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Dietary fats and prevention of type 2 diabetes

Ulf Risérus[a], **Walter C. Willett**[b], and **Frank B. Hu**[b]

a*Clinical Nutrition and Metabolism, Department of Public Health and Caring Sciences, Faculty of Medicine, Uppsala University, Sweden*

b*Departments of Nutrition and Epidemiology, Harvard School of Public Health, and Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA, USA*

Abstract

Although type 2 diabetes is determined primarily by lifestyle and genes, dietary composition may affect both its development and complications. Dietary fat is of particular interest because fatty acids influence glucose metabolism by altering cell membrane function, enzyme activity, insulin signaling, and gene expression. This paper focuses on the prevention of type 2 diabetes and summarizes the epidemiologic literature on associations between types of dietary fat and diabetes risk. It also summarizes controlled feeding studies on the effects of dietary fats on metabolic mediators, such as insulin resistance. Taken together, the evidence suggests that replacing saturated fats and trans fatty acids with unsaturated (polyunsaturated and/or monounsaturated) fats has beneficial effects on insulin sensitivity and is likely to reduce risk of type 2 diabetes. Among polyunsaturated fats, linoleic acid from the n-6 series improves insulin sensitivity. On the other hand, long-chain n-3 fatty acids do not appear to improve insulin sensitivity or glucose metabolism. In dietary practice, foods rich in vegetable oils, including non-hydrogenated margarines, nuts, and seeds, should replace foods rich in saturated fats from meats and fat-rich dairy products. Consumption of partially hydrogenated fats should be minimized. Additional controlled, long-term studies are needed to improve our knowledge on the optimal proportion of different types of fats to prevent diabetes.

1. Introduction

Dietary composition could play a significant role in improving insulin sensitivity and reducing risk of diabetes and its complications [1]. The role of dietary fat in type 2 diabetes has been of clinical interest for many decades. Kinsell et al. were probably the first to report that type of fat consumed could influence insulin action in humans [2]. In a case report, a patient with type 1 diabetes required less exogenous insulin after substituting safflower oil rich in n-6 FA for triglycerides rich in saturated fatty acids (SFA) and oleic acid. Through our daily dietary intake, we ingest a variety of fatty acids (FAs) with different chain-length and numbers of double bonds. The most abundant dietary FAs are oleic acid, linoleic acid, palmitic acid, and stearic acid. These are reflected in plasma and tissue lipids. Thus, dietary fatty acid composition, to a large extent, determines the relative availability and storage of FAs in tissues [3].

The aim of this paper is to review the role of different types of dietary fat on insulin sensitivity and diabetes risk, and to update previous reviews on this topic [4-6]. Since there are no long-

Corresponding author: Dr Ulf Risérus, Clinical Nutrition and Metabolism, Department of Public Health and Caring Sciences, Uppsala Science Park, 75185, Uppsala, Sweden, Tel: +46186117971, Fax: +46186117976, E-mail: ulf.riserus@pubcare.uu.se.

term randomized trials on the effect of dietary fat quality on diabetes risk, this review will focus on the effect of dietary FAs on surrogate endpoints, e.g., insulin sensitivity in randomized controlled interventions, and the relation of dietary fats to diabetes incidence in epidemiologic studies. In controlled feeding studies, test diets are typically isocaloric and differ only in dietary fat quality. However, such studies are usually small and of short duration, and thus, can only evaluate intermediate endpoints, e.g., insulin sensitivity.

Epidemiologic studies, on the other hand, are typically large, with long follow-up periods. Some of these studies have used objective methodology to assess dietary fat quality with biomarkers of FA intake, e.g., serum FA composition. Other studies have assessed dietary fat quality using food records or questionnaires. Both types of studies will be discussed, but the latter have previously been reviewed in detail [5], and therefore, will only be briefly updated here.

2. Epidemiological studies

2.1. Assessment of dietary FA intake

In that the composition of several FAs in serum lipids or tissues reflects the composition of dietary FAs, they can be used as objective and reliable biomarkers of the relative FA content of the diet [7-10]. FAs that cannot be synthesized endogenously from carbohydrates are the best biomarkers of FA intake. These include polyunsaturated fatty acids (PUFA), such as linoleic acid (n-6) and α-linolenic acid (n-3), *trans* fatty acids (TFA), and odd numbered FAs, e.g., 15:0 and 17:0 [11]. Excellent biomarkers are also available for long-chain n-3 FAs found in oily fish. Conversely, SFA (except SFAs with an odd number of carbon atoms) and monounsaturated fatty acids (MUFA) are usually considered weaker biomarkers since they reflect not only dietary intake, but also, to some extent, de novo lipogenesis.

The ability to assess the source of FAs and food patterns is an advantage offered by food records or food frequency questionnaires. For example, increased MUFA intake (i.e., oleic acid) could be due to either high consumption of meats and dairy products, or non-hydrogenated vegetable oils (e.g., rapeseed oil and olive oil). This may explain why observational studies found a positive association between monounsaturated fat and insulin concentrations, [5] while a large controlled intervention showed that replacing SFA with MUFA led to improved insulin sensitivity [12].

The lipid fraction or tissue in which FAs are measured should be considered when interpreting biomarkers of FA intake. Depending on which FAs are being studied, the activity of enzymes responsible for desaturating and elongating FAs can also influence FA composition [13]. In addition, the FA composition in tissues can be affected by genetic, hormonal and lifestyle factors [13].

FA ratios, i.e., product-to-precursor ratios, have been used in several epidemiological studies as markers for desaturase enzyme activities, and recently, as indirect markers of saturated fat intake, e.g., the 16:1n-7/16:0 ratio [14] [15]. This ratio may be a better marker of saturated fat intake than serum palmitic acid proportions alone [14], but further research is needed on the potential use of ratios as markers of dietary intake. It should be noted that biomarkers of FAs provide data as percentages of total FAs, not absolute amounts.

2. 2. Cross-sectional studies of dietary fat and diabetes

Many cross-sectional or case-control studies have compared dietary fat intake of diabetic patients and healthy subjects. In the multinational, multicentre study of the Mediterranean Group for the Study of Diabetes, dietary surveys were conducted in 6 countries. The results showed that recently-diagnosed diabetics had both higher relative intake of total fat and SFA

from animal fat sources compared with healthy controls. Furthermore, subjects with undiagnosed type 2 diabetes had significantly higher intake of saturated fat compared with controls [16]. The latter is relevant because these subjects did not have the chance to change their diet due to diagnosis of type 2 diabetes or dietary treatment [16].

The problem of confounding still remains. Nonetheless, these data are in line with a Dutch study on patients with newly-diagnosed diabetes; subjects who had a higher intake of total fat (40% energy, E), and in particular, saturated fat (15% E) [17]. It should be noted that cross-sectional observational studies investigating links between dietary fat quality and prediabetes/diabetes require cautious interpretation due to several sources of bias, e.g., change of diet due to obesity or prediabetes, or failure to make detailed adjustments for adiposity or physical activity.

2.3. FA biomarkers, insulin resistance, and diabetes risk

2.3.1. FA biomarkers and insulin sensitivity: cross-sectional studies—Cross-sectional studies that use the clamp technique to measure insulin sensitivity and FA composition in skeletal muscle show a direct relation between the proportion of long-chain PUFA and insulin action [18]. In contrast, the more saturated the muscle membrane, the more insulin resistant the individual [18]. A cross-sectional study in Pima Indians reported similar outcomes [19], i.e., an inverse association between the amount of n-3 FAs and insulin resistance.

The Uppsala Longitudinal Study of Adult Men (ULSAM) included 2,322 50-year-old men at baseline who have been followed for 35 years, with detailed metabolic measurements approximately every 10 years. Cross sectional data at age 70 suggest that there is no link between n-3 FA composition (in skeletal muscle phospholipids and serum cholesterol esters) and insulin sensitivity. Rather, they demonstrate a FA composition in serum cholesterol esters and skeletal muscle phospholipids; a composition associated with insulin resistance and characterized by high proportions of palmitic (16:0), palmitoleic (16:1n-7) and dihomo-γ-linolenic (20:3 n-6) acids and a low proportion of linoleic acid (18:2n-6) [13,20]. A smaller cross-sectional study also found a negative correlation between SFA in serum phospholipids and insulin sensitivity in healthy subjects. Conversely, there was a positive relation between linoleic and arachidonic acid and insulin action [21]. In a Finnish population-based study, a FA pattern with high palmitic and palmitoleic acid, and low linoleic acid in cholesterol esters, has been associated with glucose intolerance and type 2 diabetes [22].

2.3.2. FA biomarkers and diabetes: prospective studies—Several prospective studies suggest that a FA pattern that reflects high intake of saturated fat and low relative intake of linoleic acid predicts type 2 diabetes. A prospective study of the ULSAM cohort, in which 50-year-old men were followed for 10 years, showed that diabetes incidence during follow-up was related to the FA composition of serum cholesterol esters at baseline [23]. The differences in serum FA composition were highly significant in subjects who remained normoglycemic (n = 1,753) compared with those who later developed type 2 diabetes. The men who developed diabetes had higher proportions of SFA and palmitoleic acid, a low proportion of linoleic acid, and a relatively high content of gamma-linolenic (18:3n-6) and dihomo-gamma-linolenic (20:3, n-6) acids in the serum cholesterol esters. The outcome was also similar after adjustment for differences in body mass index (BMI) [23]. In line with the cross-sectional analyses of ULSAM, there were no associations between n-3 fatty acids in serum and diabetes incidence during follow up.

In a Finnish prospective cohort study, middle-aged normoglycemic men (n = 895) were followed for 4 years [24]. Those who developed impaired fasting glucose (IFG) (n = 56) or type 2 diabetes (n = 34) during follow-up had higher proportions of esterified and non-esterified

saturated FAs and decreased proportions of polyunsaturated FAs at baseline. Logistic regression analyses adjusted for age, obesity, and fasting lipid, glucose, and insulin concentrations showed that men with proportions of non-esterified and esterified linoleate in the upper third had nearly half the risk for developing IFG or diabetes compared with those in the lower third [24]. A prospective study (9-year follow-up) in 2,909 American subjects 45-64 years of age also showed that those who developed diabetes during follow-up (n = 252) had a higher proportion of SFA in serum cholesterol esters and phospholipids [25]. These results were consistent with the studies by Vessby et al. and Laaksonen et al. [23,24]. The association remained after adjustments for age, sex, BMI, waist-to-hip ratio, alcohol intake, cigarette smoking, physical activity, education, and parental history of diabetes. Diabetes incidence was positively associated with the proportions of palmitic (16:0), palmitoleic (16:1n-7), and dihomo-gamma-linolenic (20:3n-6) acids, and inversely associated with the proportion of linoleic acid in cholesterol esters. In phospholipids, there was a positive association between SFA (palmitic and stearic acid) and diabetes risk [25].

The potential role of SFA intake in the development of diabetes is also in line with recent data from the ULSAM cohort. These suggest that saturated fat intake among 50-year-old men independently predicts insulin resistance 20 years later, a finding reflected by an elevated 16:1n-7/16:0 ratio in cholesterol esters [15]. In prospective studies, most of the associations remained after adjusting for several lifestyle factors, including physical activity, smoking, and obesity.

A recent prospective study with nested case-cohort analyses (Melbourne Collaborative Cohort Study) investigated both dietary FA intake reported by food frequency questionnaire as well as FA composition of plasma phospholipids in relation to type 2 diabetes in 3,737 adults [26]. Total SFA in phospholipids and reported dietary intake were positively related to diabetes incidence. Plasma linoleic acid was inversely associated with diabetes incidence, but dietary intake of linoleic acid showed a positive association [26]. This contradictory result could reflect measurement error in self-reported dietary intake. However, lack of adjustment for total energy intake may also lead to biased estimates. Further study is needed to determine the extent to which reduced plasma linoleic acid proportions might reflect metabolic dysfunction (i.e., reduced delta-6 desaturase activity).

2.4. Self-reported dietary intakes and diabetes risk: prospective studies

Several prospective studies using food records or questionnaires to assess dietary fat intake have been summarized in prior reviews by Hu et al. [5] and Lichtenstein and Schwab [6]. Although not entirely consistent, prospective data from self-reported dietary intake generally support those from studies that use biomarkers, i.e., those that suggest an inverse association between n-6 PUFA intake and diabetes risk [5,6]. For example, the Nurses' Health Study—with 84,204 women aged 34-59 prospectively followed for 14 years (2,507 diabetes cases during follow-up)—showed that PUFA intake assessed by a validated food frequency questionnaire was inversely and significantly associated with incidence of type 2 diabetes, whiles MUFA or SFA intake was not related to diabetes risk after adjusting for (BMI) and other covariates [27]. Risk reduction related to PUFA was maximized when PUFA replaced trans fatty acid (TFA) intake. In the same cohort, a low polyunsaturated to saturated fat (P/S) ratio was independently related to an increased risk of cardiovascular disease in women with type 2 diabetes [28].

In this study, a 5% replacement of SFA with MUFA or carbohydrates is associated with respective risk reduction of cardiovascular disease in diabetics of 37% and 22%. Nuts, an important food source of PUFA and MUFA in this population, have been associated with lower risk of diabetes in women even after adjusting for fibre intake and various lifestyle factors [29]. Twelve-year data from the Health Professionals Follow-up Study—with 42,504 men aged

40-74 years (1,321 diabetes cases during follow-up)—showed that SFA intake was associated with increased risk of diabetes independent of cereal fibre intake and established risk factors, but not BMI [30]. In addition, multivariate analyses showed that regular processed meat consumption was related to increased diabetes risk. PUFA intake was not significantly associated with diabetes risk in the whole population, but there was an inverse relation between the intake of linoleic acid and diabetes incidence among men under the age of 65 and in normal-weight subjects. In the Iowa Women's Health Study, incidence of type 2 diabetes during 11 years of follow-up was independently and inversely associated with vegetable fat intake reported by a food frequency questionnaire [31]. There was also an inverse relation between diabetes incidence and substitution of PUFA for SFA. These associations remained significant after adjusting for obesity and fat distribution, physical activity, and smoking. In addition, there was a significant positive association between animal fat intake and diabetes incidence, which was also independent of obesity and lifestyle factors [31].

In the European prospective investigation of the Cancer Norfolk Study, diet was assessed by semiquantitative food frequency questionnaire [32]. Of the 23,631 men and women who were followed, 414 subjects developed diabetes during 3-7 years. An increased dietary P/S ratio was associated with a reduced risk of diabetes independent of various lifestyle factors, but not of obesity and central fat distribution [32]—a finding similar to the results from the Health Professionals Follow-up Study [30]. It should be noted that studies measuring serum FA composition or other prospective data using reported dietary fat intake found similar relations with diabetes, but obesity did not mediate the associations [23,24] [31]. It could also be argued that obesity lies in the causal pathway between fat intake and diabetes, and thus, it would not be appropriate to routinely adjust for BMI when examining relations between dietary fat quality and diabetes.

Epidemiological data on n-3 FA intake and diabetes risk and insulin sensitivity have been somewhat inconsistent [5], but prospective cohort studies that have examined the association between long chain n-3 FA and type 2 diabetes generally show no appreciable association.

2.5. Trans fatty acids (TFA) and diabetes

The adverse effects of trans fatty acids (TFA) on cardiovascular disease are well-established [33,34], but their role in the development of type 2 diabetes has not been as widely investigated. The Nurses' Health Study is the largest and most detailed epidemiologic study because of the many repeated assessments of diet [27]. It showed a positive association between TFA intake and risk of diabetes, with a clear dose-response relation. Small epidemiologic studies or those that did not include repeated measures of diet, did not indicate a positive association [31]. Although it is not proven that inflammation is a causative factor in diabetes development, mounting evidence suggests that TFA increases inflammatory cytokines that are related to risk of diabetes [35].

2.6. Dairy fat, insulin resistance, and diabetes

Dairy fat contains high amounts of SFA (~70% of milk fat is SFA). In addition to lauric acid (12:0), cow's milk is also abundant in short-chain and medium chain FA with 4-10 carbons as well as odd numbered FAs, e.g., 15:0 and 17:0. In a cross-sectional study of elderly Swedish men, dairy fat intake was inversely associated with several metabolic anomalies, including elevated fasting plasma glucose concentrations [36]. It was also significantly correlated with 15:0 and 17:0 in serum lipids, which can be considered biomarkers of dairy fat intake. In contrast, plasma phospholipid concentrations of 15:0 were inversely related to incidence of type 2 diabetes in a case-cohort study with 4 years of follow-up [26]. Pereira et al. found that among young adults who were overweight at baseline (but not among leaner individuals), dairy

consumption was also inversely related to the incidence of metabolic factors associated with insulin resistance [37].

In the Health Professionals Follow-up Study, a dietary pattern characterized by higher dairy intake, especially low-fat dairy intake, was related to a reduced risk of type 2 diabetes in men [38]. A dietary pattern rich in low-fat dairy products has also been associated with lower risk of type 2 diabetes in middle-aged or older women [39]. It is not clear which components of dairy products contribute to the observed benefit. A stronger association with low-fat or fat-free dairy suggests that dairy fat is unlikely to have independent protective effects against diabetes.

3. Controlled dietary interventions

3.1. Overview

No long-term randomized controlled studies on the relation between the quality of dietary fat and diabetes risk exist. Thus, we have to rely on short-term studies on the effects of dietary FAs on surrogate endpoints, e.g., insulin sensitivity, insulin secretion, or glycemic control. FAs may not only act through alterations of cell-membrane FA composition and function, but also through short-term alterations of gene expression and enzyme activities. Vessby reviewed several randomized controlled short-term studies conducted in the 1990s, mainly in healthy subjects [4]. These lasted up to 4 weeks [40-43], except for one study in hypertensive subjects, which had a duration of 16 weeks [44]. All of these studies directly measured insulin sensitivity by euglycemic clamp or minimal modelling, and had isocaloric test diets that differed only in dietary fat quality. Limitations included short duration and small sample size. Overall results from these studies showed no significant effect of SFA, MUFA, or PUFA on insulin sensitivity [4].

Two other studies compared PUFA with MUFA in subjects with either impaired glucose tolerance (IGT) [45] or type 2 diabetes [46]. Outcomes showed no significant differences in insulin sensitivity despite significant changes in plasma FA composition. Notably, the study on patients with diabetes lasted only 24 days, with the proportion of total fat in the test diets increased from a baseline of 34% E to ~40% [46]. The other study lasted for 8 weeks, but differed in the proportion of total dietary fat and carbohydrates, complicating a direct comparison between the two test diets [45]. Several additional studies have been conducted in the past few years. These tend to show somewhat more positive results, possibly because of their greater statistical power. Still, minor variations in population demographics and type of fat source can contribute to differences in outcomes. Below, we describe some of the latest studies in more detail.

3.2. Role of monounsaturated fats

In a randomized controlled crossover study in 25 healthy subjects, isocaloric diets were consumed for 4 weeks, with all diets prepared in a metabolic kitchen [47]. There were no differences in insulin sensitivity between diets rich in SFA, MUFA, or trans fat (9% E either as palmitic acid, oleic acid and 18:1 trans, respectively, with total fat ~28% E). However, in the subgroup of overweight subjects, SFA reduced insulin sensitivity (by 24%) compared with MUFA. This decrease, however, was not statistically significant, possibly due to a small number of subjects in the subgroup (n = 7). This finding indicates that type of fat might be more important in subjects with an “insulin resistant phenotype,” but the premise needs further investigation in larger studies.

The KANWU study is the largest randomized controlled clinical trial to date [12]. This multicentre trial included 162 healthy participants recruited from 5 different countries. Subjects received isocaloric diets that differed only in fat quality; both the SFA diet (17% E from SFA,

14% E from MUFA, 6% E from PUFA) and the MUFA diet (23% E from MUFA, 8%E from SFA, 6% E from PUFA) had a total fat intake of 37% E. All subjects were supplied with edible fats to be used as spreads on bread, for cocking, and as dressings. Core foods, such as margarines, oils and a range of other staple items, were provided. Subjects did not know which diet they were on.

The main finding was that substitution of MUFA for SFA improved insulin sensitivity, which was impaired on the SFA diet (-10%, P = 0.03) but did not change on the MUFA diet (+2%, NS) (P = 0.05 for difference between diets). A second important finding was that subjects with higher total fat intake (i.e., >37%E) did not obtain a beneficial effect from MUFA. This outcome is consistent with results from a controlled lifestyle intervention where changes in estimated desaturase activities (derived from plasma FA composition) were related to changes in insulin sensitivity only in subjects with a total fat intake below 35.5% E [48]. This potential interaction between fat quality and quantity needs further investigation, especially since overall evidence does not suggest that total fat intake alone plays an important role in determining insulin sensitivity.

In line with the KANWU study, a controlled short-term trial in healthy subjects (n = 59) reported impaired insulin sensitivity in those who consumed a SFA-enriched diet compared with those who consumed a MUFA-rich diet [49]. The total fat content of the test diets was 38% E. The same group recently conducted another controlled crossover study in insulin resistant (n = 11) offspring of obese diabetic patients. Again, the results indicated that a diet rich in MUFA improved insulin sensitivity compared with a diet rich in SFA [50]. These effects were observed despite the short intervention period (28 days) and the relatively high intake of total fat.

3.3. Role of polyunsaturated fats

Linoleic acid is the most abundant PUFA in the diet. In a randomized trial by Summers et al., a diet rich in PUFA n-6 (e.g., linoleic acid) improved insulin sensitivity when compared with a SFA-rich diet after only 5 weeks [51]. It should be noted that more than half of the participants were obese or had type 2 diabetes. Another significant finding was a reduction of visceral fat when SFA was replaced by PUFA, but it is unclear whether the reduction mediated the improved insulin sensitivity.

This study indicates that it may be possible to influence insulin sensitivity within 4-5 weeks by changing fat quality alone [47,49-51]. It also suggests that FAs could affect insulin sensitivity by other mechanisms (e.g., gene expression) rather than by changes in cell membrane FA composition, which entails a longer process. Despite the important long-term effects of FAs on insulin action, there are few data from randomized clinical trials. Therefore, large prospective epidemiological studies with extended follow-up may have a particularly important role in the evaluation of long-term effects of FA on the risk of diabetes.

Data from controlled feeding studies in patients with diabetes are also very limited. Heine and colleagues conducted a randomized crossover study in subjects with type 2 diabetes almost 2 decades ago [52]. Diets were isocaloric and total fat content was approximately 38% E. Two 30-week periods with different dietary P/S-ratios (0.3 vs. 1.0) were compared in 14 patients (completers). The differences in diets were achieved by substitution of linoleic-acid-enriched oils and margarines with SFA; other nutrients were kept constant. Insulin sensitivity was assessed by calculating metabolic clearance rate (MCR) from insulin dose response curves [53].

During the high P/S diet, insulin-mediated glucose disposal at physiologic insulinemia increased significantly (32%) compared with the low P/S diet. However, at higher insulin

infusion rates, the MCRs of glucose were not significantly different between diets [52]. Since the total fat content was high (38%), it is possible that a beneficial effect of the high P/S-diet was underestimated [12,48]. Nevertheless, this study is important since it suggests a potential long-term benefit from the substitution of SFA with n-6 PUFA. This outcome is in line with recently-reported short-term findings [51].

3.4. Role of n-3 FA from fish

Animal experiments indicate that intake of fatty acids from the n-3 family, from fish oils in particular, have a beneficial effect on insulin sensitivity in rats [54], but not in healthy humans [12] or in subjects with type 2 diabetes as shown in several controlled studies [4,55]. These results are consistent with those from a recent study in which n-3 supplementation (3.5% E) for 14 weeks had no effect on high-molecular weight adiponectin concentrations in moderately obese subjects [56]. Insulin sensitivity, however, was not measured in that study. Moreover, a recent report indicated that high doses of n-3 FA (fish oil) may even impair insulin action in subjects with type 2 diabetes [57].

3.5. The n-6/n-3 ratio and insulin resistance

The few available studies on the n-6/n-3 FA ratio suggest that it does not play a major role in the development of insulin resistance and type 2 diabetes [58]. In particular, controlled intervention studies show that n-6/n-3 ratio has no impact on insulin action [59,60]. In contrast (as discussed above and as previously pointed out by others [61]), lowering the intake of linoleic acid may actually increase both diabetes and cardiovascular risk [33,61]. Although it is believed that n-6 FAs are proinflammatory compared with n-3 FAs, this hypothesis is not supported by clinical or epidemiologic data in humans. Rather, some data show that linoleic acid is inversely related to plasma C-reactive protein concentrations [62,63], and might have anti-inflammatory effects by down-regulating NF kappa B [61].

3.6. Trans fatty acids and insulin resistance

Data from controlled feeding studies on the effects of TFA on insulin sensitivity in humans have been inconsistent [64], but the duration of these studies is relatively short. In monkeys, a 5-year controlled study found that TFA feeding (versus oleic acid) caused insulin resistance and impaired glucose metabolism [65].

Conjugated linoleic acid (CLA)—a group of 18:2n-6 conjugated *trans* FAs found in dairy fat and partially hydrogenated vegetable oils—may have diabetogenic effects in humans. Data demonstrate that the *trans*10*cis*12-CLA isomer, in doses of 1% E, impairs insulin sensitivity in abdominally obese men with the metabolic syndrome [66]. In fact, *trans*10*cis*12-CLA is the most potent FA known with regard to impaired insulin sensitivity, at least in prediabetic subjects with the metabolic syndrome [64].

Impaired insulin action has been closely linked to CLA-induced lipid peroxidation and inflammation [67], but other mechanisms, such as ectopic fat accumulation and downregulation of peroxisome proliferator activating receptors (PPARs) may also be involved. Although the potential diabetogenic effect of CLA is mainly ascribed to *trans*10*cis*12-CLA, a commercial CLA isomer mixture caused impaired insulin sensitivity in subjects with type 2 diabetes [68]. In addition, data show that the cis9trans11-CLA isomer found in dairy fat may cause modest impairment of insulin sensitivity in abdominally obese individuals [69].

4. Dietary fats and diabetes: potential mechanisms

Mechanisms underlying the relation between dietary FAs and incidence of diabetes are still unclear, but the traditional view has been that dietary fat quality mainly affects cell membrane

FA composition and, consequently, cell membrane function [70]. The FA composition of cell membranes is thought to alter several cellular functions, including membrane fluidity, ion permeability, and insulin receptor binding/affinity; functions affected by translocation of glucose transporters interacting with second messengers [71]. Such alterations could, in turn, affect tissue and whole body insulin sensitivity.

More recent experimental data also point toward other mechanisms that involve direct regulatory effects on gene expression and enzyme activity [72]. SFA and MUFA, for example, have minimal effects on lipogenic gene expression, while PUFA (arachidonic acid > eicosapentaenoic acid > docosahexaenoic acid > linoleic acid) suppresses lipogenic expression in vitro [73], partly by binding to and activating nuclear receptors, such as PPARγ [74]. SFA also affects enzyme activities, inflammatory gene expression, and transcription factors that may contribute to its effects on glucose metabolism [75]. As discussed above, the potential benefit of linoleic acid in preventing diabetes may also be related to its potential anti-inflammatory effects [61,62]. This hypothesis requires further investigation in controlled clinical studies. Finally, a diet high in unsaturated long-chain n-6 and n-3 FA may inhibit hepatic lipogenesis and stimulate hepatic FA oxidation, which may improve hepatic insulin sensitivity [72].

In vitro studies and animal experiments suggest that FAs could act directly on insulin-sensitive tissues [58]. In several experiments, PUFAs (e.g., linoleic acid and n-3 FAs) have suppressed lipogenic gene expression and enhanced oxidative metabolism. Conversely, SFAs—palmitic acid, in particular—have had an opposite effect [72,76]. Recently, non-esterified or free fatty acids (FFA) have been identified as ligands for orphan G-protein coupled receptors (GPCRs) that may also mediate some effects of dietary FAs on insulin action and secretion.

It has been suggested that FFA play a critical role in physiological glucose homeostasis [77]. GPR40 and GPR120 are activated by medium and long-chain FFAs. While the former, in particular, may mediate effects of FAs on insulin secretion [78,79], GPR41 and GPR43 can be activated by short-chain FFA [80]. Both groups of FAs are abundant in fat from dairy sources. GPCRs are, therefore, potentially interesting as novel targets for diabetes prevention and treatment.

Another interesting receptor family in this context is the Toll-Like Receptors (TLR). TLRs could be a mediating link between FAs, inflammation and insulin resistance [81]. In vitro studies have shown especially that the saturated FA lauric acid (12:0) initiates TLR4 signaling in macrophages [82-84], but has also been shown that other SFA (14:0, 16:0 and 18:0) could activate TLR4 which in turn trigger inflammatory responses by activating IKK/NF-$_{\kappa}$B pathway and stimulate macrophage production of cytokines [85]. The TLR4 signaling pathway has been identified as a key mediator of deleterious effects of palmitic acid including inflammation, impaired endothelial NO signaling and insulin signal transduction [86]. These experimental studies thus suggest that TLRs are influenced differently depending on the type of FA.

5. Conclusions

Available data from controlled intervention studies suggest beneficial effects on insulin sensitivity when SFA and TFA are replaced with MUFA or PUFA. Outcomes from observational studies using serum biomarkers of dietary fat intake or dietary questionnaires are consistent with those from controlled studies of insulin sensitivity; both suggest that replacing SFA and TFA with PUFA will lower the risk of type 2 diabetes. More controlled long-term studies with sufficient power are needed to identify the optimal dietary FA composition to reduce risk of type 2 diabetes.

Improving fat quality should be considered part of a dietary lifestyle strategy to prevent or manage type 2 diabetes. In practice, replacing fats from red meats and butter with non-hydrogenated vegetable oils and margarines rich in MUFA and/or PUFA should be encouraged to improve insulin sensitivity and reduce diabetes risk. Such dietary fat composition also lowers cardiovascular risk by reducing the serum LDL/HDL ratio and triacylglycerols [33,34].

Besides plant-based oils, nuts and seeds are also excellent sources of both MUFA and PUFA. There is stronger evidence for a potential protective effect from n-6 fatty acids (i.e., those rich in linoleic acid) than for n-3 fatty acids, but more research is needed. Few data are available on the effects of dietary fat quality in individuals with diabetes, and the optimal proportion of SFA, MUFA, and PUFA remains uncertain. Future studies are needed to investigate the interaction between dietary fat quantity and quality with regard to insulin action and metabolic control.

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Abbreviations

FA
: fatty acid

SFA
: saturated fatty acids

MUFA
: monounsaturated fatty acids

PUFA
: polyunsaturated fatty acids

E
: energy

P/S
: polyunsaturated fatty acid/saturated fatty acid

ULSAM
: Uppsala Longitudinal Study of Adult Men

BMI
: body mass index

MCR
: metabolic clearance rate

IGT
: impaired glucose tolerance

IFG
: impaired fasting glucose

PPAR
: peroxisome proliferator activating receptor

CLA

conjugated linoleic acid

FFA

free fatty acids

GPCRs

G-protein coupled receptors

References

1. Mann JI. Nutrition recommendations for the treatment and prevention of type 2 diabetes and the metabolic syndrome: an evidenced-based review. Nutr Rev 2006;64:422–427. [PubMed: 17002238]
2. Kinsell LW, Walker G, Michaels GD, Olson FE. Dietary fats and the diabetic patient. N Engl J Med 1959;261:431–434. [PubMed: 14409236]
3. Hodson L, Skeaff CM, Fielding BA. Fatty acid composition of adipose tissue and blood in humans and its use as a biomarker of dietary intake. Prog Lipid Res 2008;47:348–380. [PubMed: 18435934]
4. Vessby B. Dietary fat and insulin action in humans. Br J Nutr 2000;83 Suppl 1:S91–96. [PubMed: 10889798]
5. Hu FB, van Dam RM, Liu S. Diet and risk of Type II diabetes: the role of types of fat and carbohydrate. Diabetologia 2001;44:805–817. [PubMed: 11508264]
6. Lichtenstein AH, Schwab US. Relationship of dietary fat to glucose metabolism. Atherosclerosis 2000;150:227–243. [PubMed: 10856515]
7. Zock PL, Mensink RP, Harryvan J, de Vries JH, Katan MB. Fatty acids in serum cholesteryl esters as quantitative biomarkers of dietary intake in humans. American journal of epidemiology 1997;145:1114–1122. [PubMed: 9199541]
8. Aro A. Fatty acid composition of serum lipids: is this marker of fat intake still relevant for identifying metabolic and cardiovascular disorders? Nutr Metab Cardiovasc Dis 2003;13:253–255. [PubMed: 14717056]
9. Bingham S. The dietary assessment of individuals; methods, accuracy, new techniques and recommendations. Nutr Abstr Rev (Ser A) 1987;57:705–742.
10. Goris AH, Westerterp-Plantenga MS, Westerterp KR. Undereating and underrecording of habitual food intake in obese men: selective underreporting of fat intake. Am J Clin Nutr 2000;71:130–134. [PubMed: 10617957]
11. Glatz JF, Soffers AE, Katan MB. Fatty acid composition of serum cholesteryl esters and erythrocyte membranes as indicators of linoleic acid intake in man. Am J Clin Nutr 1989;49:269–276. [PubMed: 2916448]
12. Vessby B, Unsitupa M, Hermansen K, Riccardi G, Rivellese AA, Tapsell LC, Nalsen C, Berglund L, Louheranta A, Rasmussen BM, Calvert GD, Maffetone A, Pedersen E, Gustafsson IB, Storlien LH. Substituting dietary saturated for monounsaturated fat impairs insulin sensitivity in healthy men and women: The KANWU Study. Diabetologia 2001;44:312–319. [PubMed: 11317662]
13. Vessby B, Gustafsson IB, Tengblad S, Boberg M, Andersson A. Desaturation and elongation of Fatty acids and insulin action. Ann N Y Acad Sci 2002;967:183–195. [PubMed: 12079847]
14. Warensjo E, Risérus U, Gustafsson IB, Mohsen R, Cederholm T, Vessby B. Effects of saturated and unsaturated fatty acids on estimated desaturase activities during a controlled dietary intervention. Nutr Metab Cardiovasc Dis. 2008
15. Risérus U, Arnlov J, Berglund L. Long-term predictors of insulin resistance: role of lifestyle and metabolic factors in middle-aged men. Diabetes Care 2007;30:2928–2933. [PubMed: 17644620]
16. Thanopoulou AC, Karamanos BG, Angelico FV, Assaad-Khalil SH, Barbato AF, Del Ben MP, Djordjevic PB, Dimitrijevic-Sreckovic VS, Gallotti CA, Katsilambros NL, Migdalis IN, Mrabet MM, Petkova MK, Roussi DP, Tenconi MT. Dietary fat intake as risk factor for the development of diabetes: multinational, multicenter study of the Mediterranean Group for the Study of Diabetes (MGSD). Diabetes Care 2003;26:302–307. [PubMed: 12547853]

17. van de Laar F, van de Lisdonk E, Lucassen P, Tigchelaar J, Meyboom S, Mulder J, van den Hoogen H, Rutten G, van Weel C. Fat intake in patients newly diagnosed with type 2 diabetes: a 4-year follow-up study in general practice. Br J Gen Pract 2004;54:177–182. [PubMed: 15006122]
18. Borkman M, Storlien LH, Pan DA, Jenkins AB, Chisholm DJ, Campbell LV. The relation between insulin sensitivity and the fatty-acid composition of skeletal-muscle phospholipids. N Engl J Med 1993;328:238–244. [PubMed: 8418404]
19. Pan DA, Lillioja S, Milner MR, Kriketos AD, Baur LA, Bogardus C, Storlien LH. Skeletal muscle membrane lipid composition is related to adiposity and insulin action. J Clin Invest 1995;96:2802–2808. [PubMed: 8675650]
20. Vessby B, Tengblad S, Lithell H. Insulin sensitivity is related to the fatty acid composition of serum lipids and skeletal muscle phospholipids in 70-year-old men. Diabetologia 1994;37:1044–1050. [PubMed: 7851683]
21. Pelikanova T, Kazdova L, Chvojkova S, Base J. Serum phospholipid fatty acid composition and insulin action in type 2 diabetic patients. Metabolism 2001;50:1472–1478. [PubMed: 11735096]
22. Salomaa V, Ahola I, Tuomilehto J, Aro A, Pietinen P, Korhonen HJ, Penttila I. Fatty acid composition of serum cholesterol esters in different degrees of glucose intolerance: a population-based study. Metabolism 1990;39:1285–1291. [PubMed: 2246969]
23. Vessby B, Aro A, Skarfors E, Berglund L, Salminen I, Lithell H. The risk to develop NIDDM is related to the fatty acid composition of the serum cholesterol esters. Diabetes 1994;43:1353–1357. [PubMed: 7926311]
24. Laaksonen DE, Lakka TA, Lakka HM, Nyyssonen K, Rissanen T, Niskanen LK, Salonen JT. Serum fatty acid composition predicts development of impaired fasting glycaemia and diabetes in middle-aged men. Diabet Med 2002;19:456–464. [PubMed: 12060056]
25. Wang L, Folsom AR, Zheng ZJ, Pankow JS, Eckfeldt JH. Plasma fatty acid composition and incidence of diabetes in middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) Study. Am J Clin Nutr 2003;78:91–98. [PubMed: 12816776]
26. Hodge AM, English DR, O'Dea K, Sinclair AJ, Makrides M, Gibson RA, Giles GG. Plasma phospholipid and dietary fatty acids as predictors of type 2 diabetes: interpreting the role of linoleic acid. Am J Clin Nutr 2007;86:189–197. [PubMed: 17616780]
27. Salmeron J, Hu FB, Manson JE, Stampfer MJ, Colditz GA, Rimm EB, Willett WC. Dietary fat intake and risk of type 2 diabetes in women. Am J Clin Nutr 2001;73:1019–1026. [PubMed: 11382654]
28. Tanasescu M, Cho E, Manson JE, Hu FB. Dietary fat and cholesterol and the risk of cardiovascular disease among women with type 2 diabetes. Am J Clin Nutr 2004;79:999–1005. [PubMed: 15159229]
29. Jiang R, Manson JE, Stampfer MJ, Liu S, Willett WC, Hu FB. Nut and peanut butter consumption and risk of type 2 diabetes in women. Jama 2002;288:2554–2560. [PubMed: 12444862]
30. van Dam RM, Willett WC, Rimm EB, Stampfer MJ, Hu FB. Dietary fat and meat intake in relation to risk of type 2 diabetes in men. Diabetes Care 2002;25:417–424. [PubMed: 11874924]
31. Meyer KA, Kushi LH, Jacobs DR Jr, Folsom AR. Dietary fat and incidence of type 2 diabetes in older Iowa women. Diabetes Care 2001;24:1528–1535. [PubMed: 11522694]
32. Harding AH, Day NE, Khaw KT, Bingham S, Luben R, Welsh A, Wareham NJ. Dietary fat and the risk of clinical type 2 diabetes: the European prospective investigation of Cancer-Norfolk study. American journal of epidemiology 2004;159:73–82. [PubMed: 14693662]
33. Erkkila A, de Mello VD, Risérus U, Laaksonen DE. Dietary fatty acids and cardiovascular disease: an epidemiological approach. Prog Lipid Res 2008;47:172–187. [PubMed: 18328267]
34. Hu FB, Willett WC. Optimal diets for prevention of coronary heart disease. Jama 2002;288:2569–2578. [PubMed: 12444864]
35. Mozaffarian D. Trans fatty acids - effects on systemic inflammation and endothelial function. Atheroscler Suppl 2006;7:29–32. [PubMed: 16713393]
36. Smedman AE, Gustafsson IB, Berglund LG, Vessby BO. Pentadecanoic acid in serum as a marker for intake of milk fat: relations between intake of milk fat and metabolic risk factors. Am J Clin Nutr 1999;69:22–29. [PubMed: 9925119]
37. Pereira MA, Jacobs DR Jr, Van Horn L, Slattery ML, Kartashov AI, Ludwig DS. Dairy consumption, obesity, and the insulin resistance syndrome in young adults: the CARDIA Study. Jama 2002;287:2081–2089. [PubMed: 11966382]

38. Choi HK, Willett WC, Stampfer MJ, Rimm E, Hu FB. Dairy consumption and risk of type 2 diabetes mellitus in men: a prospective study. Archives of internal medicine 2005;165:997–1003. [PubMed: 15883237]
39. Liu S, Choi HK, Ford E, Song Y, Klevak A, Buring JE, Manson JE. A prospective study of dairy intake and the risk of type 2 diabetes in women. Diabetes Care 2006;29:1579–1584. [PubMed: 16801582]
40. Schwab US, Niskanen LK, Maliranta HM, Savolainen MJ, Kesaniemi YA, Uusitupa MI. Lauric and palmitic acid-enriched diets have minimal impact on serum lipid and lipoprotein concentrations and glucose metabolism in healthy young women. J Nutr 1995;125:466–473. [PubMed: 7876922]
41. Louheranta AM, Turpeinen AK, Schwab US, Vidgren HM, Parviainen MT, Uusitupa MI. A high-stearic acid diet does not impair glucose tolerance and insulin sensitivity in healthy women. Metabolism 1998;47:529–534. [PubMed: 9591742]
42. Fasching P, Ratheiser K, Schneeweiss B, Rohac M, Nowotny P, Waldhausl W. No effect of short-term dietary supplementation of saturated and poly- and monounsaturated fatty acids on insulin secretion and sensitivity in healthy men. Ann Nutr Metab 1996;40:116–122. [PubMed: 8773736]
43. Louheranta AM, Turpeinen AK, Vidgren HM, Schwab US, Uusitupa MI. A high-trans fatty acid diet and insulin sensitivity in young healthy women. Metabolism 1999;48:870–875. [PubMed: 10421228]
44. Toft I, Bonaa KH, Ingebretsen OC, Nordoy A, Jenssen T. Effects of n-3 polyunsaturated fatty acids on glucose homeostasis and blood pressure in essential hypertension. A randomized, controlled trial. Ann Intern Med 1995;123:911–918. [PubMed: 7486485]
45. Louheranta AM, Sarkkinen ES, Vidgren HM, Schwab US, Uusitupa MI. Association of the fatty acid profile of serum lipids with glucose and insulin metabolism during 2 fat-modified diets in subjects with impaired glucose tolerance. Am J Clin Nutr 2002;76:331–337. [PubMed: 12145003]
46. Brynes AE, Edwards CM, Jadhav A, Ghatei MA, Bloom SR, Frost GS. Diet-induced change in fatty acid composition of plasma triacylglycerols is not associated with change in glucagon-like peptide 1 or insulin sensitivity in people with type 2 diabetes. Am J Clin Nutr 2000;72:1111–1118. [PubMed: 11063437]
47. Lovejoy JC, Smith SR, Champagne CM, Most MM, Lefevre M, DeLany JP, Denkins YM, Rood JC, Veldhuis J, Bray GA. Effects of diets enriched in saturated (palmitic), monounsaturated (oleic), or trans (elaidic) fatty acids on insulin sensitivity and substrate oxidation in healthy adults. Diabetes Care 2002;25:1283–1288. [PubMed: 12145222]
48. Corpeleijn E, Feskens EJ, Jansen EH, Mensink M, Saris WH, de Bruin TW, Blaak EE. Improvements in glucose tolerance and insulin sensitivity after lifestyle intervention are related to changes in serum fatty acid profile and desaturase activities: the SLIM study. Diabetologia 2006;49:2392–2401. [PubMed: 16896932]
49. Perez-Jimenez F, Lopez-Miranda J, Pinillos MD, Gomez P, Paz-Rojas E, Montilla P, Marin C, Velasco MJ, Blanco-Molina A, Jimenez Pereperez JA, Ordovas JM. A Mediterranean and a high-carbohydrate diet improve glucose metabolism in healthy young persons. Diabetologia 2001;44:2038–2043. [PubMed: 11719836]
50. Paniagua JA, Gallego de la Sacristana A, Romero I, Vidal-Puig A, Latre JM, Sanchez E, Perez-Martinez P, Lopez-Miranda J, Perez-Jimenez F. Monounsaturated fat-rich diet prevents central body fat distribution and decreases postprandial adiponectin expression induced by a carbohydrate-rich diet in insulin-resistant subjects. Diabetes Care 2007;30:1717–1723. [PubMed: 17384344]
51. Summers LK, Fielding BA, Bradshaw HA, Ilic V, Beysen C, Clark ML, Moore NR, Frayn KN. Substituting dietary saturated fat with polyunsaturated fat changes abdominal fat distribution and improves insulin sensitivity. Diabetologia 2002;45:369–377. [PubMed: 11914742]
52. Heine RJ, Mulder C, Popp-Snijders C, van der Meer J, van der Veen EA. Linoleic-acid-enriched diet: long-term effects on serum lipoprotein and apolipoprotein concentrations and insulin sensitivity in noninsulin-dependent diabetic patients. Am J Clin Nutr 1989;49:448–456. [PubMed: 2923077]
53. Heine RJ, Bilo HJ, van der Meer J, van der Veen EA. Sequential infusions of glucose and insulin at prefixed rates: a simple method for assessing insulin sensitivity and insulin responsiveness. Diabetes Res 1986;3:453–461. [PubMed: 3549121]
54. Storlien LH, Kraegen EW, Chisholm DJ, Ford GL, Bruce DG, Pascoe WS. Fish oil prevents insulin resistance induced by high-fat feeding in rats. Science 1987;237:885–888. [PubMed: 3303333]

55. Kabir M, Skurnik G, Naour N, Pechtner V, Meugnier E, Rome S, Quignard-Boulange A, Vidal H, Slama G, Clement K, Guerre-Millo M, Rizkalla SW. Treatment for 2 mo with n 3 polyunsaturated fatty acids reduces adiposity and some atherogenic factors but does not improve insulin sensitivity in women with type 2 diabetes: a randomized controlled study. Am J Clin Nutr 2007;86:1670–1679. [PubMed: 18065585]
56. Kratz M, Swarbrick MM, Callahan HS, Matthys CC, Havel PJ, Weigle DS. Effect of dietary n-3 polyunsaturated fatty acids on plasma total and high-molecular-weight adiponectin concentrations in overweight to moderately obese men and women. Am J Clin Nutr 2008;87:347–353. [PubMed: 18258624]
57. Mostad IL, Bjerve KS, Bjorgaas MR, Lydersen S, Grill V. Effects of n-3 fatty acids in subjects with type 2 diabetes: reduction of insulin sensitivity and time-dependent alteration from carbohydrate to fat oxidation. Am J Clin Nutr 2006;84:540–550. [PubMed: 16960167]
58. Risérus U. Fatty acids and insulin sensitivity (review). Curr Opin Clin Nutr Metab Care 2008;11:100–105. [PubMed: 18301083]
59. Griffin MD, Sanders TA, Davies IG, Morgan LM, Millward DJ, Lewis F, Slaughter S, Cooper JA, Miller GJ, Griffin BA. Effects of altering the ratio of dietary n-6 to n-3 fatty acids on insulin sensitivity, lipoprotein size, and postprandial lipemia in men and postmenopausal women aged 45-70 y: the OPTILIP Study. Am J Clin Nutr 2006;84:1290–1298. [PubMed: 17158408]
60. Giacco R, Cuomo V, Vessby B, Uusitupa M, Hermansen K, Meyer BJ, Riccardi G, Rivellese AA. Fish oil, insulin sensitivity, insulin secretion and glucose tolerance in healthy people: is there any effect of fish oil supplementation in relation to the type of background diet and habitual dietary intake of n-6 and n-3 fatty acids? Nutr Metab Cardiovasc Dis 2007;17:572–580. [PubMed: 17127043]
61. Willett WC. The role of dietary n-6 fatty acids in the prevention of cardiovascular disease. Journal of cardiovascular medicine (Hagerstown, Md 2007;8 Suppl 1:S42–45.
62. Petersson H, Basu S, Cederholm T, Risérus U. Serum fatty acid composition and indices of stearoyl-CoA desaturase activity are associated with systemic inflammation: longitudinal analyses in middle-aged men. Br J Nutr 2007:1–4.
63. Petersson H, Lind L, Hulthe J, Elmgren A, Cederholm T, Risérus U. Relationships between serum fatty acid composition and multiple markers of inflammation and endothelial function in an elderly population. Atherosclerosis. 2008
64. Risérus U. Trans fatty acids and insulin resistance. Atherosclerosis (Suppl) 2006;7:37–39.
65. Kavanagh K, Jones KL, Sawyer J, Kelley K, Carr JJ, Wagner JD, Rudel LL. Trans fat diet induces abdominal obesity and changes in insulin sensitivity in monkeys. Obesity (Silver Spring) 2007;15:1675–1684. [PubMed: 17636085]
66. Risérus U, Arner P, Brismar K, Vessby B. Treatment with dietary trans10cis12 conjugated linoleic acid causes isomer-specific insulin resistance in obese men with the metabolic syndrome. Diabetes Care 2002;25:1516–1521. [PubMed: 12196420]
67. Risérus U, Basu S, Jovinge S, Fredrikson GN, Arnlov J, Vessby B. Supplementation with conjugated linoleic acid causes isomer-dependent oxidative stress and elevated C-reactive protein: a potential link to fatty acid-induced insulin resistance. Circulation 2002;106:1925–1929. [PubMed: 12370214]
68. Moloney F, Yeow TP, Mullen A, Nolan JJ, Roche HM. Conjugated linoleic acid supplementation, insulin sensitivity, and lipoprotein metabolism in patients with type 2 diabetes mellitus. Am J Clin Nutr 2004;80:887–895. [PubMed: 15447895]
69. Risérus U, Vessby B, Arnlov J, Basu S. Effects of cis-9, trans-11 conjugated linoleic acid supplementation on insulin sensitivity, lipid peroxidation, and proinflammatory markers in obese men. Am J Clin Nutr 2004;80:279–283. [PubMed: 15277146]
70. Storlien LH, Pan DA, Kriketos AD, O'Connor J, Caterson ID, Cooney GJ, Jenkins AB, Baur LA. Skeletal muscle membrane lipids and insulin resistance. Lipids 1996;31 Suppl:S261–265. [PubMed: 8729130]
71. Ginsberg BH, Brown TJ, Simon I, Spector AA. Effect of the membrane lipid environment on the properties of insulin receptors. Diabetes 1981;30:773–780. [PubMed: 6266903]
72. Clarke SD. The multi-dimensional regulation of gene expression by fatty acids: polyunsaturated fats as nutrient sensors. Curr Opin Lipidol 2004;15:13–18. [PubMed: 15166803]

73. Yoshikawa T, Shimano H, Yahagi N, Ide T, Amemiya-Kudo M, Matsuzaka T, Nakakuki M, Tomita S, Okazaki H, Tamura Y, Iizuka Y, Ohashi K, Takahashi A, Sone H, Osuga Ji J, Gotoda T, Ishibashi S, Yamada N. Polyunsaturated fatty acids suppress sterol regulatory element-binding protein 1c promoter activity by inhibition of liver X receptor (LXR) binding to LXR response elements. J Biol Chem 2002;277:1705–1711. [PubMed: 11694526]
74. Evans RM, Barish GD, Wang YX. PPARs and the complex journey to obesity. Nat Med 2004;10:355–361. [PubMed: 15057233]
75. Rioux V, Legrand P. Saturated fatty acids: simple molecular structures with complex cellular functions. Curr Opin Clin Nutr Metab Care 2007;10:752–758. [PubMed: 18089958]
76. Staiger H, Staiger K, Haas C, Weisser M, Machicao F, Haring HU. Fatty acid-induced differential regulation of the genes encoding peroxisome proliferator-activated receptor-gamma coactivator-1alpha and -1beta in human skeletal muscle cells that have been differentiated in vitro. Diabetologia 2005;48:2115–2118. [PubMed: 16132959]
77. Winzell MS, Ahren B. G-protein-coupled receptors and islet function-implications for treatment of type 2 diabetes. Pharmacology & therapeutics 2007;116:437–448. [PubMed: 17900700]
78. Itoh Y, Kawamata Y, Harada M, Kobayashi M, Fujii R, Fukusumi S, Ogi K, Hosoya M, Tanaka Y, Uejima H, Tanaka H, Maruyama M, Satoh R, Okubo S, Kizawa H, Komatsu H, Matsumura F, Noguchi Y, Shinohara T, Hinuma S, Fujisawa Y, Fujino M. Free fatty acids regulate insulin secretion from pancreatic beta cells through GPR40. Nature 2003;422:173–176. [PubMed: 12629551]
79. Briscoe CP, Tadayyon M, Andrews JL, Benson WG, Chambers JK, Eilert MM, Ellis C, Elshourbagy NA, Goetz AS, Minnick DT, Murdock PR, Sauls HR Jr, Shabon U, Spinage LD, Strum JC, Szekeres PG, Tan KB, Way JM, Ignar DM, Wilson S, Muir AI. The orphan G protein-coupled receptor GPR40 is activated by medium and long chain fatty acids. J Biol Chem 2003;278:11303–11311. [PubMed: 12496284]
80. Covington DK, Briscoe CA, Brown AJ, Jayawickreme CK. The G-protein-coupled receptor 40 family (GPR40-GPR43) and its role in nutrient sensing. Biochemical Society transactions 2006;34:770–773. [PubMed: 17052194]
81. Kim JK. Fat uses a TOLL-road to connect inflammation and diabetes. Cell Metab 2006;4:417–419. [PubMed: 17141623]
82. Lee JY, Sohn KH, Rhee SH, Hwang D. Saturated fatty acids, but not unsaturated fatty acids, induce the expression of cyclooxygenase-2 mediated through Toll-like receptor 4. J Biol Chem 2001;276:16683–16689. [PubMed: 11278967]
83. Lee JY, Zhao L, Youn HS, Weatherill AR, Tapping R, Feng L, Lee WH, Fitzgerald KA, Hwang DH. Saturated fatty acid activates but polyunsaturated fatty acid inhibits Toll-like receptor 2 dimerized with Toll-like receptor 6 or 1. J Biol Chem 2004;279:16971–16979. [PubMed: 14966134]
84. Lee JY, Plakidas A, Lee WH, Heikkinen A, Chanmugam P, Bray G, Hwang DH. Differential modulation of Toll-like receptors by fatty acids: preferential inhibition by n-3 polyunsaturated fatty acids. J Lipid Res 2003;44:479–486. [PubMed: 12562875]
85. Shi H, Kokoeva MV, Inouye K, Tzameli I, Yin H, Flier JS. TLR4 links innate immunity and fatty acid-induced insulin resistance. J Clin Invest 2006;116:3015–3025. [PubMed: 17053832]
86. Kim F, Pham M, Luttrell I, Bannerman DD, Tupper J, Thaler J, Hawn TR, Raines EW, Schwartz MW. Toll-like receptor-4 mediates vascular inflammation and insulin resistance in diet-induced obesity. Circulation research 2007;100:1589–1596. [PubMed: 17478729]