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EFFECTS OF FAT-MODIFIED DIETS ON CHOLESTEROL AND LIPOPROTEIN METABOLISM

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INTRODUCTION

The role of dietary fat and cholesterol in the pathogenesis of hyperlipidemia and its associated risk for cardiovascular disease (CVD) has been the topic of numerous reviews and considerable debate. The relative merit of a fat-modified "prudent diet" in reducing plasma lipid levels has been examined intensively for over thirty years; the majority of these studies have used

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plasma lipid and lipoprotein levels as the study end point. In addition, there are numerous studies evaluating the effects of fat-modified diets on whole-body cholesterol and lipoprotein metabolism in normolipidemic and hyperlipidemic individuals. These metabolic studies provide essential data not only on diet-induced changes in plasma lipid levels but also on the efficacy of dietary changes in altering the body's handling of lipoprotein cholesterol as related to atherogenesis and, more importantly, on the mechanisms by which dietary changes alter plasma lipid levels and CVD risk.

OVERVIEW

Previous reviews in this series have discussed dietary cholesterol metabolism (23), lipoprotein metabolism (20), and cholesterol biosynthesis (76). This review concentrates on changes in cholesterol and lipoprotein metabolism in man resulting from implementation of fat-modified diets. Emphasis is placed on the effects of dietary changes similar to those proposed by the American Heart Association (25), which recommends:

1. Caloric intake to achieve and maintain desirable weight.
2. Reduction in dietary saturated fat to 10% of calories.
3. Increase in polyunsaturated fats to 10% of calories.
4. Reduction of total fat intake to 30% of calories and increase of complex carbohydrate intake.
5. Reduction of dietary cholesterol intake to less than 300 mg/day.

Any discussion of the impact of dietary changes on sterol and lipoprotein metabolism in man requires consideration of the overall dynamics of these metabolic pathways. Sterol balance studies have shown that the rate of whole-body cholesterol synthesis averages 11–13 mg/kg-day on a modest cholesterol diet and that cholesterol absorption averages 55%. For a 70-kg man on a typical North American diet the daily synthesis of cholesterol would be approximately 840 mg, and the absorption from a dietary intake of 450 mg/day would be 250 mg/day. Under these conditions the production rate of cholesterol, endogenous synthesis plus absorbed dietary cholesterol, is approximately 1100 mg/day. The rate of bile acid synthesis is approximately 3–4 mg/kg-day and constitutes the major catabolic product of cholesterol. Each day approximately 1000 mg of biliary cholesterol enters the intestinal tract and half is reabsorbed. Other than in patients with familial combined hyperlipidemia, the rates of cholesterol and bile acid synthesis are relatively constant among normolipidemic subjects and patients with various forms of hyperlipidemia irrespective of their plasma cholesterol levels.

The metabolism of the plasma lipoproteins is a complicated process in that the production rates and fractional catabolic rates (FCR) of the various

lipoprotein fractions are a function of the type of hyperlipidemia the patient may exhibit. For a normolipidemic subject with average plasma cholesterol and triglyceride levels, the production rate of very low-density lipoprotein (VLDL) apoprotein B (apoB) is 9–15 mg/kg-day with a FCR rate of 4.5–14 day^{-1}. Low-density lipoprotein (LDL) apoB production averages 7.5–14 mg/kg-day with a FCR of 0.29–0.46 day^{-1}. There exists in the literature a large degree of variation for these kinetic values of VLDL apoB and LDL apoB production and turnover in control subjects. Much of the variability is due to patient-to-patient heterogeneity, methodological differences, and the type of kinetic model applied to the data.

OBESITY AND CALORIC INTAKE

Obesity, especially androgenic obesity, has been shown to be an independent risk factor for CVD (28, 37); in addition, obesity contributes to a number of the other risk factors for CVD, e.g. glucose intolerance, hypertension, and hyperlipidemia. Obesity results in a number of alterations in whole-body cholesterol and lipoprotein metabolism and these changes usually create a more atherogenic metabolic pattern for cholesterol and the lipoproteins.

Obesity and Cholesterol Metabolism

Obesity is characterized by increases in the rates of cholesterol synthesis (32, 40, 51, 66) and biliary excretion of cholesterol, associated with increased lithogenicity of the bile (4, 8, 54) and expanded body cholesterol pools (21). Some studies suggest that the bile acid synthesis rate and fecal excretion are also increased in obese subjects (58). It has been calculated that the increase in cholesterol synthesis in obesity is approximately 20 mg/day for each excess kilogram of body fat (51). Quantitation of whole-body cholesterol synthesis rates on a body weight basis demonstrates that obese patients produce approximately the same amount of cholesterol per day, 12–14 mg/kg-day (40); however, the increase in whole-body cholesterol synthesis cannot be accounted for by the cholesterol synthetic capacity of adipose tissue, which is no more than 1 mg/kg-day (52, 78). Whether increased cholesterol synthesis in obesity occurs in the liver or other body tissues has not been clearly established (3, 5, 17). Irrespective of the source of the increased production rate, it is clear that obese patients have an elevated cholesterol synthesis that can be reduced to within normal levels by weight reduction (51).

Weight reduction not only decreases the rate of cholesterol synthesis, it also reduces the hypersecretion of biliary cholesterol while maintaining a normal phospholipid and bile acid output (8). During active weight loss, the bile of obese patients remains supersaturated, apparently because of an increased mobilization of adipose tissue cholesterol stores (8). This mobilization would

be predicted to decrease the expanded mass of the slowly turning over pool of cholesterol characteristic of obese subjects (61).

There is little doubt that significant changes in whole-body cholesterol metabolism can be achieved through weight reduction—changes that are beneficial in reducing CVD and gallstone risks not only by lowering plasma lipid levels but also by reducing cholesterol synthesis, biliary secretion, and the size of body cholesterol pools.

Obesity and Lipoprotein Metabolism

Reported studies of VLDL and LDL metabolism in obese patients include subjects with various degrees of obesity, with and without hypertriglyceridemia. There is some debate regarding the extent of overproduction of VLDL triglyceride and VLDL and LDL apoB in obesity, in large part due to the variety of quantitative presentations of the data. On a total body weight basis the production rates of VLDL triglyceride and VLDL and LDL apoB in obese patients are not profoundly elevated; however, as noted by Grundy et al (26), the increased adiposity is not a site of VLDL synthesis and therefore the data should be presented using ideal weight or fat-free body mass as the denominator in normalized VLDL synthesis rates.

Studies by a number of investigators have shown that obese subjects overproduce VLDL triglycerides (26, 69, 74) and apoB (16, 32, 34), and that weight reduction can significantly reduce these elevated production rates (19, 69). It is reported that obese, hypertriglyceridemic subjects exhibit both an overproduction and a reduced clearance of VLDL, while those with normal triglyceride levels express only an overproduction (26). There appears to be a direct relationship between plasma triglyceride levels and VLDL triglyceride production rates (35, 74); however, this is not uniformly observed (26). The FCR for VLDL triglyceride and apoB are decreased only in obese subjects with hypertriglyceridemia (19, 26, 34, 35). The fraction of VLDL directly converted to LDL, as opposed to the fraction directly removed, is reported to be increased in the obese state (19, 35). Two studies report that obese subjects remove significantly higher amounts of VLDL apoB from the circulation without conversion to LDL apoB (16, 34). These findings may relate to whether the study subjects had elevated plasma LDL levels, since it appears that one mechanism for maintaining a normal LDL level when VLDL production is increased is to reduce the direct conversion of VLDL to LDL (34). Most of the reported abnormalities in VLDL metabolism associated with obesity can be normalized by weight reduction (19, 69). Two potential causes of the overproduction of VLDL in obesity are the increased free fatty acid flux and the increased insulin levels associated with obesity; these stimulate VLDL synthesis (26).

LDL metabolism is also altered in the obese patient. There is a higher

protein-to-cholesterol ratio in the LDL particle (19, 32) and a trend toward higher LDL production rates, whether calculated on an ideal body weight or actual body weight basis (19, 32, 34). Studies suggest that the FCR for LDL apoB is also increased in obese patients (16, 19, 32, 34), although this finding rarely reaches statistical significance in individual studies. Weight reduction can significantly reverse these metabolic patterns (19). The increase in plasma LDL levels following weight reduction in obese patients arises from a decrease in the FCR and a corresponding increase in the direct secretion of LDL (19).

DIETARY CHOLESTEROL

The effects of dietary cholesterol on plasma lipoprotein cholesterol levels have been reviewed by McGill (46) and Grundy (23). It should be noted that the majority of studies investigating the effects of dietary cholesterol on cholesterol and lipoprotein metabolism have used relatively high dietary cholesterol intakes (>1000 mg/day) as compared to low baseline cholesterol intakes (<200 mg/day). In addition, most studies investigating the effects of dietary cholesterol on lipoprotein metabolism have not quantitated the mass of cholesterol absorbed, which can account for much of the wide variability in observed responses (48). An additional complicating factor is that the effects of a dietary cholesterol challenge differ significantly between patients depending upon the amount of cholesterol absorbed per kg body weight, because the rate of endogenous cholesterol synthesis, and hence the body's capacity to handle dietary cholesterol, is a function of body weight. With these considerations in mind, the currently available findings do not provide sufficient data to evaluate how reducing the present dietary cholesterol intake will affect whole-body cholesterol and lipoprotein metabolism.

Dietary Cholesterol and Cholesterol Metabolism

There is abundant evidence that increasing dietary cholesterol intake changes the various mechanisms maintaining whole-body cholesterol homeostasis in man: cholesterol absorption and synthesis, biliary excretion, bile acid synthesis, and tissue accumulation. The data demonstrate a pronounced heterogeneity among individual patients in the quantitative significance of each of these responses to a dietary cholesterol challenge; however, the evidence supports the concept that having precise feedback suppression of endogenous cholesterol synthesis as a primary metabolic response allows the patient to maintain a constant plasma cholesterol level and to avoid accumulation of excess cholesterol in body tissues.

The first reports of sterol balance studies on high cholesterol intakes demonstrated that the body's mechanisms for compensation include (*a*) decreased fractional absorption of cholesterol once the intake level exceeds 1500 mg/day (72); and (*b*) decreased endogenous synthesis and increased biliary re-excretion of absorbed dietary cholesterol, which are the two primary compensatory responses (72). Studies by Nestel & Poyser (57) of nine subjects using moderate intakes of cholesterol (250 versus 750 mg/day) demonstrated that the compensatory mechanisms equalled the increase in absorbed cholesterol and that a rise in plasma cholesterol was observed only when endogenous cholesterol synthesis was not sufficiently suppressed by the increased flux of dietary cholesterol. In a few patients, an additional mechanism to compensate for a high-cholesterol diet is increasing fecal bile acid excretion; however, this is apparently a minor compensatory response (41, 44, 57).

Studies feeding very high amounts of dietary cholesterol (up to 3.5 g/day) have demonstrated that some patients accumulate the absorbed dietary cholesterol in body tissues (44, 72, 73) and, upon resumption of a low cholesterol intake, these accumulated stores of cholesterol can be mobilized for eventual fecal excretion (73). Studies by Maranhao & Quintao (44) in patients fed low- and high-cholesterol diets (50 vs 1350 mg/day) reported that six of the thirteen subjects exhibited no increase in plasma cholesterol levels and that the compensatory mechanisms, primarily a decrease in endogenous cholesterol synthesis, equalled the increase in absorbed dietary cholesterol. Those patients exhibiting a rise in plasma cholesterol due to the high-cholesterol diet failed to compensate effectively for the increased cholesterol flux. Interestingly, baseline level of plasma cholesterol or the presence of familial hypercholesterolemia has little effect on whether a patient has precise or imprecise compensatory mechanisms (44, 45). Precise compensatory responses to dietary cholesterol (i.e. decreased endogenous synthesis) exist in most genetically distinct populations (27, 47, 87).

Studies of the effects of dietary cholesterol on cellular sterol synthesis have demonstrated that dietary cholesterol reduces the activity of mononuclear leukocyte 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (53) and the rate of acetate incorporation into sterols (49). Studies by McNamara et al (49) found that the decrease in mononuclear leukocyte sterol synthesis was directly related to the amount of dietary cholesterol absorbed, and this reduction was significantly greater in those subjects who did not exhibit a rise in plasma cholesterol levels (52 of 75) while it was much less in those patients who were diet sensitive. The data from most of the studies are consistent with the concept that those subjects showing the greatest reduction in endogenous cholesterol synthesis in response to a dietary cholesterol challenge have a negligible increase in plasma cholesterol concentrations.

Reported effects of dietary cholesterol on biliary lipid concentrations are contradictory; some investigators have observed an increase in biliary cholesterol saturation (14, 39), while others have reported that dietary cholesterol has no effect on the saturation index (1, 15). From the sterol balance studies one would predict that an increase in dietary cholesterol intake in patients who either lack precise feedback suppression of endogenous synthesis or who exhibit a substantial increase in biliary re-excretion of absorbed dietary cholesterol would result in an increased biliary cholesterol saturation. In contrast, patients who increase bile acid synthesis in response to a dietary cholesterol challenge might be expected to have a reduced biliary saturation index. The heterogeneity of compensatory responses to a dietary cholesterol challenge probably accounts for the contradictory results reported for the effects of dietary cholesterol on biliary lipid concentrations (1, 14, 15, 39).

Dietary Cholesterol and Lipoprotein Metabolism

Studies by Nestel and coworkers (56, 59) demonstrated that an increased dietary cholesterol intake (200 versus 1700 mg/day) altered both the composition and metabolism of VLDL and intermediate-density lipoproteins (IDL). These metabolic ward studies were carried out for one week on the low cholesterol intake and four weeks on the high intake. In one study (56) the high cholesterol intake increased plasma HDL and apoA1 levels ($n = 8$) but did not significantly increase total, VLDL, LDL, or apoE concentrations; in the other study (59) a similar high cholesterol intake did increase total plasma cholesterol in four patients fed a diet with a low ratio of polyunsaturated to saturated fat (P/S). The data demonstrate that a high cholesterol intake does not alter the apoB flux in VLDL but does increase the turnover of IDL apoB by 50% in 5 of 8 patients (59), although this was not observed in the previous study (56). In 3 of 6 patients, dietary cholesterol increased the percentage of VLDL that bound to a heparin affinity column and may represent plasma accumulation of IDL particles (56).

Two studies have investigated the effects of dietary cholesterol on plasma LDL kinetics. Packard et al (70), fed 7 subjects either 110 or 905 mg cholesterol/1000 cal per day on a low P/S diet (0.17) and reported that the high dietary cholesterol intake increased total, LDL, and HDL cholesterol levels. LDL composition was unchanged, indicative of a larger apoLDL plasma pool. Kinetic studies indicate that a high dietary cholesterol intake increased LDL synthesis by 23% while reducing the fractional catabolic rate (FCR) by 10%. The reduction in the FCR was due to a decrease in the receptor-mediated uptake of LDL; however, there was a significant increase in the absolute amount of LDL degraded by receptor-independent mechanisms (70). In a similar study, using moderate amounts of dietary cholesterol

during the challenge period, Ginsberg et al (18) fed five volunteers a diet with 40% of calories as fat and a P/S ratio of 0.4. They reported that shifting dietary cholesterol intake from 150 to 500 mg/1000 kcal had no effect on plasma cholesterol levels and did not alter the synthesis and FCR of apoB in either VLDL or LDL. VLDL triglyceride metabolism was also unaffected by the increase in dietary cholesterol intake. In this study (18) all five volunteers were nonresponders to the moderate dietary cholesterol challenge and thus probably possessed precise feedback suppression of endogenous cholesterol synthesis.

Two additional studies support the concept that very high dietary cholesterol intakes suppress LDL catabolism in humans. Mistry et al (53) found that increasing dietary cholesterol intake by 1500 mg/day for 14 days increased total, IDL, LDL, and HDL cholesterol levels, reduced mononuclear leukocyte LDL degradation by 74%, and increased the cholesterol content of these cells by 17%. Similar results have been reported by Applebaum-Bowden et al (6), who compared the effects of a dietary cholesterol intake of 137 versus 1034 mg/day on mononuclear leukocyte LDL degradation in nine subjects and found an 11% increase in plasma LDL levels associated with a 41% reduction in cellular LDL receptor activity; the observed decrease in cellular LDL degradation occurred irrespective of changes in plasma cholesterol levels.

A different approach to investigating the effect of absorbed cholesterol on plasma LDL metabolism was taken by Kesaniemi & Grundy (33), who treated six patients with neomycin, an inhibitor of cholesterol absorption. The subjects were fed a low-cholesterol diet (113 mg/day); thus the major drug effect was a reduction in biliary cholesterol absorption. The FCR of LDL was unchanged and the rate of apoLDL synthesis lowered by 28% during neomycin administration. The results parallel the findings of Packard et al (70) of an increased apoLDL synthesis when the flux of cholesterol through the liver is increased during cholesterol feeding. The data suggest that the primary response of the lipoprotein metabolic pathways to changes in delivery of absorbed cholesterol to the liver is an alteration in apoLDL synthesis, possibly with a concomitant changes in LDL uptake by receptor-mediated mechanisms.

An increased dietary cholesterol intake has been reported to alter both the composition and cellular lipoprotein receptor interaction of plasma HDL (42). Feeding 4–6 eggs per day for 4 weeks results in a HDL particle with enhanced binding capacity to cellular LDL receptors and with an increased content of apoE. This HDL with apoE (HDLc) particle may function in reverse cholesterol transport, which is necessitated by a high-cholesterol diet, and may be involved in an anti-atherogenic role in response to a tissue overload with cholesterol (43).

An increase in absorbed dietary cholesterol alters lipoprotein metabolism.

The effects of a modest dietary cholesterol reduction on the synthesis and turnover of the various lipoproteins, however, appear to be minimal. The data suggest that a very high dietary cholesterol intake reduces the receptor-mediated degradation of LDL even when plasma cholesterol levels are not increased; similar data during modest cholesterol intakes indicate no change. As discussed above, similar responses are seen for cholesterol synthesis and indicate that most patients possess precise feedback regulation of both cholesterol synthesis and lipoprotein metabolism in response to a moderate increase in dietary cholesterol.

DIETARY FAT QUALITY

Numerous studies have shown that plasma lipoprotein levels can be significantly changed by the quality of dietary fat (31). This section reviews the effects of dietary fat quality, the polyunsaturated-to-saturated fat (P/S) ratio, on lipoprotein and cholesterol metabolism in man. In the following section the effects of changes in dietary fat quantity, which also include changes in carbohydrate quantity, on sterol and lipoprotein metabolism, are considered.

Dietary Fat and Cholesterol Metabolism

A number of studies have investigated the effects of dietary fat quality on whole-body cholesterol metabolism in an attempt to determine whether cholesterol absorption, synthesis, catabolism, or tissue flux are responsible for the cholesterol-lowering effect of an increase in dietary fat P/S ratio. Most of the data indicate that polyunsaturated fat intake has a transient effect on whole-body cholesterol metabolism by increasing fecal steroid excretion; however, the long-term intake of a high P/S diet does not alter whole-body cholesterol metabolism.

The first sterol balance studies in humans fed saturated versus polyunsaturated fats suggested that polyunsaturated fats increased fecal excretion of both neutral and acidic steroids (10, 55) although this was not a consistent finding (7, 81). Studies by Grundy & Ahrens (24) in eleven patients fed various combinations of saturated and polyunsaturated fats failed to support the theory that polyunsaturated fats increase fecal steroid excretion. The debate regarding the effect of a high P/S fat diet on sterol balance continued in the literature with reports of increased fecal steroid excretion and of no effects on whole-body cholesterol synthesis (22, 60, 63–65, 68, 80). Grundy (22) reported that an increase in the P/S ratio of the diet increased fecal steroid excretion in a group of hypertriglyceridemic patients, whereas no such increases are observed in normolipidemic and hypercholesterolemic subjects (24, 80).

The responses of the cholesterol homeostatic mechanisms to an increase in the dietary fat P/S ratio vary substantially from patient to patient and are

dependent on both the type of lipidemia the patient exhibits and the duration of the study. Nestel et al (68) suggested that the increased fecal steroid excretion in response to a high P/S fat diet may be a transient response that persists until a new steady state in cholesterol metabolism has been achieved. The currently available data supports this concept. One consistent finding is the absence of any effect of a high polyunsaturated fat diet on dietary cholesterol absorption (24, 68).

The effects of a high P/S fat diet on biliary composition and bile lithogenicity have been studied by a number of investigators (13, 22, 84); some studies indicate an increased biliary cholesterol saturation on a high P/S diet while others find no effect. The pattern of changes in biliary composition upon shifting from a low to high P/S diet probably reflect patient differences. Obese and/or hypertriglyceridemic patients who are at increased risk of gallstone formation under most conditions are more responsive to an increase in the dietary fat P/S ratio, whereas nonobese, nonhypertriglyceridemic patients do not respond to an increase in dietary fat P/S by increasing biliary cholesterol excretion. Care should be taken in altering the dietary fat quality of patients susceptible to gallstone development because increased bile lithogenicity is more likely to occur in these patients due to an increase in dietary fat P/S ratio.

Dietary Fat and Lipoprotein Metabolism

In man, polyunsaturated fat tends to lower and saturated fat to increase plasma cholesterol levels (31). Studies of lipoprotein composition demonstrate that a shift from a low to a high P/S ratio of dietary fat does not alter the composition of the lipoproteins (38, 83) but rather lowers plasma lipoprotein cholesterol levels by reducing VLDL and LDL apoB production rates. Cortese et al (11) reported that shifting the P/S ratio of a 45% fat diet from 0.12 to 3.8 reduced the VLDL and LDL apoB production rates by 31 and 23% respectively, without altering the FCR. Kraemer et al (36) found that a dietary shift from P/S 0.2 to 2.0 had no consistent effect on VLDL triglyceride synthesis. Similar results have been reported by Turner et al (82), who found that shifting the P/S ratio of dietary fat from 0.2 to 8.0 decreased the LDL apoB production rate by 13% while not significantly decreasing the FCR in normolipidemic or type II hypercholesterolemic subjects. In contrast, Shepherd et al (80) reported that a dietary fat change from P/S 0.25 to 4.0 resulted in a 9% increase in the FCR of LDL without altering the production rate. In another series of studies, Shepherd et al (79) found that a change in dietary fat quality from a P/S ratio of 0.25 to 4.0 altered the composition, thermotropic properties, and subfraction distribution of HDL and reduced the synthesis but not the FCR of apoA1. Addition of fish oil n-3 fatty acids to the diet also reduces plasma VLDL and LDL levels, primarily by reducing the

production rates of VLDL and LDL apoB and VLDL triglycerides; the FCR of LDL apoB is unaltered by dietary fish oil (30, 67).

Overall, the patterns of the findings indicate that a large shift in dietary fat P/S reduces VLDL and LDL apoB production to a greater extent than any observed increase in the FCR. Most of the studies, however, used pronounced shifts in fat P/S values, ranging from a low of 0.12 to as high as 8.0. The available data provide little information on the potential changes in lipoprotein production and turnover that might occur from a modest shift in dietary fat P/S.

DIETARY FAT AND CARBOHYDRATE QUANTITIES

Studies investigating the effects of dietary fat quantity on cholesterol and lipoprotein metabolism must be considered as changes in dietary fat intake and also as modifications in the percentage of calories from carbohydrate since dietary fat calories are replaced with carbohydrates in all studies. Consequently any responses of whole-body sterol and lipoprotein metabolism should be interpreted as the combined effects of reducing fat (either saturated or polyunsaturated) and increasing carbohydrates (simple or complex). Most published studies have used wide ranges of these two dietary components, even to the extent of using fat-free diets. The effects of a 10–15% increase in carbohydrate intake and a similar decrease in dietary fat on sterol and lipoprotein metabolism therefore are not easily interpreted.

Dietary Fat and Carbohydrate Quantity and Cholesterol Metabolism

Whyte et al (86) studied the effects of high polyunsaturated fat versus high sucrose intakes on sterol balance in four patients fed each diet for two weeks. They reported that the shift to a low-fat, high-carbohydrate diet increased fecal bile acid excretion and decreased fecal neutral steroid excretion; overall sterol balance was unchanged. Similar findings have been reported by Andersen & Hellstrom (2) for patients ingesting a high-fat versus a high-carbohydrate diet. The increased bile acid excretion on a high-carbohydrate diet is directly related to an increased synthesis of cholic and chenodeoxycholic acids and an increased biliary excretion (2). In almost all cases, plasma cholesterol levels did not change while plasma triglyceride levels were increased by intake of the high-carbohydrate diets. In contrast, Cummings et al (12) reported higher fecal bile acid excretion on a high-fat (41% calories) as compared to a high-carbodydrate (68% calories) diet. The dietary shift to a high-carbohydrate diet in this study, however, also resulted in a decreased cholesterol intake and a higher P/S ratio of the dietary fat (12).

Schreibman & Ahrens (77) fed patients diets containing 15% of calories as

protein and either 70 or 20% cottonseed oil, with the remaining calories derived from dextrose. The shift to a high-carbohydrate diet increased fecal acidic sterol excretion without changing neutral steroid output, had an inconsistent effect on plasma cholesterol levels, and increased plasma triglycerides in all cases. Four subjects fed a 40% fat versus a fat-free diet exhibited a decreased fecal steroid excretion during the fat-free period, principally because of a reduction in neutral steroid excretion. All patients fed the fat-free diet had increased plasma cholesterol and triglycerides levels due to the high carbohydrate intake.

Biliary flow and composition are also altered by increasing dietary carbohydrate intake at the expense of fat calories. A high-carbohydrate diet results in an increased flow rate for cholesterol and bile acids (85) with an accompanying decrease in biliary cholesterol and phospholipid molar percentage, while the relative concentration of bile acids is increased (2). It appears that the change in biliary flow rates and composition results primarily from the decreased fat intake rather than from an increased intake of refined carbohydrates. Werner et al (85) reported that increasing sucrose intake in 12 subjects did not alter the flow rate or molar composition of cholesterol, bile acids, or phospholipids of the bile.

Dietary Fat and Carbohydrate Quantity and Lipoprotein Metabolism

Reducing the quantity of dietary fat while increasing carbohydrates has a pronounced effect on the metabolism of all the lipoprotein fractions, especially for VLDL triglyceride and apoB metabolism because of the carbohydrate-induced hypertriglyceridemia. VLDL apoB synthesis has been reported to increase from 17 to 71% by dietary carbohydrates (11, 29, 62), although one report indicates no change (50). The FCR for VLDL apoB is reported to decrease from 3 to 46% (29, 50, 62). It is uniformly agreed that a high-carbohydrate diet increases VLDL triglyceride synthesis while reducing its FCR (50, 71, 75).

Studies of the effects of a high-carbohydrate diet on LDL apoB metabolism are conflicting. Two groups reported a 15 to 46% increase in the FCR (11, 62) while another found no change (50); both groups were using similar ranges of calories from dietary carbohydrate (45% vs 70 or 80%). In all reports, however, there were relatively few patients studied and all studies observed substantial heterogeneity in the responses (11, 50, 62). A low-fat, high-carbohydrate diet reduces LDL production rates by an average of 20% (11). The effect of a high-carbohydrate diet on HDL metabolism in normolipidemic subjects is to increase the FCR of HDL apoA1 (8–39%); reported changes in HDL apoA1 synthesis vary from no change to an 11% increase (9, 88). Studies in hypertriglyceridemic subjects report no effect of a high-carbohydrate diet on HDL apoA1 production or FCR (88).

The overall responses of the lipoproteins to a shift in calories from fat to carbohydrates are an increased VLDL level due to an increase in VLDL synthesis and reduced turnover accompanied by an increase in the turnover of HDL apoA1. The metabolic effects on LDL metabolism are debatable; however, as noted by Melish et al (50), a shift to a high-carbohydrate diet is associated with a decrease in the proportion of VLDL directly converted to LDL, which may account for some of the conflicting data. An additional variable between studies is the kinetic model used in the data analysis of VLDL kinetics. In all of the reported studies the changes in LDL metabolism in response to the high carbohydrate intake were highly variable.

SUMMARY AND DISCUSSION

The goal of this review was to characterize the changes in whole-body sterol and lipoprotein metabolism resulting from a fat-modified diet, including dietary changes that might reflect the metabolic response to implementation of a "prudent diet." Unfortunately there are only limited data from studies using dietary changes within the physiological ranges, i.e. changing from a pattern similar to the current dietary intake to one with limited total fat, saturated fat, and cholesterol intakes. It is difficult with the currently available data to predict the metabolic changes in a nonhyperlipidemic population in response to modest dietary changes, especially when considering the large degree of heterogeneity that has been demonstrated in the responses to the more dramatic dietary interventions used in most of the studies discussed here. This metabolic heterogeneity, combined with the numerous conflicting reports of the consequences of dietary interventions, makes generalizations difficult.

There is also the complicating factor of the variations in study design and data presentations; formula diets versus solid food; normalizations of data by total body weight, ideal weight, and fat-free weight; substitution of simple versus complex carbohydrates in studies of dietary fat quantity; and the use of subjects with various forms of hyperlipidemia and wide ranges of ideal body weights. What is clearly lacking in the data base for defining the effects of fat-modified diets on cholesterol and lipoprotein metabolism as related to dietary recommendations and the general public are studies using modest dietary interventions and normolipidemic subjects fed diets that mimic the types of diets presently consumed and recommended.

With the above-mentioned considerations in mind, and the limitations imposed on the available data by restricting it to "real life" dietary changes, Table 1 attempts to summarize the potential effects of a fat-modified diet on cholesterol and lipoprotein metabolism in normolipidemic subjects. It is clear that the most consistent benefit in terms of altering an atherogenic metabolic pattern is achieved by weight reduction of the obese individual. The metabolic changes achieved by reducing dietary cholesterol intake and total fat calories

and by increasing the P/S ratio are inconsistent and variable. Unfortunately, there is almost no data base to evaluate dietary effects of a complete fat-modified diet, within the ranges of a "prudent diet," on cholesterol and lipoprotein metabolism in either hyperlipidemic or normolipidemic subjects.

It is apparent that the biomedical community needs more information on the metabolic consequences of a fat-modified diet on cholesterol and lipoprotein metabolism in man in order to develop a model of the overall dynamics of these pathways and the potential benefits to be achieved by recommending

Table 1 Effects of a "real life" fat-modified diet on cholesterol and lipoprotein metabolism[a]

	Dietary intervention			
	Body weight	Dietary cholesterol	Fat P/S ratio	Fat calories
	Obese	450	0.45	40%
Metabolic	to	to	to	to
response	lean	<300	1.00	30%
Plasma level				
Cholesterol	0 to −	0	−	−
Triglyceride	−	0	0 to −	0
Synthesis				
Cholesterol	−	0 to −	0	0
Bile acids	0 to −	0 to +	0	+
Biliary cholesterol				
Flow	−	0 to +	?	+
Molar %	−	0	0	−
Biliary bile acids				
Flow	0	0	?	+
Molar %	0	0	0	+
VLDL-TG				
Synthesis	−	0	0	+
FCR	0	0	0	−
VLDL apoB				
Synthesis	-	0	−	0 to +
FCR	0	0	0	0 to −
LDL apoB				
Synthesis	+	0 to +	−	−
FCR	-	0 to −	0 to +	+
HDL				
Synthesis	?	?	−	0 to +
FCR	?	?	0	+

[a] + = Increase; 0 = no change; − = decrease; ? = unknown.

that the public alter its dietary pattern as a means of reducing mortality from cardiovascular disease.

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