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Review Article Open Access

Dietary fatty acid composition and metabolic syndrome: a review

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Article History
Received:
17/05/2014
Revised:
06/08/2014
Accepted:
08/09/2014

Keywords:
Dietary fat,
Dyslipidemia,
Fatty acid,
Insulin resistance,
Metabolic syndrome

A B S T R A C T

Diet as a part of lifestyle plays a pivotal role in the development of metabolic syndrome and its consequences. Fatty acid composition as a part of dietary intake affects blood fatty acid concentrations, insulin sensitivity and different metabolic pathways associated with the occurrence and consequences of the metabolic syndrome. The aim of this review is to evaluate the effects of dietary fatty acid composition on metabolic syndrome (MetS) and its components. A search was conducted through PubMed, Google scholar and Science Direct using keywords including metabolic syndrome, MetS, diet, fatty acid composition, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, omega3, omega6 and fish oil, insulin resistance, hyperlipidemia, obesity and blood glucose. We included English articles published from 1995 to 2014. Based on the results of the studies reviewed, intake of saturated fatty acids by increasing LDL-C, total cholesterol and oxidized LDL and arterial stiffness was associated with increased insulin resistance and metabolic syndrome. In contrast, supplements containing omega-3 and monounsaturated fatty acids such as fish and rapeseed oil can reduce the risk of metabolic syndrome and its consequences risk factors by lowering triglycerides, cholesterol, inflammation and oxidative stress. Low intake of saturated fatty acids and monounsaturated fatty acids with increased intake of omega-3 polyunsaturated fatty acids may be useful in reducing the risk of metabolic syndrome and its consequences.

Introduction

Metabolic syndrome (MetS), which is also known as "syndrome X," was first described by Reaven in his 1988 Banting Lecture [1]. Based on different definitions of *International Diabetes Federation* (IDF), *National Cholesterol Education Program* Adult Treatment Panel III (NCEP ATP III) and World Health Organization (WHO), the syndrome is characterized by central obesity, insulin resistance, dyslipidemia and hypertension [2-4]. This syndrome is highly related to risk factors of cardiovascular diseases and type 2 diabetes mellitus [5-7]. In most countries, about 20–30% of adult populations are predisposed to MetS because of its relation to obesity and lifestyle changes [3,4,8,9]. Although the pathogenesis of the MetS is not completely understood, it involves a complex interaction

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between genetic and lifestyle factors such as diet and physical activity [7-11]. Diet, a lifestyle factor which has changed in the past decades, is considered to play major role in the increase in prevalence of obesity. Observational and intervention studies suggest that the quality of dietary fats may affect MetS' components such as obesity, insulin resistance and dyslipidemia [12-14]. Therefore, in the past decade much attention has been given to the effects of the quality of dietary fat, independent of its total amount [9,12,15].

Lipids serve the body not only as major metabolic fuels, but also as membrane signaling transducers and modulators of nuclear transcription factors. Lipid homeostasis is well connected with other pathways of metabolism. Accordingly an unbalanced lipid state is often related to some abnormalities such as obesity, insulin resistance and hypertension, therefore the most and important part of lipids that are found in foods are fatty acids [16-18].

Fatty acids are long-chain hydrocarbons that can be separated into four categories: saturated, monounsaturated, polyunsaturated, and trans fats [19].

Because of important effects of fatty acids on health, many studies have been performed to understand their role on incidence, progress and results of many diseases and syndromes such as MetS. Essential fatty acids such as omega-3 fatty acids, serve important cellular functions and are a necessary part of the human diet because the body has no biochemical pathway to produce these molecules on its own [18,19]. Studies have indicated that saturated fats worsen, while monounsaturated and polyunsaturated fats improve insulin sensitivity, dyslipidemia, central obesity, cardiovascular and mental disorders' risk factors [9,12,20,21].

Role of dietary fatty acid composition in the incidence and progress of MetS and its components has been a controversial topic for decades and remained unresolved duo to the lack of comprehensive studies. Therefore, the aim of this review is to investigate epidemiological and clinical studies on the role of dietary fatty acid composition including saturated, monounsaturated and polyunsaturated fats on MetS and its components such as insulin sensitivity, blood lipids, blood pressure, central obesity, glucose tolerance and the factors related to these components such as inflammation and oxidative stress. We searched through PubMed, Google scholar and ScienceDirect using keywords including metabolic syndrome, MetS, diet, fatty acid composition, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, omega3, omega6 and fish oil, insulin resistance, hyperlipidemia, obesity and blood glucose. In this review we included English articles published from 1995 to 2014.

1. Saturated fatty acids

Saturated fatty acids (SFA) are long-chain carboxylic acids with no double bonds between the individual carbon atoms of the fatty acid chain such as palmitate and stearate which found especially in animal fats. Foods high in SFA include fast foods, processed foods, high-fat dairy products, red meats, and pork. Currently, increasing consumption of total and saturated fat is alarmingly higher than the latest dietary recommendations [22,23].

Results of studies indicate that a high intake of fat, particularly fat rich in saturated fatty acids influences central obesity, insulin sensitivity, fasting glucose concentrations, inflammation processes, and factors which can progress Mets or worsen it [24-28]. However, fat effects on some factors such as arterial function has remained uncertain [29]. Several interventional studies have demonstrated that lipid profiles could be affected by changes to the quality and quantity of fat in the diet, in particular total plasma cholesterol can be lowered by reductions in dietary, total or saturated fat [30]. However these profiles could be improved by substituting monounsaturated fatty acid (MUFA) and polyunsaturated fat (PUFA) for SFA [31].

Ebbesson et al. examined the association of the red blood cell (RBC) content of three types of SFAs (including myristic, palmitic and stearic) with insulin resistance and glucose metabolism and found that myristic acid content of RBCs was positively associated with fasting insulin, 2h insulin and homeostasis model assessment-estimated insulin resistance (HOMA-IR). Palmitic acid content of RBCs was associated with 2h glucose and 2h insulin and stearic acid content of RBC was associated with fasting glucose. Their study supported the hypothesis that blood SFA concentrations are associated with insulin resistance and glucose intolerance and they are significant risk factors for type 2 diabetes [32]. Some other studies with similar findings reported that individuals with the MetS and insulin resistance possess a plasma fatty acid composition characterized by high levels of SFAs such as 16:0, palmitoleic acid

(16:1, n-7] and dihomo-γ-linolenic (20:3, n-6) acids, whereas the levels of polyunsaturated acids (PUFAs; 18:2, n-6) are typically low [33,34]. It worth mentioning that an acute rise in SFAs is able to increase insulin secretion whereas unsaturated fatty acids are ineffective, and chronically elevated SFAs inhibit insulin secretion and lead to an increased rate of β-cells apoptosis in the pancreas [15].

The study which was conducted within the framework of the Tehran Lipid and Glucose Study (TLGS) demonstrated an association between dietary fatty acid intake and the prevalence of risk factors for the metabolic syndrome. They showed positive trend over quartiles of SFA intake with low-density lipoprotein-cholesterol (LDL-C) and triglycerides (TG). Also an inverse association was found between high-density lipoprotein-cholesterol (HDL-C) and SFA and PUFA intakes. Lastly, they demonstrated a significant association of different kinds of fatty acids and risk of the MetS in this population, except for the total PUFA intake [35]. In a population-based cross-sectional study Hekmatdoost et al. showed that increased consumption of dietary total fat, especially SFAs, was associated with a higher risk of metabolic syndrome in Tehranian adults [9]. A study comparing women with a diet high in SFAs to women whose diet was low in total fat or high in MUFAs and PUFAs, demonstrated that total cholesterol and LDL-C levels were lower in those women whose diet had high unsaturated fatty acids content. The HDL-C concentrations in women whose diet was high in SFAs was 15% higher than in those whose diet was low in SFAs [36]. This contrast with results of other studies may be because of reducing SFAs without altering the amount of unsaturated fatty acids in the diet. Moreover, the effect of SFA on promoting the MetS could be explained by its effect on the stimulation of toll-like receptors in different tissues such as the liver, muscle, adipose tissue and immune cells [37]. Moreover, dietary SFA has been reported to increase the expression of proinflammatory gene expression, which increases the risk of the MetS [38]. Nago and Yanagita have reported that medium-chain TG might decrease the risk of the MetS through suppressing fat deposition and preserving insulin sensitivity [39].

Corella et al. investigated the association between high intake of SFAs and fat mass, obesity-associated gene and body mass index (BMI) and showed that high, but not low, intakes of SFA modulate the association between the obesity-associated gene and BMI in American populations [40].

Finally, high intake of SFAs can lead to metabolic abnormalities such as insulin resistance, high concentration of blood cholesterol and LDL-C, obesity, inflammation and other probably incidence of MetS.

2. Monounsaturated fatty acids

Monounsaturated fatty acids (MUFA) are chemically classified as fatty acids containing a single double bond including *cis* and *trans*-configuration. The *cis*-isomers are the predominant form of MUFA in food sources. The most common *cis*-configured MUFA in daily nutrition is oleic acid followed by palmitoleic acid and vaccenic acid. The most frequently consumed dietary oils rich in MUFA are canola and olive oils [41].

Studies have shown that consumption of dietary MUFA promote healthy blood lipid profiles, regulate blood pressure, improve insulin sensitivity and controlled glucose levels [42,43]. Moreover, newer data suggest the oxidation and metabolism of dietary MUFA influences body composition and ameliorates the risk of obesity [43,44]. These kinds of dietary fats studied especially in Mediterranean diets with more consumption of olive oils, were found to have an inverse association between intake of MUFA and risk of chronic heart disease (CHD) [19]. However, debates continue on the optimal dietary fatty acid composition and the evidence supporting MUFA as the healthy dietary fatty acid is weak. Even considering food sources of MUFA (plant vs. animal), there is little evidence to support recommendations to increase dietary MUFA for coronary heart disease (CHD) prevention [45].

An interventional study with three diet groups including low (L-MUFA), moderate (M-MUFA) and high (H-MUFA) amounts of MUFAs, assessed the effects of replacing dietary SFAs with MUFAs, on concentrations and subclass distributions of VLDL, intermediate-density lipoprotein, LDL, HDL and VLDL apolipoprotein B kinetics. Their finding suggested that replacing dietary SFAs with MUFAs may increase insulin resistance because fasting insulin concentrations and homeostatic model assessment (HOMA) scores were significantly higher after consumption of the M-MUFA and H-MUFA diets, than after consumption of the L-MUFA diet [46].

Palomaki et al. investigated the effects of dietary rapeseed oil and butter on serum lipids in a clinical trial and showed that the level of oxidized LDL (ox-LDL), total cholesterol and LDL-C decreased significantly in the dietary rapeseed oil group compared to the butter group, while HDL-C levels remained unchanged. Low density lipoprotein particles enriched with MUFA seemed to be resistant against oxidation; since MUFAs are the main fatty acids in rapeseed oil. This protective effect may contribute to the decreased level of oxidized LDL-C [7]. Egert et al. examined the effects of high-fat and low-fat diets rich in MUFA on CVD risk factors in healthy non-obese men and women and showed that the size of the major LDL fraction, the LDL susceptibility to oxidation and the plasma concentrations of oxidized LDL were significantly reduced by both diets, while ox-LDL/LDL-C ratio and serum TG were not significantly affected by the diets [47]. Gill et al. showed that plasma cholesterol concentrations decreased in a dose-dependent manner with increasing intakes of dietary MUFAs. Plasma TG, HDL-C, $VLDL_1$, $VLDL_2$ and intermediate-density lipoprotein were not significantly affected by the dietary intervention. However, concentrations of atherogenic LDL-III were 25% lower after the H-MUFA diet than after the L-MUFA diet. The present dietary intervention had a neutral effect on HDL-cholesterol concentration, as well as on the subclass distributions of HDL and LDL-C, because the concentrations and kinetics of TG-rich $VLDL_1$ particles were not significantly affected by the fatty acid composition of the diet [46]. It is now well established that HDL-C concentrations and HDL-C and LDL-C subclass distributions are related to the metabolism of large TG-rich lipoproteins. Thus, in the absence of changes to $VLDL_1$, disturbances of these lipoprotein variables should not occur.

In another study on modification of postprandial oxidative stress with dietary fat, the high MUFA diet improved postprandial oxidative stress parameters in patients with MetS, which helped to reduce the inflammation and had cardioprotective effects especially in subjects with MetS [12].

Imamura et al. investigated prospective associations between long-chain MUFA exposure, assessed as objective biomarkers in plasma phospholipids, and incident CHF in two independent US cohorts, a cardiovascular health study (CHS) and an atherosclerosis risk in communities (ARIC) study. They found that higher circulating levels of 22:1 and 24:1 fatty acids, with apparently diverse dietary sources were associated with incident congestive heart failure (CHF) in two independent cohorts, suggesting possible cardio toxicity of long-chain MUFA in humans [48].

Based on the results of studies, dietary MUFA can reduce concentration and oxidation of plasma LDL-C and prevent inflammation especially if it is replaced with SFAs.

3. Polyunsaturated fatty acids

Polyunsaturated fatty acids (PUFA) are fatty acids with more than one double bond, which play an essential role in the body as sources of energy and components of cell membranes, including two major groups: omega-3 and omega-6 fatty acids. They have been studied extensively for their effects on health and several diseases such as CHD, type 2 diabetes, cancer cachexia, asthma, and dementia [6,19,49-51]. Previous studies have shown that omega-3 and omega-6 fatty acids have different effects on lipid metabolism, particularly with regard to plasma TG, LDL-C, HDL-C and lipoprotein subclasses [52].

An intake of long-chain omega-3 PUFAs (LC-PUFAs) in the range of 3 to 6 g/d, in the form of eicosapentaenoic acid (20:5n_3; EPA) and docosahexaenoic acid (22:6n_3; DHA) supplements, has been shown to decrease plasma VLDL and TG concentrations and to increase LDL particle size and the concentration of HDL_2 cholesterol [53].

3.1. Omega-3 polyunsaturated fatty acids

Over the last 20 years, randomized controlled trials and epidemiological studies have demonstrated high intakes of EPA and DHA (>2 g/day) to have positive effects on endothelial function, vascular reactivity, blood pressure, inflammation, and plasma lipid levels [49,54-56].

In one crossover study, omega-3 fatty acids improved hypertriglyceridemia, while the combination therapy with niacin and omega-3 fatty acids had additive effects on TG, HDL and LDL-C size [57]. Results of another study demonstrated that the absolute variation of PUFA had an important inverse correlation with TG and other components of MetS, whereas cholesterol concentration was not affected by the variation [58].

Result of study of adult Puerto Rican

participants, divided into 4 groups based on their dietary fatty acid patterns (SFA/dairy, omega-3 fatty acid/fish, very long chain SFA/ PUFA/oils, MUFA/trans), showed that SFA/dairy pattern was inversely associated with fasting serum glucose concentrations; the omega-3 fatty acid/fish pattern was associated with lower odds of Mets but not with lower blood pressure [24]. In another similar study the very long chain SFA/ PUFA/oils pattern was found to be related to smaller waist circumference that plays a central role in MetS [9].

Mirmiran et al. in their study conducted within the framework of the TLGS investigated whether the background dietary intake of omega-6 fatty acids modulates the effects of EPA, DHA and α-linolenic acid (ALA) on the risk of the MetS and its components. Their findings showed that intakes of EPA and DHA were associated with a lower risk of high serum TG concentrations, regardless of the background intake of omega-6 fatty acids. In addition, ALA intake with a high or low omega-6 fatty acids intake decreased the risk of an enlarged waist circumference and the MetS. The dietary intake of omega-6 fatty acids also decreased the risk for the MetS, but they found no association between omega-3 fatty acids intake and the omega-6/omega-3 ratio and the MetS in Tehranian adults. The ALA intake was found to be inversely associated with the MetS, irrespective of the background intake of omega-6 fatty acids in adults [6].

Another study investigating whether omega-3 fatty acids improved arterial health and inflammatory responses showed that fish oil omega-3 fatty acids increased plasma and red blood cells EPA and DHA, but no beneficial changes were observed in the markers that were measured for hemodynamics, MetS or inflammatory effects[5].

3.2. Omega-6 polyunsaturated fatty acids

Omega-6 fatty acids, are one type of PUFAs in foods, especially vegetable and fish oils. Compared to human studies these kinds of fatty acids have been investigated mostly in animal models, with more focus on the ratio of omega-6 to omega-3 or other fatty acids. Some studies have tried to find the relationship between omega-6 fatty acids and the components of MetS or its risk factors. Findings of a study showed that an imbalance in dietary omega-6 and omega-3 PUFAs may be a contributory factor to the insulin resistance and related blood lipid abnormalities of the MetS [59].

One study conducted within the framework of the OPTILIP study, examined the effects of altering the ratio of dietary omega-6 to omega-3 fatty acids on insulin sensitivity, lipoprotein size, and postprandial lipemia and demonstrated that decreasing the omega-6/omega-3 does not influence insulin sensitivity or lipase activities in older subjects. However, reduction in plasma TG after an increased intake of omega-3 fatty acids resulted in favorable changes in LDL size [56]. Another study investigating whether a high background dietary intake of omega-6 PUFA attenuates the effects of fish-oil supplementation on insulin sensitivity and associated blood lipids of the MetS in Indian Asians showed that the background dietary omega-6 PUFA concentration did not modulate the effect of fish-oil supplementation on blood lipids or insulin sensitivity in this ethnic group [59]. Results of the Rodriguez et al. study examining the possibility of an association between insulin resistance and long-chain omega-6 PUFAs in erythrocyte phospholipids of type 2 diabetics, indicated that formation of long-chain omega-6 fatty acids from 18:2 omega-6 by desaturation-elongation is impaired under insulin resistant conditions and reduced desaturase activities may be involved. They had suggested that insulin-mediated activation of Delta5 and Delta6 desaturases may not occur in insulin resistant conditions [60].

Mata et al. examined the modification of LDL oxidation and change in coronary smooth muscle cell DNA synthesis with MUFA and PUFA omega-6 fatty acid-enriched diets, and found that the MUFA-enriched diet reduced smooth muscle cell DNA synthesis and LDL levels and protected LDL from oxidation. They suggested that an oleic acid-rich Mediterranean diet could be better than omega-6 or omega-3-rich diets in the prevention of atherosclerosis [61]. One randomized controlled trial that examined the effects of omega-6 fatty acids, compared with SFAs, on liver fat, lipoproteins, and inflammation in abdominal obesity, demonstrated that omega-6 fatty acids compared with SFAs, reduced liver fat and modestly improved metabolic status, without weight loss. Also high omega-6 fatty acids intake did not cause any signs of inflammation or oxidative stress [62].

Tulk et al. examined the acute effect of modifying the omega-6 /omega-3 PUFA ratio of a SFA oral fat tolerance test (OFTT) on

postprandial TG and inflammatory responses in men with MetS and found that neither time nor treatment affected circulating C-reactive protein (CRP) concentrations. Thus, decreasing the omega-6 PUFA content of a high-SFA OFTT did not drastically change postprandial TG or inflammatory responses in men with MetS [63].

An association has been reported between omega-6 PUFAs and inflammation responses. The mechanism which explains this association is that high intakes of omega-6 PUFAs leads to increased production of eicosanoids and lipoxins, and the eicosanoids from omega-6 PUFAs are biologically active in very small amounts, and if formed in large amounts, they contribute to inflammatory responses that can lead to accumulation of fats, obesity and insulin resistance and high proliferation of cells [64].

Conclusion

Recent studies indicate that high consumption of dietary fat especially SFA might worsen the components of MetS specially insulin resistance and inflammation process. Consumption of PUFAs including omega-3 and omega-6 sources such as fish oil or vegetable oils like rapeseed oil and replacing SFA with MUFA and PUFA can improve insulin resistance, blood lipids, central obesity, blood pressure and accordingly incidence or consequences of MetS. It seems that we should pay more attention not only to the quantity of dietary fats but also to the quality of dietary fatty acids composition in designing a healthy dietary plan. More studies should be carried out about the relationship of dietary fatty acid composition with all components of MetS to understand the effects of such fatty acids on onset or progress of MetS.

Acknowledgements

We would like to thank Ms. N. Shiva for critical editing of English grammar and syntax of the manuscript.

Conflict of interest: The authors declared no conflict of interest.

Source of funding: None

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