



Dietary Fat and the Genetic Risk of Type 2 Diabetes

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Abstract

Purpose of Review We review recent evidence of the relationship between dietary fat intake and risk of type 2 diabetes (T2D), the role of epigenetic alterations as a mediator of this relationship, and the impact of gene-dietary fat interactions in the development of the disease. Based on the observations made, we will discuss whether there is evidence to support genetic personalization of fat intake recommendations in T2D prevention.

Recent Findings Strong evidence suggests that polyunsaturated fatty acids (PUFA) have a protective effect on T2D risk, whereas the roles of saturated and monounsaturated fatty acids (SFA and MUFA) remain unclear. Diets enriched with PUFA vs SFA lead to distinct epigenetic alterations that may mediate their effects on T2D risk by changing gene function. However, it is not currently known which of the epigenetic alterations, if any, are causal for T2D. The current literature shows no replicated evidence of genetic variants modifying the effect of dietary fat intake on T2D risk.

Summary There is consistent evidence of a protective role of PUFA in T2D prevention. No evidence supports genetic personalization of dietary recommendations in T2D prevention.

Keywords Dietary fat · Fatty acid composition · Gene · Genetic risk · Epigenetics · Type 2 diabetes

Introduction

Type 2 diabetes (T2D) is an increasingly common disorder that contributes substantially to the global burden of chronic disease [1–3]. Currently, more than 400 million people worldwide suffer from T2D, and the incidence rate is predicted to increase by more than 50% by 2040, primarily due to increased life expectancy and the adoption of Western lifestyles. Hence, T2D constitutes one of the greatest current threats to global public health.

Dietary fat intake is considered an important modifiable risk factor of T2D. Public health guidelines generally recommend reducing the intake of saturated fatty acids (SFA) and replacing them with unsaturated fat [4, 5]. However, current evidence concerning the association between dietary fatty acid composition and T2D risk is inconsistent. Furthermore, it has been speculated that the effect of dietary fat on T2D risk may vary between individuals depending on genetic variation and that the identification of the genetic variants that modify the impact of fat intake on T2D risk could enable the development of “personalized diets.”

Here, we will review the existing evidence of the relationship between dietary fat intake and T2D risk, epigenetic alterations as a mediator of this relationship, and the role of gene-dietary fat interactions in the development of T2D (Fig. 1). Based on the observations drawn from the literature, we will discuss whether there is evidence to support genetic personalization of fat intake recommendations in the prevention of T2D.

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Dietary Fat and Risk of T2D

Dietary fatty acid composition is thought to play an important role in the development of T2D [4, 5]. However, there is still great uncertainty regarding the optimal dietary fatty acid

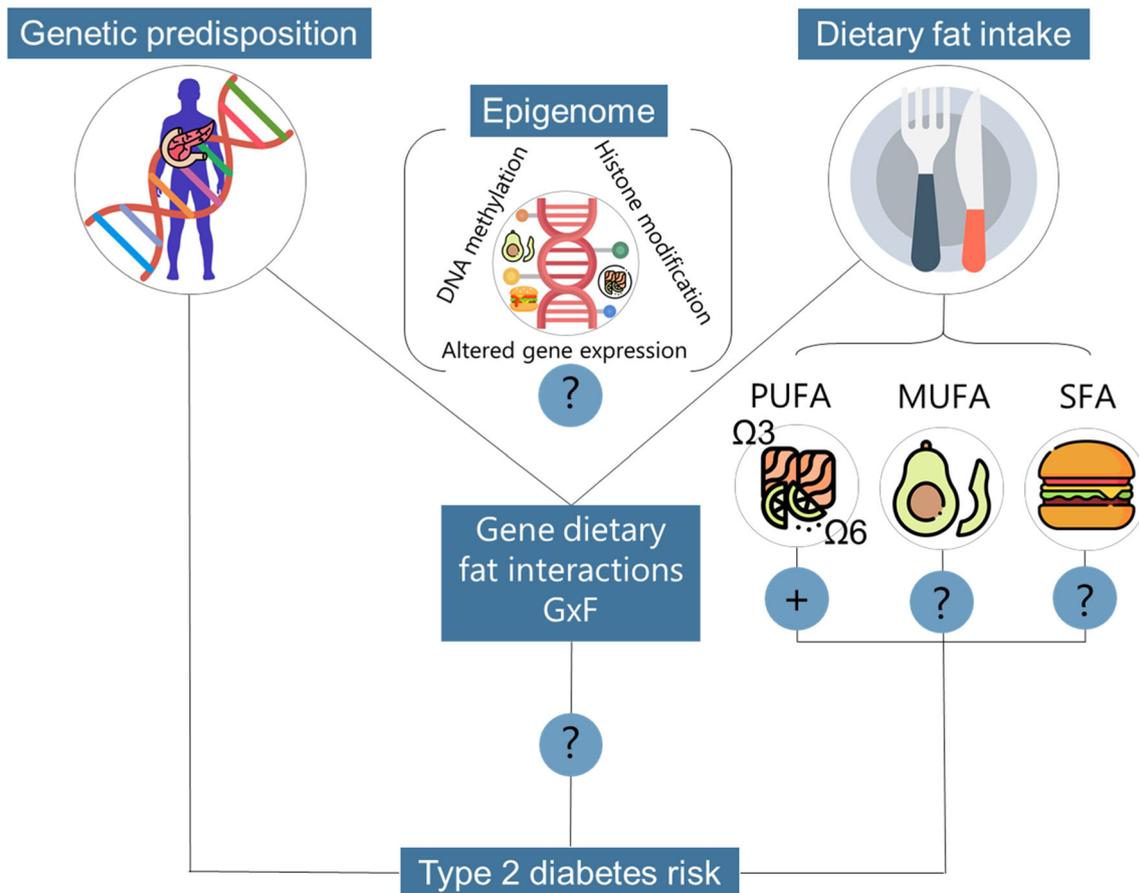


Fig. 1 Interplay between genetic predisposition and dietary fat intake in the development of type 2 diabetes. Multiple genetic variants have been found associated with an increased risk of type 2 diabetes (T2D) in genome-wide association studies (GWAS). Changes in dietary fat intake lead to epigenetic alterations and corresponding changes in gene expression. However, it remains unclear whether these alterations are causal for T2D. The literature supports a protective role of

polyunsaturated fatty acids (PUFA) in T2D development, whereas the effects of saturated and monounsaturated fatty acids (SFA and MUFA) remain uncertain. Many interactions between genetic variants and dietary fat intake (GxF interactions) on T2D risk have been reported in the literature, but robust replication studies have not supported the initial evidence. Icons made by Freepik, Eucalypt, Smashicons, Vectors Market, and Surang from www.flaticon.com

content to prevent T2D [6]. The strongest evidence concerning the relationship between dietary fat and T2D risk comes from meta-analyses of prospective cohort studies of incident T2D and randomized controlled trials (RCTs) of surrogate endpoints of T2D, such as fasting glucose and insulin sensitivity. The strengths of prospective cohort studies are large sample sizes and long follow-up periods that allow analysis of incident T2D as the outcome. However, the assessment of dietary intake is most often carried out using food records and questionnaires that are affected by reporting bias and inaccurate assessment of fat intake from mixed dishes and prepared foods [7]. Direct measurement of fatty acid concentrations from the circulation or tissues avoids biases relating to self-report of dietary intakes, but the measured concentrations may not only reflect dietary intake but also endogenous metabolic processes [8, 9]. On the other hand, RCTs allow controlling for caloric intake and the composition of diet, but are compromised by small sample size and short duration that only allow evaluation of intermediate endpoints of T2D.

Evidence regarding the relationship between dietary fat quality and T2D risk is mostly consistent between prospective cohort studies and RCTs. A recent meta-analysis of individual-level, self-reported dietary data from 102,350 adults, of whom 20,015 developed incident T2D, showed no significant association between SFA or *trans*-fat intake and T2D, whereas higher intake of total polyunsaturated fatty acids (PUFA) and omega-6 PUFA was associated with a lower risk of T2D and higher monounsaturated fatty acid (MUFA) intake with a higher risk [10••]. The negative results concerning SFA intake and T2D risk agree with literature-based meta-analyses of prospective cohort studies [4, 11, 12], as well as with the only RCT on dietary fat modification and incident T2D published thus far, where a reduction in SFA intake as part of overall dietary fat reduction was not associated with T2D risk among 48,835 postmenopausal women [13]. The protective effect of PUFA on T2D risk is similarly consistent with literature-based meta-analyses of cohort studies on incident T2D [14] and with results from RCTs that have shown improvements in glycemic

control when SFA are replaced with PUFA [15]. The meta-analyses of individual-level data of circulating concentrations of PUFA in 39,740 adults have indicated that it is the plant-derived omega-6 linoleic acid (18:2) and omega-3 alpha linolenic acid (18:3) that are specifically associated with lower T2D risk, whereas no protective effect has been found for other PUFA [16, 17].

The effect of MUFA on T2D risk may be confounded by the source of dietary MUFA. While a detrimental effect of higher MUFA intake on incident T2D risk was observed in the abovementioned meta-analysis of 102,350 adults who self-reported their dietary intakes [10], it is important to note that MUFA intake in populations from North America and non-Mediterranean European countries that constituted the study population is driven by the consumption of meats and dairy products. In contrast, RCTs studying the replacement of SFA with MUFA have shown improvements in insulin sensitivity when MUFA has been derived from plant-based sources [18–20].

While nutritional recommendations generally advise reduction of SFA intake, recent studies suggest that the effects of SFA on T2D risk may depend on the carbon chain length of the fatty acids. An analysis of the circulating concentrations of long-chain SFA myristic acid (14:0), palmitic acid (16:0), and stearic acid (18:0) among 12,403 incident cases of T2D and 16,154 randomly selected controls showed an association with increased T2D risk [21]. In contrast, circulating concentrations of odd-chain SFA (15:0 and 17:0), specific for milk fat, were associated with a decreased risk of T2D, and these findings were subsequently confirmed in a meta-analysis of 63,682 adults of whom 15,158 developed incident T2D [22]. The circulating concentrations of very long-chain SFA arachidic acid (20:0), behenic acid (22:0), and lignoceric acid (24:0) found in peanuts and macadamia nuts also showed a protective effect on T2D risk [23]. However, very long-chain SFA are also produced endogenously, and their observed protective effect on T2D risk may thus reflect both higher dietary intake of these fatty acids and improved fatty acid metabolism. Likewise, the observed detrimental effect of long-chain SFA on T2D risk may partly reflect impaired fatty acid metabolism [21].

The beneficial effect of dairy fat on T2D risk is supported by results from literature-based meta-analyses of prospective cohort studies utilizing self-reported dietary data [24]. However, no impact of high vs. low consumption of dairy foods on fasting glucose or insulin resistance was found in a meta-analysis of published RCTs [25]. Furthermore, no evidence of a causal effect of dairy intake on T2D risk, fasting glucose, or insulin resistance was found in Mendelian randomization studies utilizing the lactase LCT-13910 variant as a genetic instrument for dairy intake [26–28]. The inconsistencies between findings from prospective cohort studies vs RCTs and Mendelian randomization studies suggest that the observational results may be confounded by other dairy

components (vitamin D, calcium, protein etc.), processes related to fermentation of dairy foods or other factors.

Taken together, there is consistent evidence on the benefit of PUFA in T2D prevention, whereas the effects of SFA subtypes and MUFA in T2D prevention remain uncertain.

Fat Intake, Epigenome, and Risk of T2d

Several recent studies highlight that changes in fat intake may result in short- and long-term epigenetic alterations in the pancreas and other tissues that are critical for glucose homeostasis, which may mediate the effects of dietary fats on T2D risk by modifying gene function [29]. In vitro, exposure of clonal beta-cells to high levels of the SFA palmitic acid (16:0) for 48 hours was associated with an increase in histone acetyl transferase (HAT) activity and altered histone acetylation that regulates chromatin accessibility [30]. In human pancreatic islets, exposure to high levels of palmitic acid led to impaired insulin secretion and affected the expression of 290 genes with a corresponding change in DNA methylation [31].

In human intervention studies, a five-day high-fat diet was associated with changes in DNA methylation and gene expression patterns in human skeletal muscle cells [32, 33]. The changes were partly reversible by returning to control diet [32, 33]. A seven-week SFA-rich diet led to elevated liver and visceral fat accumulation compared with PUFA-rich diet despite similar weight gain, and adipose tissue DNA methylation of 4875 CpG sites was affected differently between the two diets [34]. While both SFA and PUFA overfeeding led to an increase in DNA methylation overall, SFA overfeeding increased the mean methylation of 125 genes by > 1%, while PUFA overfeeding changed the mean methylation of as many as 1797 genes. On the other hand, SFA overfeeding altered the adipose tissue expression of 22 genes, whereas no significant changes in adipose gene expression were found in response to PUFA overfeeding [34]. Finally, it has been shown that methylation levels also differ in blood samples of preadolescents according to their intake of PUFA or SFA [35].

Overall, evidence points to widespread effects of dietary fat on epigenetic regulation in tissues that are important for metabolism and, furthermore, that these epigenetic alterations differ depending on fatty acid composition of the diet. However, it remains unclear which of the identified epigenetic modifications, if any, are causal or predictive for T2D development.

Gene-Dietary Fat Interactions and T2d Risk

Twin, family, and population studies suggest a strong heritable component for T2D [36–39]. The progress in identifying the genetic risk variants that contribute to this heritability was

very slow at first, due to the lack of study approaches that could uncover genetic variants with modest or low effect sizes that are now known to characterize the genetic architecture of T2D [40]. In 2005, the development of chip-based genotyping arrays made it possible to initiate genome-wide association studies (GWAS) which, to date, have identified hundreds of independent genetic variants associated with T2D, explaining up to 50% of T2D heritability [41–46].

The success of GWAS of T2D has also spurred a discussion about using genetic findings to personalize recommendations for dietary fat intake in T2D prevention. The first step in the development of such recommendations is to identify the genetic variants and genes that are sensitive to changes in dietary fat intake and thus could predict individual responses to specific dietary modifications in the prevention of T2D. Over the last 15 years, many promising interactions between genetic variants and dietary fat intake on T2D risk have been reported in epidemiological studies [47]. However, a recent systematic replication effort in the EPIC-Interact Consortium, including 21,148 adults, of whom 9403 developed incident T2D, was not able to replicate any of the published interactions [47]. The lack of success in replicating interactions could, in part, reflect insufficient statistical power. Other studies have attempted to improve power by combining T2D risk alleles into a genetic risk score and examining the interaction between the score and dietary fat intake. In the largest meta-analysis of this kind, including individual-level data from 102,350 adults, of whom 20,015 developed incident T2D, no significant evidence of interaction between genetic predisposition to T2D and dietary intake of total fat, SFA, MUFA, total PUFA, omega-6 PUFA, omega-3 PUFA, or *trans*-fat was seen [10].

It has been proposed that the genetic variants identified in GWAS for association with T2D risk may not be the same variants that interact with lifestyle factors, because the effects of the identified T2D risk variants are rather homogenous across populations [48]. Genome-wide studies of gene-fat interactions could allow discovery of genetic loci with weak or no marginal effect on T2D risk. However, to our knowledge, no such studies have been published to date.

Taken together, there are currently no known replicated interactions between genetic variants and dietary fat intake on T2D risk. Hence, there is no indication for personalized recommendations regarding dietary fat intake and prevention of T2D based on genetic variation at present. RCTs of T2D have demonstrated that healthy diet, together with weight loss and regular exercise, is effective in the prevention of T2D in high-risk individuals [49, 50]. Current findings support these interventions to be deployed independent of the estimated genetic predisposition of an individual, as genetic burden does not seem to modify the effectiveness of the interventions.

Conclusions

There are still major gaps in the evidence regarding the relationship between dietary fat intake and T2D risk. Strong evidence supports a protective role of PUFA in T2D prevention, whereas more studies are needed to elucidate the effect of SFA and MUFA on T2D risk. Dietary fat modifications lead to specific epigenetic alterations that could mediate the effects of dietary fat on T2D risk. However, it is not yet known whether these alterations are causal for T2D development. No interactions between genetic variants and fat intake on T2D risk have so far been robustly replicated. Overall, there is no evidence to support tailored dietary fat recommendations based on individual genetic risk profile to prevent T2D.

Compliance with Ethical Standards

Conflict of Interest Germán D. Carrasquilla and Hermina Jakupović declare that they have no conflict of interest. Tuomas O. Kilpeläinen reports grants from Novo Nordisk Foundation.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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