [7], are the foundations of the modern nutritional management of type 1 diabetes. However, due to errors in estimating carbohydrate contents of the meals [8], and variation in the absorption of the injected insulin [9], reaching postprandial normoglycaemia is often a challenge [10]. It is therefore not surprising that suboptimal HbA_{1c} levels are frequently reported among individuals with type 1 diabetes [11].

Because of dissatisfaction with suboptimal glycaemic control related to the adherence to higher carbohydrate diets, some individuals with diabetes have once again turned to carbohydrate restriction as a means to tackle glycaemia. While most of the current observations have been from patients with type 2 diabetes [12], also individuals with type 1 diabetes may benefit from carbohydrate restriction as an adjunct to insulin treatment. Unlike seen in the Diabetes Control and Complications Trial where reduction in HbA_{1c}, that followed the intensification of insulin therapy, was burdened by concomitant increase in the risk of hypoglycaemia [13], such risk has not been associated with improved glycaemia achieved by carbohydrate restriction [14–16]. Instead, restricting dietary carbohydrate intake has rather lead to lower variability in the blood glucose levels [15,16].

Presuming unchanged energy requirement, reduction in carbohydrate intake needs to be accompanied by an increase in the intake of at least one other macronutrient. In practice, this is often fat [17], as protein requirement mainly depends on the urinary and faecal nitrogen loss, and protein required for tissue growth [18]. This has raised concerns whether adherence to such a high-fat diet would have negative consequences for cardio-metabolic risk factors [19–21]. This study was undertaken to explore the frequency of adhering to low-carbohydrate diets in a sample of Finnish individuals with type 1 diabetes. Additionally, our goal was to investigate the association between low-carbohydrate diet and cardiovascular risk factors.

2. Methods

The study subjects, in this cross-sectional study, were participants in the nation-wide multicentre Finnish Diabetic Nephropathy (FinnDiane) Study. The aim of the FinnDiane Study is to identify risk factors for diabetes complications in adult ($\geq$18 years) individuals with type 1 diabetes. Participants were recruited from over 80 centres around Finland (see the electronic supplementary material for a list of the centres). Type 1 diabetes was defined as diabetes onset before the age of 40 years, and permanent insulin treatment, initiated within a year from the diagnosis. Of the FinnDiane Study participants, we included in the current analyses those who had completed a diet record for a minimum of 3 days with plausible energy intake [5020–14,600 kJ/d (1200–3500 kcal/d)], whose estimated glomerular filtration rate (eGFR) was $\geq$60 ml/min/1.73 m^2, and who showed no signs of acute infection (high-sensitivity C-reactive protein, hsCRP, $\leq$10 mg/l). The Ethics Committee of The Helsinki and Uusimaa Hospital District approved the study protocol. The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all participants upon study entry.

2.1. Variables and measurements

At the study visit the participants were thoroughly investigated, as previously described [22]. In brief, the participants' weight and height were measured in light clothing without wearing shoes. Height was measured using a wall-mounted stadiometer. Waist and hip circumferences were measured using an inelastic tape measure. Waist circumference was measured at the midway between the lowest rib and iliac crest, while the hip circumference was measured with the subject standing with feet close together, around the widest portion with the tape measure parallel to the floor. Body mass index (BMI; weight in kg/height in m^2), waist-to-hip ratio (waist circumference/hip circumference), and body adiposity index (BAI; [hip circumference in cm/height in $m^{1.5}$] $-$ 18) were calculated. Following a minimum of ten-minute rest, blood pressure was measured twice using a digital blood pressure monitor (Omron M6, OMRON Healthcare UK Ltd, Milton Keynes, UK). In case the two measurements differed by over 10 mmHg a third measurement was conducted, in which case the two measurements closest to each others were used. Mean of the two measurements was used in the analyses. HbA_{1c} was measured locally using a standardized assay. Serum lipid, lipoprotein, and creatinine concentrations were centrally determined at the laboratory of the Helsinki University Hospital from early morning blood samples. As participants had type 1 diabetes, fasting was not required, but light breakfast was allowed to prevent or treat hypoglycaemia. The serum creatinine concentration was used to calculate eGFR [23]. Serum hsCRP concentration was measured by immunoassay (Modular analyzer, Roche, Indianapolis, USA). The attending physician recorded information on the participant's current medication use and diabetes complications on a standardized form. Acute myocardial infarction, coronary bypass, stroke, amputation, and peripheral vascular disease were coded as hard cardiovascular event. Retinal laser treatment was an indication of severe diabetic retinopathy. Insulin dose was self-reported. The method to obtain self-reported data on physical activity has previously been

published [24]. In short, participants retrospectively reported the frequencies, average durations, and intensities of 21 common leisure-time physical activities over the past 12 months. From these reports, we calculated the metabolic equivalent of task hours (METh) by multiplying the duration of the activity by the activity- and intensity-specific metabolic equivalent. The METh was treated as a continuous variable in the multivariable models.

2.2. Dietary intake

The methods to study dietary intake, in the FinnDiane Study, have previously been described [4]. Briefly, at the study visit participants were asked to complete a validated diet questionnaire [25]. Upon returning the questionnaire, participants were sent a 3-day diet record. The allocated 3 days covered two weekdays and one weekend day, and continuation of habitual dietary practices was emphasised. The recording was repeated after a 2–3 months' interval with the aim at obtaining a total of 6-day recording with some seasonal variation. AivoDiet software (version 2.0.2.3, AIVO, Turku, Finland) was used to calculate energy and nutrient contents of the participants' diets, as reported in the records. Mean nutrient intakes from either 3-day (if only available) or 6-day record were calculated. In the same record, participants also reported self-monitored blood glucose (SMBG) values. From these reports, mean and coefficient of variation (CV, standard deviation divided by mean) of the measured values were calculated for each participant.

For investigating the association between low-carbohydrate intake and health, we took two separate approaches. First, in order to utilise the data from the whole population, we calculated a carbohydrate-to-fat ratio using the percentages of energy (E%) derived from carbohydrates and fats. The higher the ratio, the higher the carbohydrate intake in relation to fat intake. This ratio was used as a continuous variable in the analyses. Second, based on the calculated carbohydrate intake, individuals with low carbohydrate intakes (<130 g/day or <26 E%, as described in the paper by Feinman et al. [17]) were identified. These individuals were compared to sex-, diabetes duration- and eGFR-matched controls, selected from a pool of participants in the highest quintiles of carbohydrate intakes (>253 g/day or >48 E%). This matching was done to ensure that the two populations would be as similar as possible, so that potential differences in these variables would not obscure the observations.

2.3. Statistical analyses

All analyses were conducted using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp, Armonk, NY, USA), and alpha value was set to 5% (two-tailed test). Means ± standard deviations, medians (interquartile ranges), and frequencies (%) were used to describe the study sample in normally distributed, non-normally distributed, and categorical observations, respectively. The between-group comparisons, in these respective variables, were conducted with independent samples t-test, Mann-Whitney U test, and Chi-squared test. Multivariable generalized linear regression analysis was applied when investigating the association between

carbohydrate intake (either the carbohydrate-to-fat ratio or the low-carbohydrate status) and the cardio-metabolic risk factors. Models were adjusted for a number of background variables (sex, diabetes duration, eGFR, insulin dose, physical activity, BMI), medication related to the given outcome, and a number of dietary variables (energy, alcohol, fibre) considered important for the outcomes of interest. Data from men and women were analysed together, except in case of variables with known sex differences (e.g. waist-to-hip ratio and cholesterol).

3. Results

Data were available from 902 individuals (44% men; mean ± standard deviation age 47 ± 13 years) (Table 1). The median BMI of the sample was 25.2 kg/m^2 and HbA$_{1c}$ 63 mmol/mol (7.9%). Mean (min, max) daily carbohydrate intakes of the whole sample were 205 g (65 g, 482 g) and 42 E% (17 E%, 60 E

Table 1 – Basic characteristics and cardio-metabolic risk factors of the total study sample.

	n 902
CHO-to-fat ratio	1.17 (0.95–1.46)
Men (%)	44.1
Age (years)	47 ± 14
Diabetes duration (years)	28 (18–39)
Insulin dose (IU/kg)	0.55 (0.42–0.70)
Retinopathy (%)	28.4
eGFR (ml/min/1.73 m^2)	101 (89–112)
Hard CV event (%)	11.2
BMI (kg/m^2)	25.2 (23.0–27.8)
HbA$_{1c}$ (mmol/mol)	63 (55–71)
HbA$_{1c}$ (%)	7.9 (7.2–8.6)
SMBG mean	8.0 (6.8–9.3)
SMBG CV	0.42 (0.34–0.49)
SBP (mmHg)	135 (124–149)
DBP (mmHg)	76 (70–83)
hsCRP (mg/l)	1.1 (0.5–2.3)
Triglycerides (mmol/l)	0.91 (0.71–1.24)
Men	n 398
WHR	0.93 (0.89–0.98)
BAI	23.5 (21.7–25.9)
Total CHOL (mmol/l)	4.40 (3.93–5.00)
Non-HDL CHOL (mmol/l)	2.90 (2.43–3.45)
HDL-CHOL (mmol/l)	1.49 (1.24–1.77)
HDL3-CHOL (mmol/l)	0.76 (0.61–0.91)
Women	n 504
WHR	0.83 (0.79–0.87)
BAI	28.6 (25.7–32.1)
Total CHOL (mmol/l)	4.63 (4.11–5.15)
Non-HDL CHOL (mmol/l)	2.87 (2.40–3.33)
HDL-CHOL (mmol/l)	1.72 (1.44–2.03)
HDL3-CHOL (mmol/l)	0.75 (0.63–0.93)

Data are presented as median (interquartile range), frequency, or mean ± standard deviation. CHO-to-fat ratio, calculated from percentages of energy derived from carbohydrates and fats; eGFR, estimated glomerular filtration rate; Hard CV event, hard cardiovascular event; SMBG, self-monitored blood glucose; CV, coefficient of variation; SBP, systolic blood pressure; DBP, diastolic blood pressure; hsCRP, high-sensitivity C-reactive protein; WHR, waist-to-hip ratio; BAI, body adiposity index; CHOL, cholesterol.

%). Mean (min, max) daily fat intakes of the total population were 79 g (28 g, 208 g) and 36 E% (20 E%, 61 E%).

3.1. Carbohydrate-to fat ratio

Based on the percentages of energy derived from carbohydrates and fats, there was a median (interquartile range) carbohydrate-to-fat ratio of 1.17 (0.95–1.46). In the multivariable analyses, higher carbohydrate-to-fat ratio was associated with higher variability of the SMBG, and higher systolic and diastolic blood pressure (Table 2). In men and women, higher carbohydrate-to-fat ratio was associated with lower HDL3-cholesterol concentration. In men, higher carbohydrate-to-fat ratio was additionally associated with a lower waist-to-hip ratio, while in women it was associated with lower total and HDL-cholesterol concentration. Dietary carbohydrate-to-fat ratio was not associated with BMI, body adiposity index, glycaemic control, or the concentrations of hsCRP, triglycerides, and non-HDL cholesterol.

3.2. Low-carbohydrate intake vs. higher carbohydrate intake

Low-carbohydrate diet (<130 g/day or <26 E%) was endorsed by 69 (7.6%) individuals. In all, 69 sex-, diabetes duration-, and eGFR-matched controls with higher carbohydrate intake were identified for the 69 individuals with low-carbohydrate diet (Table 3). These two groups were comparable with respect to age and complication status. Men with low carbohydrate intakes had higher WHR, total cholesterol concentration, non-HDL cholesterol concentration, and HDL3-cholesterol concentration compared to men with higher carbohydrate intakes. Women with lower carbohydrate intakes had lower BAI, and higher total, HDL-, and HDL3-cholesterol concentrations.

Those in the low-carbohydrate group reported lower total energy and fibre intake, but higher alcohol intake (Supplementary Table 1). Instead, protein intake per body weight was comparable between the two groups. In the multivariable analyses, individuals with lower carbohydrate intakes had lower BMI, lower variability of the SMBG values, and lower diastolic blood pressure (Table 4). Men in the low-carbohydrate group had higher total and non-HDL cholesterol concentrations, while women had lower BAI and higher HDL-cholesterol concentration.

4. Discussion

Adherence to a low-carbohydrate diet was not common, in the current sample. Only 7.6% of the total population was considered low-carbohydrate adherents, with carbohydrate intakes below either 130 g/day or 26 E% [17]. Compared to sex-, diabetes duration-, and eGFR-matched individuals with higher carbohydrate intakes, those with low carbohydrate intake had significantly lower BMI, had lower variability of the SMBG values, and had lower diastolic blood pressure. In

Table 2 – The multivariable association between carbohydrate-to-fat ratio and cardio-metabolic risk factors.			
	B	95% Wald Confidence Interval	P
Men and women			
Body mass index	−0.111	−0.867–0.645	0.774
HbA$_{1c}$	0.845	−1.623–3.313	0.502
SMBG mean	0.013	−0.345–0.370	0.945
SMBG CV	0.041	0.016–0.065	0.001
Systolic blood pressure	4.334	1.188–7.480	0.007
Diastolic blood pressure	2.471	0.725–4.217	0.006
hsCRP	−0.110	−0.450–0.231	0.528
Triglycerides	−0.052	−0.166–0.061	0.368
Men			
Waist-to-hip ratio	−0.024	−0.046 to −0.002	0.029
Body adiposity index	0.542	−0.358–1.442	0.238
Total cholesterol	−0.168	−0.418–0.081	0.186
Non-HDL cholesterol	−0.072	−0.313–0.169	0.558
HDL-cholesterol	−0.082	−0.196–0.032	0.158
HDL3-cholesterol	−0.067	−0.126 to −0.009	0.023
Women			
Waist-to-hip ratio	−0.007	−0.023–0.010	0.416
Body adiposity index	0.538	−0.746–1.822	0.412
Total cholesterol	−0.255	−0.476 to −0.034	0.024
Non-HDL cholesterol	−0.089	−0.290–0.112	0.386
HDL-cholesterol	−0.144	−0.262 to −0.027	0.016
HDL3-cholesterol	−0.121	−0.181 to −0.060	<0.001

SMBG, self-monitored blood glucose concentration; CV, coefficient of variation, hsCRP, high-sensitivity C-reactive protein. All models are adjusted for sex, diabetes duration, eGFR, insulin dose, total energy intake, fibre intake, alcohol intake, and physical activity. HbA$_{1c}$, SMBG mean, SMBG CV, SBP, DBP, hsCRP, and triglyceride analyses are additionally adjusted for BMI. Moreover, lipid and hsCRP analyses are additionally adjusted for lipid lowering medication, and blood pressure analyses are additionally adjusted for antihypertensive medication. Generalized linear regression.

	Low-CHO diet n 69	High-CHO diet n 69	P
Table 3 – Basic characteristics and cardio-metabolic risk factors of the study sample divided by the carbohydrate intake status.			
CHO-to-fat ratio	0.75 (0.60–0.91)	1.59 (1.48–1.87)	<0.001
Men (%)	31.9	31.9	1.000
Age (years)	51 ± 11	49 ± 14	0.262
Diabetes duration (years)	35 ± 14	32 ± 14	0.325
Insulin dose (IU/kg)	0.52 (0.42–0.67)	0.56 (0.40–0.71)	0.472
Retinopathy (%)	41.2	32.4	0.374
eGFR (ml/min/1.73 m^2)	92 ± 17	96 ± 15	0.163
Hard CV event (%)	10.1	17.6	0.226
BMI (kg/m^2)	25.0 (23.4–27.9)	25.6 (23.6–29.6)	0.311
HbA$_{1c}$ (mmol/mol)	60 (53–72)	65 (55–72)	0.208
HbA$_{1c}$ (%)	7.6 (7.0–8.7)	8.1 (7.2–8.7)	0.208
SMBG mean (mmol/l)	8.2 (6.8–9.8)	7.7 (6.8–9.5)	0.681
SMBG CV (mmol/l)	0.39 ± 0.13	0.42 ± 0.12	0.138
SBP (mmHg)	139 (127–151)	139 (129–150)	0.696
DBP (mmHg)	75 ± 9	78 ± 9	0.101
hsCRP (mg/l)	1.1 (0.5–2.3)	1.2 (0.5–2.6)	0.939
TG (mmol/l)	0.95 (0.69–1.25)	0.97 (0.68–1.30)	0.995
Men	n 22	n 22	
WHR	0.96 ± 0.07	0.92 ± 0.06	0.040
BAI	25.0 ± 4.8	24.1 ± 2.9	0.463
Total CHOL (mmol/l)	4.79 (3.99–5.27)	4.27 (3.76–4.64)	0.010
Non-HDL CHOL (mmol/l)	3.28 ± 0.89	2.79 ± 0.44	0.033
HDL-CHOL (mmol/l)	1.71 ± 0.57	1.48 ± 0.50	0.163
HDL3-CHOL (mmol/l)	0.91 ± 0.26	0.72 ± 0.23	0.022
Women	n 46	n 46	
WHR	0.85 ± 0.06	0.85 ± 0.07	0.962
BAI	29.3 ± 4.5	32.3 ± 5.4	0.004
Total CHOL (mmol/l)	4.89 (4.49–5.51)	4.46 (3.84–4.88)	0.002
Non-HDL CHOL (mmol/l)	3.08 ± 0.91	2.89 ± 0.68	0.277
HDL-CHOL (mmol/l)	1.96 ± 0.56	1.55 ± 0.36	<0.001
HDL3-CHOL (mmol/l)	0.86 ± 0.23	0.73 ± 0.23	0.009

Data are presented as median (interquartile range), frequency, or mean ± standard deviation. Low-CHO diet, low-carbohydrate diet, <130 g/day or <26 E%; High-CHO diet, higher carbohydrate diet, sex-, diabetes duration- and eGFR-matched controls identified from a pool of participants in the highest quintile of carbohydrate intake (>253 g/day or > 48 E%); CHO-to-fat ratio, calculated from percentages of energy derived from carbohydrates and fats; eGFR, estimated glomerular filtration rate; Hard CV event, hard cardiovascular event; SMBG, self-monitored blood glucose concentration; CV, coefficient of variation; SBP, systolic blood pressure; DBP, diastolic blood pressure; hsCRP, high-sensitivity C-reactive protein; TG, triglycerides; WHR, waist-to-hip ratio; BAI, body adiposity index; CHOL, cholesterol.

women with lower carbohydrate intakes, lower BAI and higher HDL-cholesterol concentrations were observed, while in men low-carbohydrate diet was associated with higher total and non-HDL cholesterol levels. In the whole population, we investigated the association between dietary carbohydrate-to-fat ratio and cardio-metabolic risk factors. In these analyses, higher carbohydrate intake in relation to fat was associated with higher blood glucose variability and higher systolic and diastolic blood pressure, and lower HDL3-cholesterol concentrations. Furthermore, in men, higher carbohydrate-to-fat ratio was associated with lower waist-to-hip ratio, and in women it was associated with lower total and HDL-cholesterol concentrations.

The association between adherence to a low-carbohydrate diet and glycaemic control, in type 1 diabetes, has been reported in a number of previous papers. In an online survey including 316 children and adults with type 1 diabetes, who voluntarily adhered to a low-carbohydrate diet, an average HbA$_{1c}$ of 39 mmol/mol (5.7%) was reported [14]. This excep-

tional glycaemic control was achieved with an average daily carbohydrate intake of 36 ± 15 g, without an increase in the frequency of hypoglycaemias. In another observational study, the mean HbA$_{1c}$ of 11 adults with type 1 diabetes, following a diet with <55 g of carbohydrates per day, was 35 mmol/mol (5.4%) [21]. Nielsen et al described their observations from a total of 48 individuals with type 1 diabetes who took part in an educational course to reduce daily carbohydrate intake to ≤75 g per day [26]. Three months after the start of the course, a significant reduction in HbA$_{1c}$ was reported. Moreover, unlike in those not adherent, a significant improvement in glycaemic control was evident among the continuously adherent participants also four years after the course. Randomized trials with low-carbohydrate diets in type 1 diabetes are scarce. In one small study, 10 subjects with type 1 diabetes were randomly assigned either to a standard carbohydrate counting course or to the same course with additional instructions to achieve and maintain a diet with a daily carbohydrate intake of 50–75 g [27]. At the end of the 12-week

Table 4 – The multivariable analyses investigating the association between carbohydrate intake status and cardio-metabolic risk factors.

	Low-CHO diet n 69		High-CHO diet n 69		
	Mean	95% CI	Mean	95% CI	P
Men and women					
BMI (kg/m^2)	25.6	24.1–26.8	27.8	26.5–29.1	0.030
HbA$_{1c}$ (mmol/mol)	61.4	58.0–64.8	64.6	60.8–68.3	0.278
SMBG mean (mmol/l)	8.3	7.7–8.8	8.3	7.7–8.9	0.902
SMBG CV (mmol/l)	0.38	0.34–0.42	0.45	0.41–0.49	0.030
SBP (mmHg)	136	132–141	142	137–147	0.188
DBP (mmHg)	74	72–77	79	76–81	0.048
hsCRP (mg/l)	1.9	1.4–2.5	1.9	1.3–2.5	0.962
Triglycerides (mmol/l)	1.18	1.02–1.34	1.03	0.85–1.20	0.277
Men					
WHR	0.95	0.93–0.98	0.95	0.92–0.99	0.969
BAI	25.3	23.5–27.2	24.9	22.4–27.4	0.813
Total CHOL (mmol/l)	5.08	4.68–5.48	4.00	3.46–4.55	0.007
Non-HDL CHOL (mmol/l)	3.42	3.12–3.72	2.71	2.26–3.15	0.021
HDL-CHOL (mmol/l)	1.67	1.46–1.88	1.58	1.29–1.86	0.658
HDL3-CHOL (mmol/l)	0.89	0.80–0.98	0.82	0.69–0.96	0.500
Women					
WHR	0.85	0.82–0.87	0.86	0.83–0.88	0.692
BAI	29.0	27.1–31.0	33.1	31.1–35.2	0.014
Total CHOL (mmol/l)	4.90	4.57–5.23	4.52	4.20–4.84	0.162
Non-HDL CHOL (mmol/l)	3.00	2.74–3.25	3.03	2.77–3.28	0.884
HDL-CHOL (mmol/l)	1.91	1.73–2.10	1.54	1.36–1.73	0.014
HDL3-CHOL (mmol/l)	0.85	0.76–0.94	0.76	0.67–0.85	0.199

Data are presented as adjusted means and standard errors. Low-CHO diet, low-carbohydrate diet, <130 g/day or <26 E%; High-CHO diet, higher carbohydrate diet, sex-, diabetes duration- and eGFR-matched controls identified from a pool of participants in the highest quintile of carbohydrate intake (>253 g/day or >48 E%); SMBG, self-monitored blood glucose concentration; CV, coefficient of variation; SBP, systolic blood pressure; DBP, diastolic blood pressure; hsCRP, high-sensitivity C-reactive protein; WHR, waist-to-hip ratio; BAI, body adiposity index; CHOL, cholesterol. All models are adjusted for sex, diabetes duration, eGFR, insulin dose, total energy intake, fibre intake, alcohol intake, and physical activity. HbA$_{1c}$, SMBG mean, SMBG CV, SBP, DBP, hsCRP, and triglyceride analyses are additionally adjusted for BMI. Moreover, lipid and hsCRP analyses are additionally adjusted for lipid lowering medication, and blood pressure analyses are additionally adjusted for antihypertensive medication. Generalized linear regression.

intervention HbA$_{1c}$, in the carbohydrate restriction group, was significantly reduced from a mean of 63 to 55 mmol/mol (7.9 to 7.2%), with no change in the control group. Albeit weight loss was not promoted, in that study, a 6.3% and 0.5% weight reduction was observed in the intervention and control group, respectively. In the current study, we also looked at the relation between carbohydrate intake and a number of variables related to body weight. Here we noticed that individuals with higher carbohydrate intakes had higher BMI, and women with high carbohydrate intakes had higher BAI compared to those adhering to a lower carbohydrate diet. Contrary to these observations, higher carbohydrate intake in relation to fat was in men associated with lower waist-to-hip ratio. As carbohydrate restriction is sometimes used as a weight-loss method [28], our cross-sectional observations could indicate that carbohydrate restriction is more prevalent among men with a desire to lose weight.

Intensified insulin therapy, in the Diabetes Control and Complications Trial, resulted in improved glycaemic control, but was only accomplished by simultaneous increase in the risk of hypoglycaemia [13]. It has been suggested that improving glycaemic control without increasing the risk of hypoglycaemia may only be achieved by reducing glycaemic variability [29]. Of interest, adhering to a low-carbohydrate diet

and diets with lower carbohydrate-to-fat ratio, in the current study, were associated with reduced variability in the blood glucose measurements. This could be of clinical importance as large blood glucose variability has been suggested to play a key role in the pathology of end-organ damage in diabetes [30]. Reduced glycaemic variability has also been reported in other studies of low-carbohydrate diets [15,16,21]. In addition to improved glycaemia and reduced glycaemic variability, low-carbohydrate diets have been associated with longer time spent in euglycaemia, and less time in hypoglycaemia [15].

Besides their effects on glycaemia, low-carbohydrate diets have also been associated with improved HDL-cholesterol levels [14,25,28,31], lower triglyceride concentrations [14,25,28,31], and reduced blood pressure [31]. The current observations with lower blood pressure and higher HDL-cholesterol concentration, associated with diets lower in carbohydrates in relation to fats, are in line with these reports. However, these beneficial effects are sometimes opposed by observations of increased total and/or LDL-cholesterol concentrations [14,21,31], which have raised concern of long-term safety of low-carbohydrate diets [21]. In the current study, higher total cholesterol and non-HDL cholesterol concentrations were observed in 22 men in the low-carbohydrate arm. Instead, in women, higher

carbohydrate-to-fat ratio was associated with lower total cholesterol levels. However, this association seemed to be explained by lower HDL-cholesterol concentrations, instead of lower non-HDL cholesterol concentrations. In previous studies, high fat intake has shown to give rise to the larger-sized LDL-cholesterol particles, which are sometimes considered less atherogenic than the smaller and denser particles [32,33]. Larger LDL-cholesterol particles can, however, also be associated with increased coronary disease risk, particularly in the setting of normal or low triglyceride levels [32]. Longitudinal trials are, therefore, needed to assess the cardio-metabolic effects of low-carbohydrate diets.

Considering the low number and the small size of the published studies in this field, a large sample of well-defined individuals with type 1 diabetes is a major strength of the current study. However, there are also important limitations to be acknowledged. The study is cross-sectional, and can therefore only reveal associations between dietary intake and health variables. Despite considering a number of confounders in the analyses, residual confounding from variables not accounted for may remain. As participants were volunteers, some selection bias may also be evident. It is likely that individuals more interested in health and diet are over-represented in the current sample. Due to the changes in cardiovascular risk factors and dietary intake related to emerging diabetic kidney disease, we excluded those with eGFR < 60 ml/min/1.73 m^2. Therefore, the current observations may only be generalized to individuals with type 1 diabetes and fairly well preserved renal function. The assessment of dietary intake with a self-reported record has its limitations, such as over- and under-reporting of food items generally considered healthy and unhealthy, respectively. Whether such misreporting would have affected the macronutrient proportions of the diets, is not known. While, with a 417 g (or 43 E%) range, we were able to capture great diversity in the carbohydrate intake, the current results may only be applied within the observed range, and not in higher or lower carbohydrate intakes. With the methods applied, we were not able to distinguish between low and high glycaemic index carbohydrates. Due to this shortcoming, the results only reflect the total carbohydrate intake. It should also be noted that using the grams/day criteria (<130 g/day) for a low-carbohydrate diet, identifies not only those attempting to adhere to a low-carbohydrate diet, but also any light eaters. Women, for example, on average eat less than men. Moreover, with longer diabetes duration, emergence of various health concerns can affect dietary intake. By taking sex, diabetes duration and eGFR into account, we ensured that the two groups were comparable with regards to these basic characteristics. Finally, while the number of low-carbohydrate adherents was modest, in the current study, by using the carbohydrate-to-fat ratio we were able to include the whole population in the analyses, and to see whether the relative distribution of the two macronutrients played any role in the health markers.

In conclusion, lower carbohydrate intake and lower dietary carbohydrate-to-fat ratio were associated with a number of beneficial metabolic observations, such as lower variability in the blood glucose concentrations, lower blood pressure, and higher HDL-cholesterol concentration. However, in men

adherence to low-carbohydrate diet was associated with higher total and non-HDL cholesterol concentrations, and higher waist-to-hip ratio. Large randomized controlled trials are needed to reveal the long-term risks and benefits of low-carbohydrate diets in type 1 diabetes.

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Authorship

All authors took part in designing the study. A.J.A. analysed the data, and wrote the first draft of the paper. A.J.A. and P.-H.G. had the primary responsibility for the final content. All authors have contributed to the writing and approved the final manuscript.

Declaration of Competing Interest

Professor Per-Henrik Groop has received grants from Eli Lilly and Roche, is an advisory board member for AbbVie, Astellas, Astra Zeneca, Boehringer-Ingelheim, Cebix, Eli Lilly, Janssen, MSD, Medscape, Mundipharma, Novartis, Novo Nordisk, and Sanofi. He has received lecture honoraria from Astellas, Astra Zeneca, Boehringer-Ingelheim, Eli Lilly, Elo Water, Genzyme, MSD, Mundipharma, Novartis, Novo Nordisk, PeerVoice, and Sanofi. All other authors declare no conflicts of interest.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.107818.

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