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Cross-sectional association between the isocaloric replacement of carbohydrates with protein and fat in relation to fat compartments distribution and hepatic lipid content in recent-onset type 1 and type 2 diabetes

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Abstract

Background Diets restricted in carbohydrates may be beneficial for diabetes management. However, without reducing energy intake, carbohydrate restriction results in increased protein and fat intake. Understanding how this macronutrient substitution is associated with adipose tissue distribution is important to prevent diabetes progression. Therefore, the aim was to investigate the isocaloric substitution of carbohydrates with fat and protein in relation to subcutaneous (SAT) and visceral adipose tissue (VAT) and hepatic lipid (HL) content in individuals with recent-onset type 1 (T1D) and type 2 diabetes (T2D), accounting for macronutrient quality.

Methods This cross-sectional analysis includes participants with T1D ($n=137$) and T2D ($n=170$) from the German Diabetes Study (GDS). Dietary macronutrient intake was derived from dietary information assessed with a validated food frequency questionnaire. SAT and VAT were measured with magnetic resonance (MR) imaging, while HL content with ^{1}H MR spectroscopy. Isocaloric substitution analyses based on multivariable linear regression models were conducted to examine the replacement of total and higher glycemic index (GI) carbohydrates in energy percent (En%) with total fat, monounsaturated (MUFA), polyunsaturated (PUFA), and saturated fatty acids (SFA), and protein in regard to SAT, VAT and HL content.

Results In individuals with T1D, substituting carbohydrates with total fat was not associated with SAT, while substituting carbohydrates with protein demonstrated higher SAT [β (95% CI) per 5 En%: 3100 cm^3 (25, 6200)]. In individuals with T2D, replacing carbohydrates with total fat or protein showed no association with SAT and VAT. However, substituting carbohydrates with PUFA was associated with lower VAT [-970 cm^3 (-1900, -40)] and HL content [-3.3%

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(-6.9, 0.4)], while replacing carbohydrates with SFA was associated with higher HL content [2.4% (-0.6, 5.4)]. Substituting carbohydrates with protein was associated with lower HL content in individuals with T2D [-2.4% (-4.9, 0.0)], mainly driven by plant-based protein. There were no substantial differences between the replacement of total and higher GI carbohydrates.

Conclusions The quality of substituted nutrients may play an important role for adipose tissue and HL accumulation in individuals with T2D. Particularly, integrating PUFAs and plant-based proteins into the diet seems beneficial for VAT and HL content.

Keywords Isocaloric substitution, Food frequency questionnaire, Carbohydrates, Fat, Protein, Glycemic index, Subcutaneous fat, Visceral fat, Hepatic lipid content, Diabetes

Introduction

In the last years a growing number of studies has investigated the associations of macronutrient intake in regard to diabetes management and progression. There is a large body of evidence that diets restricted in carbohydrates are effective for body weight reduction and improvement of glycemic and blood lipid markers in individuals with type 2 diabetes (T2D) [1]. In addition, the importance of carbohydrate quality in the prevention of T2D, as well as in type 1 diabetes (T1D) and T2D management is becoming more widely acknowledged [2, 3]. The most common method to evaluate carbohydrate quality is using the glycemic index (GI), which is a measure that ranks carbohydrates in foods based on their postprandial glycemic response after consumption compared to the same amount of reference carbohydrate (e.g., glucose solution or white wheat bread) [4]. Previous studies showed that diets high in GI were associated with a higher risk of T2D and cardiovascular diseases (CVD) [5]. Moreover, there is evidence that low-GI diets can improve glycemic control, blood lipids and body weight in individuals with diabetes [1, 6]. As a consequence, current guidelines recommend the adherence to low GI diets for individuals with T2D [7, 8].

However, when the intake of carbohydrates in the diet is reduced while keeping the overall energy intake constant, the intake of fat and protein intake increases, which might also have an impact on human health. For example, while total fat intake was not associated with risk of T2D and CVD [9–11], a higher intake of polyunsaturated fatty acids (PUFA), and particularly omega-3 (n-3) PUFA, was related to lower risk of CVD [12]. In contrast, there was no association between the intakes of monounsaturated (MUFA) and saturated fatty acids (SFA) and the incidence of T2D and CVD [9–11]. However, there is an indication that the intake of plant-based MUFA might be superior to animal-based MUFA [13], and certain SFA, namely odd-chain and very-long chain SFA, were associated with a lower risk of T2D, CVD, and mortality in the general population [14–16]. In regard to protein intake, previous findings suggested that plant-based rather than animal-based protein was beneficially associated with cardiometabolic health in the general population [17], and a substitution of carbohydrates with plant-based protein was linked to lower mortality in individuals with T2D [18].

Recently, findings of a substitution analysis conducted in a population free of diabetes indicated that the replacement of foods with higher GI carbohydrates (e.g., fried potatoes, sugar sweetened beverages, starchy vegetables) by foods with lower GI (e.g., whole grains, fruit and non-starchy vegetables) was associated with weight loss, and thus, may play a crucial role in long term weight management [19]. Moreover, substituting carbohydrates with total and animal-based protein was linked to an increase in body weight in individuals with T2D, whereas no weight change was observed for plant-based protein [20]. However, it is important also to consider body fat distribution, as higher accumulations of subcutaneous (SAT) and visceral adipose tissue (VAT) and hepatic lipid (HL) content are risk factors for insulin resistance and comorbidities, such as CVD [21]. This is particularly important in the context of diabetes progression, given that majority of individuals with T2D are overweight or obese, and the prevalence of overweight also increases in T1D [22, 23]. In this context, findings of a previous substitution analysis in the general population indicated that the isocaloric replacement of carbohydrates with fat was related to a higher accumulation of VAT and HL [24].

However, studies that investigated intake of nutrients and its influence on adipose tissue distribution in persons with diabetes are scarce. No study has yet investigated the isocaloric substitution of carbohydrates with fat and protein and specific subtypes in relation to accumulation of adipose tissue and HL content in a diabetes population. Thus, the aims of this study were to investigate 1) the associations between macronutrient intake and SAT, VAT and HL content and 2) the isocaloric substitutions of carbohydrates with fat and protein (accounting for the macronutrient quality) in association with SAT, VAT and HL content in individuals with recent-onset T1D and T2D.

Methods

Study design and study population

In this study, we used data from the German Diabetes Study (GDS), which is an ongoing prospective observational study including participants aged 18 to 69 years with a diagnosis of T1D or T2D within the last year according to the criteria of the American Diabetes Association (ADA) [25]. The study is performed according to the Declaration of Helsinki, was approved by the ethics board of the University of Düsseldorf (ref. 4508) and registered at Clinicaltrials.gov (NCT01055093). All participants provided their written informed consent and underwent a comprehensive examination at baseline. The study design, cohort profile as well as inclusion and exclusion criteria of the GDS have been previously described in detail [26].

We conducted a cross-sectional analysis, including participants enrolled in the study center in Düsseldorf with available baseline data on dietary intake between August 2012 and July 2023 with data on magnetic resonance imaging (MRI) and proton magnetic resonance spectroscopy (^{1}H-MRS) examinations ($n = 530$). Participants with missing data on outcomes ($n = 186$) and covariates ($n = 25$), as well as with implausible daily total energy intake (< 800 or > 4000 kcal for men, < 500 or > 3500 kcal for women) ($n = 12$) were excluded [27], resulting in a final study population of 137 participants with T1D and 170 participants with T2D (Supplementary Fig. 1). The study is reported according to the STROBE-nut guideline [28].

Data collection

Dietary assessment

Data on dietary intake were obtained from a validated semiquantitative food frequency questionnaire (FFQ) [29]. With the FFQ, information about the participants' habitual food consumption frequencies was collected for 148 food items within the last year. Consequently, for each participant the daily nutrient intake in grams was calculated according to the German Food Code and Nutrient Data Base based on the reported frequencies in combination with assigned portion sizes for each food item [29, 30]. In order to take the quality of carbohydrates into account, information from an extended validated questionnaire was used to calculate the GI and differentiate between higher (GI > 55) and low GI (GI ≤ 55) carbohydrates [31, 32].

In this study, we focused on carbohydrates (total, higher GI, low GI), total fat, MUFA (total, animal- and plant-based), PUFA (total, n-3 and n-6 PUFA), SFA (total, even-chain, odd-chain and very-long-chain SFA), and protein (total, animal- and plant-based). A detailed description of carbohydrate, MUFA, PUFA, SFA and protein subtypes is listed in Supplementary Table 1.

Outcome assessment

In this study, SAT, VAT and HL content were investigated as outcome measures. Participants underwent an examination, using a clinical 3-T magnetic resonance scanner (Achieva dStream, X-Series, Philips Healthcare, Best, The Netherlands) after overnight fasting. SAT and VAT volumes [cm^3] were quantified using a whole-body MRI, by employing T1-weighted axial fast spin-echo and post-processed by a trained operator using SliceOmatic® v5.0 software (Tomovision, Montreal, Canada) [33]. HL content was quantified via ^{1}H-MRS by using single voxel stimulated echo acquisition mode as previously described [33].

Covariate assessment

Information on age, sex, smoking status and type of diabetes treatment were collected during a face-to-face interview [26]. Anthropometric measures including body weight and height were assessed by qualified personnel using calibrated instruments, such as a weighing scale (SECA 285; SECA, Hamburg, Germany) and stadiometer [26]. The body mass index (BMI) was then calculated as the quotient of body weight and height in square. Physical activity within the past 12 months was assessed via the validated Baecke questionnaire [34, 35]. With this data, we generated a physical activity index including the domains"physical exercise in leisure"and"leisure and locomotion activities", resulting in a continuous score between 0 (lowest) and 10 (highest) points [36]. For socioeconomic status (SES), we used a composite index that comprised the domains education level, occupational status and household income and ranged between 3 and 21 points (higher values indicate higher SES) [37]. Information on alcohol intake and total energy intake were obtained from the FFQ [29].

Statistical analysis

Continuous variables were described as mean and standard deviation (for normally distributed variables) or as median and interquartile range (for skewed variables). Categorical variables were described as numbers with percentages.

Associations between macronutrient intake and SAT, VAT and HL content were investigated using multivariable linear regression models to determine β-coefficients with 95% confidence intervals (95% CI). In addition, non-linear dose–response curves were modeled for these associations using restricted cubic splines with three knots (10 th, 50 th, and 90 th percentiles). The substitution analyses based on

multivariable linear regression models were conducted to investigate the isocaloric replacement of macronutrients associated with SAT, VAT and HL content. In order to perform the substitution analyses in an isocaloric setting, daily nutrient intake was transformed as energy percent [En%]. For this, mean energy values of 9 kcal/g were assumed for fat and subgroups of fat, as well as 4 kcal/g for protein, carbohydrates and their subgroups, respectively. In detail, we examined following substitution models: First, the replacement of carbohydrates with total fat, MUFA, PUFA, SFA and protein (all per 5 En%); and second, in more detail, the replacement of higher GI carbohydrates with low GI carbohydrates, animal-based and plant-based MUFA, n-3 and n-6 PUFA, even-chain SFA, animal-based and plant-based protein (all per 1 En%), as well as odd-chain and very-long-chain SFA (both per 0.1 En%) (Supplementary Fig. 2) [20, 24, 38].

Substitution analyses were performed according to the methods suggested for nutritional epidemiology applying the partition model approach conducted in one linear regression model [39, 40]. Using this method, the model includes both the substituting variable (e.g., +5 En% of protein) and the substituted variable (e.g., −5 En% of carbohydrates), but also the remaining nutrient (in this case: total fat), which is kept on a constant level. Subsequently, the hypothetical "substitution effect" results in the subtraction of the β-coefficient of the substituting variable minus the β-coefficient of the substituted variable. Thus, the difference in the β-coefficients can be interpreted as the outcome measure of a 5 En% increase in protein at the expense of carbohydrates.

All analyses were adjusted for following covariates that were selected a priori based on the literature: age [years] and sex [male/female], smoking status [current non-smoking/smoking], physical activity [continuous], SES [continuous], energy intake [kcal/d, continuous], and alcohol intake [g/day, continuous] (model 1). Only analyses including individuals with T2D were further adjusted for diabetes treatment [no pharmacological treatment/non-insulin pharmacological treatment/insulin treatment], since most of the individuals with T1D (~ 89%) were treated with insulin. In the substitution analyses, the models also included mutual adjustment for complementary nutrient intake [En%]. In sensitivity analysis, we additionally adjusted for BMI [kg/m^2] to control for the impact of body weight status for these associations (model 2).

All analyses were performed in SAS® version 9.4 (SAS Institute, Cary, NC, USA) and forest plots were conducted in Stata 14.1.

Results

The characteristics of the included study participants are shown in Table 1. Compared to individuals with T1D, individuals with T2D were older (52 vs. 37 years), had a higher BMI (31 vs. 25 kg/m^2), consumed less alcohol (3.4 vs. 7.8 g/day) and were more likely on non-insulin treatment (61 vs. 6%) instead of insulin (9 vs. 88%). Participants with T2D tended to have a lower total energy intake than participants with T1D (2130 vs. 2330 kcal/day), whereas the distribution of macronutrients was similar between both diabetes types. Both individuals with T1D and T2D reported a low-moderate intake of carbohydrates (T1D: 37 En%, T2D: 36 En%) and a high intake of total fat (T1D: 45 En%, T2D: 46 En%). Protein intake was 15 En% (T1D) and 16 En% (T2D), respectively. Moreover, compared to persons with T1D, persons with T2D had higher SAT (23,400 vs. 16,300 cm^3) and VAT volumes (3900 vs. 1100 cm^3) as well as HL content (6.2 vs. 0.3%).

Association between macronutrient intake and SAT, VAT and HL content

In both individuals with T1D and T2D, no distinct associations were observed between intake of carbohydrates and SAT, VAT and HL content (Supplementary Table 2). The non-linear dose–response curve indicated a positive association with HL content in T2D, with highest values at 30–40 En% of carbohydrates (Supplementary Fig. 3), mainly driven by higher GI carbohydrates [β (95% CI) per 1 En%: 0.2% (0.0, 0.4)] (Supplementary Table 2).

Total fat intake was not associated with SAT, VAT or HL content in individuals with T1D (Supplementary Table 2, Supplementary Fig. 4). However, in a more detailed analysis, a higher intake of animal-based MUFA was linked to higher SAT volume [per 1 En%: 750 cm^3 (200, 1300)] (Supplementary Table 2). In individuals with T2D, there was no distinct association between total fat intake and SAT and VAT; however, we found a positive non-linear association between total fat intake and HL content, with the highest levels at 40–50 En% (Supplementary Fig. 4). Higher intakes of PUFA and very-long-chain SFA were associated with lower SAT and VAT volumes, but imprecisely estimated expressed as wide 95% CIs (Supplementary Table 2). Furthermore, findings showed lower HL content for a higher intake of plant-based MUFA [per 1 En%: −0.6 (−1.1, −0.1)], PUFA [per 5 En%: −3.2% (−6.0, −0.5)], both n-3 and n-6 PUFA, and very-long-chain SFA [per 0.1 En%: −2.1 (−4.3, 0.0)], respectively. Conversely, higher intakes of SFA [per 5 En%: 2.8% (0.6, 4.9)], as well as even-chain [per 1 En%: 0.7% (0.2, 1.3)] and odd-chain SFA [per 0.1 En%: 1.4% (0.2, 2.6)] were associated with higher HL content.

Table 1 Characteristics of GDS study participants with recent-onset type 1 and type 2 diabetes

	Type 1 Diabetes ($n = 137$)	Type 2 Diabetes ($n = 170$)
Age [years]	37.1 ± 11.4	52.2 ± 8.6
Sex [female/male]	41%/59%	37%/63%
BMI [kg/m^2]	25.2 ± 4.2	31.2 ± 5.8
< 25 kg/m^2	57%	14%
25–30 kg/m^2	30%	27%
≥ 30 kg/m^2	13%	59%
Socioeconomic status	14.0 ± 2.6	14.4 ± 2.7
Lower class	6%	2%
Middle class	53%	55%
Upper class	41%	43%
Smoking status		
Current	26%	25%
Former	29%	35%
Never	45%	40%
Physical activity score	6.2 ± 1.6	5.7 ± 1.2
Alcohol intake [g/day]	7.8 (1.8, 17.2)	3.4 (0.6, 11.4)
Diabetes medication		
No medication	6%	30%
Non-insulin medication	6%	61%
Insulin medication	88%	9%
Total energy [kcal/day]	2330 ± 700	2130 ± 660
Carbohydrate intake [En%]	36.7 ± 7.3	36.3 ± 6.8
Higher GI carbohydrate intake [En%]	21.2 ± 6.7	20.7 ± 6.5
Low GI carbohydrate intake [En%]	15.6 ± 4.9	16.4 ± 5.0
Total fat intake [En%]	45.4 ± 7.1	45.9 ± 6.6
MUFA intake [En%]	16.9 ± 3.3	16.7 ± 2.9
Plant-based MUFA intake [En%]	5.2 ± 2.8	5.1 ± 2.8
Animal-based MUFA intake [En%]	8.4 ± 2.5	8.3 ± 2.5
PUFA intake [En%]	8.1 ± 2.1	8.8 ± 2.6
n-3 FA intake [En%]	1.3 ± 0.6	1.5 ± 0.8
n-6 FA intake [En%]	6.8 ± 1.7	7.3 ± 2.1
SFA intake [En%]	17.5 ± 3.0	17.4 ± 3.0
Even-chain SFA intake [En%]	14.3 ± 2.4	14.2 ± 2.3
Very-long-chain SFA intake [En%]	0.26 ± 0.06	0.26 ± 0.07
Odd-chain SFA intake [En%]	0.35 ± 0.10	0.35 ± 0.11
Protein intake [En%]	15.6 ± 2.4	16.1 ± 2.8
Plant-based protein intake [En%]	3.5 ± 1.0	3.5 ± 0.9
Animal-based protein intake [En%]	9.7 ± 3.0	10.3 ± 3.3
Subcutaneous adipose tissue [cm^3]	16,300 (11,600, 22,300)	23,400 (16,600, 32,300)
Visceral adipose tissue [cm^3]	1100 (510, 2400)	3900 (2800, 5100)
Hepatic lipid content [%]	0.3 (0.0, 1.1)	6.2 (2.4, 13.3)

BMI body mass index, *En%* energy percent, *GI* glycemic index, *MUFA* monounsaturated fatty acids, *PUFA* polyunsaturated fatty acids, *SFA* saturated fatty acids

A higher protein intake was associated with higher SAT volume in individuals with T1D [β (95% CI) per 5 En%: 3200 (200, 6300) cm^3] (Supplementary Table 2 and Supplementary Fig. 5). Differentiation between the source of protein showed that a higher intake of animal-based protein was positively associated with SAT volume [per 1 En%: 690 (220, 1200) cm^3], while a higher intake of plant-based protein was inversely associated with SAT volume [per 1 En%: −1600 (−3000, −150) cm^3] (Supplementary Table 2). In individuals with T2D, there was also a positive association between protein (both animal- and plant-based) and SAT, however, imprecisely estimated.

In contrast, higher protein intake was linked to lower HL content in T2D (Supplementary Fig. 5).

Substitution analysis in association with SAT volume

For the substitution of carbohydrates with total fat, MUFA, PUFA or SFA, no distinct associations were observed in T1D or T2D (Fig. 1). Replacing carbohydrates with protein was associated with higher SAT, especially in T1D [β (95% CI) per 5 En%: T1D: 3100 cm^3 (25, 6200); T2D: 2300 cm^3 (−740, 5400)].

In a more detailed analysis, the substitution of higher GI carbohydrates with low GI carbohydrates was not associated with SAT in both diabetes types (Fig. 1). There was an indication for individuals with T1D that the replacement of higher GI carbohydrates with even-chain SFA was associated with higher SAT [per 1 En%: 1400 cm^3 (−290, 3200)], while the replacement with very-long-chain SFA was linked to lower SAT [per 0.1 En%: −4200 cm^3 (−8500, 180)]. However, the 95% CI was wide. In individuals with T2D, the substitution of higher GI carbohydrates indicated an association with higher SAT, when replaced with animal-based and plant-based protein [per 1 En%: 680 cm^3 (−65, 1400); 2400 cm^3 (−86, 4800)].

In sensitivity analysis additionally adjusting for BMI, the positive association of substituting carbohydrates with protein did not longer exist for both T1D and T2D, (Supplementary Table 3). The remaining associations were attenuated after further adjustment for BMI.

Substitution analysis in association with VAT volume

For VAT, no associations were found in individuals with T1D when replacing carbohydrates with fat or protein (Fig. 2). In individuals with T2D the substitution of carbohydrates with total fat was not associated with VAT; however, replacing carbohydrates with MUFA was associated with higher VAT [per 5 En%: 1200 cm^3 (230, 2200)] and replacing carbohydrates with PUFA with lower VAT [per 5 En%: −970 cm^3 (−1900, −40)]. A similar tendency was observed for SFA [per 5 En%: −630 cm^3 (−1400, 100)]. For the replacement of carbohydrates with protein no distinct association was found in T2D.

When replacing higher GI carbohydrates with low GI carbohydrates, no associations were detected for VAT in T1D and T2D (Fig. 2). In individuals with T1D, the estimates were small and 95% CIs wide for the associations of the replacement of higher GI carbohydrates with fat, but there was an indication for lower VAT when higher

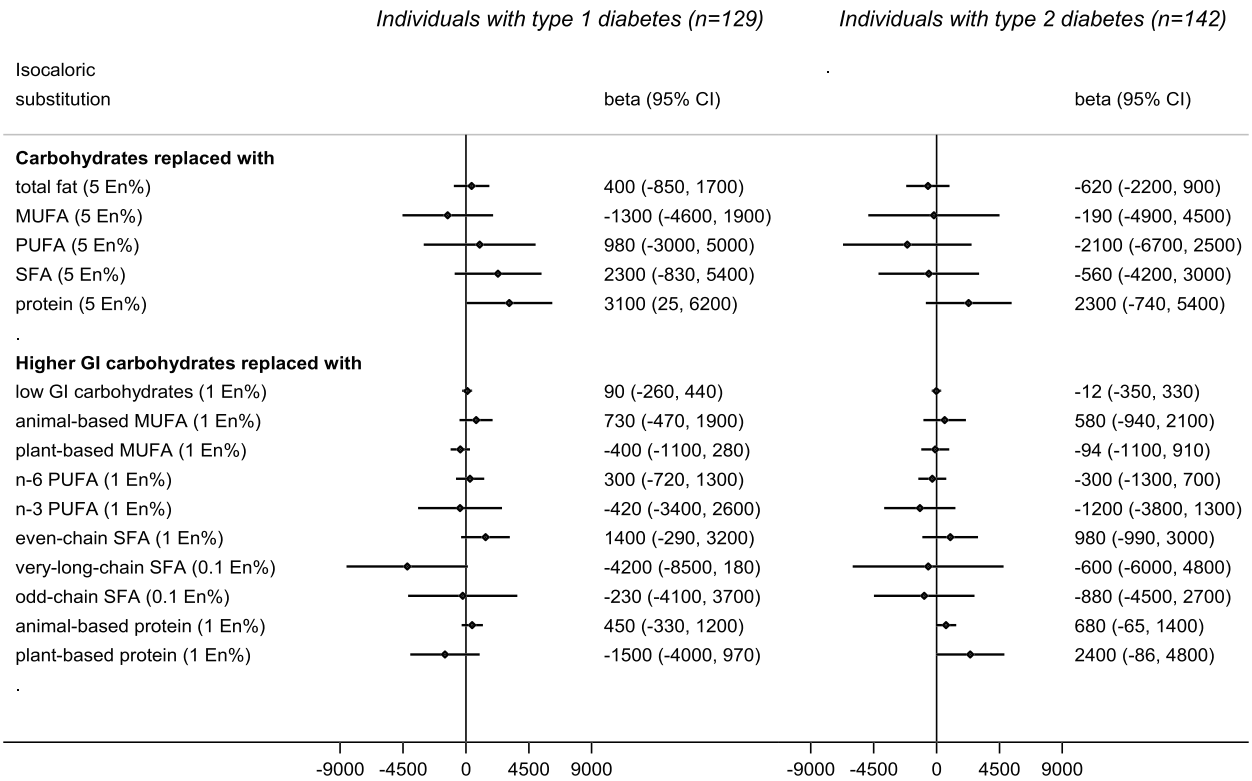

Fig. 1 Cross-sectional isocaloric substitution of carbohydrates and higher GI carbohydrates and its association with subcutaneous adipose tissue volume [cm^3]. Models are adjusted for age, sex, smoking status, physical activity, socioeconomic status, energy intake, alcohol intake, diabetes medication (only for T2D) and complementary nutrient intake

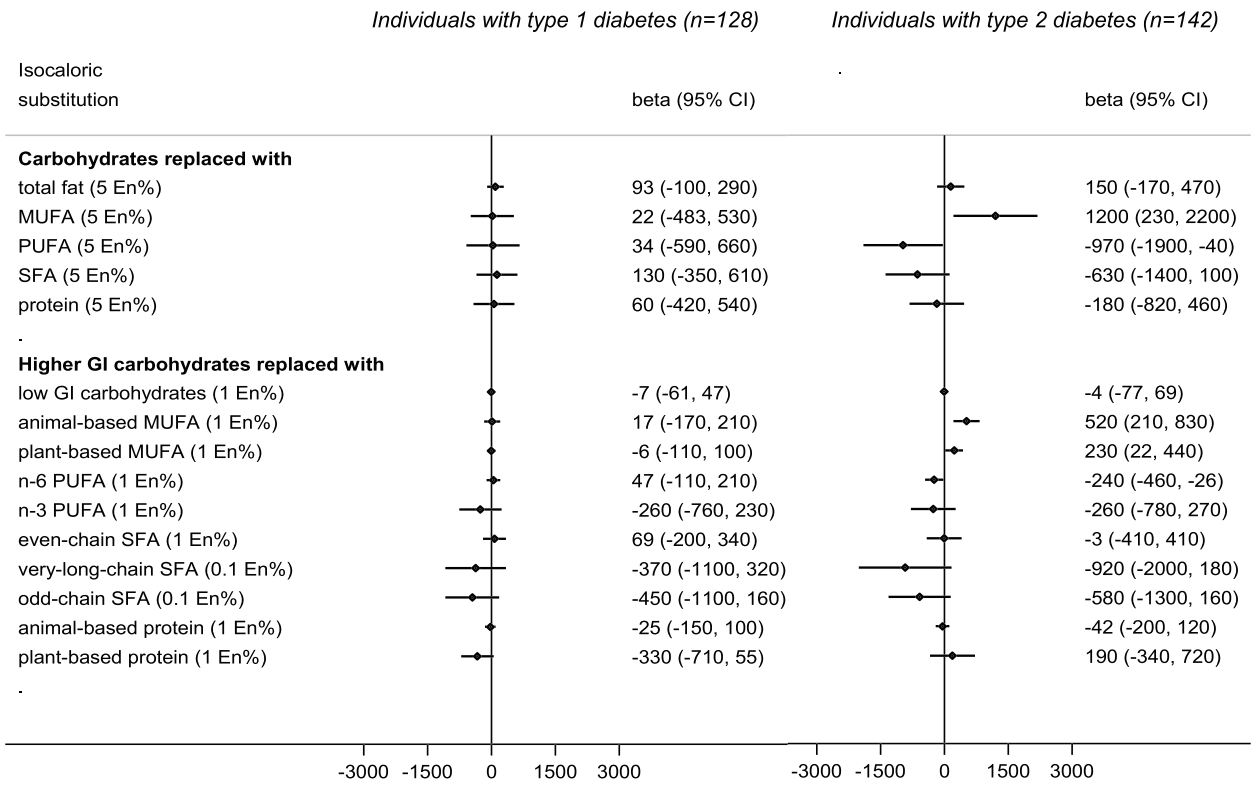

Fig. 2 Cross-sectional isocaloric substitution of carbohydrates and higher GI carbohydrates and its association with visceral adipose tissue volume [cm^3]. Models are adjusted for age, sex, smoking status, physical activity, socioeconomic status, energy intake, alcohol intake, diabetes medication (only for T2D) and complementary nutrient intake

GI carbohydrates were substituted with plant-based protein [per 1 En%: −330 cm^3 (−710, 55)]. In individuals with T2D, substituting higher GI carbohydrates with both animal-based and plant-based MUFA was associated with higher VAT [per 1 En%: 520 cm^3 (210, 830); 230 cm^3 (23, 440)]. In contrast, we observed lower VAT when replacing higher GI carbohydrates with n-6 PUFA [per 1 En%: −240 cm^3 (−460, −26)] and very-long-chain or odd-chain SFA [per 0.1%: −920 cm^3 (−2000, 180); −580 cm^3 (−1300, 160)]. The replacement of higher GI carbohydrates with animal-based or plant-based protein was not associated with VAT.

In general, the adjustment for BMI did not substantially change the findings for VAT (Supplementary Table 4). Some of the associations were more precisely estimated, evidenced by narrower 95% CIs.

Substitution analysis in association with HL content

No associations were found with regard to HL content for any of the substitutions in individuals with T1D (Fig. 3). In individuals with T2D, replacing carbohydrates with total fat was not associated with HL content. However, substituting carbohydrates with PUFA was associated with lower HL content [per 5 En%: −3.3% (−7.0, 0.3)], while the replacement with SFA was linked to higher HL content in T2D [per 5 En%: 2.4% (−0.6, 5.4)]. In addition, the replacement of carbohydrates with protein was associated with lower HL content [per 5 En%: −2.4% (−4.9, 0.0)].

In more detailed analysis, the substitution of higher GI carbohydrates with lower GI carbohydrates was not associated with HL content (Fig. 3). Substituting higher GI carbohydrates with n-6 and n-3 PUFA was in both cases associated with lower HL content in T2D [per 1 En%: −0.9% (−1.7, −0.1); −1.2% (−3.2, 0.8)]. We found a positive association for HL content when replacing higher GI carbohydrates with even-chain SFA [per 1 En%: 1.4% (−0.1, 2.9)], and inverse associations for HL content for the replacement of very-long-chain SFA or odd-chain SFA [per 0.1 En%: −3.6% (−7.5, 0.2) and −2.7% (−5.4, 0.0)]. In regard to protein, particularly replacing higher GI carbohydrates with plant-based protein was related to lower HL content [per 1 En%: −2.8% (−4.7, −0.8)].

Further adjustment for BMI did not substantially change the findings in regard to HL content (Supplementary Table 5).

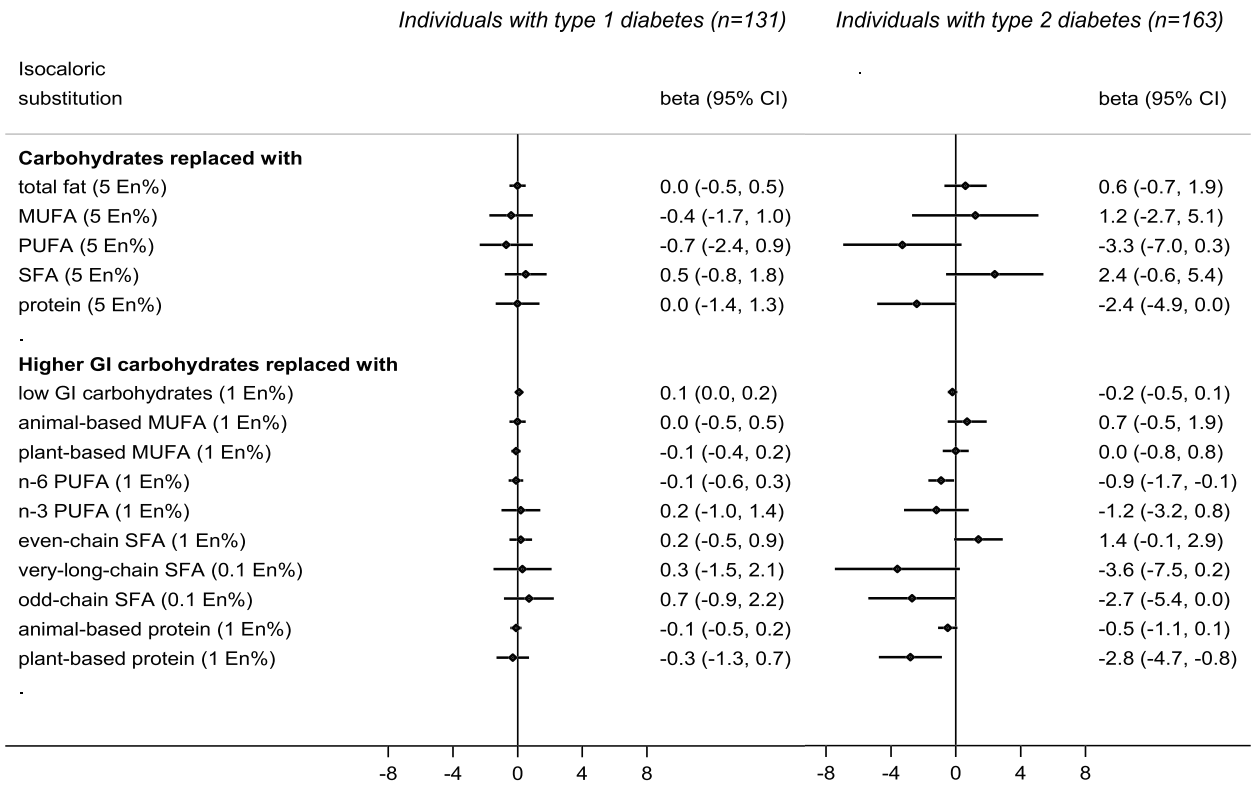

Fig. 3 Cross-sectional isocaloric substitution of carbohydrates and higher GI carbohydrates and its association with hepatic lipid content [%]. Models are adjusted for age, sex, smoking status, physical activity, socioeconomic status, energy intake, alcohol intake, diabetes medication (only for T2D) and complementary nutrient intake

Discussion

This study demonstrates that the accumulation of adipose tissue and HL content is not solely determined by the macronutrient composition, but may also be influenced by the substituted quality of nutrients. Particularly in individuals with T2D, replacing carbohydrates with PUFA, and accordingly higher GI carbohydrates with n-3 and n-6 PUFA, was linked to lower VAT volumes and HL content. Moreover, the replacement of higher GI carbohydrates with plant-based protein, and very-long-chain and odd-chain SFA was associated with lower HL content, whereas a substitution with even-chain SFA was linked to higher HL content in T2D.

In comparison with findings of a previous cross-sectional study in the general population, showing that replacing carbohydrates with total fat was linked to higher VAT and liver fat content [24], our results were more divergent. On the one hand, we also found higher VAT in T2D, when replacing carbohydrates with MUFA, and accordingly higher GI carbohydrates with both animal- and plant-based MUFA. Additionally, replacing carbohydrates with SFA, particularly higher GI carbohydrates with even-chain SFA, was associated with higher VAT and HL content in our study. However, on the other hand, our results suggest that the replacement of carbohydrates with PUFA, and the replacement of higher GI carbohydrates with n-3 and n-6 PUFA, as well as very-long-chain and odd-chain SFA was associated with lower VAT and HL content, particularly in individuals with T2D.

These discrepancies suggest that it is essential, which specific nutrients are substituted for carbohydrates, with consideration of their quality. Moreover, the source of the nutrients may be of importance. For instance, even-chain SFA are mainly found in animal products (e.g., red meat, hard cheese) and tropical oils (e.g., coconut oil, palm oil), while common sources for very-long-chain SFA are canola oil, peanuts, peanut butter and macadamia nuts, and odd-chain SFA are a proxy for the consumption of dairy products [41, 42]. Consequently, different fatty acids might potentially influence health outcomes in different ways. In this context, previous studies investigating circulating SFA biomarkers have shown that higher levels of total and even-chain SFA were associated with a higher risk of developing T2D and CVD [14, 15]. In addition, findings from randomized controlled trials (RCTs) indicated that the intake of total SFA can rapidly increase hepatic lipid storage, serum lipids and energy

metabolism, and thus, induce insulin resistance [43, 44]. In contrast, higher levels of circulating odd-chain and very-long-chain SFA were associated with a lower risk of T2D, CVD and mortality in large cohort studies [14–16, 41, 42].

Moreover, in regard to the substitution of carbohydrates with PUFA, our results align with the present state of research. Findings of a systematic review and meta-analysis of RCTs showed that replacing carbohydrates with PUFA was associated with improved glycemia, insulin resistance, and insulin secretion capacity, particularly in individuals with diabetes [45]. In general, particularly n-3 PUFA are attributed to be beneficial in the context of inflammation and CVD incidence and mortality [12], but interestingly, effect estimates were similar in our study replacing higher GI carbohydrates with n-3 or n-6 PUFA, respectively. However, our findings on the substitutions with MUFA need more discussion. A previous meta-analysis of RCTs found that a higher intake of MUFA might be favorable with respect to fat mass and blood pressure in persons not only restricted to diabetes [46]. Similar beneficial findings were observed in a substitution analysis in individuals with T2D with regard to weight change after five years when carbohydrates were replaced with MUFAs [47]. Beyond that, there is evidence that especially animal-based MUFA may be associated with visceral adiposity and weight gain, whereas plant-based MUFA was not associated with changes in body weight [48, 49]. In our study, we found higher VAT volumes, when higher GI carbohydrates were replaced with animal-based MUFA, but interestingly also with plant-based MUFA. However, no associations were found for the substitution with MUFA and HL content. Thus, our findings align with the results of a RCT that indicated that MUFA may induce acute insulin resistance but has no deleterious effects on hepatic lipid and energy metabolism [50].

In terms of protein intake, our findings suggest that the replacement of carbohydrates with protein was linked to higher SAT volumes, especially in individuals with T1D. However, this association diminished after controlling for BMI, which might be explained due to the strong correlation between SAT and BMI [51]. In contrast, our findings suggest that replacing carbohydrates with protein, and especially higher GI carbohydrates with plant-based protein, was associated with lower HL content in individuals with T2D. Hence, our findings are similar to the results of a previous substitution analysis in individuals with T2D, where the substitution of carbohydrates with plant-based protein was beneficial with respect to weight change compared to the substitution with animal-based protein [20]. In addition, a systematic review and meta-analysis of RCTs in individuals with diabetes found that replacing animal-based protein with plant-based protein was associated with more beneficial levels of HbA1c, fasting glucose and fasting insulin [52]. In regard to VAT and HL content, the findings of a previous cross-sectional study in the general population showed that adhering to a plant-based diet was associated with lower VAT, but not with liver fat [53]. However, in this study plant-based protein was only a fragment of the investigated diet and thus, this may explain the differences compared to our findings. In individuals with T1D, no associations were found for HL content when replacing carbohydrates with proteins (or fats), which might be mainly explained by the fact that in our study individuals with T1D had very low HL content (median: 0.3%).

In terms of carbohydrate quality, current guidelines suggest dietary recommendations towards a higher intake of low GI carbohydrates for diabetes management [7, 8]. However, our findings showed no associations for replacing higher GI carbohydrates with low GI carbohydrates for SAT, VAT and HL content, respectively. These findings are of interest in light of previous studies indicating that diets with a higher GI were associated with poorer glycemic control, blood lipids and body weight in individuals with diabetes [1, 6]. Moreover, findings from a RCT demonstrated that following a low-GI diet for two weeks can already reduce HL content in overweight individuals [54]. However, the intake of higher GI carbohydrates is relatively high in this cohort (~ 21 En% in both T1D and T2D) and an increase in low GI carbohydrate intake could potentially reduce the accumulation of adipose tissue and HL content. In addition, recent guidelines stated that a reduction of SFA is recommended for the dietary management of diabetes [8]. Indeed, we observed that a substitution of (higher GI) carbohydrates with total and even-chain SFA was linked to higher HL content; however, the replacement with very-long and odd-chain was associated with lower HL content. Thus, the quality and source of nutrient of the substitutes might be also crucial.

According to our results the integration of PUFAs, odd-chain and very-long-chain SFA, and plant-based protein may be considered for diabetes management in the future. This might have the potential to avoid accumulations of VAT and HL content, which is associated with an impaired glucose and lipid metabolism, insulin resistance, and several comorbidities, and thus, can induce diabetes progression [21].

One of the strengths of the GDS cohort is its inclusion of individuals with a short known duration of overt T1D and T2D within one year after their diagnosis with detailed phenotyping, including MRI-measured SAT and VAT volumes, as well as ^{1}H-MRS-measured HL content. Moreover, this was the first time that comprehensive

substitution analyses were performed to investigate the replacement of carbohydrates in relation to SAT, VAT and HL content in individuals with T1D and T2D. In addition, the quality of carbohydrates according to their GI was taken into account, using data from an extended validated questionnaire [31]. However, our study had some limitations as well. First, due to the observational study design, no actual substitutions of macronutrients were carried out in the study participants, and thus, it is not possible to draw conclusions about causality. Therefore, residual confounding cannot be excluded, although potential confounders were considered in our analyses. Second, dietary intake was assessed via self-reports and reporting bias cannot be ruled out. This applies especially for unhealthy foods, since participants, in particular overweight and obese individuals, tend to underreport their true intake [55]. Beyond that, measurement errors could have particularly occurred in subtypes of carbohydrates and fatty acids, since only the main food sources are included on a food group level in the FFQ, which potentially led to difficulties in quantifying the true intake. However, the quantification into higher GI and low GI carbohydrates has previously been validated [31]. Third, since participants were recently diagnosed with diabetes, the diagnosis may have prompted changes in the dietary behavior which may not have yet affected the outcome variables. This might have caused an underestimation of the association in our cross-sectional analyses. In addition, potential selection bias cannot be ruled out due to the comprehensive GDS protocol and its exclusion criteria, and thus, these findings might not be transferable to all individuals with diabetes.

Conclusions

The findings indicated that replacing carbohydrates with PUFA was associated with lower VAT volumes and HL content, particularly in individuals with T2D. Moreover, the substitution of higher GI carbohydrates with odd-chain and very-long-chain SFA, as well as plant-based protein, demonstrated an association with lower HL content in T2D. Consequently, it appears that not only nutrient composition, but also its quality, may play a relevant role in adipose tissue accumulation and HL content, particularly in individuals with T2D.

Abbreviations

ADA	American Diabetes Association
BMI	Body mass index
CI	Confidence interval
CVD	Cardiovascular disease
En%	Energy percent
FFQ	Food frequency questionnaire
GDS	German Diabetes Study
GI	Glycemic index
HL	Hepatic lipid
^{1}H-MRS	Proton magnetic resonance spectroscopy
IDF	International Diabetes Federation
MASLD	Metabolic dysfunction-associated steatotic liver disease
MRI	Magnetic resonance imaging
MUFA	Monounsaturated fatty acids
PUFA	Polyunsaturated fatty acids
RCT	Randomized controlled trial
SAT	Subcutaneous adipose tissue
SFA	Saturated fatty acids
SES	Socioeconomic status
T1D	Type 1 diabetes
T2D	Type 2 diabetes
VAT	Visceral adipose tissue

Supplementary Information

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Supplementary Material 1.

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Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the first author used ChatGPT as a support of the writing process to improve readability. After using this tool, the author reviewed and edited the content as needed and takes full responsibility for the content of the publication.

Authors' contributions

AL, SS and MR conceptualised the idea for the analysis. VSH, YK, SK, OPZ, KSW and RW collected the data. AL performed the statistical analyses with the support of ES, JG, KSW, AB and SS. AL and SS wrote the manuscript. AL, ES, SS, AB, CH, OK and MR contributed to the interpretation and discussion of the results. AL and SS are guarantors 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. All authors read and approved the final manuscript.

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Data availability
Data described in the manuscript, code book, and analytic code will be made available upon request pending application and approval.

Declarations

Ethics approval and consent to participate
The study is performed according to the Declaration of Helsinki, was approved by the ethics board of the University of Düsseldorf (ref. 4508) and registered at Clinicaltrials.gov (NCT01055093). All participants provided their written informed consent.

Consent for publication
Not applicable.

Competing interests
AEB is a member of the International Carbohydrate Quality Consortium (ICQC), a member of the Scientific committee of the transnational governance of the Nutri-Score system, a member of the Scientific Advisory Council for Agricultural Policy, Nutrition and Consumer Health Protection, Federal Ministry of Food and Agriculture Germany and a co-author of the popular cookbook "Nordisch abnehmen". Her research is supported by grants from the German Research Foundation (BU 1807/3-2 & BU 1807/8-1), and the European Joint Programming Initiative "A Healthy Diet for a Healthy Life" and from the ERA-NET Cofund HDHL INTIMIC (GA No. 727565 of the EU Horizon 2020 Research and Innovation Programme). The research of CH is supported by grants from the German Research Foundation (DFG) and the European Community (HORIZON-HLTH-2022-STAYHLTH-02-01: Panel A) to the INTERCEPT-T2D consortium. RW reports honoraria for lectures/presentations/speaker's bureaus from Eli Lilly, Boehringer Ingelheim, NovoNordisk and Sanofi Aventis; travel support from NovoNordisk; honoraria for advisory boards from Eli Lilly and Akcea Therapeutics. MR received fees consulting, lecturing or serving on advisory boards from Astra Zeneca, Boehringer-Ingelheim, Echosens, Eli Lilly, Merck-MSD, Madrigal, Novo Nordisk, Madrigal and Target RWE and has performed investigator-initiated research with support from Boehringer-Ingelheim, Novo Nordisk and Nutricia/Danone to the DDZ. The research of MR is supported by grants from the German Research Foundation (DFG; RTG/GRK 2576), the European Community (HORIZON-HLTH-2022-STAYHLTH-02-01: Panel A) to the INTERCEPT-T2D consortium, BMG, MKW, BMBF and the Schmutzler-Stiftung.

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