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The Role of Saturated Fats in Coronary Heart Disease

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Editorial

The role of saturated fatty acids (SFA) in coronary heart disease (CHD) is widely debated in both the scientific literature and in the public arena [1-27]. Clinical trials have reached conflicting conclusions and the national and international nutrition committee recommendations vary. Some of the recent best- selling health books propose that we eat more saturated fat and to wear shirts labeled with "eat more fat" or "butter is back" [27].

The SFA relationship to CHD is complex and is the result of the SFA source, their structural heterogeneity, the carbon length, the replacement nutrient(s), the microbiome composition, the genotypic and phenotypic expression to the SFAs, insulin resistance, body composition and the systemic inflammation status [1-5]. Individual long-chain saturated fatty acids (LC-SFA) exhibit unique biological properties. Dietary saturated fat absorption varies depending on chain-length and the associated food matrix. The *in vivo* metabolism of saturated fatty acids varies depending on the individual fatty acid, genetics and the nutritional state of the individual [1-5]. In addition, it is critical to consider the effects of SFA on serum lipids, inflammation, adhesion molecules, oxidative stress, vascular immune dysfunction, fibrinolytic activity, thrombotic risk, macrophage foam cell formation, LDL receptor activity, stimulation of the toll- like receptors (TLR 2 and TLR 4), nuclear factor (NF-κB) dependent inflammatory gene expression and the enzymatic desaturation of SFA to monounsaturated fatty acids (MUFA) [1-5].

The dietary SFA intake does not entirely predict changes in serum lipids, CHD risk or SFA status in an individual as measured by the SFA content in serum cholesterol esters and erythrocytes [1,6-8]. High SFA status, not high SFA intake, is more likely to be associated with an increased CHD risk [6]. Stearate (C-18) has little effect on lipids due and may have variable effects on CHD risk to its rapid desaturation to MUFA by stearoyl-CoA Δ-9-desaturase (SCD) which is genetically determined [1-3].

Endogenous SFA synthesis, especially that of palmitic acid (16:0) from carbohydrates, contributes to the SFA status [1,6-8]. A diet low in SFA, but high in refined carbohydrates, spares SFA at the expense of de novo synthesis of SFA from abundant dietary carbohydrate. However, if the diet is low in carbohydrates, then the dietary SFA is directly used for energy production. Long chain fatty acids (LCFA) enhance gastrointestinal growth of gram negative bacteria and lipopolysaccharide (LPS) uptake, which increases gut permeability, gut inflammation, immune activation of gastrointestinal T-cells, post prandial endotoxemia, and infection risk with sulphite-reducing organisms and other pathobionts at the microbial-epithelial interface which promotessignificant gastrointestinal inflammation and immune dysregulation. In addition, dietary SFA induce CHD that is related to their effects on insulin resistance, obesity, nonalcoholic liver disease and thrombosis secondary to reduction in the release of tissue plasminogen activator [4,6,9-11]. SFA, as opposed to MUFA, also increase NADPH oxidase, reduce detoxification of radical oxygen species (ROS) due to decreased activity of catalase, glutathione peroxidase (GPx), superoxide dismutase (SOD 1) and thioredoxin reductase (TxNRD1) [4,6,9].

Recent clinical reviews have shed new light on the role of SFA in CHD [12-19]. Over 600,000 subjects were evaluated in a meta-analysis of 32 trials that included 17 observational studies of fatty acid (FA) biomarkers, 32 observational studies of FA intake and 27 randomized controlled clinical trials (RCCT) of FA supplementation [12]. SFA intake increased CHD overall by 6%, but the highest association of CHD risk occurred with palmitic- C-16 and stearic FA- C-18, based on circulating FA biomarkers. In the observational studies, based on the highest to lowest tertiles of dietary intake of constituent fats, SFA increased CHD by 2%, trans fat (TFA) intake increased CHD by 16%, omega 6 FA increased CHD by 1%, long chain omega 3 polyunsaturated fats (LC-PUFA) decreased CHD by 7% and MUFA decreased CHD by 1% [12]. The estimates for circulating fatty acids and CHD showed an increase in CHD of 6% with SFA, increase in CHD of 6% with MUFA, decrease in CHD

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of 16% with LC-PUFA, decrease in CHD of 6% with omega 6 FA and an increase in CHD of 5% with TFA [12]. In the randomized, control trials of FA supplementation, the risk for CHD was reduced by 3% for alpha-linolenic acid, decreased by 6% for LC-PUFA and reduced by 11% with omega 6 FA [12].

A 12-year study of 35,957 subjects, in which SFA intake was measured with a food-frequency questionnaire, a lower CHD risk was found. This risk reduction was related to the sums of grams per day of butyric (C-4) through capric acid (C-10) (SCFA), the sum of grams of pentadecylic (pentadecanoic C-15) through margaric acid (heptadecanoic C-17), myristic acid -C-14 (LCFA) and SFA from dairy [13]. However, concomitant cholesterol-lowering therapy, trans-fat intake and a limited variation in SFA and PUFA intake likely confounded the data which makes any conclusions regarding SFA and CHD impossible.

In a meta-analysis of three large cohort studies that included the health professionals follow-up study (HPFS), the nurses' health study (NHS-1) and the NHS-2, an isocaloric energy replacement at 5% from saturated dairy fat with polyunsaturated fatty acids (PUFA) or vegetable fat was associated with a 24% and 10% reduction in CHD risk, respectively, but isocaloric energy substitution of other animal fat with dairy fat increased CVD risk by 6% [14]. The reduction in CHD with replacement of SFA with isocaloric energy with PUFA, MUFA, TFA, omega 6 FA, whole grains, vegetable or plant proteins, refined carbohydrates, high fructose corn syrup or starches will depend on the percent of energy being replaced [14,15]. The replacement of 1% of energy from SFAs with PUFAs lowers LDL cholesterol and is likely to produce a reduction in CHD incidence of 2% to 8% [14].

In the recent, large prospective, longitudinal cohort studies of 115,782 men and women in the HPFS (34 year follow-up) and the NHS (38 year follow-up) a significant positive correlation between SFA intake and CHD rates was noted [15]. SFAs accounted for 9.0% to 11.3% of energy intake and consisted primarily of lauric acid (12:0), myristic acid (14:0), palmitic acid (16:0), and stearic acid (18:0). Comparing the highest to the lowest groups of individual SFA intakes, the increased incidence of CHD was 7% for 12:0, 13% for 14:0, 18% for 16:0, 18% for 18:0, and 18% for all four SFAs combined (p=0.05 to p=0.001). The reduction in CHD after isocaloric replacement of 1% energy from 12:0-18:0 was 8% for PUFA, 5% for MUFA, 6% for whole grains and 7% for plant proteins.

The PRE vención con DIeta MED iterránea (PREDIMED) 6 year prospective study included 7,038 participants with a high CVD risk (MI, CVA or death from CV causes) demonstrated that dietary consumption of SFA and trans fatty acid (TFA)were associated with a higher risk of CVD by 81% and 67% respectively from the highest to the lowest quintiles. The hazard ratio (HR) for CVD in the highest quintile of total fat, MUFA and PUFA compared to those in the lowest quintile was 0.58, 0.50 and 0.68 respectively. The intake of PUFAs and MUFAs reduced the risk of CVD and death. The isocaloric replacement of SFAs or trans-fats with MUFAs and PUFAs was inversely associated with CVD [19]. SFA from pastries and processed foods were associated with a higher risk of CVD [19].

The importance of low SFA, high MUFA and PUFA diet was again emphasized in the 4.8 year primary prevention (PREDIMED diet). The rate of major cardiovascular events from MI, CVA or total CV deaths was reduced by 30% with nuts and 30% with extra virgin olive oil (EVOO). The reduction in CVA was 39% (p<0.003) with a 33% reduction from EVOO and a 46% reduction from nuts. The reduction in MI was 23% (p=0.25) with a 20% reduction from EVOO and a 26% reduction from nuts. The total CV deaths were reduced by 17% (p= 0.8) [20].

The following conclusions can be made based on the present available clinical studies [1,12-27]:

1. The association between SFA and CHD depends on the SFA status, biomarkers and the carbon length of the SFA as well as the dietary SFA intake. These measured variables result in a different risk of CHD due to SFA. The larger prospective studies demonstrate significant associations with a 2% to 18% increase in CHD risk with C12-C18 SFA but not with C4-C10 SFA. The greatest risk of CHD is with the LCFA, palmitic, stearic and myristic acid but also a significant risk in CHD with lauric acid (MCFA). The SCFA (C4-C10, butyric-capric) do not increase CHD risk.

2. SFA of different carbon chain length (C12-C18, lauric, myristic, palmitic and stearic) have varied effects on serum lipids. LCFA have adverse effects on insulin resistance, metabolic syndrome, type 2 diabetes mellitus, obesity, thrombotic risk, vascular function and stroke, whereas SCFA are neutral.

3. The source of SFA differs in the macronutrient, micronutrient and phytonutrient composition which directly influences the CHD risk.

4. Isocaloric replacement of SFA or dairy fat with PUFA reduces CHD by 8% to 25%. Isocaloric replacement of SFA (dairy fat) with vegetable fat reduces CHD by 10%. Whereas the 5% energy intake substitution of other animal fat with dairy fat was associated with 6% increased CHD risk.

5. Replacing SFA with refined CHO, high fructose corn syrup, or starches at isocaloric (ISC) amounts increases insulin resistance, glucose, serum lipids such as LDL-C and TG, uric acid and increases CHD by up to three fold.

6. Replacing SFA or dairy fat with whole grains or non refined CHO at ISC amounts reduces CHD/CVD by 6% to 9%

7. Replacing SFA with MUFA at isocaloric amounts lowers the risk of CHD by 5% to 15%.

8. Replacing SFA with plant proteins at isocaloric amounts reduce CHD by 7%.

9. Trans-fat intake at isocaloric amounts increases CHD 16%.

10. Omega 6 FA at isocaloric amounts has minimal impact on CHD.

Patients should be counselled to replace LCFA with PUFA, MUFA, SCFA, whole grains and plant proteins. Genetic factors contribute to the risk of CHD related to the dietary intake of C-18 FA. It is not possible to recommend the safest amount of dietary consumption of SFA, especially LCFA, at this time but studies suggest it should be well below 9% of total caloric intake. SFA are diverse compounds and are not created equal and have variable effects on CHD risk depending on many factors. Therefore, the concept that SFA is good or bad must be tempered with fact and avoid "lumping" SFA into one category related to CHD. In addition, we should avoid a reductionist approach to dietary recommendations. The effect of the human diet on CHD is best understood in relation to the totality of the diet and not a single macronutrient. Dietary guidelines should

recommend foods and dietary patterns that improve CHD based on a scientific, clinically applicable and comprehensive approach. Sugars, refined carbohydrates, high fructose corn syrup, starches and trans-fatty acids significantly increase the risk of CHD. Omega 6 FA appears to be neutral on CHD risk. Whereas omega 3 FA, MUFA, fermented foods, fiber, fruits and vegetables and the traditional Mediterranean diet reduce CHD/CVD [20].

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