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Trans Fatty Acids and Atherosclerosis-effects on Inflammation and Endothelial Function

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Abstract

The current diet and lifestyle are commonly known contributing factors of atherosclerosis, which is the underlying disorder in patients with cardiovascular disease. An identification of any kinds of foods that may exert the cardioprotective or cardiotoxic influence and deeper understanding their molecular mechanisms of action has become an object of interest due to their importance. Through largely epidemiological evidence, trans fatty acids (TFAs) intake has been associated with a variety of the cardiovascular complications, including atherosclerosis. The excessive intake of TFAs has detrimental effect on lipid profile. However, the association between the consumption of TFA and the risk of cardiovascular disease are much greater, than predicted by the effect on serum lipids alone, suggesting that the TFAs intake may also affect the other, non-lipid risk factor. Evidences from many studies indicate, that TFA induce the inflammatory response and endothelial dysfunction. In the following review we present a current knowledge concerning the chemistry of TFAs, their dietary source, their association with cardiovascular disease and the possible mechanisms explaining their effect on atherosclerosis.

Keywords: Atherosclerosis; Cardiovascular disease; Trans fatty acids; Endothelial dysfunction

Introduction

Cardiovascular disease, in particular coronary heart disease, is the principal cause of mortality worldwide. Atherosclerosis is the underlying disorder in the majority of patients with coronary heart disease. The development of atherosclerotic plaque in the arteries is a result of multiple risk factor including both non-modifiable risk factor (family history gender and age) and modifiable risk factor which are associated with life style choice, particularly poor diet habits [1-3]. In recent years, the eating habits of highly industrialized societies changed radically thanks to new technologies in the food industry, that allow consumption of products containing large amounts of trans fatty acids.

Trans fatty acids are unsaturated fats, that contain at least one double bound [4]. In contrast to naturally occurring unsaturated fatty acids, which have the cis configuration (hydrogen atoms on the same side of the acyl chain), TFAs contain at least 1 double bound in the trans configuration (hydrogen atoms on opposite sides of the acyl chain). The type of bond affects the shape of the fatty acid chain. A cis bond creates a bent chain, whereas trans results in much straighter molecules similar to that of saturated fatty acids. Although the chemical composition of a cis and Trans fat may be identical, this change in the configuration will induce obvious effects on the packing of the lipid in, for example, phospholipid bilayer and on the function of both lipids and proteins in a membrane structure.

Recently, the use and presence of TFA in the diet has been the object of much public health discussions. This article focuses on TFAs as modifiable dietary risk factor for atherosclerosis, reviewing the evidence for lipid and non-lipid effects.

Sources of dietary trans fatty acids

Trans fatty acids occur naturally in ruminant fats, in which small amount of TFAs are produced by bacteria in the stomach of grass grazing sheep and cattle [5]. Therefore, sheep and cattle meats as well as dairy products (cheese, milk and butter) contain ruminant trans fatty acids (rTFAs). The most dietary trans fatty acids are the result of industrial processing by partial hydrogenation of vegetable or fish oils to produce partially hardened fats and food products [4,6]. During the partial hydrogenation of vegetable oils a number of double bonds is reduced, while approx. 30-50% of unsaturated fatty acids are transformed from cis into trans. Hydrogenation is used by food industry to increase their viscosity (changing vegetable fats from a liquid to a semi-liquid or solid) and/or extend their shelf life (decreasing susceptibility to oxidation). It also increases the fat's melting point, making the product more suitable for frying.

The main fatty acid formed in the process of vegetable oil solidification is elaidic acid (C18:1, trans-9) [7]. However, the process of frying or baking food in vegetable oils results in the generation of linoelaidic acid (C18:2; trans-9,12) [8]. The high temperature accompanying this process causes the conversion of the double bond from the cis configuration into the trans one. Major dietary sources of the industrial TFA include margarines (1.2-7.85% TFA content per weight basis), snacks such as biscuit, cakes and popcorn (5-10%) and frying oils (23-30%) [8]. The most predominant trans isomer in rTFA is vaccenic acid (C18:1; trans-11) [9]. A smaller amount of conjugated linolenic acid (C18:2; 9-cis,11-tras)(CLA) can also be formed from vaccenic acid.

TFAs effect on cardiovascular risk factor

Growing evidence indicates, that increased consumption of industrial TFAs may be important modifiable risk factor in development of cardiovascular diseases, because they are associated with a higher risk of cardiovascular morbidity and mortality [10,11].

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Based on results from very well documented observational studies, the industrial TFAs consumption increases the risk of coronary heart disease on a per-calorie basis than any other dietary macronutrients, including saturated fatty acids [12,13]. A meta-analysis of 4 prospective cohort studies involving 140000 subjects showed, that a 2% increase in the consumption of TFAs was associated with the 23% increase in the incidence of CHD [14]. The Nurse Health Study found a 33% increase in the incidence of CHD among those participants in the highest quintile of TFA intake, compared with those in the lowest quintile [14]. A meta-analysis of prospective studies showed a 24, 20, 27 and 32% higher risk of myocardial infarction or death from cardiovascular disease for a 2% of the TFAs intake energy isocalorically replacing carbohydrate saturated fatty acids (SFA), cis-monounsaturated fatty acids (MUFA) and cis-polyunsaturated fatty acids (PUFA), respectively [15]. An evaluation of the TFA intake associated with mortality over 25 years in the seven countries study and Health Professionals Follow-up Study reported a positive correlation between trans fatty acids consumption and a risk of death from cardiovascular disease [16,17]. A strong correlation between the TFA intake and the coronary heart disease risk was confirmed in studies using biomarkers of a tissue concentration of TFAs. It was demonstrated, that TFAs concentration in plasma phospholipids and erythrocytes is associated with an elevated risk of cardiovascular diseases [18,19]. The Cardiovascular Health Study showed that elaidic acid concentration in plasma phospholipids was adversely associated with total mortality, mainly due to the increased risk of cardiovascular disease [20]. So far, there are merely few studies evaluating the serum concentration of TFAs. Recently it has been shown, that serum TFAs (elaidic and linoelaidic acids) concentration was elevated in young patients with coronary artery disease [21]. Moreover, serum TFA level had positive correlation with the body mass index, LDL-cholesterol, triglicerides and apoB48 and an inverse correlation with age and HDL-cholesterol.

The studies showed, that replacing a 2% of energy from carbohydrates with *Trans*-fat nearly doubled the relative risk of coronary heart disease [22]. Whereas a replacement of a 5% of energy from carbohydrates with saturated fat was associated with a 1.47-fold increase in relative risk. These results suggest on a gram-for-gram basis, that trans fat was associated with an approximately 15-times greater risk of coronary heart disease, than with the saturated fat. These results are somewhat ironic because commercial partially hardened fats, which are main source of trans fats, were originally introduced into the diet as a means to lower the risk of cardiovascular disease from saturated fat intake.

On the other hand the removal of TFAs from our diet has resulted in improvements in cardiovascular disease. After that Danish Government introduced a statuory provision for a limit of the amount of iTFAs acceptable in food, a 60% decline in cardiovascular diseases in Denmark was observed [23]. Mozaffarian and colleagues [13] estimated that a reduction of the commercial trans fat intake from 2.1% of energy to 1.1% or 0.1% of energy could prevent 72,000 or 228,000 cardiovascular deaths per year in the United States, respectively. These results leave no doubt that trans fats have a significant, adverse effects on cardiovascular diseases.

By contrast, the results from observational studies concerning the intake of TFA and coronary heart disease demonstrate, that the rTFA intake has either not been associated with or has been negatively associated with the risk of cardiovascular disease [24].

Trans fatty acids: lipid profiles and lipoprotein metabolism

One important factor in the pathogenesis of atherosclerosis is disorders of lipid metabolis and positive correlation between plasma cholesterol or LDL and atherosclerosis is now well documented. Therefore, the potential for dietary TFAs to alter or promote this relationship was a possible mechanism for deleterious effects of TFAs on the cardiovascular system. The influence of trans fat on blood lipids has been well documented and reviewed [15,25,26]. The consumption of TFAs increases total and LDL cholesterol in the same way as the consumption of saturated fatty acids. Compared with MUFA and PUFA or SFA diet, the TFA intake decreases HDL-cholesterol. In meta-analysis of 13 randomized controlled trials observing the effect of isocaloric replacement of PUFA MUFA or SFA with TFA, a significant increase in LDL-cholesterol, total cholesterol to HDL-cholesterol ratio, the ratio of apolipoprotein B to apolipoprotein A and lipoprotein a was observed. Other studies have shown an increase in serum triglycerides and a reduction in size of the LDL particle. All of these changes in blood lipids caused by TFAs intake represent the independent risk of cardiovascular diseases.

The mechanisms responsible for this alternation seem to be associated with the modulation of the liver function and metabolism of lipoprotein. In cultured human hepatoma cell lines, TFAs increased the LDL/HDL ratio, apolipoprotein A: apolipoprotein B apoA to apoB) ratio and cholesterol content both in LDL and HDL particles in comparison to SFA [27]. Moreover, TFAs increased a hepatic secretion of VLDL and their particle size.

The observed effect of TFAs on hepatoma cells may be partially responsible for the increase of LDL cholesterol and small dense LDL, which has been associated with a higher risk of cardiovascular disease than the large LDL [28].

Compared to PUFA and SFA, a consumption of TFAs increases the plasma activity cholesterol ester transfer protein, the main enzyme responsible for the transfer of cholesterol ester from HDL to very low density lipoprotein (VLDL) and LDL [13]. This may explain the changes occuring in lipid profile in people consumed diets rich in trans fatty acids.

TFAs not only decrease plasma levels of HDL-cholesterol, but also may change the antiatherogenic activities of HDL. Recently it has been shown, that reconstituted HDL containing the elaidic acid lost its antioxidant ability and induced the highest uptake of oxyLDL into human macrophages [29].

Atherosclerosis and trans fatty acids

The studies above mentioned provided an indirect evidence of an atherogenic effect of TFAs. However, this had never been demonstrated until the study by Bassett and colleagues [30]. They showed, that supplementation of the diet of LDL receptor deleted mice with an industrial trans fat, elaidic acid, resulted in the independent and direct stimulation of atherosclerosis. Furthermore, they also shown, that an addition of elaidic acid to a cholesterol-supplemented diet did not induce an additive effect.

Unexpectedly, in the study performed in the same model of experimental atherosclerosis a surprising anti-atherogenic action by the ruminant TFA, the vaccenic acid was detected [31]. A significant decrease in the area of the atherosclerotic plaques covered in the aortas from LDL receptor deleted mice was observed, when diets were supplemented with cholesterol and vaccenic acid in comparison to diets supplemented with both cholesterol and elaidic acid, or just cholesterol alone.

Atherosclerosis is initiated by the subendothelial retention of low-density lipoprotein (LDL), followed by physicochemical modifications such as oxidation [32,33]. Macrophages located in the arterial intima layer present several scavenger receptors, that uptake modified LDL. Progressive macrophage lipid accumulation leads to foam cell formation. Lipid-laden macrophages release many of chemoattractants and inflammatory mediators, leading to a lesion progression. Macrophage lipid homeostasis is determined by the balance between the cholesterol uptake and the efflux of excess cholesterol to extracellular acceptors, such as high density lipoprotein (HDL) and apolipoprotein A-I (apo A-I) [34]. HDL particles or apoA-I interact with cells to promote the efflux of cholesterol from arterial macrophages via binding to ATP-binding transporters A-1 (ABCA-1) and G-1 (ABCG-1. Fournier at al. [35] reported that elaidic but not vaccenic acid reduced the ABCA1-mediated cholesterol efflux from the mouse and human unloaded or cholesterol-loaded macrophages, similarly to palmitic acid. A recent study conducted in LDL receptor knockout mice revealed that elaidic acid increased the lesion area, macrophage infiltration and arterial total cholesterol content [36].

Trans fatty acids and inflammation.

The vascular inflammation is a primary event in the pathogenesis of atherosclerosis [32,37]. Furthermore, an activation of inflammation can elicit acute coronary syndromes. Some inflammatory markers are key risk factors for atherosclerosis [38]. Some studies have shown, that inflammatory disease markers such as C-reactive protein (CRP) are better predictors of future cardiovascular events than lipid and lipoprotein levels alone [39].

Both, observational and randomized studies showed that TFAs have pro-inflammatory effects. It was well documented and reviewed in several papers [15,40]. The increased TFAs consumption has been associated with the increased circulating concentration of inflammatory markers, such as tumor necrosis factor (TNFα), interleukin 6 (IL-6) or CRP. In patients with the established heart disease and higher inflammatory marker level, erythrocyte membrane concentration of TFAs (a biomarker of dietary intake) were associated with higher level of IL-6, TNFα, soluble TNFα receptors and monocyte chemoatrractant protein-1. Randomized trial involving hypercholesterolemic patients showed greater production of IL-6 and TNFα in cultured mononuclear cells, gained from participants consuming a one-month diet high iTFA, compared with the cells taken from members of control group.

Monocytes/macrophages present in atherosclerotic change are a major source of inflammatory cytokines in atherosclerosis [41]. It can be speculated that pro-inflammatory treatment with TFA is the result of their modulating effect on monocyte and macrophage activity.

However, adipokines synthesized in the fat tissue are actually becoming recognized as important mediators of inflammatory pathways for this reason that they are a vital source of inflammatory mediators within the atherosclerotic process [38,42]. Therefore, it is possible, supposing that TFAs are deposited within a fat tissue, then this change in the fatty acid composition may influence the adipokine synthesis and ultimately, any inflammatory actions related to atherogenesis.

The cellular and molecular mechanisms, whereby the TFAs consumption influences the inflammatory response are not well established yet. NF-κB is the transcription factor, which plays an important role in development of inflammatory responses by up-regulating the expression of many inflammatory mediators [43]. The role of this transcription factor in the pathogenesis of atherosclerosis has been indicated by studies showing that its active form is present in atherosclerotic lesions [44]. It has been suggested, that NF-κB is a redox-sensitive transcription factor, because reactive oxygen species (ROS) may regulate its activity [45]. We have recently demonstrated that TFAs have a direct pro-inflammatory effect in endothelial cells through the ROS-dependent NF-κB activation [46]. Our results also indicate that TFAs increase the intracellular ROS production. As suggested from the studies by Cassagno and colleagues [47], a diet rich in TFAs may intensify an oxidative stress. In mice fed with the diet rich in TFAs, a reduction of plasma vitamin E levels with the concomitant increase in F_2-isoprostanes (a marker of oxidative stress in vivo) was observed. This observation may also explain the high risk of cardiovascular disease associated with the TFAs intake, because oxidative stress has been associated with a development of atherosclerosis most likely through the vascular inflammatory response [45].

Trans fatty acids and dysfunction of endothelial cells

Endothelial cell dysfunction plays a key role in the pathogenesis of atherosclerosis [48]. A hallmark of endothelial dysfunction is an impairment of a vasodilatation, which is caused by the diminished synthesis and release of NO and prostacyclin. The branchial artery flow-mediated vasodilatation (FMD) is a functional measurement of the NO-dependent vasodilatation capacity of endothelia.

The randomized study, conducted on 29 healthy volunteers subjected to a 4-week diet containing either the trans fatty acids or saturated fatty acids have shown, that TFAs contributed to the reduction of the endothelium-dependent vascular relaxation [49]. A comparison of the two diets revealed, that the diet containing trans fatty acids has led to a 29% reduction of the FMD. Iwata et al. [50] have demonstrated, that both elaidic and linoelaidic acids impaired the endothelial insulin signaling and NO production in cultured endothelial cells. On the other hand, transvacenic acid was not associated with such a response. In the cultured endothelial cells, TFAs inhibited a conversion of linoleic acid to arachidonic acid, resulting in the suppression of prostacyclin synthesis [51]. Recently published study, in which the endothelial cells were cultured in fat mixtures containing different proportions of linoleic acid and elaidic acid, showed that supermarket margarines had levels of trans fats similar to those that suppressed prostacyclin by 35-54% [52].

Endothelial dysfunction is also manifested by shifts, from the anti-adhesive to pro-adhesive phenotype, which essential for both progression of atherosclerosis, as well as for the inflammatory process taking place in the vessel wall [53]. This feature of endothelial dysfunction is associated with the appearance of adhesion molecules on their surface as mediators of interactions between cells of the vascular wall and leukocytes. Thus, these interactions are essential for the adhesion and trans-endothelial migration of leukocytes. The family of endothelial adhesion molecules includes: selectins E and P, intercellular adhesion molecule-1 (ICAM-1), ICAM-2, vascular cell adhesion molecule-1 (VCAM-1). Concentrations of soluble forms of these molecules in the serum are suitable markers of endothelial dysfunction and activity of the inflammatory process.

In the study among overweight women, the higher intake of TFAs was associated with the higher plasma levels of soluble form of ICAM and VCAM-1 [54]. There is also *in vitro* study, demonstrating that TFA play a essential role in the induction of the proinflammatory effect of TFAs on endothelial cells. We and other have been demonstrated, that TFAs treatment induced the ICAM-1 and VCAM-1 expression in cultured endothelial cells [46,55].

Endothelial dysfunction is also associated with the prothrombotic activation of the endothelial cells. Recently it was shown, that a high-TFAs induced prothrombotic phenotypic changes in the endothelial cells. Namely, in the cultured endothelial cells TFAs decreased the expression levels of antithrombotic molecules like thrombomodulin as well as the tissue factor pathway inhibitor while vice versa increased the prothrombotic molecules [56].

Potential mechanisms

Although the molecular mechanisms underlying the effect of TFA on inflammation and endothelial cell function are not well established, pathways of influence of other dietary fatty acids suggest, that effects on both cell membrane and gene transcription are likely to be important. Dietary fatty acids are incorporated into phospholipids in all cell membrane [57,58]. The fatty acid composition of the membrane can strongly exert the influence on its biophysical characteristics. In particular, unsaturated and saturated fatty acids can act as potent regulators of membrane fluidity due to differential actions of phospholipids on cholesterol affinity and incorporation [59]. Cholesterol content in the cell membrane affects many important properties of the cell membrane, such as permeability, transport functions, membrane enzyme activity, and availability of membrane components as substrates as well as conformation changes of membrane proteins [60].

Cholesterol present in the cell membrane affects the formation of lipid rafts that consist of dynamic assemblies of cholesterol, lipids with saturated acyl chains, such as sphingolipids and glycosphingolipids in the exoplasmic leaflet of the membrane bilayer [61]. They are now emerging as an important cellular signaling mechanism in the regulation of a variety of cellular functions. For instance, LPS activation of macrophage results in transient Toll-like receptor 4 (TLR4) trafficking to lipid rafts along with its cognate adaptor proteins and subsequent secretion of inflammatory cytokines and chemokines [62]. A different pro-oxidative stimuli may activate NADPH oxidation through assembling or aggregating its components bound to lipids rafts with the components present in the cytoplasm [63].

It has been proposed, that TFAs may altere subcellular pathways by incorporating into cell membranes and changing the cellular membrane fluidity. As shown by the studies of Harvey and colleagues [64], an incubation of endothelial cells with trans 18:2 and cis 18:2 leads to the incorporation of those acids into the cell membrane phospholipids. The incorporation of Trans acid was twice as high as that of the cis form. The studies by Niu and colleagues [65] indicate that phospholipids containing acyl chains in the trans form take on a configuration allowing better interactions with cholesterol. Indeed, it has been shown, that the level of cholesterol in membrane phospholipids containing TFAs was 40-80% higher than in membranes containing cis fatty acid-phospholipids [65]. Due to the membrane cholesterol levels and membrane receptors are involved in the regulation of cholesterol homeostasis, the elevation in membrane cholesterol content and the lower receptor activation induced by the presence of TFA in the membrane could represent the mechanism responsible for the elevation of LDL cholesterol in the TFA supplemented diets.

Saturated fatty acids are known to induce inflammation and endothelial dysfunction through the TLR4 activation [66], an effect that appears to be caused by a recruitment of TLR4 into lipid rafts. As mentioned above, TFA induced the prothrombogenic phenotypes of endothelial cells. The results of these studies imply, that TFA impair an endothelial antithrombogenic functions through a TLR-mediated pathway. We have shown that TFA induced the intracellular ROS production in cultured endothelial cells through the activation of NADPH oxidase. Although, we do not investigate the effect of TFA on the membrane as we speculate that changes in the cell membrane structure may be responsible for the NADPH oxidase activation.

Transforming growth factor (TGF)-β is a pleiotropic cytokine, which is implicated to protect against atherosclerosis [67]. Studies on normal mice fed a high trans fatty diet have demonstrated, that this diet cause atherosclerosis by suppressing the TGF-β responses in vascular cells via an incorporation of a diet-derived TFAs into the plasma membrane phospholipids, with a resultanting increased integration of cholesterol into plasma membranes [68]. This process may cause an accumulation of the cell-surface of TGF-β–TGF-β receptor complexes in lipid rafts, facilitating a rapid degradation of these complexes, thus attenuating the TGF-β signaling.

Similarly to other fatty acids [69], TFA may bind to nuclear receptors, including the peroxisome proliferator-acivated receptor (PPAR), liver X receptor and sterol regulatory element-binding (protein-1, regulating a gene, that affects a cardiovascular risk factor through a lipid and non-lipid-related action. In adipocytes TFAs also alter the gene expression for PPARγ, resisitin and lipoprotein lipase [70].

Still, the cellular and molecular mechanisms whereby TFAs affects the atherosclerosis and cardiovascular disease are not well established and merit further investigation.

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