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Original article

The association of substituting carbohydrates with total fat and different types of fatty acids with mortality and weight change among diabetes patients

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SUMMARY

Background: Substitution of carbohydrates with fat in a diet for type 2 diabetes patients is still debated.
Objective: This study aimed to investigate the association between dietary carbohydrate intake and isocaloric substitution with (i) total fat, (ii) saturated fatty acids (SFA), (iii) mono-unsaturated fatty acids (MUFA) and (iv) poly-unsaturated fatty acids (PUFA) with all-cause and cardiovascular (CVD) mortality risk and 5-year weight change in patients with type 2 diabetes.
Methods: The study included 6192 patients with type 2 diabetes from 15 cohorts of the European Prospective Investigation into Cancer and Nutrition (EPIC). Dietary intake was assessed at recruitment with country-specific food-frequency questionnaires. Cox and linear regression were used to estimate the associations with (CVD) mortality and weight change, adjusting for confounders and using different methods to adjust for energy intake.
Results: After a mean follow-up of 9.2 y ± SD 2.3 y, 791 (13%) participants had died, of which 268 (4%) due to CVD. Substituting 10 g or 5 energy% of carbohydrates by total fat was associated with a higher all-cause mortality risk (HR 1.07 [1.02–1.13]), or SFAs (HR 1.25 [1.11–1.40]) and a lower risk when replaced by MUFAs (HR 0.89 [0.77–1.02]). When carbohydrates were substituted with SFAs (HR 1.22 [1.00–1.49])

Abbreviations: CVD, Cardiovascular; EPIC, European Prospective Investigation into Cancer and Nutrition; FFQ, Food Frequency Questionnaire; MUFA, Mono-Unsaturated Fatty Acids; PUFA, Poly-Unsaturated Fatty Acids; SFA, Saturated Fatty Acids.

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or PUFAs (HR 1.29 [1.02−1.63]) CVD mortality risk increased. The 5-year weight was lower when carbohydrates were substituted with total fat or MUFAs. These results were consistent over different energy adjustment methods.

Conclusions: In diabetes patients, substitution of carbohydrates with SFAs was associated with a higher (CVD) mortality risk and substitution by total fat was associated with a higher all-cause mortality risk. Substitution of carbohydrates with MUFAs may be associated with lower mortality risk and weight reduction. Instead of promoting replacement of carbohydrates by total fat, dietary guideline should continue focusing on replacement by fat-subtypes; especially SFAs by MUFAs.

1. Introduction

Type 2 diabetes patients have a 2−3 fold higher risk of cardiovascular disease (CVD) [1]. However, the percentage of carbohydrates in the diet is still debated [2]. Initially, carbohydrates were avoided due to their postprandial glucose and insulin raising effects. However, carbohydrates are likely replaced by fat, which may result in unfavorable changes in blood lipid levels, and perhaps an increased mortality risk. Recently, dietary diabetes guidelines have abandoned their recommendations on lowering fat intake [4] because low-carbohydrate compared to low-fat diets improved glycated hemoglobin, fasting glucose, and triglycerides [2,3] without harmful effects in the short term [5].

In recent literature, the associations of SFAs with CVD risk are debated. For the general population, two meta-analyses of prospective studies could not detect a significant positive association between SFA intake and CVD risk [6,7]. This lack of association may be because SFAs were replaced with carbohydrates, which was not addressed by these meta-analyses. Among diabetes patients, prospective studies investigating the substitution of carbohydrates with fats in the diet are scarce. We are aware of only one study among women with type 2 diabetes that showed a 22% CVD risk reduction with isocaloric substitution of 5 energy% SFA with carbohydrates [8]. It is still largely unknown whether substitution of carbohydrates by other types of fat affects (CVD) mortality.

The substitution of carbohydrates with different types of fat may also affect body weight. Overweight is very common among type 2 diabetes patients and weight loss could reduce mortality by 25% in these patients [9]. In short term studies, both iso-caloric low-carbohydrate and low-fat calorie-restricted diets were effective on weight loss in patients with type 2 diabetes, without harmful effects from low-carbohydrate diets on blood lipids [5]. Long term effects have only been studied in the general population. Two observational studies in the EPIC cohort showed that a higher proportion of fat and fat subtypes [10] at the expense of energy from carbohydrates was not associated with weight change [11]. We are not aware of any such long-term studies among diabetes patients.

This study aimed to investigate the association between dietary carbohydrate intake and substitution with different types of fat with all-cause and CVD mortality risk in type 2 diabetes patients. We used different methods of energy adjustment (the residual, nutrient density, and energy-partition methods) because each method has a different interpretation [12]. As secondary endpoints, we investigated the associations with subsequent weight (and waist circumference) change.

2. Methods

2.1. Study population

Within the European Prospective Investigation into Cancer and Nutrition (EPIC) [13], a subcohort was defined of participants with a confirmed diagnosis of diabetes mellitus at recruitment as has been described earlier [14]. The following EPIC-centers have contributed to this project: Florence, Varese, Ragusa, Turin, and Naples (Italy), Navarra and San Sebastian (Spain), Bilthoven and Utrecht (the Netherlands), Heidelberg and Potsdam (Germany), Malmö and Umeå (Sweden), and Aarhus and Copenhagen (Denmark). Self-reports of diabetes at recruitment were confirmed by a second source of information, i.e. contact to a medical specialist or practitioner, self-reported use of medication for diabetes treatment, repeated self-report of diagnosis during follow-up or record linkage to a diabetes registry or a glycated hemoglobin (HbA1c) level above 42 mmol/mol (6%). The study was conducted according to the guideline laid down in the Declaration of Helsinki and was approved by a local ethical review committee of each centre and of the International Agency for Research on Cancer in Lyon, France. All subjects provided written informed consent.

Of 7048 initial self-reports, 5542 diabetes diagnoses were confirmed. A further 870 prevalent diabetes cases without self-reported diabetes at recruitment were identified as a result of verification efforts in other projects within EPIC. This led to a subcohort comprising 6412 individuals with confirmed diabetes at recruitment [14]. After exclusion of participants with missing dietary information ($N = 42$), participants in the highest or lowest 1% of the ratio of total energy intake/estimated energy requirement ($N = 177$), and one deceased participant with missing date of death, the analytical example for cardiovascular and all-cause mortality analysis included 6192 participants (3355 men and 2837 women).

For the analysis on weight change, participants with missing baseline weight or extreme anthropometry at recruitment or follow-up [height <130 cm, BMI <16 kg/m^2, waist circumference <40 or >160 cm and waist circumference <60 cm with BMI >25 kg/m^2] were excluded on top of the above mentioned exclusions. Furthermore, participants with extreme weight change >5 kg/year ($N = 2$) or those without follow-up data on weight or BMI ($N = 2067$ this included the cohorts of Turin and Ragusa and parts of the cohort in Naples (all in Italy)) were excluded. This analytical sample included 4123 participants (2267 men and 1856 women). For 1898 participants waist change could be analyzed.

2.2. Dietary assessment

In EPIC, usual dietary intake during the previous year was assessed at recruitment by means of self-administered country-specific validated dietary questionnaires [13], either quantitative dietary questionnaires with individual portion sizes (in France, Spain, the Netherlands, Germany and Italy, except Naples) or semi-quantitative food frequency questionnaires (in Denmark, Naples (Italy), Sweden, and the UK), that were developed and validated locally [15]. Correlation coefficients for the relative validity for carbohydrate measured with food frequency questionnaires varied from 0.46 to 0.76 in women and from 0.40 to 0.84 in men; for fat correlations varied from 0.41 to 0.63 in women and 0.31 to 0.67 in

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