Meeting Report

Saturated Fat Consumption and Risk of Coronary Heart Disease and Ischemic Stroke: A Science Update

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Abstract

At a workshop to update the science linking saturated fatty acid (SAFA) consumption with the risk of coronary heart disease (CHD) and ischemic stroke, invited participants presented data on the consumption and bioavailability of SAFA and their functions in the body and food technology. Epidemiological methods and outcomes were related to the association between SAFA consumption and disease events and mortality. Participants reviewed the effects of SAFA on CHD, causal risk factors, and surrogate risk markers. Higher intakes of SAFA were not associated with higher risks of CHD or stroke apparently, but studies did not take macronutrient replacement into account. Replacing SAFA by *cis*-polyunsaturated fatty acids was associated with significant CHD risk reduction, which was confirmed by randomized controlled trials. SAFA reduction had little direct effect on stroke risk. Cohort studies suggest that the food matrix and source of SAFA have important health effects.   © 2017 S. Karger AG, Basel

Introduction

For decades, the consumption of long-chain saturated fatty acids (SAFA; containing 12–18 carbon atoms) was thought to undermine cardiovascular health. However, recent meta-analyses of prospective observational studies [1, 2] reported that SAFA intake was associated with neither coronary heart disease (CHD) nor stroke mortality nor myocardial infarction. Instead, reduced SAFA intake that was replaced by *cis*-polyunsaturated fatty acids (PUFA) was associated with a 17% lower risk of cardiovascular events [3], which was confirmed by randomized controlled trials [4, 5]. Under isoenergetic conditions, the lack of association of SAFA per se with CHD risk could imply that the potential contribution of dietary SAFA is comparable to that of all other macronutrients together. On the other hand, SAFA consumption significantly increases the plasma concentration of low-density lipoprotein cholesterol (LDL-C) compared with mixed carbohydrates and *cis*-unsaturated fatty acids [6], potentially increasing the risk of CHD [7].

The contrasting findings have challenged current SAFA recommendations, generated vigorous debate, and

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led to consumer confusion [8, 9]. Therefore, to update and discuss the science linking SAFA consumption to the risk of CHD and ischemic stroke, 20 international experts on dietary fat and health convened in Leiden, The Netherlands, November 5–6, 2015, as guests of the International Expert Movement to Improve Dietary Fat Quality (www.theiem.org), The Netherlands Oils and Fats Industry (www.mvo.nl) and the European Palm Oil Alliance (www.palmoilandfood.eu). This updated report describes the meeting's highlights.

SAFA Background

SAFA intake is inevitable as these fatty acids occur in all fat-containing foods, for example, dairy products, butter, meats, and some vegetable fats and oils [10]. Most dietary SAFA have 12–18 carbon atoms, with foods varying in the relative amounts of individual SAFA. Palmitic (C16) and stearic acids (C18) are predominant in butter, dairy and meat products; lauric (C12) and myristic (C14) acids in butter, dairy foods, coconut, and palm kernel oils [11]. In many Western countries, in particular, SAFA intakes exceed 10%E [10, 12].

In animal fats, SAFA are mainly located at the *sn*-2 position of the glycerol backbone, whereas they are usually located at the *sn*-1 and -3 positions in vegetable fats and oils [13]. These structural differences imply important physical, metabolic, and functional distinctions, which can be removed by the technique of fatty acid randomization [14].

Coconut oil contains >80% SAFA. A common misconception is that the medium-chain SAFA in coconut oil are metabolized differently from long-chain SAFA (≥C12). However, coconut oil contains approximately 50% lauric acid and 15% myristic acid, both of which have potent LDL-C and high-density lipoprotein cholesterol (HDL-C)-raising effects [6]. The popular belief that coconut oil is healthy is not supported by scientific data [15].

SAFA have distinct metabolic functions, including protein acylation [16]. This widely occurring mechanism controls the function of diverse proteins and physiological processes. Palmitate and myristate are involved in G-protein activation and consequently in signal transduction [17]. Myristoylation may be involved in the synthesis of ceramide and consequently in sphingolipid metabolism and function [18]. In addition, by stimulating fatty acid desaturation, myristic acid may increase the conversion of essential fatty acids to their functional long-chain polyunsaturated derivatives [19]. Despite these important functions, SAFA are not essential fatty acids because they can be synthesized de novo.

SAFA-rich triglycerides (TG) confer several functional qualities to foods, including structure, plasticity, and organoleptic characteristics, such as creaminess and flavor. These qualities enhance food palatability, stability, and structure and are difficult to replace without losing important food characteristics [20]. Many of the functional qualities of SAFA depend on the underlying, space-filling, fat crystal network that generates macroscopic hardness and stabilizes the oil/water interface [21]. Differences in the fatty acid composition of the TG, for example, chain length and saturation, affect product hardness [22]. For many applications, a SAFA-rich fraction of palm oil (palm stearin) is suitable [23]. Full hydrogenation of vegetable oils rich in unsaturated fatty acids is another option, but conflicts with consumers' demand for minimal processing. Whether this demand can possibly be met by conventional selective plant breeding deserves study.

Risk Factors for CHD and Ischemic Stroke

Clinicians assess several characteristics to determine an individual's risk of CHD. Those causally related to the risk of CHD are known as risk factors. Changes in a risk factor change CHD risk in a predictable way. Established and modifiable risk factors for CHD include elevated LDL-C, high blood pressure (BP), overweight and obesity, and smoking [24]. Additional risk factors have been suggested, for example, TG and C-reactive protein, but whether they are causally related to CHD is not agreed. Mendelian randomization studies may be useful for establishing causality [25].

Substantial evidence implicates LDL-C as a causal factor in cardiovascular disease (CVD) and CHD events [7], and randomized controlled trials with LDL-lowering interventions [26] support a causal relationship between LDL-C and CHD. However, LDL-C is just one causal risk factor; consequently, many CVD patients can have LDL-C levels in the optimal range. Although observational studies often fail to demonstrate significant correlations between SAFA consumption and LDL-C levels, these do not necessarily exclude a causal relationship [27]. Thus, control of LDL-C remains a cornerstone of CHD risk management [28].

Plasma LDL-C includes the cholesterol in all LDL particles (LDL-P), which exist along a continuum of sizes and densities [29]. Small, dense LDL-P (sdLDL) contain

less cholesterol per particle, but are more strongly associated with increased CHD risk than larger, more buoyant particles [30]. Thus, the measurement of LDL-P might improve the predictability of CHD risk compared with LDL-C, particularly when LDL-C is not elevated [31].

The size distribution of LDL-P is affected by the consumption of excess energy and the macronutrient composition of the diet [32, 33]. Higher intake of SAFA was associated with increases in larger, more buoyant LDL-P [34]. In the context of the Dietary Approaches to Stop Hypertension diet [35], higher compared with lower (14%E vs. 8%E) dietary SAFA was associated with improved lipid profiles and lower BP [36] when SAFA replaced carbohydrates. Although the cholesterol content of sdLDL is useful, the overall plasma concentration of these particles may be more informative [37].

There is compelling evidence that individuals with lower HDL-C face a significantly higher risk of CHD [38], but paradoxically, higher levels are not always associated with lower CHD risk [39]. The Emerging Risk Factor Collaboration showed that the inverse relationship between HDL and CHD risk holds only for lower HDL concentrations and does not apply at higher levels. HDL is widely thought to be involved in "reverse cholesterol transport" [40], a hypothesis that has been seriously challenged [41]. Doubts about the "HDL hypothesis" and the causal involvement of HDL-C in CHD risk were strengthened by Mendelian randomization studies in individuals with genetically linked elevated HDL-C whose risk of myocardial infarction was not different from those lacking the variant gene [41, 42]. Furthermore, trials with substances increasing HDL-C levels failed to reduce cardiovascular events or increased them and mortality [43]. However, these trials were performed in patients at high risk of CHD, whose HDL may have lost its putative cardioprotective function [44, 45]. These findings favored the view that HDL functions beyond cholesterol efflux may be more important for cardiovascular protection than absolute HDL levels [46].

The third commonly assessed lipid marker of CHD risk is plasma TG, chauffeured in particles of chylomicrons and their remnants, very low- and intermediate-density lipoproteins [46, 47]. Many studies reported significant associations between fasting and nonfasting TG concentrations and risk of CHD [48, 49], but there is disagreement whether TG-rich lipoproteins constitute an independent causal risk factor [49, 50]. The difficulty in establishing causality relates to the close relationship between TG and remnant cholesterol, and the inverse relationship between TG and HDL-C concentrations in plasma, both of which are significantly associated with the risk of ischemic heart disease, but in opposite directions [51]. In addition, these relationships are confounded by lifestyle factors, such as physical activity, alcohol consumption, higher body mass index, diabetes, and by reverse causation [52, 53]. Because most cells can degrade TG, but not cholesterol, it is likely that the atherogenic part of TG-rich lipoproteins is cholesterol, not the TG itself. This implies that the plasma TG level could be a risk marker rather than a causal factor.

TG-rich lipoproteins carry 2 specific apolipoproteins on their surface, apolipoprotein A-V and apolipoprotein C-III, encoded by the genes *APOA5* and *APOC3*, respectively. *APOA5* activity lowers circulating levels of TG-rich lipoproteins and is associated with decreased risk of CHD [54, 55]. In contrast, *APOC3* activity mediates higher levels of TG-rich lipoproteins and some of its gene polymorphisms are associated with increased risk of CHD [56]. Certain variants of the *APOA5* gene diminish apolipoprotein A-V function, which leads to increased TG levels and increased risk of CHD [54]. Individuals with certain loss-of-function mutations in the *APOC3* gene had lower TG levels and a lower risk of CHD compared with non-carriers [57]. Thus, data in individuals with specific gene variants lead either to elevated or reduced TG or TG-rich lipoprotein levels, supporting a causal association between TG, remnant cholesterol, and risk of CHD. Unfortunately, there are no large randomized clinical trials that could verify this hypothesis.

A clutch of hemostatic factors and inflammatory mediators [58, 59], as well as elevated BP [60] and disturbed endothelial cell function [61], is also associated with CHD risk. Fibrinogen, a positive acute phase protein essential for clot formation, has a long and consistent association with CHD risk [62]. Its association with CHD might reflect its responsiveness to inflammation [58, 59], but clot formation and the presence of fibrin in atherosclerotic plaque suggest a more direct influence on CHD risk [63, 64]. Still, a multiethnic meta-analysis of genome-wide association studies reported no strong evidence of a causal relationship between fibrinogen and coronary artery disease, stroke, or venous thromboembolism [65]. Evidence that factor VII, also essential for clot formation, is associated with CHD is inconsistent [66, 67]. Other hemostatic factors, such as von Willebrand factor, fibrin D-dimer, and tissue plasminogen activator antigen, appear to be modestly associated with first-ever CHD [59, 68]. Several hemostatic factors associated with CHD are also associated with inflammatory markers, which may confound CHD risk analyses [69].

SAFA Consumption and Heart Health

Although higher SAFA intake might increase CHD risk by increasing plasma LDL-C [70], recent meta-analyses of prospective observational studies [1, 71, 72] reported that when compensating nutrients were not taken into account, SAFA intake was not associated with CHD or stroke mortality, all-cause mortality, or myocardial infarction. Two large, independent, prospective cohorts of US men and women confirmed this result [73][1]. In a prospective Dutch cohort, higher total SAFA consumption was related to lower risk of ischemic heart disease, but not to CHD risk [74]. In another Dutch cohort, a positive association was observed between CHD risk and palmitic acid, but not total SAFA intake [75].

Several experimental conditions and methodological shortcomings could have obscured a potential relationship between SAFA intake and CHD risk. These include limited range of SAFA intakes within cohorts, possible heterogeneity in the health effects of different fatty acids, and large measurement errors in estimating dietary SAFA intake, without the ability to discriminate among individual fatty acids [76]. The balance among different fatty acids within the fatty acid class may be important [77], as might the food sources of SAFA. Biomarker studies have reported positive associations for CHD between blood levels of even-chain SAFA and inverse associations with odd-chain SAFA, which reflect different food sources [77].

Observational [3, 73] and intervention studies [5] have shown clearly that the partial replacement of dietary SAFA with *cis*-PUFA is associated with significantly reduced CHD risk and mortality. A recent review and meta-analysis [6] of intervention studies concluded that lowering SAFA intake significantly reduced the risk of combined cardiovascular events, but not mortality. In subgroup analyses, only the partial replacement of SAFA by PUFA reduced CHD events significantly, but replacement with *cis*-monounsaturated fatty acids (MUFA), carbohydrate, or protein had no significant effect. Another review of observational and intervention studies of partially replacing SAFA with PUFA found convincing evidence of lower blood LDL-C levels and a reduced risk of CVD, especially in men [78].

According to a meta-analysis of 84 controlled trials [6], isocaloric replacement of mixed carbohydrates by a common dietary SAFA mixture markedly increased plasma LDL-C and apoB concentrations, indicating an increase in LDL-P number. In addition, levels of HDL-C and apo A-I increased and plasma TG decreased. Isocaloric replacement of carbohydrate by SAFA did not significantly affect the plasma total-C to HDL-C ratio. Data on the effect of SAFA on LDL-P composition and size are scarce, but suggest that higher SAFA consumption mainly increases the larger, more buoyant, less atherogenic LDL-P [32, 33, 79].

Compared with carbohydrates, lauric, myristic, and palmitic acids differently increase LDL-C and HDL-C levels and decrease TG concentrations, while stearic acid does not affect these lipoproteins [6]. Myristic acid has the strongest effect, but because of its much higher intake, palmitic acid has the greatest overall effect on plasma lipoprotein levels. The different effects of individual SAFA explain why dietary fats with different fatty acid compositions vary in their potency to alter lipid and lipoprotein levels.

Specific food sources of SAFA and other macronutrients appear related to CHD risk as suggested by the Multi-Ethnic Study of Atherosclerosis (MESA) [80] and a meta-analysis of milk and dairy consumption [81]. In a meta-analysis of 5 randomized controlled trials [82], cheese compared with butter intake was associated with significant reductions in LDL-C and HDL-C, but had no effect on TG. In the 10-year MESA study, a higher intake of meat-delivered SAFA was associated with greater CVD risk, whereas dairy SAFA was related to lower CVD risk [80]. The investigators estimated that the isocaloric replacement of 2%E from meat SAFA with dairy SAFA was significantly associated with a 25% lower risk of CVD. As the food matrix may also influence the kinetics of SAFA absorption [83], these results indicate that total foods are more important in terms of CHD risks than the SAFA they contain.

As reviewed some time ago [84], the consumption of dietary fat significantly increased the postprandial amounts, activation, and activity of plasma clotting factor VII, which seemed to be associated with the degree of lipemia. Interestingly, the effects of SAFA-rich fats were less pronounced than those of fats rich in MUFA, and were further reduced by fatty acid randomization.

Up-to-date comprehensive reviews covering the effects of dietary fats on platelet function and thrombosis are lacking. Systematic studies with a well-validated rat model of arterial thrombosis revealed that, compared to unsaturated fatty acids, dietary SAFA (but not stearic acid) promote an arterial thrombosis tendency [85]. Ef-

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[1] While this paper was in revision, re-analyses of these cohorts were unable to verify this finding. In contrast, a positive association between SAFA intake and CHD risk was observed [98].

fects of dietary SAFA on human platelet thrombotic functions have been studied repeatedly with inconsistent results [86]. An FAO/WHO review concluded that dietary SAFA possibly raises BP compared to unsaturated fatty acids [70]. The evidence for different effects of SAFA on flow-mediated dilatation, inflammation, and insulin sensitivity was considered unconvincing.

SAFA Intake and Ischemic Stroke

The cardinal risk factor for stroke is elevated BP. Furthermore, high BP is strongly and progressively associated with risk of CHD, heart failure, peripheral vascular disease, and other serious health conditions [87, 88]. The Prospective Studies Collaboration, a meta-analysis of data from 61 prospective studies in individuals aged 40–69 years, reported that each 20 mm of mercury increase in systolic BP above usual was associated with a more than 2-fold difference in stroke mortality and a 2-fold difference in CHD mortality [89]. A meta-analysis of 11 clinical trials of BP-lowering drugs showed that regardless of baseline cardiovascular risk, lowering the BP reduced the risk of cardiovascular events in all risk groups [87]. Overall, these data and many other studies support a causal relationship between BP and risk of CHD and stroke.

Compared with studies on CHD risk, fewer data link SAFA intakes to the risk of ischemic stroke. Moreover, the results of meta-analyses are inconsistent. When replacement nutrients were not considered, dietary SAFA were not significantly associated with the risk of ischemic stroke [1] or mixed types of stroke [2]. In a recent meta-analysis, higher SAFA intakes appeared associated with lower risks of both stroke types [90]. However, significant effects were limited to males, East Asians, participants with lower body mass index, and studies of high quality and long follow-up. A meta-analysis of 7 intervention studies concluded that SAFA reduction had no clear effect on any type of stroke [4]. Although partial replacement of SAFA by PUFA reduced stroke risk in this study by 32%, with only 4 studies and 41 stroke cases, this effect was not significant.

As dairy products are a major source of dietary SAFA, it is notable that a study of 3 large prospective studies reported that dairy fat intake was not significantly related to the risk of stroke risk [91]. In 2 large prospective cohorts, circulating biomarkers of dairy fat intake were not significantly associated with the risk of any type of incident stroke [92]. Replacement of 5%E from dairy fat with PUFA was associated with a significant 21% lower risk of stroke, whereas replacement with animal fat other than dairy increased stroke risk by 6%.

A recent systematic review and meta-analysis of 31 prospective cohort studies of dairy intake and risk of CVD, CHD, and stroke reported significant inverse relative risks for intakes of total dairy, cheese, and calcium from dairy foods and total stroke, but dose–response associations did not hold after adjustment for within-study covariance [93]. Another meta-analysis of prospective studies reported a significant inverse association between stroke and low-fat dairy and cheese consumption [94]. The investigators noted heterogeneity and publication bias in the studies on stroke.

Thus, the available evidence suggests that SAFA reduction has little, if any, direct effect on stroke risk, but that the consumption of SAFA-rich dairy foods may be associated with a lower risk of ischemic stroke. This topic deserves more thorough investigation [4].

Dietary Guidelines for SAFA

Dietary guidelines now focus on foods and dietary patterns to improve consumer understanding of more healthful food choices and to acknowledge food matrix and nutrient interactions. Examples include the Nordic Nutrition Recommendations [95], 2015–2020 Dietary Guidelines for Americans [96], and 2015 Dutch food-based dietary guidelines [97]. There is now convincing evidence that the partial replacement of SAFA-rich foods with those rich in *cis*-PUFA is associated with a significant reduction in CHD risk. Specific SAFA-rich foods such as dairy products may also be associated with lower CHD risk. Identifying healthy food choices to replace specific, less healthy ones, as in several updated dietary guidelines, may facilitate dietary modifications that lower the risk of CHD.

Summary and Conclusions

SAFA have important metabolic functions, but their consumption is not essential because they can be synthesized de novo. However, their functional properties make them virtually indispensable for the production of fat-containing foods. Dietary SAFA, when compared to carbohydrates and *cis*-unsaturated fatty acids, raise plasma LDL-C, a causal risk factor for CHD. Individual SAFA affect plasma lipoprotein levels differently, with each major dietary SAFA except stearic acid resulting in higher

levels of LDL- and HDL-C and lower levels of TG. In prospective observational studies and randomized controlled trials, higher total SAFA intakes were not associated with higher incident CHD events or mortality, but replacement nutrients were not taken into account. The effect of reducing dietary SAFA is most strongly affected by the macronutrients that replace them. The greatest reduction in CHD risk occurs when *cis*-PUFA replace dietary SAFA. In intervention studies replacement of 10%E from SAFA by *cis*-PUFA reduced CVD events by 27% [4] and the replacement of 5%E from SAFA by *cis*-PUFA decreased CHD risk by 10% [5]. Data are insufficient to confirm a significant benefit for CHD risk by substituting *cis*-MUFA for SAFA. Emerging evidence suggests that the food matrix may modify the risk of CHD associated with some SAFA-rich foods. The consumption of several dairy foods has been associated with a lower risk of CVD, but data are insufficient to justify dietary recommendations.

HDL-C levels are inversely related to CHD risk in healthy populations, but causality is presently doubted. Therefore, the clinical interpretation of the increased HDL-C associated with SAFA consumption is uncertain and warrants further research. Increasing evidence suggests that TG-rich lipoproteins may be a causal risk factor for CHD and stroke.

Other markers for CHD risk, such as LDL particle size and several hemostatic, thrombotic, and inflammatory factors lack a confirmed causal relationship to CHD risk. Consistent evidence for specific effects of SAFA on any of these markers has not been reported.

Studies on SAFA intakes and risk of ischemic stroke are inconsistent. Compared with the abundant data on SAFA consumption and risk of CHD, there is insufficient evidence to support dietary SAFA recommendations to reduce stroke risk.

In conclusion, strong evidence supports the partial replacement of SAFA-rich foods with those rich in *cis*-PUFA to lower LDL-C and reduce CHD risk.

Disclosure Statement

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