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Editorial

Saturated Fats and Coronary Heart Disease

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Editorial

Do Saturated Fats (SFA) cause Coronary Heart Disease (CHD)? The answers to this question have included, yes, no, maybe and we do not know. Multiple answers to the same question either suggest that the question is not posed correctly or that the studies are flawed and inconclusive, or both. There is a serious disconnect between the findings in the clinical trials which provide variable conclusions and the recommendations by national and international nutrition advisory committees, which are sternly against SFA consumption [1]. Therefore, the mantra for the past 50 years or more that SFA should be decreased to reduce CHD needs re-evaluation.

The SFA relationship to CHD is complex and depends on many factors [1-5]. These include the metabolic, biochemical and structural heterogeneity of these molecules (carbon length of the SFA), their source, the replacement nutrient(s) used as comparators in clinical studies, the microbiome, genetic variability, genotypic and phenotypic responsiveness to the dietary pattern in which the SFAs are consumed, the presence of insulin resistance, body composition (especially total and visceral body fat) and the systemic inflammatory state. In addition, to better analyze CHD risk, it is necessary to consider the effect of SFA on a myriad of biochemical and functional risk factors for CHD rather than focusing on the effects of SFA on lipids as a surrogate for CHD. These risk factors include inflammation (measurable by intracellular adhesion molecule-ICAM, interleukin-IL6, high sensitivity C reactive protein-HSCRP), oxidative stress, immune vascular dysfunction, fibrinolytic activity, thrombotic risk, macrophage foam cell formation, LDL receptor activity, sterol receptor element binding protein-SREBP activity, mRNA, endoplasmic reticulum-ER stress, direct ligand stimulation of the toll like receptors-TLR 2 and TLR 4 on vascular tissue and monocytes, nuclear factor- NF-kB dependent inflammatory gene expression and the metabolic conversion or desaturation of SFA to MUFA [1-5]. The SFA intake with food may not entirely predict SFA status and CHD risk in an individual [1,6-8]. The direct measurement of Fatty Acid (FA) status measured by FA in serum cholesterol esters and erythrocytes may differ significantly from assumed status based upon dietary intake analysis. Experimentally determined SFA 14:0 and 16:0 status correlates positively with increased total cholesterol (TC/HDL) ratio while FA intake does not [1,6]. The status and intake of C-18 SFA (stearic) is neutral on lipids, lauric C-12 increases LDL, HDL and lowers TC/HDL ratio, myristic C-14 and palmitic (C-16) increase LDL, linoleic acid and PUFA status. High SFA status, as previously defined, not high SFA intake is associated with an increased CHD risk whereas for linoleic acid, MUFA and PUFA both status and intake are associated with decreased TC/HDL ratio and reduced CHD risk. Stearate has little effect on lipids due to its rapid desaturation to MUFA by Stearoyl-CoA Δ-9-Desaturase (SCD). However, genetic variation in SCD may alter this conversion. In addition, foam cell formation in macrophages is reduced by PUFA in the presence of SFA [1-3].

Endogenous SFA synthesis, especially that of 16:0 from Carbohydrates (CHO), contributes to the extent to SFA status [1,6-8]. A high fat, high SFA and low CHO intake improves markers of metabolic syndrome, oxidative stress, inflammation, lipids and glucose more than does a low fat, low SFA and high CHO diet of equal caloric intake [1,6-8]. When the diet is low in SFA but high in refined CHO, dietary SFA are spared at the expense of de novo synthesis from abundant dietary CHO, but if the diet is low in CHO, dietary SFA are directly used for energy production. The conversion of CHO to SFA is also stimulated by the rapidity by which both glucose and fructose enter the body and the presence of Insulin Resistance (IR). A systemic inflammatory response is associated with increased Very Low Dense Lipoprotein-Triglycerides (VLDL-TG) and decreased TC, HDL and LDL together with compositional changes of the lipoproteins, excess of small dense LDL, increased LDL particle number (LDL-P) and dysfunctional or pro-atherogenic HDL [6]. SFA, especially Long Chain Fatty Acids (LCFA), induce inflammation related to stimulation of TLR 2 and 4, synthesis of ceramides, formation of lipid rafts and of fetuin A [6]. LCFA enhance gut colonization and growth of pathogens and pathobionts, especially gram negative bacteria that increase inflammation and infection risk at the microbial-epithelial interface. An increased SFA intake promotes Lipopolysaccharide (LPS) uptake in the gut with resultant post prandial endotoxemia, inflammation, IR, obesity and CHD [6]. The capacity of the endothelium to release tissue plasminogen activator (t-PA) is lower in middle-aged and older adults who habitually consume a diet high in SFA, and this may underlie increased atherothrombotic disease risk [4]. SFA increase NADPH oxidase, reduce Radical Oxygen Species (ROS) detoxification, catalase, glutathione peroxidase (GPx), superoxide dismutase (SOD 1) and thioredoxin reductase (TxNRD1). MUFA improves all these parameters [9]. SFA in the diet changes the conditions for microbial assemblage, increases gut inflammation and promotes the expansion of a low abundance of a sulphite-reducing pathobiont called Bilophilia Wadsworthis. This increases pro-inflammatory T helper cells (TH1) and promotes taurine conjugation of hepatic bile acids which increases organic sulfur used by these microorgansims [10].

Palmitic and stearic acid are associated with IR, type 2 diabetes mellitus (T2 DM), obesity, Non-Alcoholic Fatty Liver Disease (NAFLD), inflammation and dyslipidemia with increased TG and low HDL, whereas oleic acid (18:1 n9) is neutral and vaccinic acid

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(18:1 n7) is inversely associated with T2 DM [11].

Review of a significant body of clinical data provides the opportunity to clarify the overall effect of SFA consumption and status on direct CHD endpoints. A review of 72 clinical trials with over 600,000 patients that included 32 observational studies of FA intake, 17 observational studies of FA biomarkers and 27 Randomized Controlled Clinical Trials (RCCT) of FA supplementation over a variable period of time and amount 0 concluded the following [12]:

- Trans fat intake increased CHD by 16%.
- SFA intake increased CHD by 2% (highest risk of CHD with palmitic- C-16 and stearic FA-C-18 based on circulating FA biomarkers).
- Omega 6 FA increased CHD by 1%.
- MUFA decreased CHD by 1%.
- Omega 3 FA decreased CHD by 7%.

A prospective study lasting over 6 years and with 7038 participants with a high CVD risk (PREvención con DIeta MEDiterránea, PREDIMED) found that intake of MUFAs and PUFAs were associated with a lower risk of CVD and death, whereas intake of SFA and trans-fat were associated with a higher risk of CVD. The replacement of SFAs with MUFAs and PUFAs or replacement of trans-fat with MUFAs was inversely associated with CVD [11].

Conversely, in a Dutch population of 35,957 subjects followed over 12 years, a higher SFA intake was not associated with higher CHD risks [13]. The lower CHD risk was due to the sums of the number of grams per day of butyric through capric acid (SCFA), myristic acidC-14 (LCFA) and the sum of the number of grams per day of pentadecylic (pentadecanoic C-15) and margaric acid (heptadecanoic C-17) from dairy. In a meta-analysis of three of the largest cohort studies to date, 43,652 men in the Health Professionals Follow-Up Study (HPFS), 87,907 women in the Nurses' Health Study (NHS) I, and 90,675 women in the NHS II were evaluated [14]. The replacement of 5% of energy intake from dairy fat with equivalent energy intake from PUFA or vegetable fat was associated with a 24% and 10% lower risk of CHD, respectively, while a 5% energy intake substitution of other animal fat with dairy fat increased CVD risk by 6%.

The most recent, largest prospective, longitudinal cohort studies of 115,782 men and women in the NHS (38 year follow-up) and HPFS (34 year follow-up) found a significant positive correlation between SFA intake and CHD 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 Hazard Ratio (HR) for CHD was 1.07 for 12:0, 1.13 for 14:0, 1.18 for 16:0, 1.18 for 18:0, and 1.18 for all four SFAs combined (p values = 0.05 to 0.001]. The HR for CHD after isocaloric replacement of 1% energy from 12:0-18:0 was 0.92 for polyunsaturated fat, 0.95 for monounsaturated fat, 0.94 for whole grain carbohydrates, and 0.93 for plant proteins.

In summary, the present studies on SFA and CHD indicate the following [1,12-18]:

1. Various studies show variable results, ranging from little to no association between SFA intake and CHD risk, to a significant increase in relative risk of 7-18% depending on the carbon length of the SFA. The larger prospective studies demonstrate significant associations (p values of 0.05-0.001) between C12-C18SFA and CHD rates, but not with C4-C10 SFA.

2. SFA of different carbon chain length (C12-C18, lauric, myristic, palmitic and stearic) have varied effects on both serum lipids and risk of CHD. The greatest risk of CHD is with palmitic and stearic acid. LCFA increase risk of CHD but SCFA (C4-C10, butyric-capric) does not.

3. The source of SFA differs in the macro-, micro-and phytonutrient composition and these differences will directly affect lipids and CHD risk.

4. LCFA tend to have adverse effects on IR, metabolic syndrome, T2DM, obesity, thrombotic risk, vascular function and stroke, whereas SCFA are neutral.

5. Replacing SFA or dairy fat with PUFA reduces CHD/CVD 8%-24%. Replacing dairy fat with other animal fat increases CHD/CVD risk 6%.

6. Replacing SFA with refined CHO, HFCS, or starches at Isocaloric (ISC) amounts increase CVD/ CHD by up to 33%.

7. Replacing SFA or dairy fat with whole grains or non-refined CHO at ISC amounts reduce CHD/CVD by 6- 28%.

8. Replacing SFA with MUFA at ISC amounts lowers the risk of CHD/CVD by 1-5%.

9. Replacing SFA with plant proteins at ISC amounts reduce CHD by 7%.

10. Trans- fat intake at ISC amounts increases CHD 16%.

11. Omega 6 FA at ISC amounts increases CHD 1%.

Conclusion

From this brief review, one can conclude that increased dietary intake of SFAs with carbon length of C-12 to C- 18 is associated with an increased risk of CHD by 2-18%. Dietary guidelines should be revised and individuals should be counseled to replace some Long Chain Saturated Fatty Acids (LCSFA) with PUFA, MUFA, whole grains and plant proteins. SCFA do not show an increased risk of CHD. Genetic contributions must also be evaluated in regards to the risk of CHD with some SFA especially intake of C-18 FA. The relative percentage of SFA in the diet cannot be recommended with scientific accuracy. However, the effect of the human diet on disease expression is not best understood one nutrient at a time. With the wealth of good clinical articles currently available and particularly with the addition of the articles our editorial team will deliver in this and future issues of the Annals of Nutritional Disorders and Therapies, it is time to forgo the obsolete reductionist approach of studying individual macronutrients and their relationship to CHD. Instead, we should recommend foods and dietary patterns that improve CHD with a scientific and clinically applicable comprehensive approach. Sugars, refined carbohydrates, high fructose corn syrup (HFCS), starches and trans fatty acids significantly increase the risk of dyslipidemia and CHD. Omega 3 FA, MUFA, fermented foods, fiber, fruits and

vegetables and the traditional Mediterranean diet reduce dyslipidemia and CHD [19].

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