thematic review

Thematic review series: Patient-Oriented Research

Dietary fat, carbohydrate, and protein: effects on plasma lipoprotein patterns

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Abstract In general, under isoweight conditions, different types of dietary protein or individual amino acids have little effect on lipoprotein patterns. Dietary carbohydrate tends to increase plasma triglyceride when it displaces fat, accompanied by a decrease in HDL cholesterol concentrations. Potential differential effects of types of carbohydrate are difficult to assess because of differences in rates of absorption and confounding of dietary fiber. Saturated fatty acids increase LDL and HDL cholesterol, whereas *trans* fatty acids increase LDL but not HDL cholesterol. Unsaturated fatty acids decrease LDL and HDL cholesterol, polyunsaturated more so than monounsaturated. There has been considerable interest in the potential benefit of major shifts in dietary macronutrients on weight loss and lipoprotein patterns. Short-term data favor substituting protein and fat for carbohydrate, whereas long-term data have failed to show a benefit for weight loss. During an active weight loss period low-carbohydrate diets more favorably affect triglyceride and HDL and less favorably affect LDL cholesterol concentrations. Additional efforts need to be focused on gaining a better understanding of the effect of dietary macronutrient profiles on established and emerging cardiovascular disease risk factors, mechanisms for changes observed and contributors to individual variability. Such data are needed to allow reassessment and, if necessary, modification of current recommendations.—Lichtenstein, A. H. **Dietary fat, carbohydrate, and protein: effects on plasma lipoprotein patterns. *J. Lipid Res.* 2006.** 47: **1661–1667.**

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Dietary fat, carbohydrate, and protein are the primary energy-containing macronutrients consumed on a routine basis by humans. Dietary alcohol provides a unique category of energy and will not be considered in this review. Trendy weight loss diets that have flourished during the past decade have resulted in the generation of a considerable amount of data on how major shifts in the macronutrient content of the diet affect plasma lipoprotein patterns. These data can be used to inform dietary recommendations to minimize the risk of developing cardiovascular disease (CVD).

It is difficult to consider the independent effect of dietary fat, carbohydrate, or protein on plasma lipoprotein patterns because, in each case, in addition to contributing unique essential and nonessential nutrients, the macronutrients also contribute the majority of metabolic energy to sustain life. To maintain a stable body weight, if the intake of one macronutrient is increased or decreased, there needs to be a compensatory adjustment in one or both of the other macronutrients. Under these circumstances, the effect observed on plasma lipoprotein patterns can be attributable to either the addition of one macronutrient or the reduction of the other(s). If a single macronutrient is increased or decreased without compensatory adjustments in the amount of the other macronutrients, body weight will change and any effect on plasma lipoprotein patterns will result from changes induced by weight loss or gain, a shift in the relative energy distribution of each macronutrient, or some combination thereof (1, 2). Likewise, it is difficult to accurately assess the effect of individual components of macronutrients on plasma lipoprotein patterns. For example, under isoweight conditions, if the intake of one fatty acid increases, another energy-containing component of the diet (fatty acid, amino acid, or saccharide) must decrease.

The literature is replete with studies assessing many aspects of this topic. In is beyond the scope of the article to conduct a systematic review of the literature. The discussion will be limited to major current issues and examples provided for illustrative purposes only. Special considerations imposed by unique metabolic conditions will not be addressed.

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METHODOLOGICAL ISSUES

There are a considerable number of methodological challenges associated with studies designed to assess the effect of diet composition on lipoprotein patterns. A cursory review of these issues provides some explanation for what often seems to be the appearance at best of contradictory and discordant data and at worst of a dearth of data on timely and critical topics.

With respect to humans, there is a tremendous degree of genetic heterogeneity among individuals, the significance of which is likely to be considerable but difficult at this time to adequately quantify or manage. The amount of time humans can be subjected to strict diet control is limited, from the perspectives of cost, logistics, and subject cooperation, making it difficult to achieve a "steady state." Metabolism varies by gender and age, and within each of these categories, multiple changes (e.g., hormonal and body composition) proceed at different rates, making them difficult to factor into the final analysis. Likewise, with aging come comorbidities, which make it difficult to initiate an intervention in a well-matched cohort. And finally, but of utmost importance, ethical and humanitarian considerations limit the types and extremes of interventions and the invasiveness of the techniques that can be used to characterize and monitor outcomes. Nonetheless, data that have been generated in humans, within clearly defined contexts, have provided some of the most valuable and longstanding knowledge in the area of diet and plasma lipoprotein patterns.

With respect to nonhuman interventions, there is no ideal animal model, transgenic or knockout, or in vitro system that yields data consistently analogous to human data. This is attributable to inherent differences in such factors as the physiology of gastrointestinal tracts, the characteristics of endocrine and immune systems, the pathways and nature of lipoprotein metabolism, and differences in body composition and metabolic rates. Hence, although critical data have emerged from animal and in vitro systems, particularly with respect to questions that cannot be adequately addressed in humans, these data need to be treated as pieces of the puzzle, critical but considered with caution when out of context.

DIETARY MACRONUTRIENTS

Stable body weight

Fat. Early work focused on assessing the effect of the macronutrient content of the diet on plasma lipoprotein patterns, with specific emphasis on dietary fat and carbohydrate. It was noted early in the 1960s that diets very low in fat resulted in hypertriglyceridemia (3, 4), and this effect was later attributed to increased rates of hepatic fatty acid synthesis (5, 6) and the subsequent production of hepatic triglyceride-rich particles, such as VLDL (7, 8). It was also observed that this hypertriglyceridemia was accompanied by lower HDL concentrations. Within the context of a stable body weight, replacement of dietary carbohydrate with fat resulted in lower triglyceride and VLDL cholesterol concentrations, higher HDL cholesterol concentrations, and a lower, more favorable total cholesterol-to-HDL cholesterol ratio (2, 9–12). Additionally, the more moderate the shift in the fat-to-carbohydrate ratio of the diet, the more moderate the change in triglyceride concentrations (13). Recently, it was reported that moderate carbohydrate restriction and weight loss provide equivalent but nonadditive improvements in the atherogenic dyslipidemic pattern characterized by increased triglyceride concentrations and total cholesterol-to-HDL cholesterol ratios (14).

Protein. Until recently, there has been little work on the effect of dietary protein on plasma lipoprotein patterns. Target dietary recommendations as a percentage of energy have changed little over the years (15–19). Dietary protein falls into two categories defined by origin: animal protein, primarily meat and diary; and vegetable protein, primarily grains and legumes. For the most part, the former source of protein contributes the majority of dietary saturated fat and much of the monounsaturated fat, whereas the latter, with the exception of tropical oils (palm, palm kernel, and coconut), contributes polyunsaturated and monounsaturated fat. The implications of fatty acids accompanying the sources of protein are discussed below. Although there has been considerable interest in recent years about the absolute level of protein on plasma lipoprotein patterns, it has not been possible to untangle the independent effect of the presence of protein from that of the absence of carbohydrate and/or a change in body weight. During the past decade, attention has been focused on the potential unique properties of one type of vegetable protein, soy protein, on plasma lipoprotein patterns (20). Recent work suggests that the initial beneficial effects on plasma lipoprotein concentrations relative to other types of protein, most commonly casein, have been more modest than originally thought (21–23).

Carbohydrate. Because the majority of dietary interventions in humans have held the protein content of the diet relatively constant and varied the fat, by definition, under isoweight conditions, the carbohydrate component of the diet varied inversely with fat and protein. Hence, any observations made with respect to the fat content of the diet, as discussed above, likewise apply to dietary carbohydrate. Increases in the relative proportion of carbohydrate result in dyslipidemia, characterized by high triglyceride and VLDL cholesterol concentrations, low HDL cholesterol concentrations, high total cholesterol-to-HDL cholesterol ratios, and, in some cases, small dense LDL particles (2, 9–12, 24, 25). The extent of the response is dependent on the characteristics of the study population and the magnitude of the shift from fat to carbohydrate (1, 2, 13). There is limited information on type of carbohydrate (i.e., sucrose and starch) and plasma lipoprotein response. Diets high in starch, relative to sucrose, have been associated with lower total and LDL cholesterol and with fasting and nonfasting triglyceride concentrations in

some but not all studies (6, 26, 27). However, the area under the curve for glucose and nonesterified fatty acids has been reported to be lower in response to diets high in sucrose relative to starch (6). Confounding interpretation of these data, diets high in sugar relative to starch have been reported to increase rates of fatty acid synthesis (5), perhaps reflecting differences in the rates of absorption, secondary to the presence of dietary fiber (28). Additional work in this area is needed.

The issue of the effect of carbohydrate on the plasma lipoprotein response is further complicated by other unavoidable variables when using whole food diets, such as the type of saccharide (glucose, galactose, fructose) or the presence of fiber. In general, when the carbohydrate content of the diet declines, unless the decrease is limited to products made with highly refined foods, the fiber content of the diet also declines (29–32). Because dietary fiber has been shown to have a modest effect on reducing plasma total and LDL cholesterol concentrations (33, 34), the relative effect of a change in fiber compared with carbohydrate is difficult to attribute. The addition of fiber to equalize the amount in the diet can result in noncomparable types of fiber, further adding variability to the equation. The potential of other confounding bioactive dietary factors needs further investigation.

Body weight change

The recent interest in low-carbohydrate/high-protein diets has resulted in the generation of a considerable amount of longer term data on the effect of altering the macronutrient content of the diet within the context of weight loss and subsequent effects on plasma lipoprotein patterns. A recent meta-analysis (35) of the six trials (36–41) comparing low-carbohydrate/high-protein diets with low-fat diets for at least 6 months yielded the following results. As an aggregate, at the 6 month time point, the low-carbohydrate/high-protein diets resulted in more favorable effects on plasma triglycerides and HDL cholesterol concentrations, less favorable effects on plasma total and LDL cholesterol concentrations, and a greater decrease in body weight. In the one study in which the intervention relied on providing subjects with popular diet books and little individualized support, similar to what is frequently experienced by the general population, body weight loss and plasma lipoprotein responses were similar regardless of the recommended macronutrient content of the diet (40). In those studies for which data were available after 12 months (37, 40, 41), the more favorable effects of the low-carbohydrate/high-protein diets were maintained at a statistically significant level for plasma triglyceride but not for HDL cholesterol concentrations, whereas the less favorable effects on total and LDL cholesterol remained significant. Additionally, by the 12 month time point, the significant difference in body weights was not maintained.

In contrast to weight loss studies in overweight and obese individuals, there are limited long-term data in underweight or lean subjects on the response of lipoprotein patterns to diets differing in macronutrient content that involve weight gain. One unique short-term study addressing this issue involved the Tarahumara Indians (42). Subjects were shifted from their traditional diet of 20 energy (E) % fat, 15 E% protein, and 65 E% carbohydrate to an "affluent diet" of 43 E% fat, 10 E% protein, and 47 E% carbohydrate, at approximately twice the energy level habitually consumed. Within the context of a short-term increase in body weight, plasma total cholesterol, LDL cholesterol, and HDL cholesterol concentrations increased, as did the calculated mean total cholesterol-to-HDL cholesterol ratio.

Dietary fatty acids

It has been recognized since the 1950s that the fatty acid profile of the diet is the major determinant of plasma cholesterol concentrations (43, 44). When displacing carbohydrate from the diet, saturated fatty acids increase total cholesterol, polyunsaturated fatty acids decrease total cholesterol, and monounsaturated fatty acids have a neutral effect (43–45). It is estimated that the total cholesterol-increasing effect of saturated fatty acids is approximately twice the cholesterol-decreasing effect of polyunsaturated fatty acids, resulting in early dietary recommendations that stressed reductions in dietary saturated fat (18). More recent work has concluded that saturated fatty acids, particularly lauric (12:0), myristic (14:0), and palmitic (16:0) acids, increase LDL and HDL cholesterol, polyunsaturated fatty acids decrease LDL and HDL cholesterol, and monounsaturated fatty acids, to a lesser extent than polyunsaturated fatty acids, decrease LDL and HDL cholesterol concentrations (11, 45, 46). The total cholesterol-to-HDL cholesterol ratio is similar and more favorable for polyunsaturated and monounsaturated fatty acids than for saturated fatty acids (11). Similarly, observational data suggest polyunsaturated and monounsaturated fatty acid, relative to saturated fatty acids, intakes are associated with reduced CVD risk (47).

Saturated fatty acids. In the mid-1950s, it was also noted that not all saturated fatty acids had identical effects on plasma cholesterol concentrations. Shorter chain saturated fatty acids (6:0–10:0) and 18:0 have little effect on plasma cholesterol concentrations, whereas those with intermediate chain lengths (12:0–16:0) increase concentrations (48, 49). The minimal effect of the shorter chain fatty acids is attributed to their being absorbed directly into the portal circulation, and that of 18:0 is attributed to its high rate of conversion to 18:1, a monounsaturated fatty acid (50). The LDL cholesterol-increasing effect of the intermediate chain saturated fat is attributed to a decreased fractional catabolic rate of plasma LDL, with little effect on production rate (51, 52). Predictive equations used to estimate the effect of alterations in the major dietary fatty acid subclasses, relative to carbohydrate, assume that the plasma cholesterol-increasing effect of saturated fat is approximately twice the cholesterol-decreasing effect of polyunsaturated fat. At this time, the predicative equations have factors for saturated, monoun-

saturated, and/or polyunsaturated fatty acids and do not take into consideration the differences among individual saturated fatty acids (46, 48, 53, 54). Given that each food contains a mixture of fatty acids and the difficulty in accurately assessing the fatty acid profile of the diet, this approach is reasonable at this time. Likewise, from a dietary perspective, it is difficult to formulate recommendations on the basis of the differential effects among saturated fatty acids and CVD risk. Hence, the focus has been to recommend restrictions of total saturated fat intake (17, 19). With the rapid development of the technology for genetic modification of the fatty acid profiles of plants and animals, this approach may need to be revisited as these foods become commercially available on a large scale (55–58).

Unsaturated fatty acids. Dietary unsaturated fatty acids are categorized by the length of their acyl chains, the degree of unsaturation (number of double bonds), the position of the double bond(s), and the conformation of the double bond(s). From the perspective of diet and CVD risk, all of these factors are important in dictating the biological effects of the individual unsaturated fatty acids on plasma lipoprotein patterns. With respect to chain length, the major dietary unsaturated fatty acids range from 18 to 22 carbons, with shorter and longer chain unsaturated fatty acids occurring in relatively small amounts. Although there are multiple nomenclatures for denoting the position of the double bonds for categorical purposes, the distinction from a biological perspective is made on the basis of the location of the first double bond from the methyl end of the fatty acyl chain (as opposed to the carboxyl end). Two major dietary subclasses of polyunsaturated fatty acids are ω-6 (or n-6) and ω-3 (or n-3). These fatty acids can have an identical chemical composition but differ in the location of double bonds. They are referred to as positional isomers. In addition, the double bonds can occur in either the *cis* or *trans* configuration. *Trans* double bonds have a greater bond angle than *cis* double bonds; resulting in acyl chains with a more linear conformation, similar to a saturated than an unsaturated fatty acid. Fatty acids with an identical composition but double bonds differing in conformation are referred to as geometric isomers.

ω-3 fatty acids. Interest in the protective effect of very long-chain ω-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), on CVD began in earnest in the 1970s (59, 60). These observations have been supported by a considerable number of observational studies (61–65) and some interventional studies (66, 67). Recently, there have been a number of systematic reviews and meta-analyses of the relationship of dietary ω-3 fatty acids and CVD events. The majority of them concluded that the inverse relationship between ω-3 fatty acid intake and CVD events is significant for EPA and DHA but not for α-linolenic acid (ALA) (68–72).

The major dietary source of EPA and DHA is oily fish. A plant source of ω-3 fatty acids, ALA, can be converted to EPA, albeit at very low rates (~5%) (73). Major dietary sources of ALA are canola and soybean oils. It has been suggested that the inefficient conversion of ALA to EPA can be attributed to the limited incorporation of ALA into the hepatic phospholipid pool (74). It has likewise been suggested that the inefficient conversion of EPA to DHA can be attributed to the low rate of conversion of EPA into docosapentaenoic acid, which is necessary for the subsequent conversion to DHA (74).

It is likely that the purported beneficial effects of the very long-chain fatty acids on CVD risk are multifactorial (75). The postulated mechanisms underlying the relationship include decreased arrhythmias, lower triglyceride concentrations in hypertrigyceridemic individuals, lower blood pressure, and decreased platelet aggregation (67, 76, 77). In individuals with increased triglyceride levels, ω-3 fatty acids decrease plasma concentrations by decreasing hepatic production rates of VLDL, with little effect on fractional catabolic rates (78, 79). In some cases, an increase in LDL cholesterol concentration has been attributed to very long-chain ω-3 fatty acids, in part as a result of an increased conversion rate of VLDL to LDL (78, 80). ω-3 fatty acids decrease postprandial plasma triglyceride concentrations by accelerating the fractional catabolic rate via increased lipoprotein lipase activity (81). On the basis of the available data, the American Heart Association recommends that the general population consume at least two fish meals per week, individuals with established CVD consume 1 g of EPA plus DHA per day, and hypertriglyceridemic individuals consume 2–4 g of EPA plus DHA per day (67).

Trans fatty acids. *Trans* fatty acids, by definition, contain at least one double bond in the *trans* configuration and can be either monounsaturated or polyunsaturated. Since the early 1990s, considerable attention has been focused on the effect of *trans* fatty acids on plasma lipid and lipoprotein concentrations (82). The major source of dietary *trans* fatty acids is partially hydrogenated fats and products formulated with these fats, such as commercially prepared baked and fried foods. A smaller proportion of dietary *trans* fatty acids comes from ruminant animal fats found primarily in meat and full fat dairy products. As do saturated fatty acids, *trans* fatty acids increase LDL cholesterol concentrations (82–84). In contrast to saturated fatty acids, they do not increase HDL cholesterol concentrations. Relative to unsaturated fat, both saturated fat and partially hydrogenated fat result in higher LDL cholesterol concentrations attributable to lower fractional catabolic rates, with little change in production rates (52). Relative to saturated fat, partially hydrogenated fat results in lower HDL cholesterol concentrations attributable to higher fractional catabolic rates, with little change in production rates (52). Collectively, these changes result in a less favorable total cholesterol or LDL cholesterol-to-HDL cholesterol ratio when *trans* fat is compared with saturated fat (11, 85, 86). In some cases, *trans* fatty acids have also been reported to increase triglyceride concentrations (11, 83).

Dietary cholesterol

The link between dietary cholesterol and increased plasma cholesterol concentrations and atherogenesis was originally made in the early 20th century in rabbits (87). Although the major determinant of LDL cholesterol concentrations in humans is saturated fat (48, 53), dietary cholesterol has nonetheless been positively associated with CVD risk and both LDL and HDL cholesterol concentrations (45, 88). Estimating the absolute effect of dietary cholesterol on plasma lipoprotein concentrations has been difficult because of the high degree of variability in response among individuals (89). Nonetheless, in carefully controlled studies performed in healthy young males and females, it was demonstrated that for every additional 100 mg of dietary cholesterol, fasting plasma total cholesterol concentrations increased by 1.47 and 0.73 mg/dl, respectively, with parallel increases in LDL cholesterol and apoprotein B concentrations (90, 91). Increased levels of the cholesteryl ester transfer protein were observed at the highest levels of dietary cholesterol in males but not females. One mechanism by which dietary cholesterol alters plasma lipoprotein concentrations is by downregulating cell surface LDL receptor activity, thereby decreasing VLDL and LDL clearance from plasma and increasing the conversion rate of VLDL to LDL (92). Consistent with these data, dietary cholesterol has been reported to decrease LDL fractional catabolic rates and increase LDL production rates (93). The identification of genetic polymorphisms that alter rates of cholesterol absorption is likely to shed new light in this area (94–96).

CONCLUSIONS

It is difficult to isolate the independent effects of dietary fat, carbohydrate, and protein on plasma lipoprotein profiles. The data available are confounded by changes in body weight and alterations in the intake of two or more macronutrients necessitated to minimize body weight changes. Given the high degree of variability in response among individuals, specific recommendations for dietary fat, carbohydrate, and protein to optimize plasma lipoprotein patterns need to be made on a case-by-case basis, taking into consideration a realistic anticipated level of compliance. A considerable amount is known about the effect of fatty acid subclasses, and in some cases individual fatty acids, on plasma lipoprotein patterns and the metabolic basis for these effects. Additional efforts need to be focused on gaining a better understanding of the effect of the macronutrient content of the diet on established and emerging CVD risk factors other than lipoprotein patterns, understanding the mechanisms associated with diet induced changes in lipoprotein patterns and contributors to individual variability in response, and then to reassess and if necessary modify current recommendations.

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