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New Views on Saturated fat, Sugar, and the Cardiovascular Disease Epidemic

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Abstract: Cardiovascular disease (CVD) is the leading cause of death in the United States and Puerto Rico. For years scientists and health professionals have worked diligently to decipher the causative factors of this ailment in order to establish dietary and lifestyle recommendations that could reduce CVD risk. Reducing saturated fat intake has been a mainstay of these recommendations, but recent analyses indicate that its place on that list may not be well-deserved. The relationship between saturated fat and known independent risk factors for CVD such as systemic inflammation and hypertension is uncertain and results may be positive or negative depending on the specific inflammatory marker being measured and the study design utilized. Evidence for the role of saturated fat in cardiovascular morbidity and mortality is also hazy, and varies according to the type of saturated fat being studied and the nutrient that it is replaced with; polyunsaturated fatty acids appear to be a much better replacement nutrient that carbohydrates. Sugar on the other hand has been implicated in several observational studies and clinical trials for increasing blood pressure, provoking inflammation, and giving rise to an atherogenic lipid profile. Given what we know about how these different dietary components impact CVD morbidity and mortality, it may be time to shift focus away from saturated fat and onto the excess carbohydrates in the American diet.

Introduction

Reducing intake of saturated fat has long been exalted as one of the main strategies all Americans must adhere in order to decrease their risk of cardiovascular disease. The American Heart Association recommends that adults should try to lower their cholesterol by reducing their saturated fat intake to 5-6% of their daily caloric intake (1). This would be equivalent to 13g of saturated fat per day for someone consuming a 2000 calorie diet. One of the Key Recommendations of the 2010 Dietary Guidelines for Americans is to consume no more that 10% of total calories from saturated fat (2). Despite these persistent recommendations to limit saturated fat, data from prospective cohort studies and randomized trials do not strongly support this idea that reducing saturated fat intake will lead to a decrease in the incidence of cardiovascular disease (CVD). Furthermore, CVD incidence has decreased over the years even though intake of saturated fat (SFA) has remained quite stable from 1990 to 2006 (2) and the incidence of CVD appears to even continue this decreasing trend as of 2009 (3). Approximately 610,000 people died of cardiovascular disease complications in 2013 and this largely preventable malady remains the primary cause of fatality in the United States (4). This raises the question of what other modifiable dietary risk factors could be causing this disease, and recently researchers have been looking at

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sugar, specifically added sugar in processed foods, as the new primary risk factor for CVD.

Relationship between Saturated Fat and CVD Risk Factors: Systemic Inflammation

Inflammation is an independent risk factor for cardiovascular disease (5, 6) and inflammatory markers including C-reactive protein augment directly with the accumulation of lipids in the arterial wall and can serve as predictors of health outcomes for people with acute coronary syndromes (5). How does SFA consumption affect inflammation? According to a randomized crossover trial in which healthy men were fed 3 different diets for a period of three weeks each, when compared to a monounsaturated fatty acid (MUFA) rich diet and a polyunsaturated fatty acid (PUFA) rich diet, a diet high in SFA precedes a greater expression of mRNA genes that produce tumor necrosis factor (TNF-a) while diets high in MUFA and PUFA precede a greater expression of interleukin (IL-6) mRNA (7). Despite these differences in gene expression, there was no significant difference in plasma concentration of these inflammatory markers for the different diets.

The story becomes more complex when looking at other studies that link saturated fat and inflammation, such as a double-blind crossover study (8) of men and women over the age of 50 with high cholesterol. Subjects were fed three different diets with a period of three months allotted for each diet; one diet was high in SFA (16.7% total energy), another high in PUFA (12.5% total energy), and the third with similar levels of SFA and PUFA (8.5% and 6.3%, respectively). Protein, carbohydrate, total fat %TE and MUFA were kept consistent but the high SFA diet had almost double the amount of cholesterol (121 mg/1,000 kcal). The production of interleukin (IL)-6, an inflammatory marker for atherosclerosis (9), was lowest for the high PUFA diet and similar for the high SFA and equal SFA and PUFA diets. The intermediate diet was also high in hydrogenated oils, which may have been responsible for the inflammatory response. Tumor necrosis factor (TNF-α), another pro-inflammatory cytokine, was shown to be associated with high (>18 g/day) intake of saturated fat versus low (≤18 g/day) SFA intake (TNF-α pg/mL, high-SFA 6.9 ±4.8, low-SFA 4.2 ± 2.2, $p < 0.05$) in 42 male and female patients with heart failure and a mean age of 61 years (10). Saturated fat has been shown in vitro to induce the production of tumor necrosis factor TNF-α ($p<0.01$) (11).

Another in vitro study found that saturated fat can induce the same inflammatory pathway as Lipopolysaccharide (LPS) by signaling Toll-like receptor 4 (TLR-4), activating the transcription factor NF-KB, and producing a plethora of inflammatory cytokines, among these IL-6 and TNF- α (12). The strength of the inflammatory response varied according to the chain length of the SFA; stearic acid (C18:0) was only marginally pro-inflammatory, while lauric acid (C12:0) had the greatest inflammatory effect as measured by production of COX-2. It is also worth noting that docosahexaenoic acid (DHA), an omega-3 fatty acid, was actually able to inhibit this inflammatory response (13). In rats, a diet high in SFAs compared to a diet high in fish oil, i.e. omega-3 fatty acids, resulted in higher levels of IL-1β in serum (14).

Nevertheless, when we take a look at larger studies conducted in humans we see that if there does exist an association between saturated fat and more robust inflammatory markers such as C-reactive protein (CRP) (15-17) it is a weak one. When 4,900 adults who took part in the 1999-2000 National Health and Examination Survey (NHANES) were asked about their dietary intakes of saturated fat and tested for elevated CRP, researchers found that the association between these two variables was dubious (OR Quartile 3: 1.58, 95%CI:1.02-2.44), Quartile 4: 1.44, 95% CI 0.80-2.58) (18). Independent of total energy intake, alcohol consumption, physical activity, smoking, and body mass index, CRP levels varied widely relatively to saturated fat intake, which implies that CRP levels are driven by some other unknown factors.

From these data it is evident that the existence of a connection between saturated fat and inflammation varies depending on the inflammatory marker that is being measured.

Relationship between Saturated Fat and CVD Risk Factors: Hypertension

Hypertension is another independent risk factor for CVD (19). The Health Professionals Follow-up Study followed 30,681 healthy white American male health professionals between the ages of 40-75 years old in order to observe associations between dietary components and incidence of hypertension (20). While consumption of dietary fiber was strongly associated with a decrease in hypertension risk (RR=1.36, 95% CI 1.04-1.78), there was no association between incidence of hypertension and saturated fat intake. The Multiple Risk Factor Intervention Trial (MRFIT), a prospective cohort study of 11,342 men ages 35-57 years old who were classified as being at high risk for developing CHD, found different results (21). In this 8 year study researchers controlled for BMI, alcohol consumption, and other lifestyle factors and concluded that saturated fatty acids as a percent of

total calorie intake was positively correlated with systolic (linear regression coefficient (LRC) = 0.0104) and diastolic (LRC = 0.0882) blood pressure. These results were not supported by a randomized trial of 162 healthy subjects who ate a diet high in either SFA or MUFA for 3 months (22). SBP and DBP remained unchanged on the high SFA diet (p = 0.2084) while blood pressure decreased after the 3 month time frame (p = 0.0001). The RISCK study echoed these results in 548 subjects who were at increased risk for developing metabolic syndrome (23). After 1 month on a diet high in SFA (38% total energy), vascular health was assessed using several tests, among them femoral pulse wave velocity for aortic stiffness and flow-mediated dilation (FMD) for endothelial function. Brachial artery vasodilation, production of NO, arterial stiffness, and FMD were not affected despite high intake of SFA.

Saturated Fat and Cardiovascular Events and Mortality

A recent review of 15 non-multifactorial randomized controlled trials with a sum of about 59,000 participants looking at the effects of reducing SFA intake in order to reduce cardiovascular morbidity and mortality found mixed results (24). Risk of cardiovascular events was reduced by 17% (RR = 0.83, 95% CI 0.72-0.96) but the results for cardiovascular mortality were not as convincing (RR = 0.95, 95% CI 0.80-1.12). The evidence for reduction in risk of both fatal and non-fatal myocardial infarction was also unconvincing (RR = 0.90, 95% CI = 0.80-1.01) and the results for stroke were neutral (RR = 1.00, 95% CI = 0.89-1.12).

A systematic review of 94 randomized trials and 507 cohort studies exploring the relationship between certain dietary factors and coronary heart disease corroborate these results (25). Using the Bradford Hill guidelines for causation of CHD based on dietary exposure, saturated fat received a score of ≤ 2 based on the four criteria of coherence, consistency, strength, and temporality, which designates insufficient evidence for any causative association. Dietary components such as nuts and vegetables which can reduce CHD risk received a score of 4.

The Women's Health Initiative, an 8-year-long randomized controlled trial of 48,835 racially diverse women ages 50-79 years old was included in the previously mentioned systematic review (26). The intervention group received behavior modification counseling to increase intake of fruits and vegetables to at least 5 servings per day, intake of grains to at least 6 servings per day, and to decrease total calories from fat to 20%. The control group only received educational materials and normal healthcare. At the end of the intervention period researchers found no significant difference between intervention and control groups in terms of incidence of CVD (HR = 0.98, 95% CI: 0.92-1.05), CHD (HR = 0.97, 95% CI: 0.90-1.06), and stroke (HR = 1.02, 95% CI: 0.90-1.15).

Total saturated fat intake may be less important than the ratio of PUFA/SFA

In the MRFIT the ratio of PUFA to SFA was inversely correlated with systolic (linear regression coefficient (LRC) = - 0.1684) and diastolic (LRC = - 0.6900) blood pressure (21). This correlation was stronger than that of dietary PUFA intake alone (SBP LRC = - 0.0510, DBP LRC = - 0.0655) which may indicate that the ratio of PUFA to SFA seems to be more important that the intake of the individual nutrients for predicting hypertension risk.

Saturated fats are not a homogenous group

A meta-analysis of randomized controlled feeding trials in which CHO was iso-calorically replaced with lauric acid, myristic acid, palmitic acid, or stearic acid (C12:0, C14:0, C16:0, and C18:0 respectively) found that chain length of saturated fat can lead to unique variations in levels of (LDL-C), (HDL-C), and Total Cholesterol (TC) (27). For every percent of calories from CHO replaced by SFA, all of the fatty acids caused an increase in HDL-C with lauric acid having the strongest effect and stearic acid the weakest. Similarly, lauric acid led to the greatest increase in LDL-C followed by myristic acid and palmitic acid, while stearic acid actually generated a modest reduction in LDL-C. With respect to the ratio of TC/HDL-C, lauric acid had the most favorable impact, reducing the ratio by a factor of -0.19, followed by stearic acid and myristic acid. Palmitic acid increased the TC/HDL-C ratio. This data indicates that the sweeping recommendation to reduce saturated fat intake is unfounded because it does not take into account the protective effects that some SFAs may have on the cardiovascular system via lipid homeostasis or fatty acid balance. Coconut oil is an excellent source of lauric acid (almost 50% lauric acid) but there is a need for further research to be conducted in humans in order to determine if the consumption of this oil has real cardio-protective effects. One animal study in which rats were fed virgin coconut oil (VCO), heated palm oil, or heated palm oil plus a VCO supplement found that after 16 weeks the VCO rats had lower blood pressure and less signs of lipid peroxidation (28).

The importance of the replacement nutrient

The results of a 1,254 study meta-analysis of randomized controlled trials and prospective cohort studies indicated that the effects of reducing SFA are highly dependent on

what that nutrient is replaced with – PUFA, MUFA, or CHO – and the disease outcome that is evaluated – coronary heart disease (CHD), stroke, or type 2 diabetes (27). When saturated fats are replaced by PUFA there is a 10% risk reduction for each 5% energy substitution. The results for MUFA were not consistent, and for carbohydrates the effect was neutral.

One of the studies included in this meta-analysis was a pooled analysis of 11 cohort studies wherein researchers concluded that independent of age or sex, replacing 5% of energy from SFA with PUFA could have a modest protective effect against both non-fatal (Hazard Ratio (HR) = 0.87, 95% CI: 0.77-0.97) and fatal (HR = 0.74, 95% CI: 0.61-0.89) CHD events, while replacing 5% of energy from SFA with CHO had the potential to augment risk of non-fatal CHD events (HR = 1.07, 95% CI: 1.01-1.14) as well as fatal ones (HR = 0.96, 95% CI: 0.82-1.13) (29). Unfortunately, people tend to replace saturated fat in their diets with carbohydrates instead of MUFA and PUFA.

What about the Association between High Sugar Intake and CVD risk?

While it is known that excessive intake of refined carbohydrates is detrimental to the body being that they can increase risk of type 2 diabetes (30, 31), the relationship between CHO intake and cardiovascular disease is not as well defined. In an analysis of data collected during the National Health and Nutrition Examination Surveys (NHANES) III, IV, and V (which took place during 1988-1994, 1999-2004, and 2005-2010, respectively) researchers found a positive dose-response correlation between added sugar intake and cardiovascular disease mortality (32). The results across quintiles were as follows: reference quintile 1 (Q1) HR = 1, Q2 HR = 1.09 (95% CI: 1.05-1.13), Q3 HR = 1.23 (95% CI: 1.12-1.34), Q4 HR = 1.49 (95% CI: 1.24-1.78), Q5 HR = 2.43 (95% CI: 1.63-3.62).

The case against sugar has been substantiated by a number of observational studies and clinical trials for which the results suggest that added sugars may contribute to high blood pressure, increased heart rate, inflammation, and myocardial oxygen demand (33). Feeding sucrose-rich or fructose-rich diets to rats increases their heart rate and blood pressure (34, 35). Straight fructose consumption can reduce insulin sensitivity and consequently induce hyperinsulinemia which can cause hypertension, and as insulin resistance worsens so does the intensity of hypertension (36). Hyperinsulinemia and concurrent impaired utilization of glucose is much more prevalent among individuals with essential hypertension (80%) compared to the general population (25%) (37). A recent meta-analysis of 39 randomized controlled trials analyzing the impact of sugar consumption on blood pressure and lipid profile corroborates these findings (38); high sugar consumption (as high as 40% of total energy from CHO) was associated with an increase in both systolic (mean difference (MD): 6.9 mmHg, $p < 0.001$) and diastolic blood pressure (MD: 5.6 mmHg, $p = 0.0005$) as well as raised LDL-C and to a lesser extent HDL-C (MD: 0.12 mmol/L, $p = 0.0001$ and 0.02 mmol/L, $p = 0.03$, respectively). A positive direct association between high sugar intake and triglycerides (TG) was also noted (MD: 0.11 mmol/L, $p<0.0001$).

The increase in TG is particularly noteworthy because plasma TG levels in excess of 133 mg/dl creates a favorable environment for the conversion of large, buoyant LDL-C into small dense LDL (sdLDL) (39). An abundance of sdLDL in the blood is associated with a higher myocardial infarction risk (40). Additionally sdLDL is more susceptible to oxidation relative to large LDL particles, and they can penetrate blood vessel walls more easily due to their small size and remain there for more time as they bind to proteoglycan (39).

Conclusion

According to the largest and most recent studies on the association between saturated fat intake and cardiovascular disease risk, saturated fat is not strongly correlated with well-established CVD risk factors such as systemic inflammation and blood pressure. For cardiovascular events and mortality, combined results of both RCTs and prospective cohort studies show no benefit for reducing SFA intake as a means of improving CVD outcomes. There is a potential benefit to reducing SFA if those fats are replaced by PUFAs, but if they are replaced by carbohydrates this can have either a neutral or detrimental impact on CVD risk. When making dietary recommendations it is essential to always take into account the heterogeneity of fatty acids because their impact on lipid profile varies according to chain length. Lauric acid, which is the most plentiful fatty acid in coconuts, has been shown to be protective against CVD in rats but human studies need to be conducted in order to gain a better understanding of how short chain SFAs can be cardioprotective. Lastly, a diet high in sugar can lead to high triglycerides and set in motion a cascade of events that leads to the proliferation of sdLDL and subsequent atherosclerosis. High intake of carbohydrates may be the real primary cause of the cardiovascular disease epidemic, not saturated fat, but more research needs to be done on this topic as well.

References:

1. The American Heart Association's Diet and Lifestyle Recommendations. American Heart Association 2015.
2. USDA 2010 Dietary Guidelines. U.S. Department of Agriculture and U.S. Department of Health and Human Services 2010.
3. Honors MA, Harnack LJ, Zhou X, Steffen LM. Trends in Fatty Acid Intake of Adults in the Minneapolis - St Paul, MN Metropolitan Area, 1980–1982 through 2007–2009. J Am Heart Assoc 2014; 3: e001023.
4. Heart Disease Facts. Centers for Disease Control and Prevention; Feb 2015.
5. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation 2002; 105(9):1135–1143.
6. Albert CM et al. Prospective study of C-reactive protein, homocysteine, and plasma lipid levels as predictors of sudden cardiac death. Circulation 2002; 105(22):2595–2599.
7. Jiménez-Gómez Y, López-Miranda J, Blanco-Colio LM et al. Olive oil and walnut breakfasts reduce the postprandial inflammatory response in mononuclear cells compared with a butter breakfast in healthy men. Atherosclerosis 2009; 204(2):e70-6.
8. Lichtenstein AH, Ausman LM, Schaefer EJ, Meydani SN. Effect of hydrogenated and saturated, relative to polyunsaturated, fat on immune and inflammatory responses of adults with moderate hypercholesterolemia. J Lipid Res 2002; 43, 445-452.
9. Libby P, Ridker PM, Maseri A. Inflammation and Atherosclerosis. Circulation 2002; 105:1135-1143.
10. Lennie TA, Chung ML, Habash DL, Moser DK. Dietary Fat Intake and Proinflammatory Cytokine Levels in Patients with Heart Failure. J Card Fail. 2005; 11:613–618.
11. Suganami T, Nishida J, Ogawa Y. A Paracrine Loop Between Adipocytes and Macrophages Aggravates Inflammatory Changes Role of Free Fatty Acids and Tumor Necrosis Factor α. Arterioscler Thromb Vasc Biol. 2005; 25: 2062-2068.
12. Lee JY, Sohn KH, Rhee SH, Hwang D. Saturated fatty acids, but not unsaturated fatty acids, induce the expression of cyclooxygenase-2 mediated through Toll-like receptor 4. J Biol Chem 2001;276:16683–9.
13. Huang S, Rutkowsky JM, Snodgrass RG, Ono-Moore KD et al. Saturated fatty acids activate TLR-mediated proinflammatory signaling pathways. J Lipid Res 2012. Sep;53(9):2002-13.
14. Vijay-Kumar M, Vanegas SM, Patel N, Aitken JD et al. Fish oil rich diet in comparison to saturated fat rich diet offered protection against lipopolysaccharide-induced inflammation and insulin resistance in mice. Nutr Metab 2011; 8:16.
15. Stone PA, Kazil J. The relationships between serum C-reactive protein level and risk and progression of coronary and carotid atherosclerosis. Semin Vasc Surg. 2014; 27:138–142.
16. Haverkate F, Thompson SG, Pyke SDM et al. Production of C-reactive protein and risk of coronary events in stable and unstable angina. Lancet 1997; 349:462-466.
17. Molino-Lova R. High sensitivity C-reactive protein predicts the development of new carotid artery plaques in older persons. Nutr Metab Cardiovasc Dis. 2010; 21:776-782.
18. King DE, Egan BM, Geesey ME. Relation of dietary fat and fiber to elevation of C-reactive protein. Am J Cardiol 2003; 92:1335–1339.
19. Heart Disease and Stroke Statistics - 2014 Update. American Heart Association 2014.
20. Ascherio MA, Rimm EB, Giovannucci EL. A Prospective Study of Nutritional Factors and Hypertension Among US. Circulation 1992; 86: 1475-1484.
21. Stamler J, Caggiula A, Grandits GA, Kjelsberg M, Cutler JA. Relationship to Blood Pressure of Combinations of Dietary Macronutrients: Findings of the Multiple Risk Factor Intervention Trial (MRFIT). Circulation 1996; 94: 2417-2423.
22. Rasmussen BM, Vessby B, Uusitupa M et al. Effects of dietary saturated, monounsaturated, and n3 fatty acids on blood pressure in healthy subjects. Am J Clin Nutr 2006; 83:221– 6.
23. Sanders T, Lewis F, Frost G, Goff L, Chowienczyk P. Impact of the amount and type of fat and carbohydrate on vascular function in the RISCK study. Proc Nutr Soc 2009; 67.
24. Hooper L, Martin N, Abdelhamid A, Davey G. Reduction in saturated fat intake for cardiovascular disease. Cochrane Database Syst Rev 2015;6:CD011737.
25. Mente A, de Koning L, Shannon HS, Anand SS. A Systematic Review of the Evidence Supporting a Causal Link Between Dietary Factors and Coronary Heart Disease. JAMA Intern Med 2009;169.
26. Howard BV, Van Horn L, Hsia J et al. Low-fat dietary pattern and risk of cardiovascular disease: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. JAMA 2006;295(6):655-66.
27. Mozaffarian D, Micha R. Saturated Fat and Cardiometabolic Risk Factors, Coronary Heart Disease, Stroke, and Diabetes: a Fresh Look at the Evidence. Lipids 2010; 45(10):893-905.
28. Kamisah Y, Periyah V, Lee KT et al. Cardioprotective effect of virgin coconut oil in heated palm oil diet-induced hypertensive rats. Pharm boil 2015; 53/9(1243-9): 1744-5116.
29. Jakobsen MU, O'Reilly EJ, Heitmann BL et al. Major types of dietary fat and risk of coronary heart disease: a pooled analysis of 11 cohort studies. Am J Clin Nutr 2009; 89(5): 1425–32.
30. López-Alarcón M, Perichart-Perera O, Flores-Huerta S et al. Excessive refined carbohydrates and scarce micronutrients intakes increase inflammatory mediators and insulin resistance in prepubertal and pubertal obese children independently of obesity. Mediat Inflamm 2014; 2014: 849031.
31. Gross LS, Li L, Ford ES, Liu S. Increased consumption of refined carbohydrates and the epidemic of type 2 diabetes in the United States: an ecologic assessment. Am J Clin Nutr 2004;79:5 774-9.
32. Yang Q, Zhang Z, Gregg EW et al. Added Sugar Intake and Cardiovascular Diseases Mortality Among US Adults. JAMA Intern Med [Internet]. 2014;174(4):516-524.

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33. Dinicolantonio JJ, Lucan SC. The wrong white crystals: not salt but sugar as aetiological in hypertension and cardiometabolic disease. Open Heart 2014;1.
34. Bunag RD, Tomita T, Sasaki S. Chronic Sucrose Ingestion Induces Mild Hypertension and Tachycardia in Rats. Hypertension 1982; 5: 218-25.
35. Hwang IS, Ho H, Hoffman BB, Reaven GM. Fructose-Induced Insulin Resistance and Hypertension in Rats. Hypertension 1987; 10: 512-6.
36. Ferrannini E, Buzzigoli G, Bonadonna R et al. Insulin resistance in essential hypertension. Hypertension 1998; 32: 243-8.
37. Vasdev S, Stuckless J. Role of methylglyoxal in essential hypertension. Int J Angiol 2010; 19(2): e58–e65.
38. Morenga LA, Howatson AJ, Jones RM, Mann J. Dietary sugars and cardiometabolic risk: systematic review and meta-analyses of randomized controlled trials of the effects on blood pressure and lipids. Am J Clin Nutr 2014 Jul;100(1):65-79.
39. Packard C, Caslake M, Shepherd J. The role of small, dense low density lipoprotein (LDL): a new look. Int J Cardiol 2000; 74 Suppl 1:S17-22.
40. Austin MA, King MC, Vranizan KM, Krauss RM. Atherogenic Lipoprotein Phenotype: A Proposed Genetic Marker for Coronary Heart Disease Risk. Circulation 1990 ;82:495-506.