Diabetes & Metabolic Syndrome: Clinical Research & Reviews 13 (2019) 1643–1647

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Review

Trans fatty acids and lipid profile: A serious risk factor to cardiovascular disease, cancer and diabetes

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ARTICLE INFO

Article history:
Received 26 February 2019
Accepted 14 March 2019

Keywords:
Trans fatty acid
Atherosclerosis
Diabetes

ABSTRACT

Trans Fatty acids (TFAs) have long been used in food manufacturing due in part to their melting point at room temperature between saturated and unsaturated fats. However, increasing epidemiologic and biochemical evidence suggests that excessive trans fats in the diet are a significant risk factor for cardiovascular events as well as a risk factor for cancer and diabetes. A 2% absolute increase in energy intake from *trans*-fat has been associated with a 23% increase in cardiovascular risk. They increase the levels of low-density lipoprotein which is bad for health. Moreover, several epidemiological studies have been demonstrated that a high intake of TFAs increases the incidence of cancer and diabetes. On the other hand, total elimination of TFAs is not possible in a balanced diet due to their natural presence in dairy and meat products. Many products with almost 0.5 g *trans*-fat, if consumed over the course of a day, may approximate or exceed the 2 g maximum as recommended by the American Heart Association. The objective of the review to demonstrate the causal association between trans fatty acid intake and increase the risk of coronary heart disease through their influence on lipoprotein, association with atherosclerosis, stroke, diabetes and cancer.

1. Introduction

Trans-fatty acids (TFAs) are unsaturated fatty acids which contain leastwise one double bond in the trans configuration. TFAs are manufactured through industrial processes referred as industrial trans fatty acids (iTFA) by partial hydrogenation and deodorization of vegetable oils, and heating oil at very high temperature [1]. Elaidic acid is the prime TFA often found in partially hydrogenated vegetable oil [2]. Low levels of naturally occurring TFAs are obtained from the milk and meat of ruminant animals those are referred as ruminant trans fatty acid (rTFA) e.g., cattle and sheep [3]. The most predominant *trans*-isomer in ruminant TFA is vaccenic acid. Another TFA namely conjugated linoleic acid can be formed from vaccenic acid [4]. In general, there is wide evidence that all isomeric cis and trans fatty acids in ruminant fats and partially hydrogenated vegetables oils are efficiently absorbed and incorporated into chylomicrons with the possible exceptions of fatty acids with double bonds in the 2 to 7 positions. Once they reach the liver, chylomicron remnant triacylglycerol is taken up, repackaged and exported into the circulation in the form of low density lipoproteins [5]. Following incorporation into lipoprotein fractions, triacylglycerol is transported to the peripheral tissues, where they are hydrolyzed by enzyme lipoprotein lipase and taken up into cells. Though trans fats are edible, consumption of trans fats has been showed to increase the risk of Coronary heart disease (CHD) in part by increasing the level of low-density lipoprotein (LDL) referred as “bad cholesterol” and decreases the level of high-density lipoprotein (HDL) referred as “good cholesterol” and raising Triglycerides (TG) in the bloodstream thus promoting systemic inflammation [6] (see Table 1).

Trans fatty acids are needed generally for commercial motives in the food industries to yield semi fat foods and increase the shelf life of products like margarine, crackers, deep-fried fast foods, pancakes, omelets, etc. and can also be found in restaurants [7]. The contents of TFAs differ from one food item to another, it is tough to account their consumption in different countries. In USA it is calculated to be 2–3 energy percent, whereas some countries in Middle East and South Asia, it can be as aerial as 7 energy percent

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https://doi.org/10.1016/j.dsx.2019.03.033
1871-4021/

Table 1
Contents of TFAs in different food types.

Food type	TFA content	Food type	TFA content
Shortenings	10–33g	Salty snacks	0–4g
Margarine/spreads	0.2–26g	Cake frostings and sweets	0.1–7g
Butter	2–7g	Animal fat	0–5g
Whole milk	0.07–0.1g	Ground beef	1g
Breads/cake products	0.1–10g	Vanaspati ghee (vegetable ghee)	3.5–28g

Source: [26], American Nutrition Association, The Heart Foundation.

[8]. In South Asian region, Vanaspati ghee is the principal source of TFA. For instance, in India, Vanaspati ghee used to contain as high as 40–50% TFA [9]. In Iran, 33% fatty acids in partially hydrogenated oil were TFA [10]. Around the world, different levels of TFA intake have been accomplished due to dietary habit and varying quantities of iTFA in processed foods [1].

High intake of dietary trans fatty acids (TFA) have a strong association in increasing the risk of coronary heart disease [11]. Coronary heart disease (CHD) is commenced as a procurement of atheromatous plaque in the arteries which inflict oxygen and blood to the working heart. Development of plaque in the arteries is a consequence of abundant risk factors including infection, diabetes, smoking, physical activity, increased BMI, and high triglyceride levels [12]. Various epidemiological studies have demonstrated a potent definitive adherence between the consumption of TFA and risk of CHD [13]. It has been estimated that a 2% raise in energy consumption from TFA is linked with a 23% increase risk of CHD [7]. Due to the adverse health effects, the WHO recommends less than 1% TFA intake of total energy percent [14]. In Europe, trans fat are "nearly banned" in Denmark (less than 2%), Australia, Austria, Hungary, Iceland, Norway and Switzerland [15].

The objective of this paper is to review the causal association between trans fatty acid intake and increase risk of coronary heart disease through their influence on lipoprotein, association with atherosclerosis, stroke, diabetes and cancer. This review aims to provide a critical and up-to-date overview of current information on existing condition on *trans*-fat intake and risk of cardiovascular disease, blood lipid profile, diabetes and cancer.

2. Potential mechanism of trans fats metabolism

Trans fats seem to affect lipid metabolism by diverse pathways. In vitro, trans fatty acids alter the secretion, lipid composition, and size of Apo lipoprotein B-100 (apoB-100) particles produced by hepatic cells [16]. This alteration is assimilated in studies in humans by reduced rates of LDL apoB-100 catabolism [17], losses in the size of LDL cholesterol particles [18], increased rates of apoA-I catabolism [17], and alter in serum lipid levels [19]. In humans, the structure of trans fat increases plasma mobility of cholesteryl ester transfer protein [20], the key enzyme for the transfer of cholesterol esters from HDL to LDL and very low-density lipoprotein (VLDL) cholesterol. Such increased mobility may set out reduces in the levels of HDL and rises in the levels of LDL and VLDL cholesterol noticed with consumption of trans fatty acids [19].

The cellular mechanisms uttering trans fats to inflammatory pathways and other non-lipid pathways are not well recognized. Monocytes and macrophages, endothelial cells, and adipocytes may each perform a role. Trans fatty acids accord monocyte and macrophage reactions in humans, rising the production through monocytes of tumor necrosis factor-α (TNF-α) and interleukin-6 (IL—6) [21] and probably also levels of monocyte chemoattractant protein (MCP) [22]. Trans fats also interfere in vascular function. Trans fats have been demonstrated to raise circulating biomarkers of endothelial dysfunction [23] and to weak nitric oxide–dependent arterial dilatation [24]. Trans fatty acids also affect fatty acid metabolism of adipocytes, resulting in decreased triglyceride elevation, decreased esterification of recently synthesized cholesterol, and increased formulation of free fatty acids [25]. The effects of adiposity on the connection between consumption of trans fat and circulating interleukin-6 and C-reactive protein levels suspect that the inflammatory effects of trans fats may be partly negotiated by adipose tissue [22].

The contents of TFAs differ from one food item to another; it is tough to account their health effects and mechanism of metabolism and consumption in different countries. Trans fat content in various foods, ordered in g per 100g.

3. Trans fat, inflammation and atherosclerosis

There is competing evidence about the effect of trans fats on systemic inflammation: in an interventional study, trans fat raised markers of inflammation [27] but in other one did not [28]. There is another conflict in observational studies in two reviews of the Nurses' Health Study; two different groups of researchers have found different markers of inflammation [23].

One considerable reason of atherosclerosis is disorders of lipid metabolism and positive interrelation between plasma cholesterol and atherosclerosis is now amply certified. So, the potential for dietary TFAs to promote this.

Concern was a feasible mechanism for harmful effects of TFAs on the cardiovascular system [29]. Bassett and colleagues demonstrated that supplementation of the diet of LDL receptor deleted mice with an industrial *trans*-fat, elaidic acid, resulted in the distinct and definite incitement of atherosclerosis. Moreover, they also exhibited that coupling of elaidic acid to a cholesterol-supplemented diet did not persuade an additive payoff [30]. Abruptly, in the study conducted in the same model of empirical atherosclerosis an amazing anti-atherogenic act by the ruminant TFA, the vaccenic acid was unrolled. A momentous reduction in the area of the atherosclerotic plaques veiled 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 [31].

4. Trans fatty acids increasing risk of coronary heart disease and stroke

Individuals with higher dietary TFA intake possess increased low-density lipoprotein (LDL) levels and lowering high-density lipoprotein (HDL) levels [17]. Replacing just 2% of energy with unhydrogenated unsaturated fat instead of TFA reduce the risk of CHD by 53% [32]. Leth and colleagues found a 60% decrease in CVD risk in Denmark after the Danish Government implemented the legislation to reduce the iTFA intake (Depending on calorie basis, risk of CHD increases about 1–3% with TFA intake) [33]. A more crucial proof found from Nurses' Health Study in which CHD risk roughly doubled for each 2% increase in *trans*-fat calories consumed

[32]. Epidemiological data have provided believing proof that the inclusion of TFAs in our diet is related with an adoption of cardiovascular disease. Dietary TFAs have been associated with CHD and an increased incidence of myocardial infarction [34]. According to systemic review in 2009, there is convincing proof that intake of trans fats increases the risk of CHD [35].

Regarding South Asia, it has been concluded that about 39% of CHD cases in Iran can be reduced by replacing TFA with *cis*-unsaturated fats [10]. Indian Government has taken an attempt to prevent TFA related health problems plans to reduce TFA content in Vanaspati oil to 5% in 2013 [36]. In Pakistan there is no such legislation in reducing TFAs intake. Therefore, an alarming rise of CVD risk in Pakistan [37].

5. Trans fats adversely affect lipid profile & lipoproteins

There is a positive correlation between plasma LDL and atherosclerosis and/or CHD [38]. Although epidemiological evidence suggests that there is a positive association between TFA intake and elevated plasma LDL [17] [as well as triglycerides [39], a clear mechanism has not been established. In the human hepatoblastoma (HepG2) cell line, TFAs have been associated with increased LDL: high-density lipoprotein (HDL) ratios, increased Apo lipoprotein B: Apo lipoprotein A (apoB: apoA) ratio and increased cholesterol content in both LDL and HDL particles in comparison to saturated fats [16]. All of these outcomes have been associated with a higher risk of atherosclerosis and CHD. Similar outcomes reported by Mitmesser et al. who suggested that TFAs altered the size and composition of apoB-100 containing lipoproteins. These studies provide a basic mechanism whereby TFAs deposit cholesterol in arteries. However, it is important to recognize that these studies are primarily correlative and more concrete evidence is necessary. Furthermore, there is no distinction in these studies between rTFAs and iTFAs. These two types of TFAs are structurally different and therefore, their biological effects may also be very different [16].

Epidemiological evidence has generated conflicting results with respect to an association of TFAs with serum lipid levels. In an evidence based analysis observing the effects of isocaloric replacement of polyunsaturated fatty acids (PUFAs), saturated fatty acids (SFAs) or monounsaturated fatty acids (MUFAs) with TFAs, a significant increase in low-density lipoprotein cholesterol (LDL-C) levels, total cholesterol: high-density lipoprotein cholesterol (HDL-C) ratio and the ratio of Apo B: Apo A was observed as well as a decrease in HDL-C levels [33]. Others have shown a decrease in LDL-C particle size with consumption of TFAs as opposed to unsaturated fatty acids [18]. It is important to recognize that these studies investigated a particular isomer of TFAs associated with the hydrogenation of vegetable oils (such as the trans isomer of oleic acid); therefore, more investigation with a wider variety of TFAs may be necessary to fully understand the effect of TFAs on lipoproteins.

6. Can trans fatty acids effect on cancer?

There are very few epidemiological studies that have investigated the association of intake of vaccenic acid (VA) [40] and conjugated linolenic acid (CLA) [41] and risk of cancer. A prospective study on women (1989–2002) revealed that *trans*-fat intake supposedly associated with increased risk of breast cancer [42]. Some of the epidemiological studies that have been reported a direct association with VA concentrations in serum or erythrocytes and risk of breast cancer [40,43] or prostate cancer [44]. In Netherlands a Cohort Study, energy-adjusted intake of VA was associated with an increased risk of breast cancer [45]. There have been 4 case-control studies that have investigated CLA intake and cancer. Of these, one study has reported an inverse association with dietary intake of CLA and risk of colorectal cancer [41], and one study found significantly lower dietary intake and serum concentrations of CLA in individuals with breast cancer compared to those without breast cancer among postmenopausal women [46]. In women in the highest quartile of CLA intake, there was a 29% reduction in the risk of colorectal cancer compared to those in the lowest [41]. In the other 2 case-control studies, there was no significant association of CLA [either as dietary intake [47] or concentration of CLA incorporated into adipose tissue [48] and the risk of breast cancer]. However, in one of the studies, there was a diminished risk of having an estrogen receptor (ER)-negative tumor, in premenopausal women, when comparing the maximum quartile of CLA intake and the minimum [47]. A prospective cohort study has been demonstrated that intake of CLA is weakly related with breast cancer incidence when comparing the maximum and minimum quintiles of consumption [45].

7. Even trans fatty acid associates with diabetes

Three prospective studies have investigated the relationship between the consumption of trans fatty acids and the occurrence of diabetes. Consumption of trans fat was not significantly associated with the risk of diabetes in two of these studies - among male health professionals [49] and among women in Iowa [50]. However, the ingestion of trans fatty acids significantly related to the risk of diabetes among 84,941 female nurses who were observed for 16 years and in whom self-reported diabetes was affirmed and report on dietary intake was periodically updated [51]. After adjustment for other risk factors, trans fat consumption was positively linked with the incidence of diabetes with a risk 39% points greater in the upper quintile than in the lower quintile [13]. In the Iowa cohort, a validation study supposed that the self-reported diagnosis of diabetes was incorrect in 36% of subjects, and diet was assessed only at baseline and may have changed over time [50]. Molecular mechanisms that might account for an effect of trans fatty acids on the incidence of diabetes are not well established, but evidence of effects of trans fatty acids on metabolism in adipocytes [52].

8. Discussion

Trans fats are suspected to be nutritionally unnecessary. Epidemiologic evidence has demonstrated that they are a significant risk factor for cardiovascular disease; several studies demonstrated that a 2% increase in daily energy intake from TFAs is associated with a 23% increase in cardiovascular disease risk [53]. Trans fats have also been exhibited to have an adverse impact on serum lipids and lipoproteins, increasing cardiovascular disease risk to a greater extent [19]. A number of mechanisms for the effects of trans fats have been proposed, including increased activity of cholesteryl-ester transfer protein and increased levels of inflammatory marker [27], positive correlation with atherosclerosis [30], increased risk of CHD [33], and positive association between TFAs and elevated level of plasma LDL [17]. In case of diabetes there are both inverse [49] and positive [51] association whereas epidemiological studies demonstrated significant association between TFAs intake and risk of cancer [40,48]. In review of Nurses' Health Study, researchers have found different markers of inflammation [23]. Specific epidemiological studies demonstrated that 2% increase intake of TFAs causes two times more risk of CHD [32]. Excess intake vaccenic acid and conjugated linoleic acid the risk of cancer [41]. TFA intake is positively linked with the incidence of diabetes with a risk 39% points greater the upper quintile than in the lower quintile [13]. It is clear from several *trans*-fat related studies that dietary trans fats should be minimized. However, the presence of

trans fats in dairy and meat products will make complete elimination from a balanced diet impossible.

Food manufacturers and the food industry want alternatives to trans fats but barriers comprise supply of ingredients and unknown health sequel of new processes. Trans fats gained popularity as a means of replacing saturated fats in the diet. Nevertheless, we now know that trans fats have greater adverse health implications than the saturated fats they wanted to replace. Eradicating trans fats by returning to a high-saturated-fat diet is inappropriate. Consumers are not fully conscious of the well-established health complications of trans fats. Actually, many are disconcerted as to what fats they should or should not be eating. Many are likely consuming trans fats in excess of the maximum intake recommended by the American Heart Association [54]. The present FDA labeling requirements are a better first step in giving consumers with information on trans fats. However, given the recommendation that *trans*-fat intake be as low as possible, allowing all products with <0.5 g trans fats to claim 0 g trans fats can be misleading to many consumers. Eating four or five daily servings of foods with close to 0.5 g *trans*-fat can mean an individual who believes he/she is consuming a healthful, balanced diet is actually exceeding 1% total energy from trans fats. Greater transparency is required to allow consumers to restrict dietary trans fats more effectively. Average consumers do not understand the Nutrition Facts label, or its relation to actual portion size [55,56]. Consumer education is extremely important. In the interim, educational programs targeted at these consumers must be developed to help them determine which foods likely contain trans fats based on the presence of hydrogenated or partially hydrogenated oils in the ingredient list, as well as to more accurately estimate their portion size relative to standardized values on the Nutrition Facts panel.

9. Recommendations

Public awareness about the adverse health effects of TFAs should be increased. More study and survey should be implemented about the health hazards of TFAs, especially in South Asian countries and developing countries because of the high prevalence of CVD. National and international agencies can perform vital role in this perspective. Media can also be focusing the bad health effects of TFAs to the root level. Several plan and policies can be implemented to eliminate the available use of TFAs. The legislations of FDA and World Health Organization on TFAs consumption should be followed. Daily consumption of TFAs should be less than 1% of total energy intake. Industrial manufacturers should take measures to use alternatives of TFA in their produce food products. They should label the contents of TFAs in the packet of their products.

In South Asian countries, there should be conducted epidemiological studies on TFAs consumption and health hazards. Rules and legislations should be implemented based on the findings of the study. In Bangladesh, people are less concern about the health hazards of TFAs. So epidemiological studies should be implemented and public awareness should be increased on adverse effect of high intake of TFAs.

10. Conclusion

There is now overwhelming evidence based upon several studies, TFAs have deleterious effects on our cardiovascular health, cancer and diabetes when included in the diet in high amounts. The synergistic effect of TFAs and other dietary components, drugs and environmental factors also still needs to be investigated in order to better understand TFAs and CHD and other health hazards. The direct action of TFAs on cardio myocyte function is also unclear and may represent yet another important mechanism for the deleterious effects of TFAs. Due to the impressive preliminary outcome documented in Denmark, many other countries across the world are following their lead and creating legislation to limit the amount of iTFAs available for public consumption. However, restricting all TFA consumption may not be realistic or possible. Finding novel ways to block the atherogenic action of TFAs may be a more reasonable approach. Supplementation of the diet with flax seed, for example, can prevent the atherogenic effects of dietary iTFAs in animal models. Other dietary approaches remain to be discovered. It is also important to recognize that many of our concepts regarding TFAs do not consider other TFA isomers beyond iTFAs. Because of the intriguing positive effects of vaccenic acid consumption, the picture of the effects of TFAs as risk factors for atherosclerosis may require further study to fully reveal the effects of trans fats on cardiovascular disease. Ultimately, this may result in some changes in the enacted public legislation.

Conflicts of interest

None of the authors declare a conflict of interest.

Sources of financial support

There is no funding to be disclosed.

Acknowledgements

The authors Md. Ashraful Islama, and Mohammad Nurul Aminb contributed equally to this work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2019.03.033.

Abbreviations

TFAs	Trans fatty acids
iTFA	industrial Trans fatty acids
rTFA	ruminant Trans fatty acid
CHD	Coronary heart disease
TG	Triglycerides
LDL	Low-density lipoprotein
HDL	High-density lipoprotein
VLDL	Very low-density lipoprotein
TNF-α	Tumor necrosis factor-α
IL—6	Interleukin-6
MCP	Monocyte chemoattractant protein
PUFAs	Polyunsaturated fatty acids
SFAs	Saturated fatty acids
MUFAs	Monounsaturated fatty acids
LDL-C	Low-density lipoprotein cholesterol
HDL-C	High-density lipoprotein cholesterol
VA	Vaccenic acid
CLA	Conjugated linolenic acid
ER	Estrogen receptor

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