Fatty Acids for Cardiovascular Disorders

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Contributor: Viktoriya Shramko

Data are discussed regarding the roles of the most relevant fatty acids, such as myristic (C14:0), palmitic (C16:0), stearic (C18:0), palmitoleic (C16:1), oleic (C18:1), linoleic (C18:2), *α*-linolenic (C18:3, *ω*-3), *γ*-linolenic (C18:3, *ω*-6), arachidonic (C20:4), eicosapentaenoic (C20:5), docosahexaenoic (C22:6), and docosapentaenoic (C22:5) acid. The accumulated knowledge has expanded the understanding of the involvement of fatty acids in metabolic processes, thereby enabling the transition from basic exploratory studies to practical issues of application of these biomolecules to CVD treatment. In the future, these findings are expected to facilitate the interpretation and prognosis of changes in metabolic lipid aberrations in CVD.

Keywords: cardiovascular diseases ; ischemic heart disease ; fatty acid ; lipid metabolism

1. Introduction

Diseases of the blood circulation system, primarily ischemic heart disease (IHD), rank first in terms of the prevalence of complications and death in Westernized societies, being responsible for one of every three deaths in the United States and one of every four deaths in Europe [1][2]. The 2013 Global Burden of Disease study estimating that cardiovascular diseases (CVD) caused 17.3 million deaths globally. It accounted for 31.5% of all deaths and 45% of all non-communicable disease deaths, more than twice that caused by cancer, as well as more than all communicable, maternal, neonatal, and nutritional disorders combined [2]. In addition to systemic inflammation, oxidative stress, and disruption of lipid metabolism, which are risk factors for the development and progression of atherosclerosis and the related CVD, fatty acid (FA) metabolic abnormalities became also an important risk factor. Much attention is given to the research on FA, with particular emphasis on the their amount and type consumed, and there are studies on potential utility of FA as biomarkers of the functional state of the human body for early diagnosis of CVD and especially atherosclerosis [3][4][5][6][7][8]. In cells of human tissues, ~70 FA have been identified as components in a structure of lipids, with more than a half of these FA detected in trace amounts, a less than 0.1% proportion.

The American Heart Association/American College of Cardiology guideline has recommended to decrease intake of saturated FA (SFA) to 5% to 6% of total daily energy (calorie) intake to reduce the risk of CVD [9]. The scientific rationale for decreasing SFA in the diet has been and remains based on well-established effects to raise low-density lipoprotein (LDL) cholesterol, along with a reduction in non–high-density lipoprotein (HDL) cholesterol, a leading causes of atherosclerosis [10]. On the contrary, polyunsaturated FA (PUFA) are considered to ameliorate lipid markers, with omega-3 PUFA consumption resulting in reduction of plasma triacylglycerols (TG) and ApoB-100, which in turn reduces the concentration of LDL cholesterol [11]. Reducing SFA and replacing it with PUFA in randomized controlled trials has reduced the incidence of CVD which included myocardial infarction (MI) (fatal and non-fatal combined) and IHD events [12][13]. In Finland, a successful nationwide health project to lower the very high rate of IHD mortality, started in 1972, had as a major goal the reduction in the high intake of SFA [14]. Regarding monounsaturated FA (MUFA), the data are more limited, but in vivo studies like those of Macri et al. [15], and Alsina et al. [16], found that olive oil and fish oil, rich in MUFAs, is highly effective in decreasing the oxidization of LDL, and TG levels [17]. In the populations with very low SFA intake have very low rates of CVD [18], and members of many single populations who have low SFA high unsaturated FA intake have lower future incidence of CVD compared with those with high SFA and low unsaturated FA intake [19]. Therefore, the Dietary Guidelines recent years is to shift food choices from those high in SFA to those high in MUFA and PUFA [9][20].

As lipids constitute a major portion of the majority membranes suggest that the presence of massive concentrations of unsaturated FA within membranous structures. In addition, well recognized that the PUFA are bioactive mediators of diverse pathways involved in cellular homeostasis or, in some cases, interact with cellular macromolecules resulting in cell death [21]. These cellular responses may be a consequence of the vulnerability of unsaturated FA to diverse oxidation reactions, or radical reactions, or both. Reactive oxygen species readily bind to unsaturated FA in lipids that contain multiple double bonds (DB), “steal” electrons, and trigger a free radical chain reaction. This oxidative process usually consists of initiation (production of a FA radical), propagation (creation of a peroxyl-FA radical), and termination

(production of electrophilic carbonyls [22][23]. The free radical mediated production of electrophilic products of PUFA proceeds by autocatalysis and is, as a result, not well regulated. Thus, free radical mediated lipid peroxidation is more commonly associated with diseases of sustained oxidative stress including atherosclerosis and the related CVD [24].

In the past few years researchers have come to discordant conclusions about the relationship between dietary FA and risk of CVD [12][13][20]. This has created confusion among patients, their physicians, and the public. The objective of this review is to present of results regarding effect most relevant FA on CVD, so that understand the reasons for the divergent findings.

2. Saturated Fatty Acids (SFA)

Among FA, the structure of SFA is the stability and their physical properties depend on their molecular weight (Table 1).

Table 1. The most physiologically important saturated fatty acids.

The Notation of Fatty Acid (Number of Carbon Atoms: Number π Bonds)	Trivial Name	Systematic Name (IUPAC)	Chemical Formula
12:0	Lauric	Dodecanoic	$CH_3–(CH_2)_{10}–COOH$
14:0	Myristic	Tetradecanoic	$CH_3–(CH_2)_{12}–COOH$
16:0	Palmitic	Hexadecanoic	$CH_3–(CH_2)_{14}–COOH$
18:0	Stearic	Octadecanoic	$CH_3–(CH_2)_{16}–COOH$
20:0	Arachidic	Eicosanoic	$CH_3–(CH_2)_{18}–COOH$
22:0	Behenic	Docosanoic	$CH_3–(CH_2)_{20}–COOH$
24:0	Lignoceric	Tetracosanoic	$CH_3–(CH_2)_{22}–COOH$

SFA are resistant to oxidation. The cellular membranes and lipoproteins containing large amounts of SFA are less active functionally. Such lipoprotein particles form stable bonds with cellular receptors of lipoproteins, thus promoting disorders of the cholesterol transport system in the human body and leading to the development of the dyslipoproteinemias that contribute to atherosclerogenesis: So-called atherogenic dyslipoproteinemias [25][26].

It is believed that consumption of food with SFA is associated with increased risk of CVD according, which is mediated by increased levels in serum of total cholesterol by increasing cholesterol levels LDL cholesterol. A number of studies have shown that increased consumption of SFA is associated with both an increased incidence of IHD and the severity of atherosclerotic lesions of the arteries [13][27][28][29][30][31][32].

A recent meta-analysis, which included 15 randomized controlled trials involving over 59,000 people, assessed the effect of reduced dietary the amount of SFA on mortality and cardiovascular morbidity [13]. This systematic review suggests that reducing SFA in the diet for at least two years reduced MI and IHD events, but no effects on IHD mortality, non-fatal MIs, or stroke. This clear effect on cardiovascular events was not lost on sensitivity analyses. The reduction in cardiovascular events was clearer in subgroups with greater baseline SFA intakes, greater reduction in SFA in the intervention group, and studies with greater serum total cholesterol and LDL cholesterol reductions. Meta-regression confirmed that degree of reduction in cardiovascular events was related to degree of reduction of serum total cholesterol, and there was a modest suggestion of greater protection with greater SFA reduction or greater increase in unsaturated FAs in the diet.

Palmitic acid (C16:0) is one of the important constituent acids of TG in adipose tissue. In this regard, palmitic acid content of blood has the greatest diagnostic and prognostic significance. It is considered that palmitic acid is linked with adverse cardiovascular events [27][28], and its high consumption raises the risk of CVD. The results of the randomized crossover investigation indicate that the palmitic acid-enriched diet resulted in increased fasting plasma LDL cholesterol, and HDL cholesterol concentrations [29]. It has been shown that after a decrease in the intake of SFA, blood concentrations of palmitic acid, LDL, and glucose diminish [30]. Results of a prospective study on US females and males [31] suggest that high blood levels of palmitic FA are associated with a high risk of the onset and progression of IHD. The

prospective case-control study CIRCS [32], conducted by Japanese scientists, has yielded similar results. The LURIC study (the Ludwigshafen Risk and Cardiovascular Health study) [33] have investigated the link of SFA in the blood with overall and cardiovascular mortality among patients referred to coronary angiography. The results revealed that palmitic acid is related to a higher risk of death from CVD. Palmitic FA, by enhancing inflammation-related signaling of lipopolysaccharides in macrophages, promotes inflammation and the development of CVD [34][35][36]. In addition, inflammatory activity probably is characterized by increased production of pro-inflammatory cytokines and oxidants, leading to cellular hypertrophy and apoptosis. The findings show that elevated levels of palmitic acid and likely other SFAs can contribute significantly to cardiac damage [37].

Myristic acid (C14:0). In tissues of humans and animals, this acid is present at relatively low concentrations, on average, 1% of all FA by weight [38]. Although myristic acid is a minor plasma SFA, it has attracted growing attention because of clinical evidence suggesting its potent cholesterol-upregulating action [39]. Therefore, Fattore E. et al. [40] conducted a systematic meta-analysis, comprising a total of 51 studies with the participation of 1526 volunteers. The results of this meta-analysis show that the major dietary saturated fats (palmitic, stearic, lauric, and myristic acids) have differential effects on the lipid profile: Myristic and lauric acids increase all the cholesterol fractions (e.g., total cholesterol, LDL cholesterol, HDL cholesterol, LDL cholesterol/HDL cholesterol ratio, TG, apolipoprotein A-I, and apolipoprotein B) more than does palmitic acid, and palmitic acid increases all the cholesterol fractions more than does stearic acid. In a prospective case-control study known as CIRCS [32], blood levels of myristic acid were higher in patients with IHD than in a control group of subjects. Multivariate regression analysis uncovered a link of myristic FA with higher IHD risk.

Stearic acid (C18:0). In contrast to palmitic acid, which correlates with hypercholesterolemia (HC), it is considered that stearic SFA does not have a significant influence on lipid metabolism [41]. However, in the randomized investigations Meng H. et al. [29] and Mah E. et al. [42] the stearic acid-enriched diets resulted in lower fasting plasma LDL, HDL, and non–HDL-cholesterol concentrations. By contrast, in the randomized controlled trial Baer D. J. et al. [43] and in a study by Mensink R.P. et al. [10] consumption of stearic acid as an supplement did not affect the in blood lipids and any of the primary risk factors for cardiovascular disease. In general, the data on the influence of stearic acid on CVD are contradictory. For instance, in the prospective investigations [44][45], it has been demonstrated that high consumption of stearic acid does not correlate with a higher risk of IHD and MI. By contrast, in the prospective cohort study by Zong et al. [46] and in research Praagman et al. [47], stearic acid was found to make a major contribution to the development and course of IHD. Hunter et al. [48] have shown an independent relation of stearic FA with a higher risk of IHD, but this link turned out to be weak after normalization to the sum of other studied SFA (lauric, myristic, and palmitic acids). Harvey et al. [27] have reported that stearic acid induces apoptosis and necrosis of endothelial cells more strongly than does palmitic or myristic FA. Furthermore, those authors advanced a hypothesis that intracellular accumulation of stearic FA can be proinflammatory and lipotoxic.

Epidemiological research indicates that SFA, especially those containing 12–16 carbon atoms, have the greatest effect on the blood concentration of LDL cholesterol and therefore are often associated both with a higher risk of CVD and with the severity of atherosclerotic lesions in arteries [38][49][50][51]. Present dietary guidelines recommend keeping SFA intake at 8–10% of total energy intake for the prevention of IHD and the reduction of SFA consumption and increase of PUFA consumption is the most efficient method for the normalization of the lipid value in the blood. A change in the proportions of the ingested-with-food FA that affect the ratio of HDL cholesterol to LDL cholesterol may be more important than the simple limiting of SFA, at least myristic and stearic ones, both of which influence the HDL cholesterol level [52].

Clinical trials offer conflicting conclusions regarding the role of SFA and the risk of IHD and its clinical complications. But growing number of studies indicate that the impact of SFA on the course and mortality rates of CVD, is not so much dependent on the overall amount of SFA in the human body but rather on their ratio to unsaturated FA. A recent Cochrane meta-analysis [13] showed moderate-quality evidence that replacing the energy from SFA with PUFA reduces the risk of CVD events and MI, but no effect on all-cause mortality or IHD mortality.

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