Association of saturated fats and cardiovascular disease

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2016

Dedication

This paper is dedicated to my mother, father, and brother who have always given me love and support.

Acknowledgements

I would like to thank Nitin Puri, M.D., Ph.D., for being my advisor on this project.

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Introduction

Cardiovascular disease is a chronic disease state affecting the heart and blood vessels. Included in the broad category of "cardiovascular disease" are conditions such as ischemic heart disease, stroke, heart failure, cardiac arrhythmias, and conditions relating to the heart valves. Cardiovascular disease is the leading non communicable disease worldwide (McAloon et al., 2016). According to the World Health Organization, approximately 17.6 million individuals died from cardiovascular disease in 2012. This accounts for approximately 31% of deaths worldwide. Ischemic heart disease is responsible for 7.4 million of these deaths (McAloon et al.).

The scientist Nikolaj Nikojewitsch Anitschkow and his experimental work with rabbits is credited with showing that cholesterol was the agent involved with the atherosclerotic changes that occur in cardiovascular disease (Finking & Hanke, 1997). Studies linking dietary saturated fat intake with cardiovascular disease (CVD) date back to the 1950s with the work of Ancel Keys (Keys, 1953a, 1953b, 1956). His research included examining dietary patterns in different countries. This led to the publishing of a chart that showed death from "degenerative heart disease" was related to the amount of fat-calories consumed in the typical diets of those countries (Keys, 1953a).

However, researchers at the time pointed out a number of methodological issues surrounding the data produced by Keys (Yerushalmy & Hillboe, 1957). Chief among these concerns was the decision by the author to include data from only a limited amount of countries. While the original chart included data from six countries, at that time data was available from 22 countries. Yerushalmy & Hillboe point out that if you include the data from all of the 22 countries the association is greatly reduced. This was the beginning of a controversy that still exists today. National dietary recommendations were introduced in 1977 (Harcombe et al.,

2015). The recommendations included limiting overall fat consumption to 30% of total energy intake and saturated fats to 10% of total energy intake (Harcombe et al.).

However, Harcombe and colleagues (2015) argued that data from randomized control trials available at the time these recommendations were made did not examine these dietary targets. In addition, all of the studies used to justify the recommendations only examined men and did not include women in their designs. The authors concluded, "It seems incomprehensible that dietary advice was introduced for 220 million Americans and 56 million UK citizens, given the contrary results from a small number of unhealthy men" (Harcombe et al., p. 6).

Current dietary guidelines still recommend limiting saturated fat (U.S. Department of Health and Human Services [HHS], 2015). The American Heart Association recommends limiting saturated fatty acid intake to <7% of total energy (Lichtenstein et al., 2006). Medical and dietary recommendations view a diet high in saturated fat and cholesterol and low in consumption of polyunsaturated fat as increasing one's risk of cardiovascular disease (Skeaff & Miller, 2009). Interestingly, the 2015 guidelines stated that, "Cholesterol is a not a nutrient of concern for overconsumption" (HHS, p. 90). In addition this report did not include an upper limit on total dietary fat consumption.

These changes in the most recent dietary guidelines indicate that the medical community's knowledge of nutrition continues to evolve. Newly published research over the last decade has challenged the assumption that saturated fats are linked to cardiovascular disease (Chowdhury et al., 2014). The controversy that started in the 1950s is still present today, and this paper looks to examine the most recent studies on this topic.

Purpose

The purpose of this literature review is to examine the current medical literature studying the link between saturated fat intake and cardiovascular disease. Does the current medical literature support the positive association between saturated fat and CVD enough to justify the recommendation to restrict saturated fat intake? In addition, if current literature does not find a link between the two, then will clinicians have to reconsider the dietary recommendations they give patients in the future.

Literature Review

The main topic to be covered is the overall association between saturated fat consumption and CVD risk. During the course of this review that overall question and other subsets of questions will also be examined. One of these questions is: does the food source of saturated fat impact CVD risk? Are saturated fats from dairy more or less associated with CVD compared with saturated fats consumed from red meats (de Oliveira Otto et al., 2012)? Also, this review will look at saturated fat in comparison with other nutrients that are used as replacement nutrient. When individuals are told to limit intake of certain foods, they tend to make up the calorie difference by replacement with other foods. Considering this, questions will be addressed concerning the risk of cardiovascular disease after replacing saturated fat with polyunsaturated fat or carbohydrates. This literature review will consider past research regarding saturated fats, where our understanding of saturated fats and CVD risk is presently, and where nutritional research may be heading in the future. These questions will all impact recommendations we provide to patients throughout our careers.

Problem Statement

Are saturated fats associated with increased risk of cardiovascular disease?

Methodology

Research databases will be searched in order to find relevant studies to include in this literature review. The primary databases to be used include: PubMed, Academic Search Complete, JSTOR, and Google Scholar.

Examples of key words that will be used to search these databases: cardiovascular disease AND saturated fats, cardiovascular disease OR atherosclerosis AND dietary fat guidelines, dietary fat guidelines AND cardiovascular disease, atherosclerosis etiology, fatty acid biomarkers AND blood AND coronary disease, dairy fatty acids AND cardiovascular disease risk.

Meta-analyses, randomized controlled trials, prospective and retrospective cohort studies will all be included in this literature review. The majority of studies included will be restricted to those published in the last 10 years with emphasis on those articles published in the last 5 years. Articles dating back further than that will only be included to provide a historical perspective on the association between saturated fats and CVD. Only studies published in English will be included. There will be no restrictions in terms of where the study was conducted. Studies from different populations will be included with an emphasis on those studies examining North American populations.

Literature Review

This chapter investigates current and relevant research on the influence of dietary fat, specifically saturated fat, in the development of cardiovascular disease. It will also examine research pertaining to how the replacement of saturated fat by nutrients such as polyunsaturated fat and carbohydrate influence the risk of cardiovascular disease. Major headings in this review include 1) Saturated fat and risk of cardiovascular disease, 2) Replacement of saturated fat with polyunsaturated fat and risk of cardiovascular disease, 3) Replacement of saturated fat with carbohydrate and risk of cardiovascular disease.

Saturated Fat and Risk of Cardiovascular Disease

A recent study investigated saturated fatty acid intake from different food sources and the associated incidence of cardiovascular disease (de Oliveira Otto et al., 2012). This was a prospective cohort study whose study population were participants in the Multi Ethnic Study of Atherosclerosis (MESA). It was a broad sample size of 6814 adults of many different ethnicities between the ages of 45-84 years old. Saturated fat diet was assessed by a one hundred and twenty item food frequency questionnaire. A number of cardiovascular end points were assessed including incidence of myocardial infarction, coronary heart disease, stroke, and stroke death. The different food sources accounting for saturated fat intake were: dairy saturated fat, meat saturated fat, butter saturated fat, and plant-derived saturated fat.

The results of de Oliveira and colleagues (2012) showed that total saturated fat consumption was not associated with a higher risk of cardiovascular disease. When examining saturated fat intake by food source, saturated fat consumption derived from dairy products was not associated with a significantly higher risk of cardiovascular disease. When adjusting for

demographic and lifestyle factors increased intake of dairy saturated fat was associated with a lower risk of cardiovascular disease. However, saturated fat intake consumed from meat products was associated with an increased risk of cardiovascular disease. No associations were found for cardiovascular disease with saturated fats consumed from butter or plant products. Of interest was the finding that an isocaloric substitution of 2% of energy from meat saturated fat with equivalent energy intake of dairy saturated fat decreased cardiovascular disease risk by 25%. According to the authors this would correspond to "the replacement of ~2 oz. beef or processed meat with one glass or whole milk or 1 cup of regular yogurt" (de Oliveira et al., p. 400).

Another recent study examined serum biomarkers of dairy fatty acids with cardiovascular disease risk (de Oliveira Otto et al., 2013). The authors prospectively analyzed data obtained from the MESA study. The MESA study enrolled 6814 adults of different ethnicities (white, black, Hispanic, and Chinese) between 2000 and 2002. The current study included data from 2837 of those original participants maintaining equal proportions of the different ethnic groups. Blood samples were collected during the baseline examination. The researchers primarily focused mystic acid, pentadecanoic acid, and trans-palmitoleic acid because these saturated fatty acids cannot be synthesized by the human body (de Oliveria Otto et al.). This enables these saturated fatty acids to be used as objective biomarkers of dairy consumption (Ratnayake & Galli, 2009).

With regards to cardiovascular risk factors, the results of this study showed that higher blood levels of pentdecanoic acid and trans-palmitoleic acid were significantly associated with lower plasma triglyceride levels, and lower systolic and diastolic blood pressures (de Oliveira Otto et al., 2013). However, mystic acid was positively associated plasma triglycerides, blood pressure, and the total cholesterol to HDL cholesterol ratio. When analyzing cardiovascular

disease events such as myocardial infarction, definite or probable angina, stroke, or death from coronary heart disease the saturated fatty acid, pentdecanoic acid, was inversely associated with cardiovascular disease incidence. This association was similar across the four different ethnic groups. The other saturated fatty acids studied, mystic acid and trans-palmitoleic acid were not associated with cardiovascular disease incidence.

A recent meta-analysis by Chowdhury and colleagues (2014) also examined the association of dietary fatty acids, including saturated fatty acids, and coronary heart disease. This study not only assessed dietary fat as determined by self-report questionnaire but also looked at studies that determined dietary fat intake but measuring fatty acid biomarkers. Seventy-eight studies were identified by the authors and included in the analysis. Thirty-two studies were prospective cohort studies that examined dietary fat intake, twenty one of these studies via dietary questionnaires and eleven studies that reviewed dietary records of the participants. Nineteen prospective cohort studies were included that measured fatty acid biomarkers. Summary relative risks (RRs) were then generated by pooling the study results together. The closer to 1.00 a relative risk value is, the less likely it is to develop a disease. In this case, the disease measured was coronary heart disease.

The thirty-two studies that examined dietary fat intake included 530,525 participants and averaged a follow up period of 5-23 years. In this analysis of these studies the pooled RRs for total saturated fat was 1.02 (Chowdhury et al., 2014). The nineteen studies that recorded fatty acid biomarkers included 25,721 participants and had an average follow up period that ranged from 1.3-30.7 years. The relative risk for total saturated fatty acids was 1.06. The authors concluded based on these findings that there was essentially no association between saturated fat intake and coronary disease risk.

In addition to the previous research another meta-analysis of prospective cohort studies was conducted to examine the relationship between saturated fat intake and cardiovascular disease (Siri-Tarino, Sun, Hu, & Krauss, 2010). Twenty-one studies were ultimately identified by the authors for inclusion to determine if increased dietary intake of saturated fats increased a person's risk of coronary heart disease, stroke, and cardiovascular disease. Sixteen studies derived risk assessments for coronary heart disease and eight studies used stroke as an endpoint. In order to be included an association of saturated fat and cardiovascular disease had to be evaluated (Siri-Tarino et al.). The studies reviewed used twenty-four hour recalls, food frequency questionnaires, and multiple daily food records as assessments of dietary intake.

When pooling all of the included studies together, the relative risks of saturated fat intake with coronary heart disease and cardiovascular disease were 1.07 and 1.00 respectively (Siri-Tarino et al., 2010). The relative risk for stroke was 0.81; however, two of the eight studies examining stroke only used hemorrhagic stroke as an outcome. Since an elevated lipid profile would influence the risk of an ischemic stroke to a greater extent, these two studies were excluded and the relative risk recalculated. The relative risk excluding those two studies was 0.86. Based on these results the authors concluded that there was "insufficient evidence from prospective epidemiological studies to conclude that dietary saturated fat is associated with an increased risk of CHD, stroke, or CVD" (Siri-Tarino et al., p. 545).

A 2010 study looked into the question of whether dietary saturated fatty acid intake was associated with increased mortality from cardiovascular disease in a Japanese cohort (Yamagishi et al.). The researchers examined data collected from the Japan Collaborative Cohort Study for the Evaluation of Cancer Risk (JACC). This study comprised 58,453 men and women who filled out a food frequency questionnaire and were followed up for 14 years. The studies primary

endpoint was mortality from cardiovascular disease. The results of the study showed that saturated fatty acid intake was inversely associated with risk of total stroke, intraparenchymal hemorrhage, and ischemic stroke. No association was found between saturated fat intake and mortality from heart diseases such as ischemic heart disease, cardiac arrest, heart failure. The authors caution however that the Japanese consume far lower amounts of saturated fat in their diet compared with Western countries. As a result, one should caution the ability to generalize the results of this study to Western populations.

A 2015 meta-analysis of observational studies also examined the association of saturated fatty acids with risk of cardiovascular disease and all-cause mortality (de Souza et al.). Based on their review a 5% increase in energy from saturated fats increases all cause morality by 4.7%. However, the relative risk ratio was 0.99 for saturated fats and all-cause mortality. The relative risk ratio for saturated fat intake and total coronary heart disease mortality was 1.06. With regard to total cardiovascular disease mortality the relative risk ratio was 0.97. Based on these findings the authors found no clear association between saturated fat intake and cardiovascular disease mortality. However, the authors do caution that their study did not examine replacement nutrients. For example, they did not examine if replacement of saturated fat by another nutrient such as polyunsaturated fat would decrease the risk of cardiovascular disease mortality. The authors' primary research aim was to examine cardiovascular outcomes of higher vs. lower intakes of saturated fats.

Replacement of Saturated Fat with Polyunsaturated Fat

In 1969, a double-blind, randomized, controlled clinical trial was conducted to determine if a diet high in unsaturated fat was beneficial in preventing atherosclerosis compared with a diet

high in saturated fats (Dayton, Pearce, Hashimoto, Dixon, & Tomiyasu, 1969). A total of 846 male participants were recruited over an 8-year period. The sample population was based on middle-aged and elderly male veterans who were living in the Los Angeles Domicile. The subjects were asked to participate and after giving consent were randomized into a control group which received a conventional diet that contained roughly 40% fat calories. Animal fat was the majority of the source for the fat calories in the control group. The experimental group received a diet that was designed to substitute unsaturated fat for saturated fat. This was achieved by using vegetable oils such as corn, soybean, safflower, and cottonseed oil to replace approximately two thirds animal fat. The total fat content was still kept at 40%. The control diet contained approximately 653 mg of cholesterol which was comparable to the typical American diet at that time. The experimental diet reduced the amount of cholesterol consumed to 365 mg per day.

The effect to the two diets resulted in the experimental group having a lower serum cholesterol value compared to the control group (Dayton et al., 1969). The control group saw an immediate increase in their serum cholesterol over the first 20 months then a progressive decline over the next 6 years. In comparison, the experimental group showed an immediate decrease in their serum cholesterol followed by a consistent decline mirroring the control group. The total mean difference in serum cholesterol between the experimental and control groups was 12.7%. The primary endpoints of the trial were considered new coronary events. New coronary events included sudden death or definite myocardial infarction. Although there were more events in the control group compared to the experimental group, the results were not statistically significant. However, when the authors included the category of definite cerebral infarction, the results did become statistically significant favoring the experimental group.

The study also analyzed the autopsy results of 80% of the participants who died during the course of the study (Dayton et al., 1969). The arteries under review were for the degree of atheroma, fibrous lesions, thrombosis, ulceration, and calcification included the coronary arteries, aorta, and circle of Willis. The results of the autopsies revealed that "there was no difference in the lipid concentration of the aorta, circle of Willis, coronary atheroma or uncomplicated aortic atheroma" (Dayton et al. p. 41). In addition, there was no difference in calcium concentration of aorta between the two groups.

Ramsden and colleagues (2016) recently published a re-evaluation of recently recovered data from the Minnesota Coronary Experiment (MCE). The MCE was double blind randomized controlled trial that was conducted to test whether a diet rich in unsaturated fat, specifically linoleic acid, reduces coronary heart disease compared with a diet high in saturated fat. The sample size was large and including 9570 participants and conducted over a 5-year period from 1968-1973. The participants were men and women over the age of twenty who were admitted to a nursing home or one of six state mental health facilities. The experimental diet was designed to lower serum cholesterol. There was variability between facilities, but all of experimental diets produced significant reduction in saturated fats and significant increases in linoleic acid. Saturated fat ranged from 8.0% to 12.3% of calories with a mean 9.2% across facilities. This resulted in a reduction in saturated fats of approximately 50%. Linoleic acid was increased by 280%, ranging from 11.3% to 16.5% of calories with a mean of 13.2%. The control diet did not change saturated fat intake but did increase linoleic acid intake. The linoleic acid intake in the control diet ranged from 3.4% to 4.7% of calories. The control diet was predicted to lower serum cholesterol but to a much lesser extent than the experimental diet.

The results of the study revealed that the experimental diet did significantly lower serum cholesterol compared to the control diet (Ramsden et al., 2016). After analysis of the data, the authors found that the participants who had a greater reduction in serum cholesterol had a higher risk of death. This was mainly attributed to the subgroup of those participants aged greater than or equal to 65 years of age. In this subgroup they found that a 30 mg/dL decrease in serum cholesterol was associated with a 35% higher risk of death.

A recent meta-analysis wanted to examine diets high in the unsaturated fat, specifically linoleic acid, and the risk of coronary heart disease (Farvid et al., 2014). Prospective cohort studies were included if they provided risk or hazard ratios for dietary linoleic acid consumption and coronary heart disease endpoints. A total of 13 cohort studies were chosen for review totaling 310,602 participants. Linoleic acid consumption ranged from 1.5 to 6.4 percent of energy. For 11 of the 13 studies the relative risk ratios represent substitution the same amount of energy from linoleic acid for carbohydrates. Ten of the 13 studies were able to provide relative risk estimates of substituting the same amount of energy from linoleic acid for saturated fats. The results of this study revealed an inverse relationship between linoleic acid intake and risk of total coronary heart disease events. For every 5% increase in energy intake from linoleic acid there was an associated 10% risk of coronary heart disease events. The results also showed that there was a significant inverse association when linoleic acid replaced saturated fats in the diet (Farvid et al.). The results of this meta-analysis refute the findings of Ramsden et al. (2016) which showed detrimental effects of increasing linoleic acid consumption as a replacement for saturated fats.

Adding to these findings is meta-analysis conducted in 2010 examining the effects of replacing saturated fat with polyunsaturated fat on coronary heart disease. Mozaffarian, Micha

and Wallace (2010) specifically reviewed randomized controlled trials. These authors wanted to review trials that were randomized in their design to increase total or n-6 polyunsaturated fatty acid consumption for at least one year without other major interventions. The other major interventions would include blood pressure control, smoking control, or other dietary interventions. The trials had to have a control group without the intervention of increasing polyunsaturated fat in replacement of saturated fat. The trials also had to have data so risk ratios could be calculated for coronary heart disease events such as myocardial infarction, coronary heart disease death, or sudden death. Eight trials were included for review.

The average polyunsaturated fat consumption in the control groups ranged from 4.0 to 6.4 percent of total energy. The intervention groups polyunsaturated fat consumption ranging from 8.0 to 20.8 of total energy. After statistical analysis Mozaffarian et al. (2010) showed that replacing polyunsaturated fat for saturated fat reduced coronary heart disease events by 19%. Replacing saturated with polyunsaturated fat reduced low density lipoprotein cholesterol levels (LDL-C) without significant reduction in high density lipoprotein cholesterol (HDL-C). The authors concluded that the results "provide strong concordant evidence that consumption of PUFA, in place of SFA, lowers CHD risk" (Mozaffarian et al., p. 7).

Li and colleagues (2015) conducted a prospective cohort study that also compared saturated fat and unsaturated fat on coronary heart disease risk. This study used data obtained from the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS). The NHS is a long term study where female nurses, aged 30-55, in the United States have provided information concerning diet and lifestyle, medications, and newly diagnosed diseases at baseline and then every 2-4 years thereafter. In 1980, the women of the study started to complete a food frequency questionnaire. Data on men was obtained from the HPFS. Male health

professionals, aged 40-75, were enrolled beginning in 1986. As with the NHS the HPFS participants completed questionnaires about diet, lifestyle, and medical history. After excluding subjects with previously diagnosed cancer and cardiovascular disease, or who had provided data on their diet that was incomplete or inaccurate, the final sample included 84,628 women and 42,908 men. The results showed that replacing 5% of energy intake from saturated fatty acids with 5% of energy from polyunsaturated fat lowered a person's coronary heart disease risk by 25%. When considering both types of micronutrients that make up unsaturated fat: polyunsaturated fat and monounsaturated fat and modeling the same isocaloric substitution (i.e. 5% energy intake), replacement of saturated fat with unsaturated fat lowered one's coronary heart disease risk by 17%.

Another recent study used data obtained from the same two long term studies, the NHS and HPFS (Wang et al., 2016). This prospective cohort study included data from a total of 126,233 subjects over a follow-up period of 32 years. The authors found that replacing the same amount of energy from saturated fats with polyunsaturated fats was associated with a lower mortality from cardiovascular disease. When considering total mortality, isocaloric substitution of replacing the 5% of energy from saturated fat with the equivalent energy from unsaturated fat decreased mortality by 27% for polyunsaturated fat and 13% for monounsaturated fat.

Replacement of Saturated Fat with Carbohydrate

In 2008, Forsythe and her fellow researchers carried out a 12 week randomized controlled dietary intervention trial comparing a very low carbohydrate diet and a low fat diet on markers of inflammation. The participants of the study were 40 overweight men and women aged 18-55. "Overweight" was defined as a body mass index (BMI) >25 kg/m2. All of the participants were

required to have athrogenic dyslipidemia, which this study defined as elevated triglyceride levels and low HDL levels. Blood samples were drawn at the start of the trial to be used as a baseline and then repeated after the 12 weeks of dietary intervention. For very low carbohydrate diet, there was no restriction on intake of saturated or unsaturated fat. The subjects could consume an unlimited amount of beef, fish, eggs, and heavy creams. The low fat diet was designed to restrict saturated fat to <10% of total calories, and total cholesterol to <300 mg. The subjects were encouraged to consume whole grain carbohydrates, fruit, vegetables, low fat dairy and lean meat products (Forsythe et al., 2008). Examples of inflammatory markers that were measured included interleukin 6 (IL-6), interleukin 8 (IL-8), vascular endothelial growth factor, tissue necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), and C reactive protein (CRP).

The results of Forsythe et al. (2008) showed that the dietary saturated fat and cholesterol intake was significantly higher in the very low carbohydrate group compared to the low fat group. The very low carbohydrate group showed better responses with regard to triglyceride levels, HDL levels, and total cholesterol/HDL-C ratio levels. In addition, the very low carbohydrate diet produced better responses in its subjects for marker of inflammation. While both diets led to significant reductions if CRP levels, the very low carbohydrate group showed significantly greater reductions in TNF-α, and IL-8. There was a trend for lower IL-6 levels that did not reach significance for very low carbohydrate group. Perhaps the most interesting finding was that despite the subjects in the very low carbohydrate group consuming three times greater amounts of saturated fat, their circulating saturated fatty acids were significantly decreased compared to the low fat group.

This research was followed up with another study that assessed plasma saturated fatty acid levels with varying intakes of dietary fat all in the presence of a carbohydrate restricted diet

(Forsythe et al., 2010). This study was a randomized controlled crossover dietary intervention that included eight men, aged 38-55, all with BMIs ranging from 25-35 kg/m2. The subjects were randomized into either a carbohydrate-restricted diet that was high in saturated fat (CRD-SFA), or a carbohydrate-restricted diet that was high in unsaturated fat (CRD-UFA). After a six-week feeding period, the subjects' blood was analyzed, and then they were allowed four weeks to return to their baseline diet before crossing over to other group. The results showed that for both diets total cholesterol and LDL-C levels increased. Total cholesterol levels increased from a baseline average of 191 mg/dl to 215 mg/dl in the CRD-SFA and 192.9 in the CRD-UFA. There was an increase in LDL-C levels in both diets compared to baseline. There were significant decreases in triglyceride levels following both diets, decreasing 39% with CRD-SFA diet and 34% in the CRD-UFA diet. The total cholesterol/HDL-C ratio or the LDL/HDL ratio did not significantly change. Of note, a doubling of the saturated fat intake in the CRD-SFA diet did not increase the saturated fat content of any of the lipid fractions.

Mensink et al. (2003) also researched the differential effects of dietary fats and carbohydrates on plasma lipid biomarkers. They conducted a meta-analysis of 60 controlled trials wanted to see how replacing saturated fat with carbohydrates or replacing saturated fats with unsaturated fats impacted the total cholesterol/HDL-C ratio, LDL-C levels, and apolipoproteins. The collection of 60 trials yielded a total of 1672 volunteers with a 70/30 ratio of men to women. According to the authors, replacing saturated fats with carbohydrates did not improve the total cholesterol to HDL cholesterol ratio. Substituting either saturated fat or carbohydrate with polyunsaturated fat reduced this ratio. Replacing carbohydrates with any class of dietary fat, (i.e. saturated, polyunsaturated, or monounsaturated fat) decreased fasting

triglyceride levels. Replacing carbohydrates with saturated fat had no effect on apolipoprotein B levels.

Jakobsen et al. (2010) looked into the question of whether replacing carbohydrate intake with saturated fatty acids influenced the risk of myocardial infarction. This was a prospective cohort study in which the authors used data obtained from the Danish study: Diet, Cancer, and Health. Diet was assessed using a food frequency questionnaire. The endpoints for this study were new onset nonfatal and fatal myocardial infarctions. The final population included in this study was 53,644, 53% of which were women; the median follow-up was 12 years. The researchers found that replacing saturated fat with carbohydrate did not result in a greater risk of myocardial infarction. However, the authors further subdivided carbohydrates into those with a high glycemic index (GI) and those with a low glycemic load. When accounting for this difference in quality of carbohydrate, replacing saturated fat with carbohydrates with a high GI resulted in a significantly higher risk of myocardial infarction. When replacing saturated fats with low GI carbohydrates, there was a lowering of risk for myocardial infarction, although this result did not reach statistical significance.

In addition to researching the substitution of unsaturated fats for saturated fats by Li et al. (2015) and Wang et al. (2016) previously reported in this review, these studies also looked at the substitution for carbohydrates for saturated fats. The results of Li et al. revealed that when saturated fats replaced carbohydrates that were high in refined starches or added sugars (i.e. those with a higher GI index) there was no increased risk of coronary heart disease. Wang et al. found that when compared to carbohydrates a diet that was higher in saturated fats did not significantly raise the risk of cardiovascular disease mortality.

Discussion

Recent studies have questioned the link between consumption of saturated fats and risk of cardiovascular disease (Chowdhury et al., 2014; de Oliveira Otto et al., 2012; de Souza et al., 2015). Since beginning in the 1970s, dietary recommendations have included restriction of dietary fat, especially saturated fat, as a lifestyle modification to reduce one's risk of cardiovascular disease (Harcombe et al., 2015). The primary basis for this advice is the "diet-heart hypothesis" where studies have shown that a diet that is high in dietary fat including saturated fats raises a person's plasma cholesterol levels, including a person's low density lipoprotein cholesterol level (LDL-C) (Hu & Willet, 2002).

An important risk factor for cardiovascular disease is a person's LDL-C level. High blood cholesterol levels and high LDL-C level are viewed as causative factors in the atheroma formation that occurs in the coronary arteries leading to angina symptoms and myocardial infarctions (Stamler, Wentworth, & Neaton, 1986). In addition to this, a person's high density lipoprotein levels (HDL-C) are a preventative risk factor for cardiovascular disease (Stein & Stein, 1999). Research has also implicated that a person's total cholesterol to HDL cholesterol ratio is a more important measure of estimating a person's cardiovascular disease risk compared to the LDL-C value (Kinosian, Glick, Preiss, & Pruder, 1995; Stampfer, Sacks, Salvini, Willet, & Hennekens, 1991).

It is also true that there is significant heterogeneity among LDL cholesterol. LDL cholesterol ranges in different sizes from smaller, dense particles to larger particles (Berneis & Krauss, 2002). Having more of the smaller LDL particles is referred to as "pattern B". Greater amounts of the larger LDL particles is termed "pattern A". Studies have implicated a

preponderance of the smaller, dense LDL particles (i.e. pattern B) with a greater atherogenic risk (Rosenson, Otvos, & Freedman, 2002; St-Pierre et al., 2001).

Lipid lowering medications, the most abundant and known examples being "statins", reduce the total cholesterol and LDL-C thereby decreasing the likelihood of a cardiac event (Cholesterol Treatment Trialists' Collaborators [CTTC], 2012). Statins have been studied for many years. Random double blind placebo controlled trials have shown that the statins reduce LDL-C levels and decrease the occurrence of coronary events (CTTC). This research has further strengthened the argument reducing a person's blood cholesterol level decreases their risk of cardiovascular disease. The logic of this argument has then been applied to diet and saturated fats. If a drug reduces LDL-C cholesterol thus reducing cardiovascular disease risk, then a diet that also reduces LDL-C cholesterol via reduced saturated fat intake should have the same effect.

Cardiovascular disease, atherosclerosis in particular, is also an inflammatory disease (Ross, 1999). Medications such as statins might also decrease cardiovascular disease risk by a mechanism that reduces inflammation at the site of atheroma formation in the coronary vessels (Ridker et al., 2005). This mechanism would be an additive effect to their already well-established ability to lower blood cholesterol levels. Studies have shown that in addition to statins preventing the risk of atheroma formation, they can also stabilize an already existing atheroma (Puri et al., 2015).

The research looking into the diet heart hypothesis has produced conflicting results. While some studies have shown the increased intake of saturated fats increases the likelihood of cardiovascular disease; other studies have shown no such association (Chowdhury et al., 2014; de Oliveira et al., 2012). The studies that have found no association did not specify the replacement nutrient for saturated fats. For instance if a person were to reduce their saturated fat

intake would they replace the saturated fat with polyunsaturated fat or carbohydrates? The question of carbohydrates is further complicated by which type of carbohydrate they would replace the saturated fat with: simple or complex carbohydrates. The Western diet is currently high in carbohydrates (HHS, 2015). This has been encouraged by the same historical dietary guidelines that recommended reduced fat intake (Hite et al., 2010). Carbohydrates were thought to be a good replacement for dietary fat because carbohydrates have less calories per gram compared to fats. Advantages of this were considered to be decreased weight gain in addition to the benefits of reducing cholesterol levels via reduced saturated fat. In the decades since the dietary guidelines have advocated decreasing total and saturated fat, Americans are consuming more calories now and this increase has been mainly due to the carbohydrates (Hite et al.).

If one is to reduce their saturated fat intake it is most likely that they will replace it with carbohydrates. As this literature review has shown if one replaces saturated fat with carbohydrates from refined grains such as white bread, white rice, crackers, and cereals their risk of cardiovascular disease does not change (Li et al., 2015). However, if they replace the saturated fats with carbohydrates that are high in whole grains, their risk of cardiovascular disease decreases (Li et al.).

According to the Dietary Guidelines Advisory Committee, more than 70% of Americans consume too many refined grain products (HHS, 2015). These are the types of carbohydrates that when replacing saturated fats do not lower cardiovascular disease risk.

Research discussed in this review have shown that diets that are high in fat and low in carbohydrates decrease markers of inflammation to a greater extent compared to high carbohydrates (Forsythe et al., 2008). These markers of inflammation have been implicated in cardiovascular disease risk (Zakynthinos & Pappa, 2009). In addition, research has shown that

replacing saturated fat with carbohydrates does not improve a person's total cholesterol to HDL cholesterol ratio (Mensink et al., 2003). Finally, in individuals with the larger LDL-C particles (pattern A), a diet that reduces fat intake shifts them to pattern B (Volek, Fernandez, Feinman, & Phinney, 2008). Increased carbohydrate intake has been linked to the more atherogenic pattern B configuration (Krauss, 2005).

Research has shown benefits on cardiovascular disease risk by replacing saturated fat with polyunsaturated fat. Recent studies have shown that substituting foods high in polyunsaturated fats decrease cardiovascular disease risk (Li et al., 2015; Mozaffarian et al., 2010). Some controversy remains about the specific type of polyunsaturated fat, such as linoleic acid. Linoleic acid is an n-6 polyunsaturated fat (Farvid et al., 2014). One study reported in this review that reanalyzed data from randomized controlled dietary trials showed that greatly increased linoleic acid as the replacement polyunsaturated fat made the subjects more likely to die from cardiovascular disease (Ramsden et al., 2016). Other researchers have refuted this finding an inverse association between linoleic acid intake and risk of cardiovascular disease (Farvid et al.).

From the research presented in this literature review, the evidence looking into replacing saturated fats with polyunsaturated fats supports increasing polyunsaturated fat consumption and using it as a replacement nutrient for saturated fat would lower cardiovascular disease risk (Li et al., 2015; Mozaffarian et al., 2010; Wang et al., 2016).

The evidence shows that saturated fats are associated with cardiovascular disease but in relation to other nutrients consumed in the diet. Authors have argued that there was insufficient evidence to initiate the dietary guideline recommendations of reducing dietary fat intake (Harcombe et al., 2015). Recently a published report has shed light on the influence food

manufacturers may have had on those initial recommendations emphasizing dietary fat as a critical risk factor for cardiovascular disease rather than carbohydrates in the form of sugar (Kearns, Schmidt, & Glantz, 2016). Newly published research looking into dietary fat and cardiovascular disease has shed new light on this issue. In response, scientists that consult on the dietary guidelines have recommended lifting the upper intake restriction on dietary fat (HHS, 2015).

As a clinician it is not enough to make the general recommendation to reduce dietary fat or reduce saturated fat to improve a person's blood cholesterol levels. This would be too general of a recommendation, and based on the food options of a number of Americans, they are most likely to replace those saturated fats with simple, refined grain carbohydrates that will not lower the risk of cardiovascular disease. When making dietary recommendations we need to offer specific foods and nutrients that are preferable to saturated fats.

Conclusion

Cardiovascular disease remains a global health problem. Decades of research has been done looking into ways to reduce the incidence of cardiovascular disease. Dietary factors, such as reduction in the amount of total dietary fat and saturated fat, have been identified as a way to modify a person's risk of cardiovascular disease. Evidence presented in this review supports the conclusion of limiting saturated fat intake. The current evidence shows that replacing saturated fat with unsaturated fats and whole grains reduces a person's cardiovascular disease risk. Replacing saturated fats with carbohydrates from refined grains will not lower a person's cardiovascular disease risk.

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Abstract

Objective: This review examined the most recent research concerning the association between saturated fats and cardiovascular disease. It also examined how other nutrients such as polyunsaturated fat and carbohydrates, when used as replacement for saturated fat, influence cardiovascular disease risk. **Method:** The primary databases to be used include: PubMed, Academic Search Complete, JSTOR, and Google Scholar. Examples of key words that will be used to search these databases: cardiovascular disease AND saturated fats, cardiovascular disease OR atherosclerosis AND dietary fat guidelines, dietary fat guidelines AND cardiovascular disease, atherosclerosis etiology. **Result:** Replacing saturated fat intake with polyunsaturated fat and whole grain carbohydrates reduces risk of cardiovascular disease. When saturated fat is replaced by refined grain carbohydrates, there is no decreased risk of cardiovascular disease. **Conclusion:** Cardiovascular disease is a significant global health problem. In terms of dietary advice, recommendations should specify replacing saturated fats with polyunsaturated fats and whole grain carbohydrates.