Carbohydrate-induced hypertriglyceridemia: modifying factors and implications for cardiovascular risk

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High-carbohydrate/low-fat, isocaloric diets have repeatedly been shown to increase plasma triglyceride concentrations. The present review addresses recent developments relevant to several important unresolved issues. These include the type of dietary carbohydrate that is most likely to induce hypertriglyceridemia, predictors of individual susceptibility, modifiable physiologic factors that may mitigate the plasma triglyceride response, underlying metabolic mechanisms that are responsible for increased plasma triglycerides, and implications of altered serum lipid profiles for atherogenic risk. Although some progress has been made in this field, the central public health issue – the net effect on cardiovascular risk – remains unresolved. Curr Opin Lipidol 13:33–40. © 2002 Lippincott Williams & Wilkins.

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Abbreviations
BMI body mass index
CAD coronary artery disease

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0957-9672

Introduction
Carbohydrate-induced hypertriglyceridemia is among the key unresolved problems in contemporary public health nutrition. A central tenet of most dietary advice relating to lipids and cardiovascular disease risk for the past 40 years has been to reduce fat (and cholesterol) intake. However, diets that replace fat with carbohydrate isocalorically have been consistently observed to worsen certain elements of the plasma lipid profile (for review [1^*]). Moreover, some individuals or groups may be more susceptible than others to the adverse effects of high-carbohydrate/low-fat diets. The question must therefore be raised whether it might be more harmful than beneficial for such individuals to follow dietary recommendations for the general public. A clear understanding of the effects of high-carbohydrate diets on plasma lipids and cardiovascular risk is therefore essential. In addition to the potential health consequences of inappropriate dietary advice, confidence of the lay public in dietary recommendations may depend to a large extent on avoiding contradictory or confusing dietary pronouncements.

We recently reviewed the literature in this field up to the year 2000 [1^*], and noted several areas that remained unresolved and in which further work was needed. These included the form of carbohydrate most likely to induce hypertriglyceridemia (especially complex carbohydrate versus simple sugars, and the role of fructose); clinical predictors of carbohydrate-induced hypertriglyceridemia (i.e. who is susceptible?); physiologic factors that influence carbohydrate-induced hypertriglyceridemia (e.g. concurrent weight loss and exercise); the metabolic mechanisms that underlie the phenomenon; and, finally, atherogenicity and cardiovascular risk implications of carbohydrate-induced hypertriglyceridemia.

The present review focuses on these key questions, discussing primarily those reports that were published during the past 12–24 months. Although some insights have been gained, it is unfortunately true that most of the answers are still not known.

Role of different dietary carbohydrates in hypertriglyceridemia
Previous work led to a number of conclusions [1^*]. The increase in plasma triglyceride concentrations on increasing dietary carbohydrate is a consistent and reproducible
effect. Plasma triglyceride concentrations increase in a
dose-dependent manner, even after increases by as little
as 10% in dietary carbohydrate (i.e. there is no apparent
threshold for the effect). Simple sugars are worse
offenders than starches, and even modest changes in
the ratio of simple to complex carbohydrate (e.g. from
40%:60% to 60%:40%) can induce hypertriglyceridemia;
fructose-containing simple sugars may be the most
detrimental. Liquid diets are worse than solid food diets
for inducing hypertriglyceridemia. Finally, fiber tends to
mitigate the effects of high-carbohydrate diets.

Bantle et al. [2**] recently conducted a well-designed
study that compared isoenergetic fructose and glucose-
based high carbohydrate diets. Those investigators
reported that a 6-week diet containing 17% of energy
as fructose, as compared with a diet containing 17% of
energy as glucose, resulted in 32% higher day-long
plasma triglyceride concentrations in men. Surprisingly,
there were no differences between the two diets in
women. No differences were observed for plasma
apolipoprotein B or insulin concentrations between the
diets in men or women. Interestingly, postprandial
triglyceride effects of the fructose-based diet were
greater than effects on fasting triglyceride levels, which
is consistent with postulated direct effects of fructose on
hepatic triglyceride synthesis. Bantle et al. proposed that
differences from previous studies that failed to show
specific effects of fructose can be explained by study
design (e.g. previous comparison of fructose with
sucrose, use of outpatient menu, or supplements instead
of providing all meals to the participants).

Vidon et al. [3] evaluated the lower end of increased
carbohydrate intake. Those authors compared 55%
carbohydrate with 40% carbohydrate diets, using a
cross-over study design. Of note, the ratio of simple
sugar to complex carbohydrate was 40%:60% in both
high-carbohydrate diets, and both diets contained equal
proportions of saturated, monounsaturated and polyun-
saturated fatty acids. The authors reported no changes in
plasma triglyceride concentrations on the higher carbo-
hydrate diet, but did note improvements in LDL-
cholesterol, ratio of LDL to HDL, and oral glucose
tolerance tests with the higher carbohydrate diet. They
concluded that modest changes in dietary carbohydrate
without inclusion of simple sugars can result in broadly
beneficial effects on plasma lipids. Hudgins et al. [4*]
also showed that changing the ratio of simple sugar to
complex carbohydrate from 60%:40% to 40%:60% in
low-fat/high-carbohydrate diets prevents stimulation of
de-novo lipogenesis (see below).

In summary, recent work has strengthened the impor-
tance of the ratio of simple sugar to complex carbohy-
drate, and particularly the presence of fructose, in the
effects of high-carbohydrate/low-fat diet on plasma
triglycerides. The effects of fiber on blood lipid changes
have recently been reviewed in this journal [5] and are
not discussed here.

**Prediction of susceptibility to carbohydrate-induced hypertriglyceridemia**

An area of active investigation has been the search for
factors that identify predisposition to carbohydrate-
induced hypertriglyceridemia. Identifying such predic-
tors would be of obvious importance for individualized
diet prescription, as well as for improving our under-
standing of the pathogenesis or genetics of the
phenomenon. Research has generally focused on two
areas: presence of other cardiovascular disease risk
factors (obesity, insulin resistance, etc.); and presence
of genetically influenced lipoprotein patterns.

**Presence of other cardiovascular risk factors**

Parks et al. [6*] recently presented a statistical analysis of
baseline metabolic factors that predict carbohydrate-
induced hypertriglyceridemia. Their study was con-
ducted in patients with established coronary artery
disease (CAD) who were participating in a multifaceted
risk factor reduction trial that included the use of a very-
low-fat (10%) diet. Increases in plasma triglycerides of
10% or greater were observed in 20 out of 36
participants. Using discriminant function analysis, these
investigators identified three variables – body mass
index (BMI), fasting triglyceride concentrations, and
fasting insulin concentrations – as the best predictors of
increases in plasma triglyceride concentrations. People
with multiple risk factor syndrome are therefore most
likely to exhibit worse serum triglyceride levels on a
very-low-fat diet. However, the relationship to other
metabolic parameters, such as LDL-cholesterol, apo-
lipoprotein B concentration or body weight, were not
presented; therefore, an overall assessment of global
benefit or risk cannot be made from their model. It
should also be noted that Parks et al. used a very-low-fat
diet (10% fat). Nevertheless, the characteristics of those
who developed hypertriglyceridemia in response to the
diet were well defined by that study, and its findings are
consistent with those of prior work (e.g. increase in
serum triglycerides only in upper body obese, not lower
body obese, women when given a high carbohydrate diet
[7]).

**Presence of genetically influenced lipoprotein patterns**

Various workers have investigated the impact of
candidate genes on the response to dietary carbohydrate.
However, the impact of such factors, including apo-
lipoprotein E phenotype and apolipoprotein AI concen-
trations, has generally been small [8]. Recently, Erkkila et
al. [9] analyzed the impact of apolipoprotein E
polymorphisms on the plasma triglyceride response to
dietary sucrose in persons with established CAD. Increases in triglyceride levels were observed on high-sucrose diets only in those with the e2 allele. Those with the e2 allele also exhibited higher plasma triglyceride concentrations and lower LDL-cholesterol concentrations at baseline than did those with the e3 or e4 alleles. That study had limitations, however. It was a cross-sectional study and dietary intake was not controlled but was assessed by 4-day food records, with sucrose intake divided into tertiles. Moreover, these were patients with diagnosed CAD, who may have modified their diets before the study, thereby introducing potential bias.

Krauss and coworkers [10**,11–13] have published extensively on the role of LDL subclass patterns in predicting the response to dietary carbohydrate. Their observations are complex and worth reviewing in detail.

Several lines of evidence had indicated that small dense LDL particles (phenotypically manifested as subclass pattern B) have a significantly higher association with CAD than large buoyant LDL (pattern A) [10**]. Indeed, LDL particle size is among the most potent risk factors for CAD, conferring a threefold increased risk. The relationship between LDL subclass pattern and CAD is confounded, however, by strong correlations between subclass pattern and other CAD risks (e.g. insulin resistance, hypertriglyceridemia, low HDL). Although patterns A and B are clearly genetically influenced, penetrance may be 50% or less and the degree to which genetic control is primary or secondary (e.g. acting indirectly through changes in triglyceride metabolism) remains uncertain.

By way of providing further background, Dreon et al. [11–13] had previously reported that baseline LDL subclass pattern strongly influences the response to low-fat (20–24%) versus high-fat (40–46%) diets in healthy normolipidemic persons. In those studies the carbohydrate contained equal proportions of simple sugar and starch, and there were no differences in monounsaturates, cholesterol or fiber between diets. While on high-fat diets, men who started with the more benign pattern A showed less benefit from the low-fat/high-carbohydrate diet and prevalence of LDL subclass pattern B in a population: on 30% fat diets, pattern B has a prevalence of approximately 30% in adult males; on 10% fat diets, pattern B has a prevalence of approximately 60% in men.

The implication of these findings is that reducing dietary fat may be beneficial from the perspective of LDL-associated atherogenesis in people who start with high-risk LDL subclass patterns, but that consequences for lower risk people are ambiguous at best. Since the lower-risk pattern A group represents the majority of the population (70–90%, depending on gender and age), the potential public health nutrition implications of this model are substantial.

More recently, Dreon et al. [12] reported that further reductions in dietary fat (to 10%, from 20–24%) in men who had remained pattern A on the 20–24% fat diet further increased the number who converted to pattern B. Again, approximately one-third (12 out of 38) changed from pattern A to pattern B on the 10% fat diet. Notably, there was no further improvement in LDL-cholesterol in these 38 individuals as a whole, and in the subset who converted from pattern A to pattern B there was an increase in apolipoprotein B and triglyceride concentrations, along with a decrease in HDL. Moreover, a strong inverse correlation was observed between LDL particle size and triglyceride concentrations. Similarly, in a separate study, Dreon et al. [13] reported that children’s response to low-fat diets differs as a function of parental LDL subclass pattern. Offspring (both boys and girls) of two pattern B parents had higher likelihood of converting from pattern A to pattern B on a low-fat (10%) diet. Again, the implication was that high-carbohydrate/low-fat diets can bring out this potentially adverse LDL subclass pattern when a genetic predisposition exists. Krauss [10**] recently summarized these studies with a figure showing an inverse relationship between percentage carbohydrate in the diet and prevalence of LDL subclass pattern B in a population: on 30% fat diets, pattern B has a prevalence of approximately 30% in adult males; on 10% fat diets, pattern B has a prevalence of approximately 60% in men.

Several caveats should be noted. The presence of baseline LDL pattern B does predict a greater fall in LDL-cholesterol, but it also predicts a greater increase in serum triglyceride concentrations [10**]. Indeed, the fall in LDL correlates closely with the rise in triglycerides. Also, most studies have not shown changes in apolipo-
protein B in parallel with changes in LDL. This is important because many other studies suggest that particle number (reflected by apolipoprotein B concentration) is among the best predictors of CAD risk [14]. Finally, the atherogenicity of small dense LDL (pattern B) has only been evaluated in populations on Western, high-fat diets. Whether pattern B has the same atherogenic implications on high-carbohydrate diets remains unproved. This is especially uncertain because the risk of pattern B is strongly dependent on apolipoprotein B concentrations (i.e. on the quantity as well as quality of LDL, particles [10**]), but apolipoprotein B concentrations are less affected than are triglyceride concentrations by high-carbohydrate diets.

Thus, the LDL subclass pattern story leaves us with an exaggerated version of the original high-carbohydrate diet paradox. In pattern B persons the fall in LDL is greater, but the rise in triglyceride levels and drop in HDL are also greater; whereas in pattern A persons there is less fall in LDL and no fall in apolipoprotein B, but less increase in triglycerides; and the conversion of these latter individuals to pattern B has unproven atherogenic implications in this setting.

To sum up, individuals with the multiple cardiovascular risk factor syndrome (manifested in particular by obesity, hyperinsulinemia and hypertriglyceridemia) at baseline are more likely to experience worsening of plasma triglycerides on high-carbohydrate/low-fat diets, but the same group (manifested by LDL subclass pattern B) is most likely to improve features of their lipid profile related to LDL-cholesterol. The net consequences for cardiovascular risk therefore remain ambiguous.

Factors that influence carbohydrate-induced hypertriglyceridemia

The two modifiable physiologic factors that appear to have the greatest impact on the hypertriglyceridemic response to dietary carbohydrate are weight and exercise.

The impact of weight loss on the hypertriglyceridemic response to low-fat/high-carbohydrate diets has long been recognized as important and has led to debate concerning optimal experiment design. The study of Lichtenstein et al. [15], for example, clearly demonstrated that weight loss was required for high-carbohydrate/low-fat diets to improve the lipid profile (i.e. to decrease LDL-cholesterol without worsening triglyceride and HDL concentrations). Because most studies of switch from ad-libitum high-fat to ad-libitum low-fat diets have documented weight loss [1*], those investigators [15] criticized the use of a forced isocaloric high-carbohydrate/low-fat study design as artificial and unrepresentative of free-living physiology. This argument is convincing, although it is to some extent confounded by the observation that weight loss on low-fat diets may be greater during the transitional period (i.e. transiently, after switching from high-fat diets) than during the long term [1*]. Nevertheless, studies of long-term ad-libitum low-fat/high-carbohydrate diets have demonstrated persistent weight loss associated with no increase in serum triglyceride concentrations [16].

Little has recently been published in this important area, however. Raeini-Sarjaz et al. [17] did report results of some relevance. They compared the effects of a low-energy/low-fat diet (i.e. fat removed and not replaced) with those of a low-fat/high-carbohydrate/isocaloric diet (i.e. fat removed and replaced with carbohydrate). The former diet reduced plasma triglyceride concentrations by 23%, whereas the latter diet increased triglyceride by 23%. Both diets reduced total cholesterol concentrations. It was concluded that manipulation of dietary energy with accompanying weight loss resulted in greater benefit for serum lipids than did manipulation of fat without weight loss. In practice, however, achievement of weight loss remains an elusive goal when compared with prescription of altered diet macronutrient composition. The relevance of this study to public health nutrition is therefore uncertain.

Perhaps the most important but least well studied factor that influences the lipid response to dietary carbohydrate is exercise. It is surprising how little attention has been given to the effects of exercise, in view of two widely recognized observations: the dissonance between the international epidemiology (linking dietary fat intake to incidence of CAD in populations) and the potentially atherogenic lipid effects of low-fat/high-carbohydrate diets in the developed countries; and differences between activity levels among these populations.

A recent correspondence published in the American Journal of Clinical Nutrition is instructive in this context [18–20]. Gibney [18] stated that ‘... it seems somewhat defeatist to accept that given our sedentary lifestyles, high-carbohydrate diets should be recognized as disadvantageous because of their frequent, but not constant, association with elevated plasma triacylglycerol, low plasma HDL cholesterol and occasionally insulin resistance. These effects of high-carbohydrate diets are totally negated by moderate physical activity on the order of 30 minutes of accumulated brisk walking’ (p. 576). Willet responded [19] that ‘Gibney asserts that 30 minutes of brisk walking can totally negate the adverse metabolic effects of high-carbohydrate diets, but offers no evidence’ (p. 577).

Hardman [20] subsequently raised several arguments. First, endurance athletes have low plasma triglycerides
and high HDL concentrations, despite high percentage carbohydrate diets. Second, middle-aged men who began jogging, achieving an average of 12 miles per week, also increased carbohydrate intake from 39–44% of energy but improved HDL-cholesterol levels [21]. Third, in a randomized trial, Wood et al. [22] demonstrated greater reduction in triglyceride concentrations and greater improvements in HDL-cholesterol levels in both men and women who exercised for between 15 and 20 min/day, and followed a high-carbohydrate/low-fat diet as compared with those on high-carbohydrate/low-fat diet alone. Finally, Hardman argued that three bouts per day of 10 min walking reduced post-prandial lipemia in persons on a typical diet of Northern Ireland [23].

Clearly, more experimental data are needed that address this issue directly. Koutsari et al. [24] recently presented the results of a study that was small but nevertheless useful. Eight healthy postmenopausal women were challenged with a high-fat mixed meal after 3 days on either a high-fat diet (50% fat, 35% carbohydrate), a low-fat/high-carbohydrate diet (15% and 70%, respectively), or the low-fat/high-carbohydrate diet combined with 60 min/day brisk walking. Those investigators reported higher levels of plasma triglycerides in both the fasting (60% increased) and the post-prandial (35% increased) states following the high-carbohydrate diet. In addition, apolipoprotein B₄₈ and apolipoprotein B₁₀₀ concentrations were significantly increased following the high-carbohydrate diet. Exercise abolished or substantially mitigated all of these changes, however. Although this study was small and was carried out for only 3 days, it represents a model for future studies and supports the notion that exercise may be a potent mitigating factor in the hypertriglyceridemic response to dietary carbohydrate.

In summary, recent work has supported the hypothesis that concurrent modest exercise or weight loss may prevent the adverse effects of dietary carbohydrate on plasma lipids, but this critical area remains incompletely studied.

**Metabolic mechanisms responsible for carbohydrate-induced hypertriglyceridemia**

The metabolic mechanisms that underlie carbohydrate-induced hypertriglyceridemia remain unresolved [1•]. Hudgins et al. [4•] measured the synthesis of new fatty acids (de-novo lipogenesis) by two independent methods in obese and lean volunteers given 10% fat and 75% carbohydrate versus 30% fat and 55% carbohydrate diets. Both diets were relatively high in simple sugars (sugar:starch ratio 60%:40%). The study utilized a random-ized, cross-over design. Serum triglycerides increased significantly on the high-carbohydrate diet, to similar degrees in both lean and obese subjects, and the change in triglycerides was highly correlated with the stimulation of de-novo lipogenesis. There were no relationships between BMI, insulin or glucagon and de-novo lipogenesis or plasma triglyceride concentrations, however. Those authors concluded that high-carbohydrate/low-fat diets that are high in simple sugars stimulate fatty acid synthesis from carbohydrate, and that plasma triglyceride levels increase in proportion to the amount of fatty acid synthesis, suggesting a mechanistic link.

An important reason to compare the metabolic basis of hypertriglyceridemia induced by high-carbohydrate diets with that of hypertriglyceridemia on standard Western high-fat diets relates to their potential atherogenicity. If endogenous hypertriglyceridemia on high-fat diets carries an increased risk for cardiovascular disease [25], then it is more likely that carbohydrate-induced hypertriglyceridemia carries a similar risk if the underlying metabolic fluxes of lipoprotein particles are similar (i.e. if there is a similar metabolic and kinetic basis) than if these mechanisms differ [1•]. It is well established that hypertriglyceridemia on high-fat diets is a high-flux state that is characterized by increased production of VLDL-triglycerides and VLDL particles. The simplest question is therefore whether carbohydrate-induced hypertriglyceridemia is due to increased production or reduced clearance.

Recent publications have addressed this question, although with somewhat inconsistent results. Parks et al. [26] studied normolipidemic (plasma triglycerides 61 ± 7 mg/dl) and moderately hypertriglyceridemic (plasma triglycerides 149 ± 16 mg/dl) persons on sequential high-fat and low-fat/high-carbohydrate diets. The diets were 35% fat and 50% carbohydrate, and 15% fat and 68% carbohydrate, respectively, with 45% of carbohydrate as simple sugars in both diets.

After 5 weeks on high-carbohydrate/low-fat diets, plasma VLDL-triglyceride and VLDL-apolipoprotein B concentrations increased by approximately 60% in both groups, resulting in plasma triglyceride concentrations of 100 and 230 mg/dl in the baseline normolipidemic and hypertriglyceridemic groups, respectively [26]. Hepatic production of VLDL-triglycerides and VLDL-apolipoprotein B were measured using an endogenous labeling approach, by incorporation of infused stable isotope-labeled palmitate and leucine. On the high-fat diets, the baseline hypertriglyceridemic group exhibited more than twofold higher production rates of VLDL-triglycerides and apolipoprotein B than did the normolipidemic group, which is consistent with previous results. No differences in clearance rate or half-lives (VLDL-triglyceride half-life of approximately 1.5 h) were ob-
served. In contrast, the increase in VLDL-triglyceride concentrations and particle numbers on high-carbohydrate diets resulted from a different mechanism. The major effect of high-carbohydrate diet on VLDL-triglyceride kinetics was to reduce clearance and prolong half-life without any significant effects on production rate (although there was a nonsignificant 20% increase in the normolipidemic group). For VLDL-apolipoprotein B, mixed kinetic results were observed, with a modest 20–33% increase in VLDL-apolipoprotein B production rate (significant in the hypertriglyceridemic group) and a borderline-significant prolongation of plasma half-life in both groups. Surprisingly, significant elevations in fasting apolipoprotein B₄₈ concentrations were also observed on the low-fat/high-carbohydrate diet, reflecting a persistence of chylomicra 15 h following the last low-fat meal. This finding has since been confirmed independently [24**]. The presence of chylomicra in the fasting state might compete with VLDL-triglycerides for lipolysis and contribute to the reduced clearance of VLDL-triglycerides that was observed kinetically. Finally, the low-fat/high-carbohydrate diet reduced the metabolic contribution to VLDL-triglycerides from plasma-free fatty acids.

Parks et al. [26] concluded that the assembly, production and clearance of elevated VLDL-triglycerides in response to low-fat/high-carbohydrate diets differs from that associated with elevated triglycerides on higher fat diets. Assumption of a similar atherogenic risk for the two forms of hypertriglyceridemia may therefore be premature.

More recently, Mittendorfer and Sidossis [27*] also studied the kinetic basis of carbohydrate-induced hypertriglyceridemia. Six normolipidemic persons were studied after receiving a very-low-fat/high-carbohydrate diet (10% fat and 75% carbohydrate) or a very-high-fat/low-carbohydrate diet (55% fat and 30% carbohydrate), in a cross-over design for 2 weeks each. Simple sugars represented 47% of total carbohydrate on the high-carbohydrate diet and 40% on the high-fat diet. Plasma triglyceride concentrations were higher (80 mg/dl) on the high carbohydrate diet than on the high-fat diet (45 mg/dl). Those authors used a novel constant infusion technique to measure VLDL-triglyceride kinetics, involving reinfusion of VLDL that had been previously endogenously labeled. Triglyceride production was reported to be 65% higher on the high carbohydrate diet (0.76 versus 0.45 mg/kg per min) with no differences in clearance (1.5 ml/kg per min or a half-life of 15–20 min). Femoral artery and hepatic vein catheters were also placed, in order to estimate splanchnic uptake and oxidation of plasma ¹³C-labeled fatty acids. Marked decreases in plasma fatty acid appearance and whole-body oxidation of fat were observed, as well as reduced fractional oxidation of fatty acids taken up by splanchnic tissues (although total splanchnic uptake of nonoxidized fatty acids was not higher in the high carbohydrate diet group, at 27 versus 34 μmol/l). These authors concluded that the increase in plasma triglyceride concentrations on the high-carbohydrate diet was due to over-production, not reduced clearance, of VLDL-triglycerides.

It is of interest to compare the results of Mittendorfer and Sidossis [27*] with those of Parks et al. [26]. There are several differences in design and method that might account for the differing kinetic conclusions of those investigators. Mittendorfer and Sidossis [27*] compared more extreme diets (10% versus 55% fat) than did Parks et al. [26] (15% versus 35% fat); their dietary periods were for 2 weeks instead of 5 weeks; the normolipidemic persons had very low baseline triglyceride concentrations (45 mg/dl); and they did not measure apolipoprotein B kinetics. The methods for measuring VLDL-triglyceride kinetics also differed between the studies. The baseline values reported by Mittendorfer and Sidossis [27*] were 45 g triglycerides produced per day (as compared with 15 g/day by Parks et al. [26]) and a plasma half-life of 15–20 min (versus 1.5 h). These values represent much higher production rates and much shorter half-lives than most previous values reported in the literature, although this does not mean that their results are incorrect. Perhaps the most important differences between the studies is that kinetics in baseline hypertriglyceridemic persons on high-fat diets were not compared with those in carbohydrate-induced hypertriglyceridemia by Mittendorfer and Sidossis [27*]. Since this comparison was the central point of the study by Parks et al. [26], it is difficult to ascertain whether systematic methodologic or experimental design differences would have affected the comparison with high-fat-associated hypertriglyceridemia.

The metabolic consequences of surplus carbohydrate calories (i.e. overfeeding with carbohydrate), as opposed to isocaloric high-carbohydrate/low-fat diets, have recently been reviewed [28] and are not discussed here.

In summary, it is reasonable to conclude that high-carbohydrate diets can influence both production and removal of plasma VLDL-triglycerides, depending on the experimental conditions, but that underlying fluxes of VLDL-triglyceride particles and their potential atherogenicity may well differ between high-carbohydrate and high-fat forms of hypertriglyceridemia.

### Atherogenicity of carbohydrate-induced hypertriglyceridemia

Unfortunately, little other evidence concerning the atherogenicity of carbohydrate-induced hypertriglyceri-
Carbohydrate-induced hypertriglyceridemia

Carbohydrate-induced hypertriglyceridemia has recently been reported. Bergland et al. [29] compared HDL subpopulations during stepwise reductions in dietary fat, as part of the Dietary Effects on Lipoproteins and Thrombogenic Activities study [30]. Normolipidemic men and women were placed on diets containing 34% fat (15% saturated fat), 29% fat (9% saturated) and 25% fat (6% saturated), given for 8 weeks each. Concentrations of HDL\textsubscript{2}, the subfraction associated with reduced cardiovascular disease risk epidemiologically, fell in a stepwise manner as dietary fat was reduced (from 0.58 to 0.53 to 0.48 mmol/l). HDL\textsubscript{2} concentrations correlated inversely with serum triglyceride concentrations. HDL\textsubscript{3} concentrations were less adversely affected by reduction in dietary fat and did not correlate inversely with triglyceride concentrations. Those authors concluded that lowering dietary fat and saturated fat reduces the concentration of the most prominent antiatherogenic HDL subclass. LDL-cholesterol concentrations also fell in that study [30], as is typically observed [1\textsuperscript{st},10\textsuperscript{th}]. The ratio of LDL-cholesterol to HDL-cholesterol therefore remains relatively constant, on average, in a group that switches from high-fat to high-carbohydrate/low-fat diet. What this means for net cardiovascular risk remains a matter of speculation.

Earlier studies had also documented the potentially adverse effects of low-fat/high-carbohydrate diets on risk factors for cardiovascular disease in healthy populations. Jeppesen et al. [31], for example, compared a 25% fat/60% carbohydrate diet with a 45% fat/40% carbohydrate diet for 3 weeks in postmenopausal women. Both diets contained ratios of sugar to starch of 1:2. Fasting plasma triglyceride and VLDL-triglyceride concentrations were 50% higher and HDL concentrations were lower on the high-carbohydrate diets. Postprandial plasma triglyceride and insulin concentrations were also higher, and retinyl-palmitate clearance was delayed on the high-carbohydrate diet. Baseline resistance to insulin-mediated glucose disposal, a measure of insulin resistance, correlated with the increases in postprandial triglycerides, insulin, glucose and retinyl-palmitate concentrations, suggesting that the adverse metabolic effects of this diet related to the degree of insulin resistance present. Not all studies have reported similar adverse effects on cardiovascular risk factors, however. Vidon et al. [3], for example, reported improved oral glucose tolerance on high-carbohydrate diets.

The effects of high-carbohydrate/low-fat diets on LDL subclass patterns are discussed above. As noted, the population most likely to experience the greatest increase in plasma triglyceride concentrations is probably the same as, or overlaps with, the group that is most likely to benefit in terms of LDL particles. The net atherogenic effect and implications for cardiovascular risk cannot therefore easily be judged, even though subclass pattern clearly stratifies plasma lipid response.

In summary, this most critical question relating to carbohydrate-induced hypertriglyceridemia remains unanswered in essentially all of its most fundamental aspects.

Conclusion

What do we know about carbohydrate-induced hypertriglyceridemia, and what do we not yet know? Some conclusions appear firm. Simple sugars (especially those containing fructose) are clearly worse offenders with regard to hypertriglyceridemia than are complex carbohydrates (starches). Indeed, it is fair to say that the best established metabolic disturbance attributable to dietary sugar intake relates to plasma lipids, not plasma glucose. Also, the plasma lipid response to high-carbohydrate/low-fat diets reflects the baseline state that is present on high-fat diets; namely, the higher the baseline triglyceride concentration, the worse the response in triglyceride/HDL axis; whereas the higher the baseline LDL and the more atherogenic the baseline LDL subclass pattern, the better the response in the LDL-cholesterol/apolipoprotein B axis.

Other conclusions are less firm, although no less important to resolve. Concurrent moderate exercise may prevent the worsening of triglyceride and HDL-cholesterol concentrations. Weight loss may have a similar mitigating effect on carbohydrate-induced hypertriglyceridemia. Indeed, energy balance and sedentary lifestyle may be as important as the ratio of carbohydrate to fat in determining the triglyceride response to high-carbohydrate diets.

The most important question is unfortunately also the least well understood. Recent results have not clarified the central ambiguity in this field; namely, are the changes observed while on high-carbohydrate/low-fat diets beneficial or deleterious with regard to cardiovascular risk? The paradox of improvements in some measures at the same time as worsening of other measures leaves the net effect open to controversy. Moreover, the atherogenic significance of biomarkers established as risk factors through epidemiologic studies in populations on high-fat diets cannot be assumed to apply identically in the high-carbohydrate/low-fat dietary setting. We may need new biomarkers of atherogenic risk, or new rules for interpreting lipid parameters, when considering populations on high-carbohydrate/low-fat diets. Recent mechanistic studies that suggest different underlying lipoprotein fluxes in hypertriglyceridemia associated with high-carbohydrate diets as compared with that associated with high-fat diets only provide indirect evidence in this regard. Direct testing of
atherogenicity and cardiovascular outcomes related to carbohydrate-induced hypertriglyceridemia is among the highest priorities in contemporary public health nutrition.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
•• of outstanding interest

1 Parks E, Hellerstein M. Effects of low-fat, high carbohydrate diets on serum lipids in humans: a review of the literature. Am J Clin Nutr 2000; 71:412–433. The literature in this field is reviewed in some detail, and the central unanswered questions (many of which are discussed in the present review) are summarized.

2 Bantle J, Raatz S, Thomas W, Georgopoulos A. Effects of dietary fructose on plasma lipids in healthy subjects. Am J Clin Nutr 2000; 72:1129–1134. This well-designed study affirms the role of fructose in adverse effects on plasma triglyceride concentrations. The sex-dependent effect (triglyceride increase observed only in men) needs to be followed up. The greater impact on postprandial triglyceride than on fasting triglyceride concentrations is also important.


4 Hidgins L, Hellerstein M, Seidman C, et al. Relation between carbohydrate-induced hypertriglyceridemia and fatty acid synthesis in lean and obese subjects. J Lipid Res 2000; 41:595–604. This study confirms that simple sugars are required for induction of hepatic de novo lipogenesis by high-carbohydrate diets. Moreover, plasma triglycerides increased in proportion to the amount of fatty acid synthesis, suggesting a mechanistic link.


24 Koutsari C, Karpe F, Humphreys S, et al. Exercise prevents the accumulation of triglyceride-rich lipoproteins and their remnants seen when changing to a high-carbohydrate diet. Arterioscler Thromb Vasc Biol 2001; 21:1520–1629. Although this was a small study with a very short intervention period (3 days), the ability of 60 min moderate exercise per day to prevent or mitigate both hyperglyceridemia (lasting as well as postprandial), and increases in apolipoprotein B48 and apolipoprotein B100 was impressive.


