Review Article

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Dietary fatty acids and cardiovascular disease: a review

Raquel Eccel Prates[1,2], Anize Delfino von Frankenberg[3], Ticiana da Costa Rodrigues[1,3]

ABSTRACT

Fatty acids (FAs) can be classified into saturated (SFA), unsaturated (poly- or monounsaturated) and trans FA. Recent studies have found that both the quantity and quality of dietary FAs may influence their role in metabolic pathways. Due to their chemical composition, some FAs play a major role in the development and progression of cardiovascular disease. This is especially true for SFA and n-3 polyunsaturated fatty acids, which include marine eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The proinflammatory effects of high SFA intake may increase the risk of atherosclerosis. On the other hand, dietary n-3 intake may reduce the risk of cardiovascular disease by decreasing atherosclerosis, inflammation, and thrombotic processes. The goal of this study was to review the current literature on the role of FA intake in the prevention and risk of cardiovascular disease.

Keywords: *Fatty acids; cardiovascular disease*

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1 Graduate Program in Endocrinology, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, RS, Brazil.

2 Department of Endocrinology, Hospital de Clínicas de Porto Alegre, Porto Alegre, RS, Brazil.

3 Department of Internal Medicine, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, RS, Brazil.

Corresponding author:
Ticiana da Costa Rodrigues
E-mail: ticianacr@yahoo.com.br
Division of Endocrinology, Hospital de Clínicas de Porto Alegre
Rua Ramiro Barcelos, 2350.
90035-903, Porto Alegre, RS, Brazil.

ARTICLE SUMMARY

Strengths: The few studies linking diet and the consumption of fatty acids to cardiovascular disease increase the strength of this research. Limitations of this study: Literature review study with cross-sectional design.

INTRODUCTION

Lipids are a type of macronutrient that, like carbohydrates and proteins, are obtained from dietary sources. They are crucial to cell membrane structure (phospholipids, sphingolipids, and cholesterol) and metabolic processes such as the transportation and absorption of lipid-soluble vitamins (A, D, E and K), in addition to playing a role as precursors of hormone synthesis and components of bile[1]. Lipids stored in the form of fat are also responsible for body temperature control, organ protection, and energy storage[2].

The optimal consumption of lipids, especially fatty acids (FAs), “as a percentage of total fat intake in both healthy and sick individuals” is still a relevant and debated issue in the development of nutritional recommendations by doctors and dietitians[3]. The goal of this article was to review the role of dietary FAs in the development and prevention of cardiovascular disease (CVD).

Fatty Acids

FAs are lipids formed by carbon chains attached to hydrogen atoms with an acidic group at one end[3]. They are classified according to the number of double bonds (unsaturations) in their structure. Saturated FAs (SFAs) have no double bonds and are mostly obtained from animal fat, such as that found in red meat and dairy products[3]. The major SFAs are lauric, palmitic and stearic acids. Unsaturated FAs (UFAs), on the other hand, can be divided into monounsaturated (MUFAs) and polyunsaturated FAs (PUFAs). The former category contains acids with a single unsaturation, the most popular of which is omega 9 (oleic acid). They can be found in oils extracted from sources such as olives, avocados, nuts, and almonds[4]. PUFAs, on the other hand, have two or more unsaturations, and are most

commonly exemplified by omega-3 and-6 (n-3 and n-6)[1]. The term "omega" refers to the position of the first double bound starting from the terminal methyl group of the FA molecule[5]. The main dietary sources of PUFAs are canola oil, cold water fish, and some seeds (n-3), as well as soy oil (n-6)[1].

Unsaturated FAs also include trans FAs (TFAs), which are geometric isomers of naturally occurring acids, or *cis*-unsaturated FAs. They are similar to the latter in their molecular shape, but differ in terms of their molecular structure[6]. TFAs are naturally produced by ruminants through the partial hydrogenation and/or isomerization of *cis*-UFA from the hydrogen released during the oxidation process, catalyzed by bacterial enzymes[7]. Artificial trans fats, on the other hand, result from the partial hydrogenation of vegetable oils using hydrogen gas and a metallic catalyst[8]. Approximately 90% of dietary TFAs come from polyunsaturated vegetable oils produced by industrial hydrogenation, a process in which a hydrogen molecule is added as a catalyst to the double bond between carbon molecules[9]. This process decreases unsaturation, increases melting points, and improves oxidative stability and the functionality of semi-solid fractions, and has therefore become widely used in the food industry[9]. The addition of TFAs to processed foods improves their flavor, texture and shelf-life[10]. TFAs can be found in products such as cookies, salty snacks, pastries, microwave popcorn, biscuits, and most foods containing margarine[7].

PUFAs include essential acids (EPUFAs), which cannot be synthesized by the human body and must therefore be obtained from dietary sources. Examples of EPUFAs include linoleic (n-6) and alpha-linolenic (n-3) acids[11]. FAs in the n-6 and n-3 families, also known as omega-6 and omega-3 acids, can be obtained from the diet or produced in the body from linolenic and alpha-linolenic acids by elongase and desaturase activity[12]. Long-chain n-3 acids, including those in the EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) families, come mostly from cold water fish and seeds such as linseed and chia, and have been found to be associated with several health benefits[13]. They play an important role in anti-inflammatory processes, membrane viscosity, and general immunity[14]. DHA is present in all tissue membranes and is found in abundance in the brain and the retina. EPA and DHA are also the precursors of several metabolites and important lipid mediators whose widely studied health benefits[13,14] will be described below. Table 1 summarizes the names and chemical structure of different types of major FAs. Table 2 describes the main dietary sources of FAs with the aim of facilitating their inclusion in diet plans.

Table 2: Recommended fat intake for the prevention of chronic disease.

Fatty Acids	% TEI
Total	20 to 35%
Saturated	<10%
Polyunsaturated	6 to 11%
• Omega-6	2.5 to 9%%
• Omega-3 (EPA and DHA)	0.5 to 2%
• Omega-3 (ALA)	>0.5%
Monounsaturated	Difference value*
Trans	<1%

*Recommended levels of monounsaturated fatty acid intake were calculated as follows: total fat - (saturated + polyunsaturated + trans fatty acids) TEI - Total energy intake. Source: WHO/FAO[15].

Table 1: Dietary sources of fatty acids.

Type	Dietary Source
Saturated fatty acid	Whole milk, butter, cream, high-fat cheese (provolone, Parmesan, mozzarella), lard, bacon, high-fat meats, poultry and fish skins, coconut milk.
Monounsaturated fatty acid	Olive oil, canola oil, olives, avocados, peanuts, chestnuts, walnuts, and almonds.
Polyunsaturated fatty acid	Fish, vegetable oils (sunflower, soy, corn, canola, saffron, cotton, sesame) and seeds of oleaginous plants (chestnuts, walnuts, hazelnuts).
o Omega-6	Meats, sunflower and primrose oil, pumpkin seeds, corn, hemp, soy, sesame, borage, canola, linseed, black gooseberry, and olive oil.
o Omega-3	Fish oil (salmon, tuna, herring, sardines), linseed, chia, hemp, pumpkin seeds, black gooseberry, egg yolks, canola oil, and soy oil.
Trans Fatty Acids	Ice cream, chocolate, filled rolls, salad dressings, creamy desserts, cookies, *chicken nuggets*, *croissants,* pies, processed cake, hard margarine, and some *fast-food.*

Saturated Fatty Acids and Cardiovascular Risk

Studies performed in the 1980s and 1990s reported that the intake of saturated fats and cholesterol is associated with the presence of coronary artery disease (CAD)[16,17]. One of the possible mechanisms underlying the association between SFA intake and an increased risk of CAD is the heightened proinflammatory activity, activation of monocytes and macrophages, and the release of inflammatory markers from adipocytes[18]. However, recent epidemiological studies[19-21] have reported varying degrees of association between these concepts, ranging from a positive association to no discernible relationship[20] between dietary saturated fats and CAD-related morbidity or mortality. It is possible that the effects of dietary SFAs on the risk factors for CAD differ depending on the acid in question and on its dietary source. For instance, a diet high in stearic acid (C18;0) is more effective in reducing LDL cholesterol (LDL-c) levels than a diet enriched with palmitic acid (C16;0) or with myristic (C14;0) and lauric acids (C12;0)[22,23]. Although all of these are SFAs, palmitic acid has a stronger effect on increasing LDL-c levels than lauric acid[24].

A recent meta-analysis of prospective cohort studies of the association between saturated fats and cardiovascular disease (CVD) found no significant evidence of a relationship between dietary saturated fat and a greater risk of CAD[25]. The study in question also suggested that the beneficial effects of low-saturated fat diets on CAD risk might be explained by the high levels of polyunsaturated fats in these diets[25] rather than by the reduction in saturated fats per se. However, a recent evaluation of the data obtained from the *Sydney Diet-Heart Study* revealed that the substitution of dietary saturated fats by linoleic (n-6) acid (a PUFA) did not lead to any benefits or reductions in overall or CAD-related mortality[26].

This study also evaluated the relationship between dietary FAs and cerebrovascular disease. A recent case-control study of 297 patients with a history of stroke found that MUFAs, PUFAs, and SFAs play independent protective roles against cerebrovascular disease, while increased TFA intake leads to an increase in the risk of stroke[27]. These findings are similar to those of previous investigations, such as the Framingham Heart Study[28], which found an inverse association between SFA and stroke risk, as did the Honolulu Heart Program[29]. In both studies, total lipid intake proved to be negatively associated with the incidence of stroke but positively associated with coronary disease. Some authors suggest that SFAs may have an effect on atherosclerosis in the coronary arteries but not on cerebral arteries, since the physiopathological mechanisms responsible for atherosclerosis may differ between these vessels and therefore be differently affected by lipid intake[27,30,31].

The latest Cochrane review of the effects of saturated fats on cardiovascular outcomes suggested that a decrease in SFA intake due to reduced total lipid intake or changes in dietary lipid composition could reduce the risk of CVD by 14%, according to the results of 6-month clinical trials[32].

Monounsaturated Fatty Acids and the prevention of Cardiovascular Disease

One of the first prospective studies of the effects of MUFAs was the *Lyon Diet Heart Study*, which evaluated the beneficial effects of a Mediterranean diet in subjects with acute myocardial infarction. This study included patients under 70 years of age who survived acute myocardial infarction. They were assigned either to the intervention group (n = 289), which received guidance on the Mediterranean diet according to nutritional guidelines, including being advised to increase the consumption of fruits, fish and olive oil, and a control group (n = 295). Authors showed that the Mediterranean diet group had lower incidence of mortality and improved lipid profile[33]. There have been several recent meta-analyses[34-36] of cohort studies investigating the effects of dietary fat intake on coronary events and cardiovascular death. Skeaff and Miller[34] did not observe any effect of high-MUFA diets on the risk of coronary events or death. Jakobsen et al.[35] performed a meta-analysis of cohort studies involving 344,696 individuals and found MUFA-rich diets to be positively associated with a risk of coronary events but not with mortality. The authors stated that, in Western diets, MUFAs are predominantly obtained from animal products, which may confound the results of comparisons between dietary fat levels[35], since the most common dietary sources of MUFAs are vegetable products containing oleic acid.

Another meta-analysis of cohort studies found a significant association between MUFA intake and reduced risk of coronary disease[36]. Two additional meta-analyses of randomized clinical trials and cohort studies also reported the beneficial effects of MUFA-rich diets on the reduction of CVD, although these findings were not conclusive[37,38].

Polyunsaturated Fatty Acids and the Prevention of Cardiovascular Disease

Studies suggest that the consumption of n-3 PUFAs (EPA and DHA) extracted from fish oils could reduce the risk of CVD by decreasing atherosclerosis, inflammation, and thrombotic processes[39]. The benefits of n-3 PUFAs in reducing CVD mortality have been documented in patients who survived acute myocardial infarction[14].

A meta-analysis of randomized studies of patients with heart disease showed that dietary supplementation with up to 2g/day n-3 EPA and DHA from fish oils reduced CAD-related deaths by over 20% but had no effect on the occurrence of arrhythmia or death from other causes[40]. Based on another meta-analysis of cohort studies and clinical trials, Mozaffarian and Rimm concluded that a daily intake of 250mg EPA and DHA from natural dietary sources reduced the risk of fatal heart disease by 36%, with no additional benefit at higher doses[41]. On the other hand, two randomized, placebo-controlled trials of the effects of enriched margarine or supplementation with 1g n-3 FAs (EPA and DHA) in patients with previous cardiovascular events or with high cardiovascular risk but no actual history of heart disease found that supplementation with n-3 FAs did not lead to a significant reduction in cardiovascular events or mortality risk in these subjects[40,42].

There is still limited evidence of the protective effects of plant-derived alpha-linolenic acid (ALA). A meta-analysis of five prospective studies showed that the risk of fatal CAD was 21% lower in individuals with high ALA intake (up to 2.0g/day) than in those who consumed less than 1.2g ALA/day, with both groups obtaining this FA from dietary vegetable oils[43]. In the *Nurses' Health Study*, which involved a cohort of 76,763 women with no history of cancer or CVD, ALA intake was investigated using a nutritional questionnaire, administered at the beginning of the study in 1984 and throughout an 18-year follow-up. The study found that increased ALA intake might decrease the risk of CVD[44].

Studies of dietary n-3 levels have found that these compounds reduce vulnerability to arrhythmia by stabilizing the myocardial membrane[45,46]. These findings corroborate the inverse relationship between the dietary intake of EPA and DHA from fish and the risk of sudden heart-related death reported in both case-control and cohort studies[47,48]. Erkkilä et al.[48] randomized 33 subjects with CVD into one of three groups with varying levels of n-3 intake: an increased lean fish intake group, an increased fatty fish consumption group, or a control group. These diets were followed for a period of eight weeks. The group who ate fatty fish four times a week (approximately 1.07g/day n-3) showed a significant increase HDL cholesterol (HDL-c) in 62mg/dL relative to the control group, suggesting a beneficial health effect of fish oil PUFAs (48). The dose-response relationship between EPA and DHA intake and the risk of cardiac death has not been well established. However, some authors hypothesize that the variability of findings on the topic may be associated with the different ethnic features of the populations examined by each study[49].

A meta-analysis of randomized controlled trials that evaluated the effects of n-6 acids and of the combination of n-6 and n-3 acids criticized studies which suggest that dietary SFAs be replaced with vegetable oil omega-6 acids. The article also points out several limitations of previous meta-analyses on the topic, such as the omission of relevant trials with unfavorable outcomes, the inclusion of studies with weak design and several confounders, and a failure to distinguish between trials that selectively increased n-6 intake from those that focused on n-3 PUFA intake only[50].

Trans Fatty Acids and Cardiovascular Disease

The negative health effects of TFAs obtained from industrially produced partially hydrogenated vegetable oils have been demonstrated by several studies[6,12,21]. The main adverse effects of TFA relate to plasma lipid concentration[22]. Kummerow et al. found that the consumption of TFAs might significantly increase LDL-c while reducing HDL-c levels[51]. A one-year follow-up of a cohort of 400 patients hospitalized for CVD revealed that a reduction of only 1% (kcal/day) in dietary TFAs intake was significantly associated with decreased LDL particle number, confirming the role of the latter as a confounder-independent modifiable risk factor and marker of disease progression[52]. TFAs have also been found to lead to greater increases in the plasma concentration of triglycerides than mono or polyunsaturated fats[53]. Clinical trials have suggested that the consumption of TFAs from hydrogenated vegetable oils has a negative effect on CVD due to their hypercholesterolemic and proinflammatory effects. Strong positive correlations between erythrocyte TFAs levels (biological marker of dietary intake) and markers of systemic inflammation have also been identified in subjects with established CVD, which speaks to the proinflammatory effect of TFAs intake. TFAs consumption is also associated with an increase in circulating markers of endothelial dysfunction[54].

A meta-analysis of prospective studies performed by Mozaffarian and Rimm showed a 32% increase in the risk of acute myocardial infarction or CAD-related death for each 2% replacement of energy intake from carbohydrates, SFA, MFA and PUFAs, respectively, with TFAs[41]. A recent review of observational, cohort and randomized clinical studies[21] suggested that animal sources have become the largest dietary source of TFAs after attempts by the food industry to reduce the use of hydrogenated fats. The effects of ruminant-derived TFAs on cardiovascular risk have not yet been fully elucidated. Some epidemiological studies found no association between the intake of ruminant-derived TFAs and the risk of coronary disease, while others have found positive or even nonsignificant negative relationships between these

two factors[12]. Data on the effects of ruminant-derived TFAs on plasma lipoproteins are still scarce. A study published by Lacroix et al.[55] in the *American Journal of Clinical Nutrition* reported that the consumption of a butter enriched with TFAs from ruminant sources did not influence the concentration of LDL-c in the 61 women who took part in the study. However, women with a body mass index (BMI) of at least 25 kg/m^2 showed a reduction of 2.8% in HDL-c concentration.

RECOMMENDATIONS

The DRIs (*Dietary Reference Intakes)* for healthy adults suggest that 20 to 35% of calories in the diet should be derived from fats[56]. In 2008[15], the World Health Organization (WHO) published a *technical report* with nutrient recommendations to prevent chronic non-communicable diseases, according to the guidelines established by the Food and Agriculture Organization of the United Nations (FAO)[57]. The recommendations for fat intake (in % of total calorie intake) can be found in Table 2. According to the V Guidelines for Dyslipidemia and the Prevention of Atherosclerosis issued by the Brazilian Society of Cardiology[58], the replacement of dietary SFAs with n-6 PUFAs, so that the latter comprise 5 to 10% of total energy intake, may reduce cardiovascular risk. The guidelines also recommend a daily intake of 2-4g/day of marine n-3 FAs.

The Brazilian recommendations are similar to those of the American College of Cardiology and the American Heart Association (ACC/AHA)[59], which suggest that a daily intake of 25-30% of calories from fat can prevent cardiovascular risk in healthy individuals. The guidelines also suggest that SFAs should provide 5 to 6% of daily calories, while TFAs should make up less than 1% and cholesterol, less than 300mg. Additionally, the daily intake of MUFAs should be between 15 and 30 g and of PUFAs, between 6 and 10%; moreover, the consumption of butters, hydrogenated fats, partially hydrogenated oils, as well as lard and palm oil, should be especially avoided[59]. In contrast, recently based on the accumulated body of evidence, the US Dietary Guideline suggests that limiting fat and cholesterol intake did not produce any meaningful health benefits and that increasing a consumption of over 35% of daily calories from PUFAs and MUFAs has documented health benefits[60].

There is no consensus as to the maximum allowance of dietary TFAs. However, guidelines recommend that TFAs should provide no more than 1% of total energy intake[61]. According to resolution RDC no. 360/2006 of the Brazilian National Health Surveillance Agency (ANVISA), the trans-fat content of foods should always be listed on product labels. However, quantities of 0.2 g or less per portion can be listed as “zero”[62].

DIET THERAPY

Some studies suggest that Mediterranean diets may have beneficial effects on cardiovascular risk[63-65]. These diets are characterized by high contents of olive oil, fruits, nuts, vegetables, and cereals, moderate fish and poultry consumption, and a low intake of dairy products, red meats, processed meats, sweets, as well as moderate wine consumption[66]. A multicenter study of primary prevention in individuals at high risk of CVD in Spain compared the effects of a Mediterranean diet to those of a control diet in 7447 participants. Cardiovascular risk decreased by 30% in the Mediterranean diet group[64]. In two cohort studies, *The Nurses' Health Study* and *The Health Professionals Follow-up Study,* the consumption of nuts at least seven times a week was inversely related to the risk of cardiovascular death in both men and women[67].

Table 3 shows an example of a healthy Mediterranean diet plan developed by the authors of the present study, according to guidelines on PUFA intake and recommendations for the prevention of CVD.

FINAL CONSIDERATIONS

The nature of the relationship between FAs and CVD has changed as studies accumulate over time. The amount and types of FAs involved in the prevention and reduction of cardiovascular events is

Table 3: Sample diet for the prevention of cardiovascular disease.

Breakfast	1 cup coffee with skimmed milk + 2 slices whole-wheat bread + 1 slice white cheese + 1 tablespoon diet jam
Morning snack	1 fruit + 3 Brazil nuts
Lunch	1 plate raw and cooked vegetables with a tablespoon of olive oil + 1 portion (120g) cooked salmon + 3 tablespoons brown rice + 1 ladleful beans
Afternoon snack	½ avocado mashed with lemon juice + 10 unsalted almonds + 1 skimmed yoghurt + 1 tablespoon ground linseed or chia
Dinner	1 plate raw and cooked vegetables with a tablespoon of olive oil + 1 portion (100g) grilled chicken

still a matter of debate. The total amount of dietary fat intake does not appear to determine cardiovascular outcomes, so that dietary recommendations should focus on the types of FAs consumed. The impact of saturated fats on cardiovascular health appears to depend on their dietary source and intake. Recent studies have found MUFAs intake, especially in the form of a Mediterranean diet, to be associated with reductions in CVD. Dietary intake of n-3 PUFAs from fish plays a protective role against cardiovascular disease. However, supplementation with fish oil does not confer the same health benefits. The dietary replacement of saturated fats with n-6 FAs is still a matter of debate. There appears to be a consensus in the literature regarding the association between TFA intake and increased cardiovascular risk. As such, the intake of TFAs should be reduced by restricting the consumption of processed foods.

Disclaimer

RP, this literature review was part of her master's thesis, and she developed and designed the manuscript. AF, helped draft and revise the manuscript. TR, advisor of the author, helped design and write this article. All authors read and approved the final manuscript

Conflicts of interest

The authors declare no conflict of interest.

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