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VIEWPOINT

Dietary treatment of type 1 diabetes: Beyond carbohydrate counting to fight cardiovascular risk

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Abstract *Aims.:* Type 1 diabetes (T1D) is tied to an increased risk of cardiovascular morbidity and mortality. Dietary treatment would be an elective therapeutic strategy to fight this risk. However, it is not known what the best dietary approach is.

We revisited the currently available literature on the nutritional treatment of T1D in the light of their potential comprehensive effects on the management of cardio-metabolic risk factors (body weight, fasting and postprandial glucose and lipid metabolism).

Data synthesis.: Nutritional research in T1D is mainly focused on blood glucose control, with most of the trials aiming at evaluating the acute effects of nutrients on postprandial glycemic response. The effects of the quantity and quality of nutrients and some specific foods on other metabolic risk factors have been explored mainly in cross-sectional analysis. Very few well-designed nutritional trials evaluated the best dietary approach to comprehensively manage cardiovascular risk by targeting along with blood glucose control, overweight, fasting and postprandial dyslipidemia. Therefore, the current best practice guidance for the dietary management of cardiovascular risk in T1D is generally based on evidence from patients with type 2 diabetes.

Conclusions: Well-conducted nutritional trials specifically designed for T1D are needed to identify the best dietary treatment to fight cardiovascular risk in these patients.

1. Introduction

Recent nationwide-based registry reports in Finland show that type 1 diabetes (T1D) is still tied to an increased risk of cardiovascular morbidity and mortality [1]. Difficulties in achieving blood glucose targets both in terms of HbA1c levels and glucose variability certainly contribute to determining this excess of risk. However, epidemiological evidence highlights the role of other cardiovascular (CV) risk factors.

The spreading out of unhealthy lifestyles, likely more than the intensification of insulin therapy, is determining an increase of the prevalence of overweight and obesity in patients with T1D that parallels global trends in healthy people [2,3]. Insulin resistance associated with overweight is the driver of pro-atherogenic lipids profile and other

Abbreviations: Type 1 diabetes, T1D; Cardiovascular, CV; Body Mass Index, BMI; Waist To Hip Ratio, WHR; Waist Circumference, WC; Monounsaturated Fat, MUFA; High Carbohydrate Diet, HCD; Low Carbohydrate Diet, LCD; Very Low-Density Lipoprotein, VLDL.

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metabolic disturbances that contribute to the unfavorable cardiovascular framework in people with T1D.

Consistently, recent epidemiological evidence highlighted the role of non-HDL cholesterol as a better predictor of cardiovascular mortality in people with T1D than HbA1c [4,5].

A recent report from EURODIAB further emphasizes the multifactorial nature of cardiovascular risk in T1D showing that targeting multiple risk factors, including smoking, body mass index (BMI), physical activity, dietary habits, total cholesterol/HDL-cholesterol ratio, combined systolic and diastolic blood pressure, and HbA1c, reduced hazard ratio of cardiovascular disease compared with targeting single risk factors [6].

In this context, dietary treatment, with its multiple and coordinated mechanism of action, is one of the elective therapeutic approaches to fighting CV risk in T1D. Despite the holistic potentialities of dietary treatment, current clinical practice and guidelines emphasize the role of carbohydrate counting as the pillar of nutritional education for patients with T1D.

Whether current evidence is oriented towards a comprehensive nutritional approach for cardiovascular prevention and treatment in people with T1D is not clear. We discuss this issue, based on current available research on the relation between metabolic risk factors (overweight/obesity, blood glucose control, and fasting and postprandial dyslipidemia) and cardiovascular disease in type 1 diabetes.

2. Cardiovascular disease

The link between dietary habits and cardiovascular disease in patients with T1D has been mainly explored in cross-sectional studies. Very few data are available on cardiovascular events, while more extensive literature is available on proxies of cardiovascular disease such as intima-media thickness, carotid plaques, and arterial stiffness. A prospective evaluation of the Pittsburg Epidemiological study found no relationship between dietary patterns individuated by principal component analysis and incidence of cardiovascular events in a cohort of T1D patients [7]. The presence of carotid plaque in a high-risk population of patients with T1D was associated, in multivariate regression models, inversely with erythrocyte linoleic acid and positively with all-C18:1trans supporting the potential role of an unfavorable pattern of fat intake on CV risk [8]. In a prospective analysis, the better diet quality at baseline, as measured by the Alternate Health Eating Index score, was associated with greater Intima-Media Thickness regression after approximately two years [9]. Other reports pointed out the positive associations between unhealthy dietary patterns, such as “Full-fat cheese and eggs” and “Sweet” [10] and “soda” [11], and arterial stiffness.

Overall, these findings suggest that reducing the consumption of unhealthy foods and beverages may significantly improve CV risk among patients with T1D. Whether this evidence is consistent with findings on the effects on single CV risk factors is discussed below.

2.1. Blood glucose control

The central role of dietary carbohydrates in determining hyperglycemia was known before the discovery of insulin. At that time, carbohydrate restriction was the only possible therapeutic strategy to blunt blood glucose rises. The availability of more sophisticated strategies for the intensification of insulin therapy freed people with T1D from the therapeutic restriction of carbohydrate intake and widened their dietary choices. Therefore, people with T1D follow a variety of dietary patterns whose impact on blood glucose control is independent of the hyperglycemic effects of carbohydrates related to insulin deficiency. In this context, cross-sectional analyses highlighted how dietary patterns higher in fat and saturated fat and lower in carbohydrates were associated with worse glycemic control in T1D [12,13]. However, since in real-life adequate matching of pre-prandial insulin dosing to the carbohydrate content of meals is still highly challenging, low carbohydrate diets are becoming again an appealing alternative to decrease insulin dose, minimize glycemic variability, and reduce HbA1c levels. Nevertheless, the currently available evidence is still inadequate to draw definitive conclusions on this issue [14,15].

A relevant factor to be considered in the evaluation of the effects of dietary carbohydrates on blood glucose control is the role of carbohydrate quality. In cross-sectional analyses, the influence of carbohydrate quantity on HbA1c and glycemia is tempered by the impact of carbohydrate quality. In several reports from a wide European cohort, total dietary fiber reveals inverse associations with blood glucose control [16,17]. The impact of carbohydrate quality is still evident in people using hybrid artificial pancreas. In a recent analysis, glycemic load was a better predictor of postprandial Time In Range (blood glucose 70–180 mg/dl) at breakfast and dinner than carbohydrates amount in a cohort of 25 patients using a hybrid closed loop system [18].

In the only two randomized trials investigating medium-term dietary effects, a low glycemic index diet, high in fiber, significantly improved blood glucose control in patients with T1D compared with a diet with a high glycemic index and low in fiber [19,20].

Overall, very few randomized trials with adequate sample size and follow-up duration investigated the effects of quantity and quality of dietary carbohydrates on blood glucose control. Further research on this issue is urgently needed [21,22].

2.2. Postprandial glucose response

Beyond overall blood glucose control, rapid and large glycemic fluctuations are independently related to the development of cardiovascular complications [23]. Therefore, postprandial glucose excursions are a relevant factor in relation to cardiovascular prevention in people with T1D. Of note, postprandial glucose response is also most relevant in relation with glucose control as it directly depends on how schemes of insulin therapy and adherence to them fit with

nutritional aspects. Patients with T1D are usually trained to count and adequate insulin dosing to the carbohydrate content of meals. Although being of benefit in achieving blood glucose targets, carbohydrate counting still has relevant limitations tied to the difficulties in its implementation [24]. The spreading of continuous glucose monitoring for clinical use has highlighted further potential flaws of carbohydrate counting, making it evident how other nutrients may influence postprandial glucose response in T1D. The results of randomized trials exploring the effects of fat and protein in addition to carbohydrates on postprandial blood glucose response and the relative insulin-delivery counteracting strategies have been recently meta-analyzed by Smith et al. [25] with no conclusive results. The recommended increase in insulin/carbohydrate ratio for fat and protein ranged in different studies between 24% and 75% and was highly dependent on individual responses. Moreover, in almost the totality of trials comparing meals with different content of protein and/or fat the meals also differed in energy content. This could represent a significant bias in the interpretation of the results since in real life energy content is one of the best independent predictors of postprandial glucose response [18].

The impact of the quality of nutrients adds further complexity to the management of postprandial blood glucose response [26]. The glycemic index of foods is one of the most challenging nutritional factors to deal with in order to tame postprandial glucose variability. Indeed, high glycemic index meals lead to a fast and steep increase followed by a rapid decline of glucose levels, with a consequent risk of hypoglycemia, while low glycemic index meals induce a blunted early response and a late increase in blood glucose [27,28].

The large interindividual variability in glucose response and difficulties in properly considering the glycemic index of single foods and mixed meals make it difficult to consider carbohydrate quality in algorithms for prandial insulin dosing. High glycemic index meals are currently difficult to manage also with the available advanced technologies. The main obstacle is kinetic insulin absorption from subcutaneous tissue which is too slow relative to the timing of simple sugar absorption.

It is worth mentioning that also the quality of fat is a relevant factor in determining the feature of postprandial glucose increase, especially after meals with a high glycemic index. In a previous study from our group, using extra-virgin olive oil instead of butter blunted the early glucose response to a high glycemic index meal [28] by slowing down the gastric emptying rate and increasing GLP-1 secretion [29].

Current therapeutic strategies to manage the variability of postprandial glucose response are still inadequate. Of course, this is related to the complexity of action of the different types of nutrients and their interaction with the multitude of other determinants of postprandial glucose response. Moreover, a most challenging aspect of postprandial glucose management relates to the interindividual variability in metabolic responses [49]. Among possible factors, interesting insights from recent studies [30] suggest that microbiota composition may play a relevant role in determining individualized responses. Future research should focus on the individuation of a personalized approach to successfully deal with postprandial glucose variability in patients with T1D.

2.3. Body weight management

Observational evidence shows that dietary quality is related to BMI in patients with T1D. In the EURODIAB study [31], a) a higher carbohydrate intake was a significant independent predictor for lower BMI, waist to hip ratio (WHR), and waist circumference (WC), b) an increased saturated fat intake and a lower intake of cereal fiber predicted a higher WHR, c) a higher monounsaturated fat (MUFA) intake and a lower glycemic index of the diet were associated with lower WHR and WC, and d) moderate consumption of alcohol was associated with an increased WC. In a Canadian cross-sectional analysis, the Mediterranean dietary score was inversely associated with BMI and WC in adults with T1D [32].

Very few randomized trials of good quality are available aiming to identify the best dietary approach to fight overweight/obesity in people with T1D. A recent systematic revision of the literature [33] retrieved only four eligible studies. Two of them were randomized controlled trials comparing, in one study, two educational programs for the implementation over a 6-month period of the Mediterranean diet or a low-fat diet, and, in the other study, intermittent fasting vs. a continuous energy-restricted program on a very small sample size (5 participants per group) of people with T1D and obesity. One pre/post-test study explored the effects of seven days of fasting and 21 days of low-calorie diet. All treatments determined a significant reduction in body weight, but no significant differences were found among different approaches.

In another report, specifically reviewing the effects of low-carbohydrate diets on metabolic outcomes in type 1 diabetes, 1 randomized trial comparing a low-carbohydrate diet (103 g/die) vs. a standard carbohydrate diet (203 g/die), a pre-post intervention, and 1 case-series reported data on BMI. No significant effects of carbohydrate restriction on BMI were found in none of the explored reports [15].

Considering the increasing prevalence of overweight/obesity in people with T1D, good-quality randomized trials on the best possible dietary approach to fight obesity associated with T1D are urgently needed.

3. Dyslipidemia

3.1. Fasting plasma lipids

Observational data show that the quality of diet significantly influences the fasting lipid profile and related CV risk of people with T1D. In a longitudinal study in youth with not optimized blood glucose control, added sugar were positively and independently related to plasma triglyceride [34]. In the EURODIAB IDDM Complications

Study, energy-adjusted total and LDL-cholesterol levels increased significantly with higher intakes of total fat, saturated fat, and cholesterol and concomitant lower intake in dietary fibre [35]. Other findings suggest that the intake of specific foods may influence cardiometabolic health in youth with T1D. Sugar-sweetened beverage intake was significantly associated with higher triglyceride, and total and LDL-cholesterol concentrations, after adjusting for energy, age, diabetes duration, race/ethnicity, sex, and education in 2286 youth with T1D enrolled in the SEARCH Nutrition Ancillary Study [36]. Consumption of $\geq$2 servings of nuts per week was associated with lower odds (37.7%) of higher plasma triglyceride in a cross-sectional analysis in Finnish people with T1D [37].

Very few intervention studies have evaluated the effects of dietary changes on fasting plasma lipid profile. A longitudinal observational study with a 2.6 $\pm$ 3.3 years follow-up explored the effects of a very-low-carbohydrate ketogenic diet (<55 g carbohydrate per day) finding that despite the improvement in blood glucose control, total cholesterol, LDL cholesterol, total cholesterol/HDL cholesterol ratio, and triglycerides were above the recommended range in 82%, 82%, 64%, and 27% of participants, respectively [38].

A randomized open-label crossover trial assessed the effects of a high carbohydrate diet (HCD) vs. a low carbohydrate diet (LCD) on glycemic variables and CV risk markers in a small sample (n = 10) of patients with T1D for a very short follow-up time (1 week) finding that the LCD resulted in more time in euglycemia, less time in hypoglycemia, and less glucose variability than the HCD, without altering mean glucose and lipid levels [39]. A couple of randomized trials [40,41] also evaluated the effects of the quality of fat. In these studies, a high MUFA diet was compared with a relatively high carbohydrate diet. A high proportion of MUFA in the diet determined a better lipid profile by lowering plasma total triglycerides by 18% and very low-density lipoprotein (VLDL) triglycerides by 26% and cholesterol by 48% but also increased the number of large VLDL [40].

3.2. Postprandial plasma lipids

Postprandial alterations of plasma lipids represent an independent CV risk factor [42] and should be considered along with fasting plasma lipids for the evaluation of the overall CV risk. In individuals with T1D, the consumption of high-fat meals increases plasma triglyceride [29,43] and acutely impairs vascular function [44]. In addition, a MUFA-rich meal induces a more pronounced postprandial triglyceride response than a meal rich in saturated fat [29].

Very few studies evaluated the effects of medium-term dietary interventions changing the relative amount of carbohydrates and fat and/or the quality of fat on postprandial triglyceride response, retrieving inconsistent results. In a parallel group design study, 30 subjects were randomly assigned to a 6-month eucaloric diet higher in carbohydrate/lower in fat or a diet lower in carbohydrate/higher in MUFA, finding a lower plasma TG profile at 24-h testing in the lower-carbohydrate/higher-MUFA group [45].

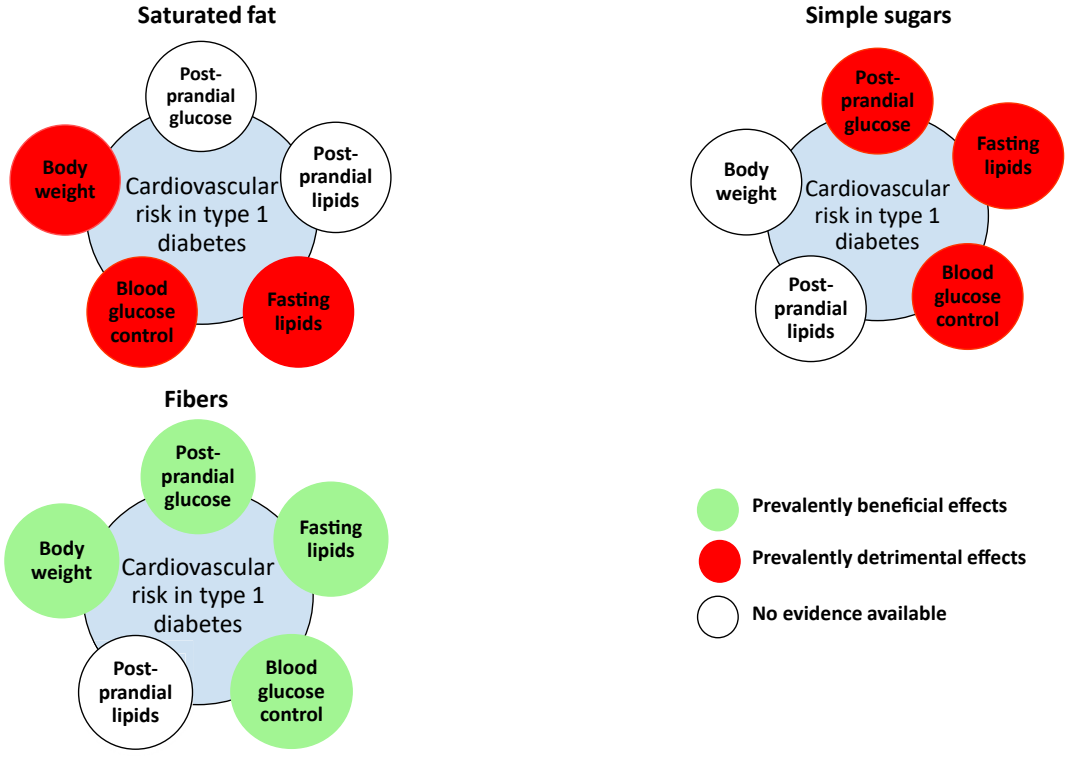

Figure 1 Qualitative representation of available evidence on comprehensive effects of diet on cardiovascular risk in patients with type 1 diabetes coming from observational studies.

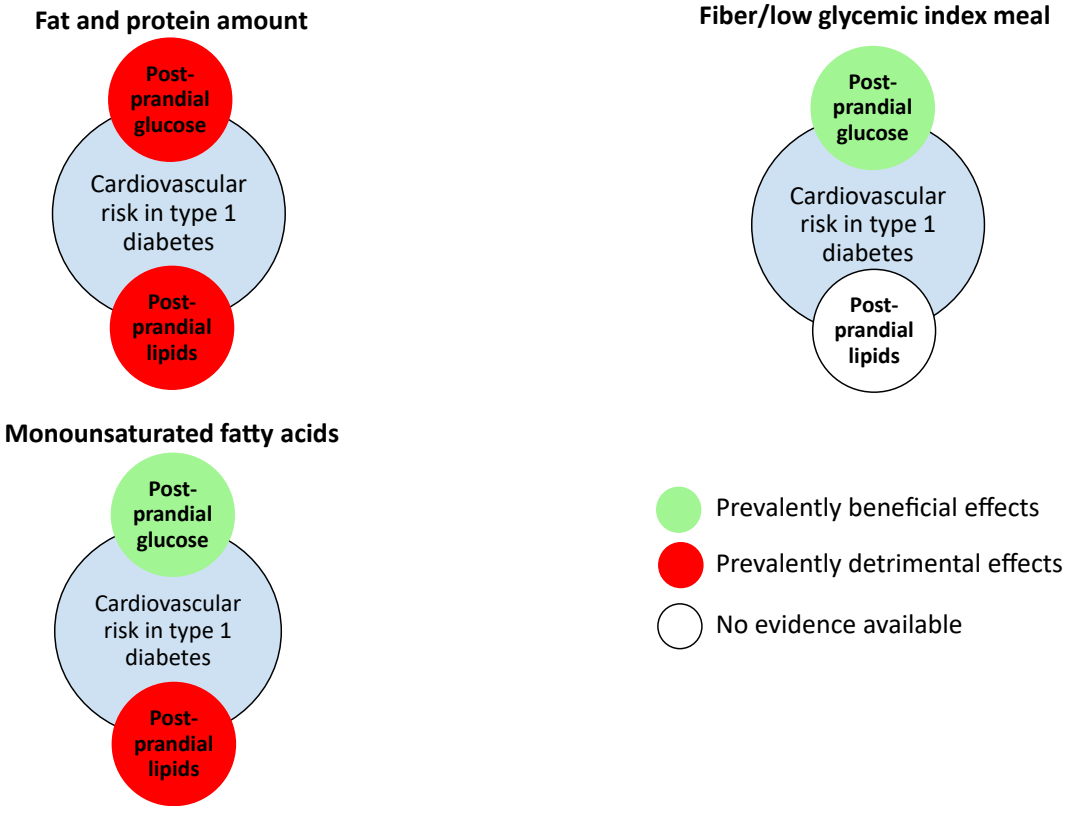

Figure 2 Qualitative representation of available evidence on postprandial blood glucose and plasma lipids in patients with type 1 diabetes coming from acute randomized trials.

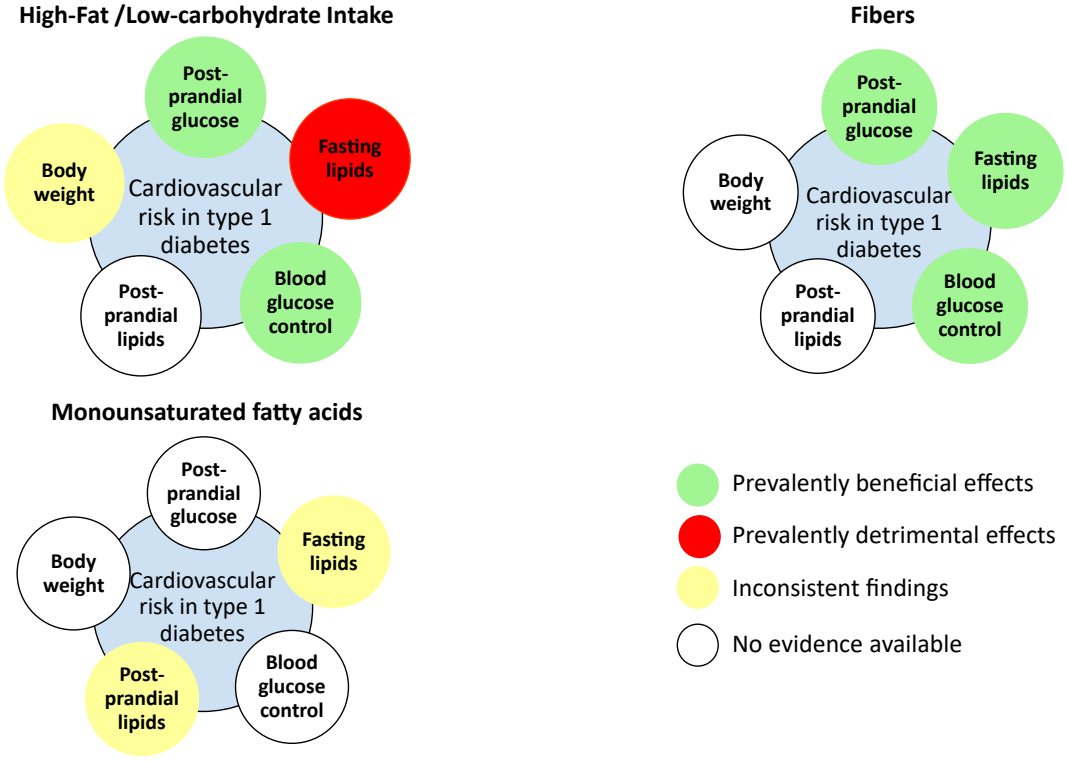

Figure 3 Qualitative representation of available evidence on comprehensive effects of diet on cardiovascular risk in patients with type 1 diabetes coming from medium-term randomized trials.

. In a 4-week randomized crossover study, triglyceride levels over 10 h, retinyl esters in chylomicrons (Sf > 400) and chylomicron remnants (Sf 100 to 400), and the total particle number (apolipoprotein B levels) in chylomicron remnants (P = .001) and small very low-density lipoprotein (Sf 20 to 100, P = .016) were higher after a high MUFA diet compared with a high carbohydrate diet [46].

4. Conclusions

Nutritional research in T1D is mainly focused on the management of postprandial glucose response. To avoid glycemic variability related to carbohydrate intake, therapeutic strategies have been recently explored aiming to manage the hyperglycemic effects of fat and protein.

Very few studies evaluated the effects of quantity and quality of nutrients also in relation to their comprehensive effects on other CV risk factors. Most of the information comes from cross-sectional and longitudinal observational studies (Fig. 1). The clearest evidence coming from these studies shows that a high intake of saturated fat and simple sugars and a low intake of dietary fibers are associated with the worst cardio-metabolic profile.

Acute studies evaluating postprandial metabolism (Fig. 2) show that fat and protein worsen postprandial glucose response. However, the quality of carbohydrates and fat used plays a relevant role in determining features of postprandial glucose response. The few studies that evaluated the effects on postprandial triglyceride show that MUFA determine a higher increase compared with carbohydrates and saturated fat.

The very few randomized trials available mainly explored the effects of varying the relative amount of carbohydrate and fat on blood glucose control, body weight, and fasting plasma lipids (Fig. 3). These trials fail to identify a comprehensive approach to CV risk reduction retrieving opposite effects on blood glucose control (usually positive) and other CV risk factors. Only a couple of randomized trials evaluated the effects of the quality of fat on postprandial lipid metabolism or the quality of carbohydrates on blood glucose control showing inconsistent results for MUFA and ameliorating effects on fasting and postprandial blood glucose control for dietary fibers (Fig. 3). It is worth mentioning that well-designed nutritional trials aimed to find the best nutritional approach to fight the mounting prevalence of obesity in T1D are completely lacking.

In conclusion, overall data show that currently available nutritional literature on T1D widely neglects the effects of diet on metabolic outcomes different from postprandial glycemia. Such a glucose/carbohydrate-centric approach is likely to obscure the deleterious effects of an overall unhealthy diet and give misleading educational messages to the patients. Therefore, a change of perspective is needed. Although the exciting progress in the development of new technologies for insulin therapy relieves patients and health care professionals from a great part of the burden related to blood glucose management, we cannot relax. T1D is not just high blood glucose levels but a complex disease with multisystemic involvement whose best care is not just making a good hormonal replacement therapy.

However, it also holds true that the implementation of long-term randomized nutritional trials in patients with T1D is particularly challenging due to the complexity of insulin therapy management and its interference with the interpretation of the outcomes. From this point of view, new technologies could be rather than a final solution, a new resource for the implementation of a more comprehensive nutritional research in T1D.

In conclusion, the current best practice guidance for the dietary management of CV risk in T1D is generally based on evidence from patients with type 2 diabetes, on data coming from acute studies, and the opinion of experts in the field. Well-controlled nutritional trials specifically designed for T1D are needed to fight CV risk in these patients.

Declaration of competing interest

The authors have no conflicts of interest to disclose.

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