PERSPECTIVE

Perspective: The Saturated Fat–Unsaturated Oil Dilemma: Relations of Dietary Fatty Acids and Serum Cholesterol, Atherosclerosis, Inflammation, Cancer, and All-Cause Mortality

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ABSTRACT

PUFAs are known to regulate cholesterol synthesis and cellular uptake by multiple mechanisms that do not involve SFAs. Polymorphisms in any of the numerous proteins involved in cholesterol homeostasis, as a result of genetic variation, could lead to higher or lower serum cholesterol. PUFAs are susceptible to lipid peroxidation, which can lead to oxidative stress, inflammation, atherosclerosis, cancer, and disorders associated with inflammation, such as insulin resistance, arthritis, and numerous inflammatory syndromes. Eicosanoids from arachidonic acid are among the most powerful mediators that initiate an immune response, and a wide range of PUFA metabolites regulate numerous physiological processes. There is a misconception that dietary SFAs can cause inflammation, although endogenous palmitic acid is converted to ceramides and other cell constituents involved in an inflammatory response after it is initiated by lipid mediators derived from PUFAs. This article will discuss the many misconceptions regarding how dietary lipids regulate serum cholesterol, the fact that all-cause death rate is higher in humans with low compared with normal or moderately elevated serum total cholesterol, the numerous adverse effects of increasing dietary PUFAs or carbohydrate relative to SFAs, as well as metabolic conversion of PUFAs to SFAs and MUFAs as a protective mechanism. Consequently, dietary saturated fats seem to be less harmful than the proposed alternatives. *Adv Nutr* 2021;12:647–656.

Statement of Significance: There is a persistent misperception that dietary saturated fats can cause or promote numerous adverse health effects and increase serum total cholesterol and LDL cholesterol. This review attempts to clarify how such misperceptions originated and describes how the dietary alternatives of polyunsaturated oils and processed carbohydrates can be more detrimental to health.

Keywords: atherosclerosis, cholesterol regulation, cancer, dietary recommendations, inflammation, lipid peroxidation, palmitic acid, polyunsaturated fatty acids, saturated fats

Introduction

The notion that dietary saturated fats raise serum cholesterol originated from the misinterpretation of several studies that showed if confined individuals consumed diets containing fats with mostly SFAs and little or no PUFAs, serum cholesterol was higher compared with when the same individuals consumed diets containing an abundance of PUFAs (1–4). When they consumed diets with a high proportion of MUFAs, serum cholesterol was intermediate. The fact that the high-MUFA diets contained an intermediate amount of PUFAs was generally ignored. One could conclude from such results that dietary saturated fats raise serum cholesterol (5), but the interpretation that PUFAs are responsible for regulating serum cholesterol is generally overlooked.

The emphasis on promoting a low-fat, low-saturated fat diet resulted in a large increase in carbohydrate consumption, and most of that increase was in the form of sugars and highly refined carbohydrates (6, 7). When dietary saturated fats are replaced with carbohydrates, there is no change in serum cholesterol when dietary PUFAs remain unchanged (8), yet replacing saturated fats with carbohydrates, especially refined carbohydrates, gives rise to proatherogenic dyslipidemia (9), as well as low-grade systemic inflammation and insulin resistance, which all increase the risk of cardiovascular disease (10). Changes in dietary saturated fat intake in adults with

metabolic syndrome resulted in no significant changes in the proportions of SFAs in any plasma lipid fractions, whereas replacement of dietary saturated fats with carbohydrates showed a direct correlation between carbohydrate intake and proportions of palmitoleate in plasma triglycerides and cholesteryl esters. Palmitoleate in plasma cholesteryl esters, plasma phospholipids, and erythrocyte membranes is a consistent predictor of type 2 diabetes and metabolic syndrome (11).

Overall mortality, and not just coronary deaths, should be the primary concern when considering dietary recommendations for the general public. Several studies from diverse populations have shown that the all-cause death rate is greater for low serum total cholesterol (<180 mg/dL) than for intermediate to moderately high serum cholesterol (180–240 mg/dL) (12–16), particularly in elderly populations (17). It is important to note that even the 2 Finnish cohorts of the Seven Countries Study, which had the highest median serum total cholesterol for all cohorts at >250 mg/dL, had more overall deaths in a subgroup of the lowest 30% of serum cholesterol than there were in the highest 30% of serum cholesterol; the latter subgroup would have had serum total cholesterol well above 250 mg/dL in those 2 cohorts (18). This was true for other cohorts in the Seven Countries Study. So the question of lowering serum cholesterol to increase longevity should be weighed on a case-by-case basis, rather than a blanket recommendation for the general population.

Numerous reports and meta-analyses support the idea that dietary saturated fats have no influence on the incidence of cardiovascular disease, coronary heart disease, type 2 diabetes, or death from all causes (9, 19–22). However, many diet and health authorities continue to stress studies that showed a decrease in serum cholesterol in response to replacing dietary SFAs with PUFAs, and conflate that to mean that dietary saturated fats increase risk of cardiovascular disease and death from coronary heart disease (23). The flaws in the studies used to support the "diet-heart" hypothesis have been documented for years, yet dietary guidelines from many sources continue to push for lower dietary intake of all saturated fats with no substantial scientific support for that policy (22, 24, 25). The fact that overall death rate is not associated with serum cholesterol concentrations, except in the extreme upper concentrations or extreme lower concentrations of serum cholesterol, should render dietary recommendations for the purpose of lowering serum cholesterol in the general population unwarranted. A summary of the potential consequences of replacing dietary saturated fats with refined carbohydrates or polyunsaturated oils is shown in **Figure 1**.

PUFA Oxidation and Lipid Peroxidation

PUFAs are important for production of a wide range of bioactive substances in the body, but like some vitamins and essential minerals, may become toxic when consumed in excess. PUFAs can be oxidized in a spontaneous chemical oxidation process that does not require enzymes and would not be regulated in cells by normal processes. This spontaneous oxidation is initiated by free radicals, reactive oxygen species (ROS), and reactive nitrogen species (RNS), which are constantly being formed in biological systems (26, 27). This free radical oxidation process, which is known as lipid peroxidation, requires molecular oxygen, and produces fatty acid peroxides, reactive carbonyl species such as malondialdehyde, as well as numerous other toxic products. The wide array of ROS, RNS, and toxic organic products formed during lipid peroxidation of PUFAs can cause mutations in DNA, which can lead to cancer (28). Lipid peroxidation can damage cell membranes and lead to cell death. The wide array of ROS and lipid peroxidation products are implicated in oxidative stress, aging, and many diseases (29, 30).

The body has many protective systems to combat lipid peroxidation, including lipid-soluble antioxidants, such as vitamin E, enzymes that eliminate ROS and RNS, and enzymes that metabolize the lipid peroxides to detoxify them (31). Lipid peroxidation of PUFAs in lipoproteins, such as LDLs, results in the oxidized LDLs being removed from the circulation by macrophages lining the arteries, leading to atherosclerosis (32, 33). Although consuming more PUFA-rich vegetable oils can lower serum total cholesterol and LDL cholesterol, it is the PUFAs in LDLs that are susceptible to lipid peroxidation, which destines that lipoprotein and its cholesterol load to the atherosclerotic deposits surrounding the arteries (34). There is also evidence that dietary oxidized PUFAs and oxidized cholesterol can lead to increased atherosclerosis (35). This leads to a conundrum: Consuming PUFAs to lower serum LDL cholesterol can also increase the chances for lipid peroxidation and consequent atherosclerosis. MUFAs are much less susceptible to lipid peroxidation, and SFAs are completely resistant because they do not contain the reactive carbon-carbon double bonds.

The point of this discussion is to stress the fact that PUFAs are not only found in vegetable oils, but also are present at low to moderate concentration in most animal fats as well. Regardless of the source, PUFAs are highly susceptible to lipid peroxidation, which can lead to atherosclerosis, heart disease, cancer, inflammation, and other unhealthy processes (30, 36). Mammals preferentially oxidize PUFAs via the β-oxidation pathway in mitochondria for ATP production, or in peroxisomes to recycle excess PUFAs into SFAs and MUFAs to eliminate a portion of these reactive nutrients

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Abbreviations used: AA, arachidonic acid; EFA, essential fatty acid; LA, linoleic acid; LT, leukotriene; NSAID, nonsteroidal anti-inflammatory drug; PA, palmitic acid; PPAR, peroxisome proliferator-activated receptor; RNS, reactive nitrogen species; ROS, reactive oxygen species; SREBP, sterol regulatory element-binding protein; TLR, Toll-like receptor.

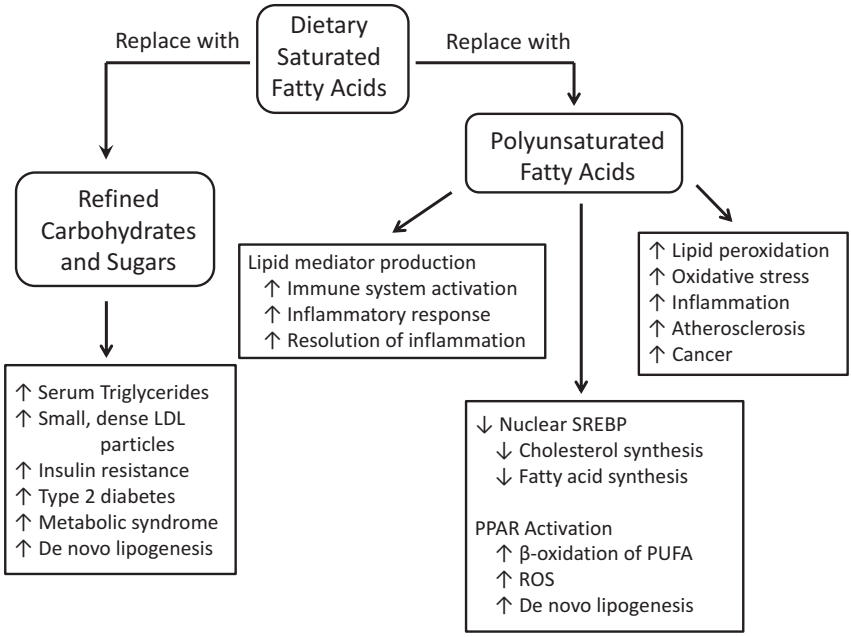

Figure 1 Some potential consequences of replacing dietary saturated fats with refined carbohydrates or polyunsaturated oils. These various physiological and health effects are described in the text. PPAR, peroxisome proliferator-activated receptor; ROS, reactive oxygen species; SREBP, sterol regulatory element-binding protein.

and prevent formation of potential toxins, particularly in the fetus and infant (see below) (37, 38). There could be many evolutionary reasons for converting PUFAs into SFAs, cholesterol, and ketones (39). Peroxidation of PUFAs in meats cooked at high temperature (40) or stored in the presence of oxygen (41) could be the reason for any association of meats with adverse health effects, whereas the saturated fat content of that food is less likely to be involved in the mechanisms for disease (42). There are often conflicting data regarding adverse health effects of foods that contain predominantly SFAs, and it is best to use a more holistic approach to dietary recommendations and food choices (22). In addition, some animal fats that are classified as saturated fats contain significant amounts of PUFAs, such as lard, which contains ~10% linoleic acid (LA), similar to palm oil and olive oil.

Fatty Acids and Serum Lipids

The primary factor that determines whether a person has low, normal, or high concentrations of serum cholesterol is genetic (43, 44). The effect of dietary fats on any individual's serum cholesterol is superimposed on the genetically determined concentration of serum cholesterol (45, 46). Numerous studies have indicated many inconsistencies in dietary responses in relation to specific gene polymorphisms (47), but the complexity of genetic variations and the broad range of gene products involved make this area of exploration rife with unpredictability and controversy. Genetic polymorphisms have been studied for several specific apolipoproteins, lipoprotein receptors, fatty acid–binding proteins, lipoprotein lipase, and other proteins involved in lipid transport (48). It is clear that focusing on apolipoproteins and their receptors is only a small aspect of the serum cholesterol picture.

The biochemical processes that determine serum cholesterol concentrations are the rate of cholesterol synthesis, especially in liver, and metabolic consumption to form numerous steroid products in the body. The expression of genes that code for enzymes that synthesize cholesterol and other lipids is regulated by a group of transcription factors known as sterol regulatory element-binding proteins (SREBPs) (49). When cholesterol concentrations are low in a cell, a series of events take place to increase the nuclear presence of SREBPs (SREBP1a and SREBP2) to promote the expression of genes for cholesterol synthesis, as well as its uptake from circulating lipoproteins (50). Insulin can also induce an increase in nuclear SREBP1 (both SREBP1a and SREBP1c), which will result in expression of genes for synthesis of fatty acids, cholesterol, and other lipids when carbohydrates are consumed in excess and stored as fat. When cholesterol concentrations are high in the cell, events occur to decrease the presence of SREBPs in the nucleus, which diminishes cholesterol synthesis and uptake from the circulation. The presence of PUFAs can decrease the amount of nuclear SREBP1 to decrease the synthesis of fatty acids, cholesterol, and other lipids, with long-chain ω-3 PUFAs showing the strongest activity in this capacity (51). SFAs and MUFAs do not have any influence on these control mechanisms.

Another class of fatty acid–activated transcription factors that promote gene expression are peroxisome proliferator-activated receptors (PPARs). Three different PPARs have been identified: PPARα, PPARβ/δ, and PPARγ. These

nuclear receptors are structurally similar, but have distinct ligand-binding properties, functions, and tissue distributions (52). All PPARs bind fatty acids, with a strong preference for long-chain PUFAs and relatively little activity with SFAs and MUFAs. PPARα is present in many tissues that rely heavily on oxidative metabolism, such as brown adipose tissue, heart muscle, skeletal muscle, and liver (53). Selectively activating PPARα with a specific agonist (WY-14,643) increased liver mass relative to body weight in rats, and decreased serum total cholesterol, HDL cholesterol, and triglycerides compared with control animals fed the same standard chow diet (54). In addition, β-oxidation occurred at a higher rate in liver, although liver contents of SFAs and MUFAs were higher, whereas PUFA content was lower, indicating a preferential oxidation of PUFAs in peroxisomes with subsequent de novo lipogenesis in PPARα agonist–treated rats compared with controls.

Treatment of rats with a selective agonist for PPARγ (rosiglitazone) had relatively little effect on liver but a significant effect on lipid metabolism in adipose tissue, resulting in lower serum triglycerides and no significant changes in serum cholesterol compared with control rats (54). In view of the fact that PPARs exhibit a strong response with PUFAs and little or no response to MUFAs and SFAs, it has become clear that PUFAs, particularly DHA and other longer-chain PUFAs, can lower serum cholesterol via PPARα. In addition, PUFA activation of PPARγ can elicit the beneficial reduction of serum triglycerides, increase adipose tissue storage of lipids, and decrease release of free fatty acids from adipose tissue. This latter mechanism explains the beneficial effects of longer-chain ω-3 PUFAs on insulin sensitivity and glucose metabolism.

Consequently when PUFAs are abundant as a result of increased dietary intake, the liver enzymes for β-oxidation of excess PUFAs in peroxisomes will help to limit the amount of PUFAs in the body to prevent excessive lipid peroxidation. In addition, many PUFA metabolites, such as eicosanoids, endocannabinoids, and the oxidized derivatives 9- and 13-hydroxyoctadecadienoic acids, will also activate PPARα in the nucleus (53). These metabolites and oxidation products of PUFAs would be an indicator of sufficient PUFAs present in body tissues to satisfy their need for synthesis of bioactive signaling agents and the excess should be eliminated. The main point of this discussion is that PUFAs, rather than SFAs or MUFAs, are responsible for regulating cholesterol metabolism, and consequently serum cholesterol and lipoprotein concentrations. The key factor is the level of PUFAs in the diet, which can influence the mechanisms for cholesterol synthesis, uptake, and distribution. Changes in the amount of SFAs or MUFAs consumed in the diet will have little or no influence on these mechanisms.

Some studies that compared olive oil (SFA:MUFA:PUFA ratio ~15:75:10) with palm oil (SFA:MUFA:PUFA ~50:40:10) found no difference in serum cholesterol concentrations of young, healthy human volunteers. Palm oil diets had much more SFAs than olive oil diets; however, because the diets contained the same amount of PUFAs, serum cholesterol did not change with these changes in dietary SFA (55, 56). It is estimated that $\leq$6–8 g/d PUFAs (8–10% of total fatty acids; 2–3% of energy) in the diet would be sufficient to satisfy normal requirements for production of bioactive products without causing adverse health effects. In addition, a ratio of ω-6/ω-3 PUFAs near 1 or 2, but certainly $<$5 would be optimum for good health (57, 58).

Importance of Palmitic Acid in Development and Physiology

Palmitic acid (PA) is the major SFA in the human diet and in the human body. The importance of PA in the development of the human fetus and infant was reviewed by the late Sheila Innis (59), who devoted much of her research to the nutrients in mammalian milk. The human baby is one of the fattest of all mammals at normal gestational birth; the adipose fat is 45–50% palmitic acid, and the baby continues to add fat during the early months of life under normal circumstances. A human baby will have ~2% PUFAs in adipose tissue at birth. Innis raised concerns that infants fed formulas with lipids coming from vegetable oils accumulated $\leq$26% LA in adipose tissue, mostly replacing palmitic acid (60), whereas LA increased to 6–8% in breast-fed infants after 7 mo (61). Mammary glands produce predominantly SFAs, regardless of the mother's dietary fat intake, and Innis raised the question of the importance of milk fatty acid composition with respect to developmental biology, and pointed out the broader implication for proper nutritional care for infants and children (59).

The unique composition of triglycerides in mammalian milk (human as well as ruminant milk) compared with vegetable oils provides clues regarding the importance of PA to infant development. Palmitate in the *sn*-2 position of glycerol of milk triglycerides improves absorption from the intestinal tract (62). The structure as well as composition of milk triglycerides ensures that newborn infants absorb an abundance of PA in the early stages of development, which is most likely evolutionarily advantageous. When infants were fed formula consisting of vegetable triglycerides, the proportion of LA increased dramatically to $\leq$46% of fatty acids in adipose tissue by 10 mo of age (63). Although increasing PUFA intake in infants can marginally lower serum cholesterol at 1 y of age (64), such manipulations in the PUFA content of infant formula and diets could have longer-term consequences that do not seem to have been followed in those cohorts.

PA is a major fatty acid in brain phospholipids, constituting 45–55% in phosphatidylcholine fractions (65). PA is used by cells to form sphingolipids, which with cholesterol and palmitoylated proteins, are important components of lipid rafts that facilitate endocytosis in caveolae, as well as numerous cell signaling pathways (66). PA is the major fatty acid in lung surfactant, and palmitoylethanolamide is a lipid mediator of intra- and intercellular signals in many cells and tissues (67).

Perhaps the greatest tragedy regarding dietary recommendations is for parents to give their children low-fat or skim

milk rather than full-fat milk. A recent review indicated that there is no evidence that full-fat milk consumption leads to obesity or cardiometabolic risk in children and adolescents (68). A recent study found that higher milk fat consumption in 3-y-old Latino children was associated with significantly lower odds for severe obesity in that population (69). Another study found significantly less adiposity at age 13 for children in the highest quartile of dairy fat consumption compared with the lowest quartile (70). Milk consumption by children and adolescents decreased by 38% between 1977 and 1996, whereas sweetened beverage consumption increased by 215% and consumption of fruit drinks increased by 189% (71). It seems the dietary recommendation to decrease milk fat consumption has caused parents to allow or even encourage children to consume more sweetened beverages under the false impression that they might be healthier for their children.

Fatty Acids and Inflammation

Inflammation can arise from an acute immune response to insult or injury, causing pain and discomfort, but generally subsides when the pathogenic insult is brought under control and injured tissue is repaired. A more subtle form of inflammation, known as low-grade systemic inflammation, occurs when immune cells infiltrate adipose tissue, especially visceral adipose tissue in obese individuals (72). Chronic systemic inflammation can lead to insulin resistance, type 2 diabetes, metabolic syndrome, atherosclerosis, and a variety of other metabolic disruptions and unhealthy conditions.

Inflammatory responses are initiated by a wide range of lipid mediators, including many eicosanoids formed from arachidonic acid (AA), the major ω-6 long-chain PUFA in membrane phospholipids of immune cells (73). The proinflammatory eicosanoids include: 5-hydroxyeicosatetraenoic acid, PGE_2, and leukotriene B_4 (LTB_4), among others. A similar array of proinflammatory eicosanoids are formed from EPA, but these are generally considered to be less provoking than the ω-6 derivatives from AA with regard to an immune response (74). Proresolving eicosanoids are formed from these two 20-carbon PUFAs, such as lipoxin A_4 and resolvin E1, among others, which actively participate in abatement of the inflammatory response. There are additional proresolving lipid mediators formed from DHA, which include resolvin D1, protectin D1, and maresin, among others (75).

The roles of PUFA-derived lipid mediators in an inflammatory response have been reviewed (73, 76, 77). Nonsteroidal anti-inflammatory drugs (NSAIDs) are effective at suppressing an acute inflammatory response because they inhibit cyclooxygenase enzymes that produce the precursors for many of the bioactive eicosanoids in the PG and thromboxane branch of eicosanoids. Steroidal anti-inflammatory drugs can be even more effective by suppressing inflammation that is resistant to NSAID treatment because they inhibit the release of long-chain PUFAs from cell membranes and diminish production of all eicosanoids, including the lipoxygenase products and the LT branch of proinflammatory agents. The eicosanoids are upstream lipid mediators, which initiate a cascade of events to release cytokines and other factors in an immune response. Peptide cytokines are generally measured as markers of inflammation because they have much longer half-lives than the lipid mediators. The point here is that it takes very little AA to trigger an immune response via its conversion to bioactive eicosanoids.

Dietary LA shows a nonlinear correlation with liver AA in rats fed fat-free background diets (78). A study in humans consuming high or low levels of LA showed a positive linear correlation with LA, but no significant changes in AA in neutrophils and plasma lipids. In that study, supplementation with fish oil (1.6 g/d EPA, 0.3 g/d DHA) resulted in reduced AA in neutrophil phospholipids (79). A review of 36 articles that studied changes in dietary LA intake and changes in tissue AA (erythrocytes and plasma/serum phospholipids) concluded that large variations in LA consumption have no significant effect on AA concentrations in those tissues (80). A recent review concluded that AA consumption can increase AA in membrane phospholipids of peripheral blood mononuclear cells (lymphocytes and monocytes) that are involved in inflammation, whereas changes in LA consumption showed no significant effect on AA in those cells (81). One would conclude from the above information that cells, particularly immune cells, regulate the synthesis of AA from LA and maintain a relatively constant concentration of AA in membrane phospholipids when humans consume a diet with $\geq$2% of energy from LA. Typical LA consumption by humans consuming a Western diet is closer to 6% of energy (82). However, EPA and DHA can reduce the concentration of AA in membrane phospholipids when they are consumed in the diet.

Fish oil supplements and ω-3 PUFAs have received the most attention with regard to dietary fats influencing arthritis symptoms, such as morning stiffness, pain, grip strength, swollen or tender joints, and reduction in the use of NSAIDs (83). One meta-analysis found significant reduction in patient-reported symptoms and use of NSAIDs with ω-3 fish oil consumption, whereas physician assessments showed no statistically significant clinical improvements (84). Study designs often have limitations, such as short duration, inappropriate placebo or control, low dose for ω-3 fish oil supplements, and not recommending a reduction in the use of ω-6 PUFA intake. Another meta-analysis of 10 randomized controlled trials found that supplementation with $>$2.7 g ω-3 long-chain PUFA per day for $\geq$3 mo duration consistently and significantly reduced NSAID consumption (85). Clinical evaluation of arthritic symptoms showed a trend toward improvement but again were not statistically significant relative to placebo controls.

There have been several recent reviews and meta-analyses regarding dietary ω-3 PUFA supplements or fish consumption effects on arthritic inflammation (86–88). The general consensus seems to be that ω-3 PUFA supplements can result in a decrease in the quantity of NSAIDs taken to relieve pain and inflammation, but there is no overall

significant effect with regard to several clinical markers of inflammation. Because some eicosanoids from EPA can be proinflammatory, albeit less so than those from AA, the differences in the degree of inflammation can be subtle. EPA can suppress the production of AA metabolites by competing with AA for incorporation into cell membranes and is considered a poorer substrate for cyclooxygenase and PG production. EPA is a relatively good substrate for lipoxygenase and LT production, although LTB_5 from EPA exhibited much less activity than LTB_4 from AA with regard to activation of leukocytes (89). Another drawback of many studies in humans is that participants might not be advised to decrease their consumption of ω-6 PUFA-rich vegetable oils while taking ω-3 PUFA supplements, and consequently continue to have a relatively large ω-6/ω-3 PUFA ratio in their overall diet.

A few studies of arthritic models in rats compared dietary saturated fats with polyunsaturated oils or supplementation with oils after arthritis was induced. When a diet containing corn oil (high in LA) was compared with beef tallow (low in essential fatty acids, EFAs), and a fish oil diet (high in ω-3 PUFAs), the corn oil diet strongly exacerbated adjuvant-induced arthritis in rats, whereas the beef tallow diet resulted in relatively little inflammation, and rats fed the fish oil diet showed an intermediate level of inflammation (90). When rats were fed an EFA-deficient diet, they showed much less adjuvant-induced inflammation compared with animals fed a control diet, but the inflammatory response was restored when rats fed the EFA-deficient diet were given a corn oil supplement after adjuvant treatment (91). Rats fed an EFA-deficient diet starting with the day of adjuvant treatment had 87% less edema in the hind foot pads compared with control rats, and edema increased when the animals on the EFA-deficient diets were given a dose of 273 mg/d LA after adjuvant treatment (92). Another study found that dietary fish oil increased inflammation relative to beef tallow for collagen-induced arthritis in rats, indicating that the ω-3 PUFAs in fish oil are proinflammatory relative to SFAs (93). These studies indicate that minimizing dietary PUFAs was beneficial in reducing arthritic inflammation in animal models. The fact that ω-3 EPA produces eicosanoids that generally have similar, albeit less potent, actions relative to ω-6 eicosanoids from AA, would explain the in vivo results of these animal studies. It is interesting that dietary DHA, but not a combination of DHA with EPA, reduced collagen-induced inflammation in rats (94), whereas oral administration of monoacylglycerol derivatives of EPA decreased the severity of adjuvant-induced arthritis in rats more than the monoacylglycerol DHA derivative (95).

There has been much discussion in the literature of the role of SFAs, particularly PA, in inflammation. There seems to be widespread misunderstanding of how PA is involved in an immune response, which stems from a study that found high concentrations (200 μM) of SFAs, but not MUFAs or PUFAs, could increase the release of inflammatory cytokines when the fatty acids were added to mouse macrophages in cell culture. PA has low solubility in water (0.2 μM), so fatty acid–free BSA was used to suspend the high concentration of fatty acids in the cell culture medium (96). The response to added PA in the cell culture medium was dependent on Toll-like receptor 4 (TLR4) activation in the macrophages. The authors tested the fatty acid–free BSA for LPS and found it to be present but negligible. Another study found that 100 μM PA added to culture media with 2% fatty acid–free BSA did not give a significant change in inflammatory cytokines, although 200 μM PA did give a significant increase (97). This level of BSA is several fold higher than albumin found in human blood, as is the concentration of PA needed to produce a significant increase in inflammatory cytokines. A later study showed that commercial fatty acid–free BSA is contaminated with lipopeptide, which activates another inflammatory TLR, TLR2 (98). Murumalla et al. (99) found that SFAs do not activate TLR2 or TLR4.

The mechanism by which TLR4 becomes activated is complex and involves dimerization of a TLR4-MD2 complex through linkage with LPS and further interaction with other membrane proteins, including myeloid differentiation factor 88 (MyD88) and CD14, to stimulate inflammatory cytokine production (100). It is unlikely that free SFAs would accomplish the same molecular interactions to activate TLR4. Membrane microdomains known as lipid rafts are involved in this process, and it has been suggested that PA augments an activated TLR4 response because it is a precursor for ceramides that constitute lipid rafts (101, 102). Ceramides are also necessary for TLR4-induced insulin resistance, which is often a consequence of low-grade inflammation arising from obesity in mice (103). It must be emphasized that the PA for ceramide synthesis is endogenous and dietary intake will have little or no influence.

Fetuin-A is a glycoprotein secreted predominantly by liver that carries free fatty acids in the blood and has been shown to activate TLR4 (104). Serum fetuin-A is high in obese diabetic humans, as well as in high-fat-diet–induced insulin-resistant mice and genetically obese (*ob/ob*) mice. Fetuin-A and TLR4 are both necessary to produce high-fat-diet–induced insulin resistance in mice (104). Fetuin-A was known from the mid-20th century to be an abundant protein in fetal calf serum (105). Fetal calf serum was used in the cell culture studies described above that showed SFAs augment TLR4-dependent increases in inflammatory cytokine production by macrophages. It is likely that fetuin-A rather than LPS was mediating TLR4 activation when SFAs were added to the culture medium in the studies described above. Little is currently known about the mechanisms that influence levels of fetuin-A in the body (106).

Dietary Fats and Cancer

Early studies found that high-fat diets in laboratory animals could increase the incidence of spontaneous and chemically induced cancers (107). It was later found that chemically induced mammary tumors in rats were augmented by dietary polyunsaturated vegetable oil compared with saturated fats in coconut oil (108). However, an epidemiological study of the incidence and rate of mortality from breast cancer in various

countries correlated with total dietary fat, rather than with any particular type of fat, that is, saturated compared with polyunsaturated (109). A recent review has described how high-fat diets can increase cancer incidence in laboratory animals, with low-grade systemic inflammation arising from the high-fat diets suggested as a contributing factor (110). The role of eicosanoids in carcinogenesis, cell proliferation, cell migration, and angiogenesis has been reviewed (111). It is generally believed that ω-3 PUFAs from fish oils can suppress the effects of ω-6 PUFA derivatives by displacing AA in cell membranes and competing with AA for metabolism to eicosanoids, in addition to the ω-3 eicosanoids often having less potent actions compared with their ω-6 counterparts. It is estimated that 20% of cancer deaths could be due to inflammation and chronic infections. There is strong evidence to support the use of anti-inflammatory drugs, both cyclooxygenase and lipoxygenase inhibitors, as anticancer drugs (112).

Lipid peroxides, ROS, and oxidative stress are associated with inflammation and are frequently invoked in tumor promotion by causing a switch in cellular metabolism (113). One of the major switches in metabolism in cancer cells is toward glycolysis as the major pathway for ATP production. This makes tumor cells more reliant on carbohydrate as an energy source. Conditions that increase carbohydrate availability, such as insulin resistance and diabetes, can promote tumor growth (114). Animal studies have shown that caloric restriction, ketogenic diets, and fasting can diminish cancer progression and metastasis (115). Although there is much interest in the use of ketogenic diets for cancer therapy in humans, the clinical evidence regarding ketogenic diets and tumor formation and progression is lacking (116). One problem might be the level of ω-6 PUFAs consumed in a ketogenic diet, which could have an adverse effect in terms of cancer therapy. The complexity of human dietary evaluation and manipulation in a free-living population makes it difficult to draw conclusions regarding dietary constituents and diseases.

Studies attempting to elucidate the role of dietary fats, whether total fats, saturated fats, or polyunsaturated oils, have been inconsistent with regard to cancer. It appears that a high caloric intake can promote cancer and cell proliferation, but evidence that cancer cells shift metabolism toward glycolysis for energy production, indicates that dietary carbohydrates would have a greater influence than dietary saturated fats on tumor promotion. Sugar, or more specifically fructose, is known to cause increased serum triglycerides, insulin resistance, and hyperglycemia (117), all of which would promote cancer.

Conclusions

Whether dietary saturated fat raises serum cholesterol or whether dietary PUFAs lower serum cholesterol might appear to be a moot point to some individuals. It is important to recognize that the focus on decreasing dietary fats resulted in a large increase in carbohydrate consumption, which has had undesirable health consequences as illustrated by the dramatic rise in obesity, type 2 diabetes, metabolic syndrome, and associated diseases. In addition, replacing saturated fats with unsaturated oils could have exacerbated diseases associated with lipid peroxidation and oxidative stress. It should not be surprising that numerous studies have tried to decipher the effects of specific dietary components on a broad range of risk factors and health effects only to obtain inconsistent results. When studying a free-living population it is impossible to separate the effects of any given dietary component from the myriad of other constituents of the diet, their respective impacts on some physiological phenomenon, and the gene–dietary constituent interactions. Because the genetic makeup of each individual is different, each can respond to any given dietary alteration in a somewhat different way (118). It can also be misleading to study manipulations of a particular line of cells in culture to understand how those cells will respond to a similar manipulation in an intact organism.

The various ways in which PUFAs, especially the ω-6 PUFAs found in vegetable oils, can augment inflammation and exacerbate a wide range of diseases associated with inflammation have been discussed here. The data are quite consistent in most animal studies, although often less convincing when dealing with humans. A major drawback in human studies is that humans generally consume relatively large amounts of ω-6 PUFAs, so any intervention that attempts to alter the amounts of PUFAs in the diet can make very little difference in the amounts of ω-6 PUFAs stored in adipose tissue or in membrane lipids. There has been some success in this respect when ω-3 PUFAs are substituted for ω-6 PUFAs in the diet. This requires more than merely supplementing the diet with ω-3 PUFAs, because dietary levels of ω-6 PUFAs are generally quite high and modest amounts of ω-3 PUFAs added to that will not be sufficient to displace the ω-6 PUFAs that are already in the body and continue to be added in the diet. Generally, it would require decreasing ω-6 vegetable oils to very low levels when supplementing with ω-3 PUFAs to see a significant effect. In addition, it is likely to take more than a month or two on a low ω-6 PUFA diet to deplete the substantial stores of LA that can be in adipose tissue as a result of a lifetime of consuming a Western diet.

Lipid peroxidation can cause oxidative stress and vice versa, and the role of these phenomena in several diseases is well documented (28, 30, 119). It is inappropriate to assign adverse effects to "dietary" saturated fats, because SFAs are chemically stable, synthesized from other nutrients in the body (notably carbohydrates and PUFAs), and are generally maintained within certain limits in most tissues according to physiological control mechanisms. On the other hand, PUFAs are unstable to chemical oxidation and their oxidation products are harmful in a variety of ways. PUFAs also form powerful signaling agents that can initiate inflammation, which can have dire health consequences, as described above. Many of the oxidized metabolites of PUFAs, especially ω-3 PUFAs, can also resolve inflammation. If saturated fats are replaced by carbohydrates in the diet, there would be

no significant improvement in serum cholesterol, and it can result in a more atherogenic lipoprotein profile. When looking at much of the data in the context of known biochemical and physiological mechanisms, it appears that saturated fats are less harmful than the common alternatives.

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