REVIEW

Dietary Fats and Health: Dietary Recommendations in the Context of Scientific Evidence[1]

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ABSTRACT

Although early studies showed that saturated fat diets with very low levels of PUFAs increase serum cholesterol, whereas other studies showed high serum cholesterol increased the risk of coronary artery disease (CAD), the evidence of dietary saturated fats increasing CAD or causing premature death was weak. Over the years, data revealed that dietary saturated fatty acids (SFAs) are not associated with CAD and other adverse health effects or at worst are weakly associated in some analyses when other contributing factors may be overlooked. Several recent analyses indicate that SFAs, particularly in dairy products and coconut oil, can improve health. The evidence of ω6 polyunsaturated fatty acids (PUFAs) promoting inflammation and augmenting many diseases continues to grow, whereas ω3 PUFAs seem to counter these adverse effects. The replacement of saturated fats in the diet with carbohydrates, especially sugars, has resulted in increased obesity and its associated health complications. Well-established mechanisms have been proposed for the adverse health effects of some alternative or replacement nutrients, such as simple carbohydrates and PUFAs. The focus on dietary manipulation of serum cholesterol may be moot in view of numerous other factors that increase the risk of heart disease. The adverse health effects that have been associated with saturated fats in the past are most likely due to factors other than SFAs, which are discussed here. This review calls for a rational reevaluation of existing dietary recommendations that focus on minimizing dietary SFAs, for which mechanisms for adverse health effects are lacking. *Adv. Nutr. 4: 294–302, 2013.*

Introduction

Since the Framingham Heart Study reported that high serum cholesterol was a major risk factor for coronary heart disease (1), there has been an aggressive campaign in the medical community to decrease serum cholesterol. It has been a widely accepted belief that dietary saturated fats and dietary cholesterol cause an increase in serum total cholesterol, as well as LDL-cholesterol (LDL-C)[2] and thereby increase the risk of heart disease if consumed (2). Over the years, it became clear that high levels of LDL circulating in the blood are susceptible to lipid peroxidation, which results in the oxidized LDL being scavenged by macrophages lining certain arteries, particularly around the heart, leading to atherosclerosis (3). Although this mechanism provides a role for high serum LDL-C causing atherosclerosis, evidence of the involvement of saturated fats is lacking, even though it is well established that a diet high in saturated fat increases serum cholesterol and a diet high in polyunsaturated oil decreases serum cholesterol (4,5). In fact, PUFAs are the components that are oxidized and generate antigenic substances that are recognized by immune cells for clearance of oxidized LDL in atherogenesis (6–8).

Numerous reports and reviews in recent years have begun to call the perceived pernicious effects of dietary saturated fatty acids (SFAs) into question. The purpose of this review is to summarize the scientific understanding as it relates to dietary fats in health and disease, particularly with regard to the innocuous nature of SFAs and the physiological effects that have implicated PUFAs in numerous disorders and diseases. The role of dietary fats in cardiovascular disease (CVD) and many other diseases is complex, yet there is a powerful inertia that has allowed the saturated fat doctrine to endure.

Dietary fatty acids and serum cholesterol

Dietary fat studies in the mid-20th century stressed the relationship of dietary SFAs and PUFAs to serum cholesterol levels with an aim toward decreasing the likelihood of the development of coronary artery disease (CAD) and premature death (4,5). Once lipoprotein fractions were separated in the blood, it became evident that LDL and VLDL were

[1] Author disclosure: G. D. Lawrence, no conflicts of interest.

[2] Abbreviations used: apo B; apolipoprotein B-100; CAD, coronary artery disease; CVD, cardiovascular disease; FH, familial hypercholesterolemia; HDL-C, HDL cholesterol; HFCS, high fructose corn syrup; LDL-C, LDL cholesterol; Lp(a), lipoprotein(a); PON1, paraoxonase 1; SFA, saturated fatty acid; SREBP, sterol regulatory element binding protein.

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the carriers of cholesterol that were most closely associated with risk of heart disease (9). Later it was found that the ratio of total serum cholesterol to HDL-C was a better indicator of heart disease risk (10). By the 1990s, the mechanisms by which dietary fats and specific types of fatty acids were regulating serum cholesterol and lipoproteins were beginning to be revealed.

A family of proteins known as sterol regulatory element binding proteins (SREBPs) were discovered in the early 1990s. These proteins move to the nucleus in cholesterol-depleted cells to alter transcription of several genes involved in lipid metabolism (11). When intracellular cholesterol levels are low, SREBP-1 promotes expression of genes for synthesis of cholesterol and LDL receptors that remove cholesterol from the circulation. When intracellular cholesterol levels are high, SREBP-1 is not activated by protease cleavage, and the genes for cholesterol production and LDL receptors are downregulated. SREBP-1 also activates promoters for genes involved in fatty acid synthesis and lipid storage (12). PUFAs, particularly docosahexaenoic acid and others to a lesser extent, regulate expression of the SREBP genes (13,14). Consequently, when PUFAs are present, there is less expression of SREBPs and enzymes for cholesterol synthesis, and the serum cholesterol pool decreases.

There appears to be a number of proteins that bind PUFAs and are involved in regulating gene expression, including a family of G protein–coupled receptors (15), as well as peroxisome proliferator–activated receptors-α and -γ, retinoid X receptors, and various other nuclear receptors (16). The liver uses a variety of these receptors or sensors for PUFAs to regulate storage and utilization versus oxidation of PUFAs (17). In this way, PUFAs can stimulate fatty acid oxidation in the liver to minimize their potential for free radical oxidation in the body when their levels are high in the diet. One must keep in mind that this complex array for regulation of expression of a wide range of genes is also subject to an even more complex array of responses to dietary PUFAs and other dietary factors.

Single nucleotide polymorphisms in genes for many of the above factors, as well as in genes for several apolipoproteins, TNFs, glutathione peroxidases, and other proteins result in a wide range of individual responses to dietary constituents. The consequences of such genetic variation can be either little change or very large changes in serum lipids and lipoproteins in response to diet, depending on an individual's genetic makeup (18). However, one should not lose sight of the fact that levels of many other proteins are being altered in the process, which can give rise to a wide array of physiological responses that influence susceptibility to many unhealthy conditions, such as CVD and cancer.

Short-chain SFAs, such as those in dairy fat and coconut oil, can also influence gene expression via interactions with various G protein–coupled receptors that are linked to several hormonal responses, including insulin and leptin, that regulate overall energy metabolism in the body (19). It is clear that there are numerous sensors that respond to dietary PUFAs and short- or medium-chain SFAs (20).

Genetic factors

Brown and Goldstein (21) received the Nobel Prize in Physiology or Medicine in 1985 for their work on genetic defects in LDL receptors of people with familial hypercholesterolemia (FH). They identified several mutations that produce nonfunctional LDL receptors, resulting in death from atherosclerosis and heart disease at an early age. Individuals with FH have serum LDL-C in excess of 300 mg/dL (or 8 mmol/L), although LDL-C may be as high as 650 mg/dL (17 mmol/L) in homozygous individuals. Goldstein and Brown (22) also identified several genes that code for other proteins involved in cholesterol transport and metabolism, such as apolipoprotein B-100 (apo B), which is a component of LDL that binds to LDL receptors. There are other proteins involved in LDL synthesis, transport, and clearance that can result in a genetic predisposition to increased serum LDL cholesterol and FH (23–25).

In the early 1990s, it was discovered that men with CVD tended to have smaller HDL particles than healthy controls (26). It was later found that LDL particle size was also significantly smaller in men with CAD than in case-matched controls (27), although another study showed the ratio of total serum cholesterol to HDL-C was a better predictor of CAD risk than LDL particle size (28). A prospective, population-based cohort study also found an increased risk of CAD in middle-aged men with smaller, dense LDL particles than in men with larger LDL particles, although the relationship did not show a linear dependence on particle size (29). It later became evident that LDL particle size was influenced by several factors and was not necessarily a useful predictor of heart disease risk; the nature of LDL is influenced by both dietary and genetic factors (30).

Lipoprotein (a) [Lp(a)] is a complex lipoprotein that has several properties in common with LDL. Like LDL and VLDL, Lp(a) contains apo B, but also contains highly variable forms of apolipoprotein(a) that strongly influence its atherogenicity and propensity to promote heart disease (31). The wide array of apolipoprotein(a) isoforms present in the human population may have caused some confusion regarding the role of Lp(a) in atherogenesis and CVD. The association of apo B with oxidized phospholipids was found to be dependent on Lp(a) (32). The presence of oxidized phospholipids and Lp(a) tend to be proinflammatory and promote atherogenesis.

Small, dense LDL particles rarely occur as an isolated condition, but are often associated with a specific phenotype that is characterized by hypertriglyceridemia, low HDL-C, abdominal obesity, insulin resistance, and other metabolic irregularities that lead to endothelial dysfunction and susceptibility to thrombosis (33). Small, dense LDL is also more susceptible to lipid peroxidation due to changes in the lipid composition, making it more atherogenic (34). LDL particles from the atherogenic phenotype contain less cholesterol and phospholipid, but more triglyceride. This phenotype is generally referred to as phenotype B and is characterized by elevated levels of apo B, which is found in LDL and VLDL (35).

There have been a host of proteins linked to lipoprotein metabolism and transport and a wide range of genetic variations identified that result in alterations of those proteins. Many are associated with HDL and larger HDL particle size, which is consistently associated with a decreased risk of CAD (36). HDL is important in reverse-cholesterol transport, bringing cholesterol from arterial deposits to the liver for processing, where it is converted to useful metabolites and eventually cleared from the body via bile secretions. A family of lipoprotein lipases, including hepatic lipase and endothelial lipase, are intimately involved in HDL metabolism. Endothelial lipase is upregulated during inflammation, a condition that increases LDL oxidation and atherogenesis (37). Genetic variation in apolipoprotein A-I, a major protein component of HDL, can result in larger but less stable HDL particles and decreased levels of circulating HDL (38). Cholesteryl ester transfer protein is generally considered to be protective, although this protein may transfer lipids from HDL to other lipoproteins that result in a less desirable serum lipid profile (39). HDL is emerging as a fascinating lipoprotein with a complex array of functions that involve both protein and lipid components. HDL has been found to influence immune function, vascular inflammation, glucose metabolism, and platelet function as well as other physiological phenomena unrelated to CVD (40).

Paraoxonase 1 (PON1) is another protein associated with HDL that exhibits esterase and lactonase enzyme activity, including metabolism of toxic organophosphorus pesticides and oxidized lipids in oxidized LDL particles. The levels of PON1 activity varies tremendously among humans, which depends to a large degree on genetic variation. However, environmental factors, such as dietary antioxidant consumption, alcohol consumption, and certain drugs can also influence PON1 activity (41). Dietary olive oil can increase levels of serum PON1 in some individuals, which is genotype dependent (42), whereas MUFAs and PUFAs can inhibit PON1 enzymatic activity (43). SFAs (palmitic and myristic) had virtually no effect on PON1 enzymatic activity. A recent study found that HDL isolated from patients with CAD lacks endothelial anti-inflammatory properties, has lower PON1 enzyme activity, and does not promote endothelial nitric oxide production (44), all of which are most likely tied to genetic rather than dietary factors.

Fatty acids involved in atherogenesis and CVD

Linoleic acid makes LDL more susceptible to lipid peroxidation and subsequent deposition of the oxidized LDL in macrophages lining the arteries (45). Several lipid peroxidation products have been shown to trigger transformation of circulating monocytes to macrophages that line the arteries and ultimately become foam cells (46,47). Lipid peroxidation products also signal cells in the arterial intima to encapsulate foam cells by surrounding them with extracellular matrix proteins and eventually calcify the matrix (48). It would stand to reason that a greater abundance of PUFAs, relative to SFAs and MUFAs, during conditions of oxidative stress would provoke atherogenesis. The fibrous cap that is formed over fatty deposits makes them inaccessible to apolipoproteins such as apolipoprotein A-I or E, which are components of HDL, the lipoprotein that removes cholesterol from these deposits (49). The protein cap is characteristic of advanced atherosclerotic plaque and erosion of this protective cap by extracellular metalloproteases can release collagen and collagen-like fragments that trigger blood platelets to initiate a blood clot, which results in myocardial infarction or stroke (3).

Because saturated fats are not susceptible to lipid peroxidation, they have not been found to be involved in these mechanisms. This begs the question of how dietary polyunsaturated oils seem to lower the risk of CAD, even though many studies have shown no such effect. One important consideration is that foods that are considered sources of predominantly saturated fats, such as meats, are often cooked at high temperatures, which can induce lipid peroxidation in the minor amounts of PUFAs present in those animal products (50–52). Oxidative stress and lipid peroxidation products are known to promote heart disease, cancer, and several other chronic diseases (53,54). High-temperature cooking can also oxidize carbohydrates, producing a range of toxic oxidation products that promote oxidative stress, type 2 diabetes, and CVD (55). The preparation and cooking methods used for foods that are traditionally classified as saturated fat foods may be producing substances from PUFAs and carbohydrates in those foods that are promoting disease.

Human food preferences tend to favor foods with both fats and sugar (56), which complicates any attempts to correlate saturated fats with disease. Sugars readily undergo oxidation, with fructose generally getting oxidized many times faster than glucose, whereas sucrose is relatively resistant to oxidation (57). The oxidation products of these monosaccharides include glyoxal, methylglyoxal, and formaldehyde. Methylglyoxal has been shown to promote endothelial dysfunction as well as hypercholesterolemia in rats (58). Methylglyoxal is also associated with increased atherosclerosis and hypertension in humans (59). Formaldehyde and methylglyoxal have been implicated in endothelial injury, oxidative stress, and angiopathy (60).

Many clinical studies show that there are fewer coronary events when polyunsaturated oils replace saturated fats in the diet (61). However, a recent meta-analysis found that interventions using mixed $\omega 3$ and $\omega 6$ PUFAs resulted in a significant (22%) decrease in CAD events compared with control diets with fewer PUFAs. However, interventions that used $\omega 6$ polyunsaturated oils with no $\omega 3$ PUFAs showed $\sim$16% more cardiovascular events compared with the control diets, although the increased number was not statistically significant (62). It would seem that even moderate amounts of $\omega 3$ PUFAs in the diet result in attenuation of inflammatory responses that are reflected in the significant reduction in coronary events observed with increasing dietary PUFAs. Of the common vegetable oils, soy oil contains $\sim$7% $\omega 3$ PUFAs and canola oil as much as 10% $\omega 3$ PUFAs, whereas corn, safflower, and sunflower oils generally contain

<1% ω3 PUFAs (63). Another systematic review found insufficient evidence to support an association (positive or negative) between CAD and several dietary factors, including SFAs or PUFAs, α-linolenic acid, total fat, meat, eggs, and milk (64).

Lipid peroxidation and inflammation

Lipid peroxidation is invoked as a mechanism for numerous adverse health effects, such as aging, cancer, atherosclerosis, and tissue necrosis. The greater in vivo susceptibility of ω6 PUFAs relative to the ω3 PUFAs, has placed the spotlight on these fatty acids as contributing to or exacerbating many ailments (68). The metabolism of arachidonic acid to bioactive eicosanoids is responsible for many of the biological processes that lead to inflammation. Indeed, steroidal and nonsteroidal anti-inflammatory drugs suppress inflammation by blocking the release of arachidonic acid from membranes or its subsequent metabolism to eicosanoids.

Studies of inflammation in rats have found that dietary manipulation of relative amounts of ω6 PUFA precursors can have profound effects on the degree of inflammation. Predominantly SFAs in the diet result in far less inflammation than diets with either ω3 (69) or ω6 PUFAs (70). Several studies have shown that dietary supplementation with ω3 PUFAs can reduce inflammation and make patients less dependent on drug therapy to manage the pain and stiffness of arthritis (71–73). Patients should be advised to minimize their intake of ω6 oils when attempting ω3 supplementation as a therapeutic approach to reduce the inflammation of arthritis and other inflammatory syndromes (74,75). Small amounts of ω3 supplements in a sea of dietary ω6 oils would have relatively little chance of changing the course of an inflammatory response. Because dietary saturated fats do not promote inflammation, it may be wiser to minimize ω6 PUFAs and consume more SFAs to reduce various types of inflammation; most sources of MUFAs contain significant amounts of PUFAs as well. There have been few scientific studies along these lines because of the misguided concern that saturated fats, even those from vegetable sources such as palm and coconut oil, would be detrimental to one's health.

The efficacy of ω3 supplements for inflammatory syndromes other than rheumatoid arthritis are less persuasive, although study designs are questioned regarding whether patients are advised to reduce their ω6 fatty acid intake (76). Fish oil supplements improved pulmonary function in some asthmatics (responders) but not in others (nonresponders). A relatively high ratio (10:1) of dietary ω6 to ω3 PUFAs resulted in diminished respiratory function in methacholine-provoked asthmatics, whereas a lower ratio (2:1) produced significant improvement in >40% of the study participants (77). A study in Japan showed beneficial effects of ω3 supplements in asthmatic children in a controlled hospital ward environment (78). A comparison of dietary saturated fats with polyunsaturated oils was not found in the literature for asthma studies. Such an approach would be logical for this life-threatening condition, in view of the benign nature of saturated fats and the fact that carbohydrates, especially sugars, may actually be augmenting the incidence of asthma (79).

Are low-fat, low-saturated fat diets healthier?

Studies with laboratory animals have shown that high-fat diets promote chemically induced cancers (80,81). A study of chemically induced mammary tumors in rats found that ω6 PUFAs promoted tumor proliferation, whereas saturated fats or ω3 PUFAs did not promote tumors as much or even suppressed tumors, depending on what one uses as a reference (82,83). Although 1 review and meta-analysis found that linoleic acid, the predominant ω6 fatty acid in vegetable oils, is not a risk factor for breast, colorectal, and prostate cancers in humans (84), there is evidence to the contrary that high intake of ω6 relative to ω3 PUFAs increases cancer risks (85–87). There are multiple processes by which ω6 fatty acids can promote carcinogenesis; production of bioactive eicosanoids from arachidonic acid is 1 mechanism (88,89). Nonsteroidal anti-inflammatory drugs as well as cyclooxygenase-2 inhibitors can suppress tumors by inhibiting production of prostaglandins, particularly those of the ω6 variety (90). Lipid peroxides are also known to promote chemically induced tumors (91), and PUFAs are highly susceptible to lipid peroxidation.

Investigators often seem to have a particular bias against saturated fats. One report showed that red meat alone was not significantly associated with colorectal cancer, although there was some increase in colorectal cancers with higher red meat intake [HR = 1.17 for highest vs. lowest intakes (95% CI = 0.92–1.49, $P_{\text{-trend}} = 0.08$)]. Processed meats were significantly associated [HR = 1.42 (95% CI = 1.09–1.86, $P_{\text{-trend}} = 0.02$)]. The authors then combined the data for red meat and processed meat to give a significant association and concluded that red and processed meat are positively associated with colorectal cancer (92). When specific types of meat were analyzed, significant risk was associated with pork [HR = 1.18 (95% CI = 0.95–1.48, $P_{\text{-trend}} = 0.02$)] and lamb [HR = 1.22 (95% CI = 0.96–1.55, $P_{\text{-trend}} = 0.03$)], but not with beef/or veal [HR = 1.03 (95% CI = 0.86–1.24, $P_{\text{-trend}} = 0.76$)]. It is interesting to note that in 1 study, beef had a much lower ratio of PUFAs to SFAs than pork, but nearly the same ratio of PUFAs to SFAs as sheep (93). The ratio of MUFAs to SFAs in beef also varies, as it does in most meats, with the ratio ranging from ~0.8 to 1.8, depending on breed and feeding practices (94).

Nitrite used in the preservation of many processed meats is known to form a carcinogen with secondary amines under acidic conditions that would prevail in the stomach (95). Others have found no association of red meat and only a very weak association of processed meat with breast cancer (96) and prostate cancer (97). Most studies find no differences in cancer risk with different types of fat, but do find associations with high levels of fat in the diet (81).

A recent meta-analysis (98) reviewed 20 studies with >1 million subjects and found that red meat was not associated with CAD events [RR = 1.00 (95% CI = 0.81–1.23, $P_{\text{-trend}} = 0.36$)].

In contrast, processed meats were associated with increased incidence of CAD [RR = 1.42 (95% CI = 1.07–1.89, $P_{\text{-trend}}$ = 0.04)]. This indicates that saturated fat per se is not increasing CAD events, but other factors are, such as preservatives used in processed meats or other dietary substances that are being consumed in conjunction with processed meats. It is important to keep in mind that meats generally contain as much MUFA as SFA. Others are beginning to challenge the saturated fat hypothesis with closer analyses of past studies (99–103).

Campaigns were waged against tropical oils (palm and coconut oils) in the early 1980s because of their high levels of SFAs, even though palm oil contains about as much MUFAs acids as SFAs and has an ample amount of PUFAs to keep serum cholesterol low. In fact, 2 studies showed that the higher ratio of SFAs to MUFAs in palm oil (1.1:1) compared with olive oil (0.22:1) had no effect on serum lipids in healthy volunteers (104,105). Palm oil and olive oil have similar amounts (~10%) of PUFAs. SFAs in coconut oil increase serum HDL-C more than LDL-C to give a more favorable lipid profile relative to dietary carbohydrates (10). Claims that tropical oils with a high SFA content increase the risk of CAD lack clear scientific evidence to that effect. Indeed, countries with high intake of tropical oils have some of the lowest rates of heart disease in the world (106).

Many of the shorter chain fatty acids found in milk fat and coconut oil have beneficial health effects. The shorter chain SFA in milk (C4–C12) are not only metabolized rapidly for energy in infants, but have been found to have important antiviral, antimicrobial, antitumor, and immune response functions (107). Lauric acid, which is present in milk and the most abundant fatty acid in coconut oil, is effective in preventing tooth decay and plaque buildup (108). Diets rich in coconut oils have also been shown to lower other risk factors for CAD, such as tissue plasminogen activator antigen and Lp(a) (109). The medium-chain SFAs in coconut oil and butterfat (milk) increase total serum cholesterol, but their positive effects on HDL-C are protective in many ways. There is also evidence that proteins, fats, and calcium in milk are beneficial in lowering blood pressure, inflammation, and the risk of type 2 diabetes (110,111). Indeed, these constituents of milk have clear beneficial effects against metabolic syndrome, which is a major factor in promoting heart disease, as well as premature death from a variety of causes (112).

There has been a spate of recent publications in the biomedical literature that question the negative perception that dairy fats are bad for health. One meta-analysis showed that participants in prospective studies with the highest consumption of dairy products had a lower RR for all-cause mortality as well as for CAD, stroke, and diabetes compared with the lowest intake of dairy products (113). Many of the studies included in the analysis started before low-fat milk was available on the market. Another review arrived at the same conclusion that consumption of dairy products is not associated with higher risk of CVD (100). Although prospective cohort studies often find a significant reduction in the incidence of CAD with a larger ratio of PUFAs to SFAs in the diet (114), there are often many other factors related to overall health that correlate with the unsaturated to SFA ratio, such as exercise, a healthier lifestyle, and more fiber and less sugar in the diet.

Less fat generally means more carbohydrate

It should not be surprising that substitution of carbohydrates (starches) for saturated fats in the diet has relatively little effect on serum lipids. Excess carbohydrates are converted to fats for efficient energy storage, and the human body synthesizes primarily SFAs from excess carbohydrates, although MUFAs are also formed. Consequently, from a physiological viewpoint, there is no reason to believe that replacing fat in the diet with carbohydrate at a constant caloric intake will improve the serum lipid profile significantly. Indeed, a low-fat, high-carbohydrate diet causes an increase in serum triglycerides and small, dense LDL particles (115), which are more strongly associated with CAD than serum total cholesterol or LDL-C. When dietary fat is replaced by carbohydrate without changing the fatty acid composition of the fat, there is no change in LDL-C or HDL-C, but there is an increase in serum triglycerides (116). However, if there is a higher percentage of PUFAs and lower SFAs in a low-fat diet, serum total cholesterol and LDL-C will decrease (117).

Young children who consumed more fruit juice than their peers were shorter in stature and had greater BMI than their peers who drank less fruit juice (118). A trend of increased fruit juice consumption by infants and children in recent years has coincided with a decrease in milk consumption (119). The rates of childhood obesity have skyrocketed since the introduction of low-fat milk, although high fructose corn syrup (HFCS) became omnipresent in foods at the same time and is more strongly associated with obesity than dietary fat (120,121). As stated previously, the short-chain SFAs in milk provide valuable antibacterial and antiviral activities, which would result in healthier children. The short-chain SFAs found in milk act as signaling agents in the immune system (122). Infections in children also correlated with higher levels of atherogenic oxidized LDL, as well as lower levels of HDL (123). It is possible that oxidized LDL and low HDL impart increased susceptibility to infection, although the combination of infections and an adverse serum lipid profile may both result from an undesirable diet, i.e., more sugar and fewer healthy fats.

Food processors generally add large amounts of sugar to fat-free or low-fat foods to make them more palatable to consumers. Fructose is 1 dietary constituent that is consistently found to have adverse health consequences, and the larger the proportion of fructose is in the diet, the more formidable the effect. The adverse effects of fructose that have been documented include increased serum triglycerides, particularly in men (124,125); increased serum uric acid, which is associated with gout and hypertension (126); increased lipid peroxidation (57) and increased oxidation of LDL (127); increased oxidative stress in animal models (128); greater risk of the development of metabolic syndrome,

including obesity, insulin resistance, hypertension, and CVD risk (129,130); increased nonalcoholic fatty liver disease (131); and increased systemic inflammation and associated renal disease (132).

There are clearly many established physiological mechanisms by which fructose increases CVD and several other diseases. Whether the source of dietary fructose is sucrose or HFCS would seem irrelevant, although sucrose is 50% fructose, whereas the most common dietary source of HFCS (soft drinks) is generally 55% fructose and ~43% glucose. Solutions of fructose are also highly susceptible to autoxidation, producing a host of toxic products (57), whereas sucrose is highly resistant to oxidation. The toxic products from fructose oxidation include formaldehyde and α-dicarbonyls. Although saturated fats have been implicated in many of the adverse health effects attributed to fructose, there is no scientific evidence to support a role for saturated fats in the physiological mechanisms. On the other hand, plausible mechanisms are proposed for all of the unhealthy conditions promoted by high fructose intake mentioned earlier.

It turns out that a high level of fructose in the diet increases plasma triglycerides, which leads to not only increased levels of VLDL and small, dense LDL particles, but increased levels of oxidized LDL, insulin resistance, and other metabolic consequences linked to metabolic syndrome and dyslipidemia (133). The mechanisms by which fructose promotes inflammation and elevated levels of uric acid and several cytokines have been reviewed (132).

Conclusions

Saturated fats are benign with regard to inflammatory effects, as are the MUFAs. The meager effect that saturated fats have on serum cholesterol levels when modest but adequate amounts of polyunsaturated oils are included in the diet, and the lack of any clear evidence that saturated fats are promoting any of the conditions that can be attributed to PUFA makes one wonder how saturated fats got such a bad reputation in the health literature. The influence of dietary fats on serum cholesterol has been overstated, and a physiological mechanism for saturated fats causing heart disease is still missing.

Various aldehydes produced in the oxidation of PUFAs, as well as sugars, are known to initiate or augment several diseases, such as cancer, inflammation, asthma, type 2 diabetes, atherosclerosis, and endothelial dysfunction. Saturated fats per se may not be responsible for many of the adverse health effects with which they have been associated; instead, oxidation of PUFAs in those foods may be the cause of any associations that have been found. Consequently, the dietary recommendations to restrict saturated fats in the diet should be revised to reflect differences in handling before consumption, e.g., dairy fats are generally not heated to high temperatures. It is time to reevaluate the dietary recommendations that focus on lowering serum cholesterol and to use a more holistic approach to dietary policy.

Acknowledgments

The sole author had responsibility for all parts of the manuscript.

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