

Carbohydrate-induced hypertriacylglycerolemia: historical perspective and review of biological mechanisms¹⁻³

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ABSTRACT Current trends in health promotion emphasize the importance of reducing dietary fat intake. However, as dietary fat is reduced, the dietary carbohydrate content typically rises and the desired reduction in plasma cholesterol concentrations is frequently accompanied by an elevation of plasma triacylglycerol. We review the phenomenon of carbohydrate-induced hypertriacylglycerolemia, the health effects of which are among the most controversial and important issues in public health nutrition today. We first focus on how seminal observations made in the late 1950s and early 1960s became the basis for subsequent important research questions and areas of scientific study. The second focus of this paper is on the current knowledge of biological mechanisms that contribute to carbohydrate-induced hypertriacylglycerolemia. The clinical rationale behind mechanistic studies is this: if carbohydrate-induced hypertriacylglycerolemia shares a metabolic basis with endogenous hypertriacylglycerolemia (that observed in subjects consuming high-fat diets), then a similar atherogenic risk may be more likely than if the underlying metabolic mechanisms differ. The third focus of the paper is on both the positive metabolic changes that occur when high-carbohydrate diets are consumed and the potentially negative health effects of such diets. The review concludes with a summary of some important research questions that remain to be addressed. These issues include the level of dietary carbohydrate that induces carbohydrate-induced hypertriacylglycerolemia, whether the phenomenon is transient or can be avoided, whether *de novo* lipogenesis contributes to the phenomenon, and what magnitude of triacylglycerol elevation represents an increase in disease risk. *Am J Clin Nutr* 2000;71:412–33.

KEY WORDS Review, carbohydrate, diet, triacylglycerols, VLDL, *de novo* lipogenesis, fat intake, hypertriglyceridemia, hypertriacylglycerolemia

INTRODUCTION

Hypertriacylglycerolemia observed with high-fat and low-fat, high-carbohydrate diets

The influence of high blood triacylglycerol concentrations on coronary artery disease risk has been the subject of intense study for the past 4 decades. In 1955 Buzina and Keys (1) observed that elevated serum triacylglycerol concentrations accelerated blood clotting. Shortly thereafter, Albrink and Man (2) and Carlson and

Bottiger (3) reported that the incidence of clinical atherosclerosis correlated better with fasting triacylglycerol concentrations than with serum cholesterol concentrations. However, in 1963 Keys and Blackburn (4) discounted this view for 2 reasons: 1) the results were obtained on the basis of estimation of triacylglycerol concentrations by difference, in which multiple errors were incorporated in the final value, and 2) analytic error. This discourse fueled further study of the production and metabolism of triacylglycerol-rich lipoprotein (TRL) particles and their effects on health.

The debate over the contribution of triacylglycerol elevation to the development of coronary artery disease has continued (5, 6), although the results of recent research, including a meta-analysis (7), support the significance of the association between blood triacylglycerol concentrations and increased atherosclerotic risk (8–10). These conclusions were drawn from data collected in large-scale clinical trials in which the average dietary fat intake was 30–40% of energy (11, 12). Whether endogenous hypertriacylglycerolemia (HPTG) with higher-fat diets increases atherosclerotic risk is not the focus of the current review, nor is the increased risk associated with low concentrations of HDL cholesterol that occur when triacylglycerols are elevated (13). Rather, the present discussion concerns a possible increase in heart disease risk when triacylglycerol concentrations are elevated as a result of lowered dietary fat and increased dietary carbohydrate. We focus on the metabolic mechanisms that lead to carbohydrate-induced HPTG because an understanding of these mechanisms may help determine whether these elevations in triacylglycerols actually increase risk. Indeed, with the current increased commercial availability of low-fat foods, this question has become an important issue in public health nutrition (14–20).

For the purpose of this review, a research diet will be termed “low-fat, high-carbohydrate” (LF-HC) if $\leq 30\%$ of the total energy was derived from fat, $\geq 55\%$ of energy was derived from

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carbohydrate, or both. This categorization is based on the fat intake recommended in the American Heart Association's Step I diet (<30% of total energy from fat) and what is viewed as a significant deviation from the average fat intake of the general population (assessed recently as 33% of energy in the Continuing Survey of Food Intakes by Individuals and the National Health and Nutrition Examination Survey; US Department of Agriculture statistics, 1994–1996). The macronutrient composition of study diets will be described as the percentage of energy from protein, followed by the percentages of energy from fat and carbohydrate. An example of this notation is 15:40:45. When available, the type of carbohydrate fed (defined by molecular size as follows: simple sugars, oligosaccharides, or polysaccharides) will also be noted, as well as whether the research diet was composed of liquid or solid foods.

Lipoprotein fractions are frequently referred to in the early literature in Svedberg units (S_f). This unit is a measure of flotation rate and can be thought of as a way of partitioning lipoprotein particles of various densities. The bulk of blood triacylglycerol is carried in 2 lipoprotein particles: chylomicrons and VLDL particles. Chylomicrons ($S_f > 400$), which are produced by the intestine, contain a major protein [apolipoprotein (apo) B-48] and carry triacylglycerol derived from ingested fat (and therefore are low in concentration in the blood during the fasting state). VLDL particles (S_f : 20–400), which are produced by the liver, contain apo B-100 and carry endogenous triacylglycerol (that which has already been assimilated or made by the body). The complete separation of the 2 TRLs from plasma is difficult because their sizes and buoyant densities overlap. Furthermore, analytic ultracentrifugation has been used to show that 20–50% of blood triacylglycerol can be carried in remnants of VLDL called intermediate-density lipoproteins (IDLs) (21). In the current literature, the acronym *TRL* is used because both chylomicrons and VLDL are isolated at $d < 1006$ g/L. In the fasting state, chylomicron concentrations should be negligible, so some early researchers referred to all particles isolated from fasting plasma at a density (d) < 1006 g/L as VLDL only. However, the consumption of LF-HC diets can be associated with elevations in fasting concentrations of VLDL, IDL, and chylomicrons, as will be described later in this review.

Identification of carbohydrate-induced HPTG

In the 1950s, carbohydrate-induced HPTG was observed during research studies in which dietary manipulations were aimed primarily at reducing blood cholesterol (22–27). To reduce serum cholesterol concentrations experimentally, the percentage of energy from dietary fat was reduced and the bulk of the energy was replaced by carbohydrate. As early as 1950, Watkin et al (22) observed that certain patients exhibited a “lipemia” with severe restriction of dietary fat intake.

In 1957 Ahrens et al (25) investigated the chemical composition of dietary fat and its effects on serum lipids. Their study is representative of much of the work published at this time in that it included a small subset of subjects ingesting LF-HC diets (4 persons who were both hypercholesterolemic and hypertriacylglycerolemic), used liquid-formula diets (casein and milk provided the protein and maltodextrins the carbohydrate), and was designed primarily to test the effect of dietary fat composition (lard, corn, and coconut oils) on serum cholesterol concentrations. Fortunately, the studies of Ahrens et al (25) included, along with the HF test diets (15:40:45), a LF-HC diet (15:10:75).

When subjects consumed the LF-HC diet for 6 wk, their triacylglycerol concentrations rose significantly, from 1.13–2.26 mmol/L (100–200 mg/dL) to as high as 8.58 mmol/L (760 mg/dL). The authors described 2 forms of primary hyperlipidemia, separable in part by the response to HC diets. In “fat-induced lipemia,” plasma clears as a result of dietary fat reduction, whereas in “carbohydrate-induced lipemia,” grossly visible lipemia is maintained when subjects are switched to LF-HC diets. Carbohydrate-induced lipemia was proposed as principally HPTG that “is a common phenomenon, especially in areas of the world distinguished by caloric abundance and obesity” (26).

In 1959 Kuo and Carson (27) studied diurnal triacylglycerol concentrations in 10 subjects who each consumed 3 formula diets: a HF diet (16:45:48), a HC diet (15:2:83), and a high-polyunsaturated-fat diet (15:60:25). These investigators were the first to comment on the relatively consistent triacylglycerol concentrations over a 24-h period (a flat curve) in subjects consuming diets extremely high in carbohydrate. They wrote, “The fruit and rice diet shows no marked postabsorptive fluctuations.” The beginning of a paradox of carbohydrate-induced HPTG was recognized: Why is it that meals low in fat, despite eliciting lower postprandial triacylglycerol curves, result in higher fasting triacylglycerol values when fed chronically?

In their now classic study, Antonis and Bersohn (28) switched the diet of South African prisoners from HF (15:40:45) to LF-HC (15:15:70). The change to HC feeding elevated triacylglycerol concentrations, which reached a maximum of about double the starting value after 3–5 wk and then declined after 3–6 mo. At the end of 8 mo, nearly all subjects had values similar to those at the beginning of the study. Thus, this study provided a second important research question regarding carbohydrate-induced HPTG: Is the HPTG effect transitory? The answer to this question is clearly relevant to the atherogenicity of this form of HPTG.

Throughout the 1960s, several investigators observed carbohydrate-induced increases in plasma glycerides in patients with elevated cholesterol, triacylglycerols, or both (26, 29–37). Interest in the topic was further stimulated when seemingly contradictory population data became available showing the low incidence of atherosclerotic disease in people who subsisted on diets in which carbohydrate was the major source of energy. Epidemiologic studies provided abundant evidence that in the rice-eating populations of the world, in which 85% of dietary energy is derived from mono- and polysaccharides, HPTG is rare (38–40). Fasting triacylglycerol concentrations in free-living populations accustomed to consuming $\geq 65\%$ of energy from carbohydrate were not higher than those in Western populations (38–40). These observations highlighted the importance of other environmental, lifestyle, and possibly genetic factors in modulating the lipid response to carbohydrate feeding and began to fuel the controversy of whether a net benefit was provided by LF-HC diets. Another highlight of the early research in this area was the emergence of lipoprotein turnover studies.

In 1965 Farquhar et al (41) validated the measurement of hepatic and plasma triacylglycerol turnover by studying the decay of radioactively labeled glycerol and palmitic acid. These investigators were among the first to apply mathematical modeling techniques to the investigation of lipoprotein kinetics in humans, an area of research that became quite active first with radioactive molecules and then with stable isotopes. Since this time, hepatic production of VLDL particles has been measured in several ways. The fatty acid moiety of triacylglycerol, the



TABLE 1
Mean triacylglycerol (TG) concentration before and after 4 d of a nonfat, liquid diet of sugars¹

Subject classification	Lipoprotein characteristics	TG before diet	TG after diet	Percentage change
		mmol/L [mg/dL]	mmol/L [mg/dL]	%
Young (<i>n</i> = 13)	Normolipidemic	0.71 (0.45–0.85) [63 (40–75)]	1.37 (0.47–2.78) [121 (42–246)]	93
Middle-aged (<i>n</i> = 10)	Normolipidemic	0.94 (0.35–1.14) [83 (31–101)]	2.08 (1.08–4.00) [184 (96–354)]	121
Type IIa/b lipoproteinemia (<i>n</i> = 8)	VLDL, ² LDL, ² ↑TC, ↑TG	1.59 (0.75–2.38) [141 (66–211)]	2.92 (1.65–3.43) [259 (146–304)]	84
Type III lipoproteinemia (<i>n</i> = 14)	IDL, ² ↑TC, ↑TC	4.13 (1.76–9.00) [366 (156–797)]	8.96 (3.07–12.29) [795 (272–1089)]	117
Type IV lipoproteinemia (<i>n</i> = 20)	VLDL, ² ↑TG	3.16 (1.22–6.91) [280 (108–612)]	6.16 (2.22–11.47) [546 (197–1016)]	95
Type V lipoproteinemia (<i>n</i> = 9)	VLDL, ² Chylos, ² ↑TC, ↑↑TG	17.50 (0.79–65.72) [1550 (70–5821)]	17.65 (1.29–38.12) [1563 (114–3376)]	0

¹ \bar{x} ; range in parentheses. TC, total cholesterol; IDL, intermediate-density lipoprotein; Chylos, chylomicrons. Adapted from Glueck et al (37).

²Primary lipoprotein particles that are elevated in the fasting state in this form of endogenous hyperlipidemia.

glycerol backbone, or the apo B moiety can all be labeled isotopically to determine the kinetics of the VLDL particle or its components. Numerous studies of VLDL turnover were designed to determine whether carbohydrate-induced HPTG resulted from an overproduction of triacylglycerol or a decrease in clearance of triacylglycerol from the blood.

In the latter part of the 1960s and through the 1970s, many studies of carbohydrate effects on triacylglycerol metabolism focused on further defining factors that influence carbohydrate-induced HPTG. These areas of investigation included the various proportions of dietary carbohydrate, the time course of the effect, the influence of mono- or disaccharides as opposed to oligo- and polysaccharides, and the effect of dietary carbohydrate on insulin resistance.

FACTORS AFFECTING TRIACYLGLYCEROL RESPONSE TO LF-HC FEEDING

This section describes factors that affect the triacylglycerol response to LF-HC feeding. These factors have been identified from studies that substituted dietary carbohydrate with fat isoenergically, keeping protein constant. As will be described later in this review, more recent research has highlighted factors that limit the magnitude of carbohydrate-induced HPTG, such as the tendency for subjects to voluntarily reduce their food intake, which is followed by weight loss. It should be kept in mind, however, that for all of the studies described in this section, efforts were made to maintain subject body weight. Usually, subject body weight was monitored and dietary energy increased if a subject was losing weight during the study.

How low does fat have to be? How high does carbohydrate have to be?

Decreasing fat without increasing carbohydrate (ie, replacing dietary fat with protein) does not appear to elevate triacylglycerol (42). This suggests that it is the addition of carbohydrate, not the removal of fat, that is associated with HPTG in persons consuming LF-HC diets. Carbohydrate-induced HPTG was shown to occur when dietary fat was as high as 30% of energy (43). Weisweiler et al (44) stated that replacing as little as 10% of the fat with carbohydrate profoundly altered the components of VLDL. This repre-

sents a switch from a HF diet (15:35:50) to a HC diet (15:25:60). An overview of the literature suggests that a dietary change from 15:40:45 to 15:35:50 is usually not sufficient to cause carbohydrate-induced HPTG unless the HC diet is fed as a liquid formula high in monosaccharides (43). In general, the greater the increases in dietary carbohydrate (and the greater the reduction in fat), the greater the increase in triacylglycerol (45). Furthermore, the greater the dietary change, the greater the percentage of subjects that will have elevated triacylglycerol concentrations (46).

What is the magnitude and time course of the effect?

Investigators have reported that the triacylglycerol response is highly variable among subjects consuming diets high in carbohydrates (30, 37, 47). For example, Glueck et al (37) studied healthy persons with mean triacylglycerol and cholesterol concentrations of 0.78 mmol/L (69 mg/dL) and 4.27 mmol/L (165 mg/dL), respectively (37). The responses of these subjects are representative of many other studies of healthy subjects (48–50). Persons with fasting triacylglycerol concentrations <1.13 mmol/L (100 mg/dL) experienced absolute elevations of 0.5–1.14 mmol/L (40–101 mg/dL) after 4 d of a liquid HC diet (Table 1). The carbohydrate-induced HPTG only rarely resulted in triacylglycerol concentrations >2.26 mmol/L (200 mg/dL). Also presented in Table 1 are data for subjects with various forms of hyperlipidemia (ie, those who had elevated triacylglycerols, cholesterol, or both). In 72 of 75 subjects studied, dietary change produced or exacerbated the HPTG, with the exception of patients with type V hyperlipoproteinemia, whose responses varied greatly (30, 37). Persons with type II a/b, III, and IV lipoproteinemia can experience absolute elevations in triacylglycerol of >2.26 mmol/L (200 mg/dL). Although attempts have been made to identify subject characteristics [eg, baseline lipid concentration, age, and body mass index (BMI)] that will reliably predict the degree of triacylglycerol elevation, these efforts have been met with only partial success.

One important but not completely answered question relates to the adaptability of humans to LF-HC diets. How long it takes for carbohydrate-induced HPTG to develop depends on the concentration of dietary carbohydrate fed, the kind of carbohydrate fed (mono- or polysaccharide), the physical form of the diet (liquid or solid), and the presence of fiber in the diet. The type



TABLE 2
Effect of different sugars on triacylglycerol (TG) concentration¹

	Starch (n = 6)	Sucrose (n = 6)	Liquid glucose (n = 6)	Maltose (n = 5)	Glucose (n = 6)
Baseline TG					
(mmol/L)	1.86 ± 0.20	1.67 ± 0.09	1.70 ± 0.24	1.68 ± 0.17	1.92 ± 0.32
(mg/dL)	165 ± 18	148 ± 8	151 ± 21	149 ± 15	170 ± 28
Dietary TG ²					
(mmol/L)	1.95 ± 0.30	2.19 ± 0.27 ³	1.75 ± 0.35	1.58 ± 0.21	1.70 ± 0.42
(mg/dL)	173 ± 27	194 ± 24 ³	155 ± 31	140 ± 19	151 ± 37

¹ $\bar{x} \pm \text{SEM}$. Adapted from MacDonald (56).

²After 5 d of consuming the prepared diets.

³Significantly different from baseline, $P < 0.05$.

of dietary carbohydrate may be more important than the amount of carbohydrate. Indeed, Glueck et al (37) fed monosaccharide-containing diets devoid of fat and found in 40 of 60 subjects that peak triacylglycerol concentrations occurred before 7 d of carbohydrate feeding. Similar findings were observed by Lees and Fredrickson (47). By contrast, Kuo and Bassett (32) fed whole-food, LF-HC diets (15:2:82) and found that most subjects' triacylglycerol concentrations stabilized in 4–6 wk. However, the triacylglycerol concentrations of 2 subjects took as long as 10–18 wk to stabilize.

In a recent investigation of 42 patients with type 2 diabetes, Garg et al (51) compared two 6-wk isoenergetic dietary phases in a randomized crossover study. Both diets, a high-monounsaturated-fat diet (15:45:40) and a HC diet (15:30:55), contained similar contents of sucrose (10% of energy) and fiber (11 and 15 g/d for the HF and HC diets, respectively). The mean fasting triacylglycerol concentration of subjects consuming the HF diet was 1.91 ± 0.82 mmol/L (169 ± 73 mg/dL), which was significantly lower than that of subjects consuming the HC diet (2.27 ± 0.98 mmol/L, or 201 ± 87 mg/dL). Half of the subjects consumed the HF diet first, followed by the HC diet. In an extension of the study, a subset of these subjects continued to consume the HC diet for an additional 8 wk (ie, HC feeding for 14 wk total). Carbohydrate-induced HPTG did not resolve after the additional 8 wk (average triacylglycerol concentration: 2.30 ± 1.10 mmol/L, or 204 ± 97 mg/dL). Indeed, the SD of the triacylglycerol concentration was higher at 14 wk, suggesting greater variability among the subjects as the study went on. Thus, in the isoenergetic situation, the mean triacylglycerol concentration remained elevated for at least several months while HC diets were consumed.

Effects of monosaccharides and polysaccharides

The induction, or exaggeration, of HPTG by feeding different forms of carbohydrates was emphasized by Kuo and Bassett (32), who performed tightly controlled, metabolic ward feeding studies in which a diet (21:28:51) was fed to 5 atherosclerotic patients and 2 hypercholesterolemic, normotriacylglycerolemic boys aged 9 and 18 y. Dietary carbohydrate as starch improved, and dietary sugar aggravated, the HPTG in the patients and induced HPTG in the boys. Because of changes in the composition of the fatty acids in plasma lipids, the authors speculated that sugar-induced HPTG arose primarily from active endogenous lipogenesis. This study not only emphasized the differences between the various forms of carbohydrate (monosaccharides compared with starch), but also raised the question of whether dietary carbohydrate is converted to fat in humans.

Several groups examined the effect of exchanging starches for sugars on serum triacylglycerol concentrations in healthy persons whose triacylglycerol and cholesterol concentrations are not elevated with ad libitum diets (32, 52, 53). MacDonald (54–57) published numerous short-term studies in which groups of subjects were switched from self-selected (presumably HF) diets to those in which $\approx 70\%$ of the energy was either uncooked cornstarch, mono- and disaccharides, or mixtures of the 2. Practically no fat was fed over the 5-d dietary periods (Table 2). Of the 5 sugars fed, only sucrose elevated triacylglycerol significantly.

These important early findings with nonfat diets are supported by later studies that included dietary fat. Hodges and Krehl (33) and Hirsch (58) conducted a series of experiments in which high-starch and high-sugar diets were fed alternately to groups of 4–8 healthy subjects living in a metabolic unit. Switching from a starch-based diet (18:15:67; 13% of energy from sugars and 54% from carbohydrate from cereals, vegetables, breads, and fruit) to a sugar-based diet (13:15:72; 58% of energy from sugars, syrups, preserves, and jellies) significantly elevated triacylglycerol from 1.29 to 2.07 mmol/L (114 to 183 mg/dL). The authors reasoned that triacylglycerol was elevated because large amounts of sugar may have been absorbed so rapidly from the intestine that the normal pathways for carbohydrate metabolism were overloaded. Thus, other metabolic pathways (eg, the hexose monophosphate shunt) were used that may favor the synthesis of fatty acids. Most of the triacylglycerol-raising effects of sucrose were attributed to its content of fructose (46). Indeed, it is now widely believed that in humans the metabolism of large amounts of fructose increases the synthesis of triacylglycerol and its release into the plasma in VLDL (59).

Numerous studies have shown that the hypotriacylglycerolemic effects of whole foods are influenced by the fiber content of the diet (60, 61). The beneficial effects of fiber were well documented in key studies showing that the fiber source (eg, legumes, grain, fruit, or vegetables) is an important factor in moderating carbohydrate-induced HPTG (62, 63). Because the most pronounced influences of dietary fiber are exerted in the fed state (60, 64), these findings suggest that studies of postprandial metabolism should be encouraged to investigate the influence of fiber on carbohydrate-induced HPTG.

The effect of various sugars on lipid metabolism remains an extremely active area of inquiry. Several recent reviews applicable to this topic can be found in the proceedings of a 1994 workshop titled the Nutritional and Health Aspects of Sugars. Included in the proceedings are comprehensive reviews of sugars and lipid metabolism (46), weight regulation (65), and blood glucose control (66). In summary, if the carbohydrate content of



a HC diet is primarily made up of monosaccharides, particularly fructose, the ensuing HPTG is more extreme than if oligo- and polysaccharides are fed (46). Purified diets, whether based on starch or monosaccharides, induce HPTG more readily than diets higher in fiber in which most of the carbohydrate is derived from unprocessed whole foods.

Is carbohydrate-induced HPTG associated with changes in insulin sensitivity?

A seminal study of the effect of dietary carbohydrate on glucose tolerance was published in 1935 by Himsworth (67), who reported improved glucose tolerance after daily carbohydrate intakes of 63% and 75% of energy in healthy subjects. Others reported similar findings (68–71). Significant reductions in fasting blood glucose and insulin, and improvements in results on oral-glucose-tolerance tests, were observed in 9 healthy control subjects and 13 patients with mild diabetes after they had consumed a HC (15:0:85) liquid formula diet (a mixture of dextrans and maltose) for 10 d (71). The investigators concluded that the critical determinant in the effect of HC feeding was the presence of available insulin of either endogenous or exogenous origin. Leclerc et al (72) reported no change in glucose tolerance in 7 healthy subjects switched from a HF diet (25:30:45) to a HC diet (25:11:64) for 1 wk. The HC diet consisted of whole foods (the starch was derived primarily from fruit, bread, and rice). Although direct measurements of insulin sensitivity were not made, these investigators concluded, “unless dramatic changes are introduced, glucose tolerance and substrate oxidation are not affected by increasing carbohydrate-derived energy in the diet of normal men and women.”

In an oft-cited study by Knittle and Ahrens (30), diabetic and healthy control subjects consumed very HF (15:70:15), typical Western (15:40:45), and HC liquid formula (15:0:85; glucose provided 100% of the carbohydrate) diets under metabolic ward conditions. The goal was to investigate changes in insulin action and glucose metabolism after an intravenous dose of tolbutamide, an insulin secretagogue. Although true paired comparisons during HC and HF feeding were available for only 3 subjects for insulin data and 5 subjects for glucose curves, these limited data support the conclusion that carbohydrate induction worsened glucose metabolism in sensitive individuals. However, the investigators' conclusions should be considered in light of the small sample size and the fact that the HC diet was a liquid formula. The baseline triacylglycerol concentrations of the subjects included in the paired comparison were high (2.3–52 mmol/L, or 200–4600 mg/dL), suggesting extreme dietary responsiveness.

A recent review by Daly et al (73) reported no worsening of blood glucose concentrations with HC diets if the subjects were healthy and not overweight. The strongest evidence that HC diets worsen glucose metabolism was generated in studies of diabetic and insulin-resistant subjects conducted by Reaven (18). Whether LF-HC diets are appropriate for persons with type 2 diabetes is still quite controversial (74) and will not be discussed here.

In summary, the results of studies of the effect of HC feeding on glucose metabolism in healthy subjects are conflicting, primarily because the HC diets contained different quantities and types of sugars. These studies have shown, however, that higher postprandial glucose concentrations do not result in higher fasting glucose concentrations. Whether chronic elevations in postprandial glucose concentrations lead to insulin resistance in the long run is unknown and is important to determine.

Which lipoprotein particles are elevated in carbohydrate-induced HPTG?

As described above, different classes of TRLs could contribute to the elevation in triacylglycerols associated with carbohydrate feeding. As early as 1955, Hatch et al (23) used the ultracentrifugal patterns of lipoproteins to identify carbohydrate-induced elevations in the concentrations of species with an S_f of 20–100 (VLDL and IDL). Throughout the late 1950s and 1960s, investigators noted an increase in particles that floated in the $d < 1006$ g/L fraction (VLDL and chylomicrons) (24, 75), as well as in β -lipoproteins of $d < 1019$ g/L (IDL, VLDL, and chylomicrons) (30, 47). In 1963 Bierman (34) described the accumulation of a new lipoprotein particle that contained more than twice the cholesterol content expected in primary (chylomicrons) or secondary (VLDL) particles. Presumably, Bierman was describing the appearance of the remnants of VLDL or chylomicrons, particles thought to evolve during hydrolysis of triacylglycerol in the plasma compartment. With respect to the content of triacylglycerol in other lipoproteins, it was shown that LDL also carries greater quantities of triacylglycerol during carbohydrate feeding (48, 76). A paper by Krauss and Dreon (77) contains the most comprehensive analysis of the effect of a whole-food, LF-HC diet (16:24:60) on changes in lipoprotein fractions. In this study, the results of analytic ultracentrifugation showed that the mass of all fractions of VLDL (large, S_f : 100–400; intermediate, S_f : 60–100; and small, S_f : 20–60) was increased with the LF-HC diet, as was the mass of large IDL (S_f : 14–20). Contributions of TRLs containing apo B-48 were not measured. Mancini et al (48) reported that in the carbohydrate-induced state, 8–13% of the triacylglycerol in all the lipoprotein fractions was present in the $S_f > 400$ fraction. This increase in triacylglycerol with an $S_f > 400$ was surprising to the authors (48), who wrote, “this clearly must be endogenous (VLDL) triacylglycerol (not chylomicrons), for these subjects were receiving only one gram dietary fat per day, and the blood samples were obtained after a 12 h fast.”

Concentrations of apo B-48, the apolipoprotein marker of chylomicrons, are normally 6 times lower (0.01 $\mu\text{mol/L}$, or 0.3 mg/dL) than those of VLDL apo B-100 (0.06 $\mu\text{mol/L}$, or 3 mg/dL) in the fasting state. Few studies have compared the concentration of chylomicrons in the fasting state before and after HC feeding. We (50) studied 5 subjects with HPTG whose triacylglycerol concentrations were further elevated when they were switched from a HF (16:36:48) diet to a HC (15:15:70) diet. Both diets were whole food, and in both 44% of the carbohydrates were mono- and disaccharides. Sixteen-hour fasting measurements showed a significant 2.4-fold increase in TRL apo B-48, from 0.012 to 0.029 $\mu\text{mol/L}$ (0.32 to 0.77 mg/dL) with the HF and HC diets, respectively, in addition to a 2-fold increase in VLDL apo B-100 of from 0.36 to 0.68 $\mu\text{mol/L}$ (9.4 to 17.9 mg/dL). Analogous to the study of Mancini et al (48), the increase in fasting apo B-48 with chronic carbohydrate feeding was unexpected given that the night before the measurements were made the subjects ingested a very-low-fat evening meal (15% of energy as fat) and that the average half-life of chylomicrons, although variable, is estimated to be < 30 min (78). Chylomicrons are thought to be produced by the intestine constitutively, and their triacylglycerol content and size increase when fat is being absorbed (79). Because so little fat is present in meals during consumption of a 15%-fat diet, however, it might be anticipated that triacylglycerol clearance would be more efficient

for postprandial chylomicrons made after a low-fat meal than after a HF meal. This does not appear to be the case (48, 78). The accumulation of apo B-48 particles in the fasting state associated with chronic carbohydrate feeding suggests that either more chylomicrons were made in the postprandial state under this dietary condition or that the chylomicrons made were cleared less efficiently.

In summary, in the fasting state, VLDLs are the primary particles that accumulate during carbohydrate-induced HPTG, although the above data suggest that chylomicrons accumulate as well. Recent developments in analytic methods now make it possible to quantify the contents of apo B-100 and B-48 (80) in plasma. Furthermore, remnant-like particles can now be separated from plasma by immunoaffinity chromatography (81). This method may provide more quantitative data of the composition of remnant-like VLDL and apo B-48-containing particles in blood. In the present decade, numerous studies have shown that the presence of remnant particles confers increased coronary artery diseases risk in persons consuming higher fat diets and in those with preexisting disease (reviewed in reference 82). Therefore, the contribution of apo B-48 particles to carbohydrate-induced HPTG needs to be confirmed and the potential atherogenicity of this elevation in remnants needs to be explored further.

BIOLOGICAL MECHANISMS THAT CONTRIBUTE TO CARBOHYDRATE-INDUCED HPTG

Early proposed mechanisms

In 1963 Farquhar et al (83) studied the kinetics of triacylglycerol in the $d < 1006$ g/L TRL fraction of plasma in 2 patients fed 2 amounts of carbohydrate. These investigators described the direct cause of carbohydrate-induced HPTG as follows: "hepatic triacylglycerol synthesis was increased and net removal of triacylglycerol was insufficient to prevent expansion of the pool size." According to this concept, carbohydrate-induced HPTG results from both triacylglycerol overproduction and inadequate triacylglycerol clearance. But what is the underlying metabolic cause of these alterations? Triacylglycerol production was frequently measured in states of insulin resistance because insulin-resistant persons are more susceptible to carbohydrate-induced HPTG (84). Hyperinsulinemia or its associated elevations in the plasma metabolites (glucose or nonesterified fatty acids) may contribute to carbohydrate-induced HPTG. Havel (85) proposed that even a mild diabetic state might be expected to intensify HPTG resulting from some independent metabolic defect. Havel, and later Kane et al (86) and Reaven et al (87), hypothesized that adipose tissue resistance to the effects of insulin could result in failure to decrease lipolysis when insulin is elevated. In 1967 Reaven et al (88) also suggested that HPTG in most subjects resulted from an increase in the hepatic triacylglycerol secretion rate secondary to hepatic insulin resistance because insulin was shown to inhibit liver triacylglycerol secretion in healthy subjects (89, 90).

Reaven and his colleagues (88, 91–94) have contributed considerable information on the effects of carbohydrate feeding in persons with diabetes. Reaven and Olefsky (95) studied 20 men who were fed liquid HF diets (15:42:43) and HC diets (15:30:55) in which the carbohydrate was composed of dextrans and maltose. As the carbohydrate content of the diets was increased, the insulin response was magnified to a much greater extent than was the increment in blood glucose concentration. However,

Acheson et al (96) suggested that these results might be specific for refined sugars. They proposed that when glucose or glucose polymers are administered in solution, rapid glucose inflow occurs before the insulin concentrations stabilize. By contrast, when mixed meals are fed, glucose absorption proceeds more slowly so that most of the influx of glucose occurs once the body has become highly insulinized.

Howard et al (97), Reaven (18), and Kissebah et al (98, 99) proposed that the metabolic basis of carbohydrate-induced HPTG was peripheral and involved an impaired ability of insulin to lower lipolysis, which would lead to higher nonesterified fatty acid flux and increased VLDL production. Thus, the prevailing theory places peripheral insulin resistance as the "driver" of VLDL overproduction in endogenous and carbohydrate-induced HPTG, through a mechanism of reduced insulin suppression of adipose tissue lipolysis. However, carbohydrate-induced elevations in insulin could affect the liver directly because they increase triacylglycerol production and storage. Over the course of 24 h, the acute insulin inhibition of VLDL secretion could be overcome by a chronic need for the liver to export stored triacylglycerols. According to this model, long-term consumption of HC diets could lead to HPTG if higher meal-associated insulin peaks during the day resulted in eventual peripheral insulin resistance. In persons with diabetes and in those with endogenous HPTG who consume higher-fat diets, strong evidence supports the concept that hyperinsulinemia and unrestrained fatty acid flux play roles in VLDL overproduction (90, 94, 97, 98). Accordingly, these same mechanisms have been hypothesized to cause triacylglycerol overproduction during carbohydrate feeding, although no data currently exist to support this hypothesis in lean, healthy subjects consuming HC diets for longer periods of time. To assess the role of insulin resistance in carbohydrate-induced HPTG, one must first ask the question, does the phenomenon of carbohydrate-induced HPTG result from overproduction of VLDL, as occurs in hyperinsulinemic states?

Elevated production of VLDL apo B, VLDL triacylglycerol, or both

If carbohydrate-induced HPTG results from overproduction of VLDL, it could occur by 2 potentially concurrent mechanisms. First, high plasma triacylglycerol concentrations may result if the number of particles produced by the liver remains the same but each particle contains more triacylglycerol. Alternatively, HPTG could result from an increase in the number of VLDL particles produced, with each particle containing the same number of triacylglycerol molecules. These 2 mechanisms would have very different influences on the production of LDL as follows. If more triacylglycerols are secreted in the same number of VLDL particles, then the number of VLDL particles in the plasma that can potentially become LDL remains constant. Furthermore, VLDLs that have more triacylglycerols per particle do not necessarily contain more cholesterol per particle; therefore, the VLDL-cholesterol load in the blood is not increased. By contrast, if more VLDL particles are secreted, this larger number of VLDL particles in the blood could lead to an increase in LDL particle number. In addition, an increase in the number of VLDL particles secreted leads to an increase in VLDL-cholesterol secretion. It is important to discern how these 2 metabolic processes contribute to the HPTG that ensues after carbohydrate feeding.

Moreover, the contributions to HPTG of VLDL particle production compared with reduced triacylglycerol clearance are



TABLE 3
Studies of VLDL composition during carbohydrate feeding¹

Author (reference)	Subject description (prestudy or HF diet TG concentration in mmol/L)	Diets (protein:fat:carbohydrate)	TG/particle	Particle number
Schonfeld (100)	4 control subjects (1.3), 7 HPTG patients (2.7)	HF whole food: 15:40:45, HC liquid dextrin: 15:1:85	↑ 118% TG/VLDL prot	↑ 40% VLDL prot
Ruderman et al (49)	5 control subjects (1.0), 8 HPTG patients (3.5)	HF ad libitum, HC liquid dextrin: 15:1:85	↑ 50% TG/VLDL prot	↑ >100% VLDL prot
Melish et al (103)	3 control subjects (1.82), 3 HPTG patients (2.8)	HF liquid formula: 15:40:45, HC liquid dextrin: 20:0:80	NS	NS
Ginsberg et al (102)	3 HPTG patients (3.3)	HF liquid formula: 15:40:45, HC liquid dextrin: 20:0:80	NS	↑ 94% VLDL apo B
Huff and Nestel (101)	6 control subjects (1.2)	HF whole food: 14:47:39, HC, type not stated: 14:18:68	↑ 55% TG:VLDL apo B	↑ 103% VLDL apo B ² (NS)
Abbott et al (76)	7 nondiabetic subjects (1.5) ³ , 7 diabetic subjects (2.0) ³	HF whole food: 15:42:43, HC whole food: 15:21:65	NS	NS
Stacpoole et al (104)	2 control subjects (1.2), 3 FH subjects (1.5) ⁴	HF whole food: 15:40:45, HC liquid glucose: 9:1:90	ND	NS

¹FH, familial hyperlipidemic; HC, high-carbohydrate; HF, high-fat; HPTG, hypertriglycerolemic; ND, not determined; TG, triacylglycerol; VLDL apo B, apolipoprotein B; VLDL prot, total protein content of VLDL fraction.

²Increase in VLDL apo B in all subjects ($P = 0.11$); NS overall.

³Nondiabetic Pima Indians and Pima Indians with type 2 diabetes.

⁴Hyperlipidemic subjects were heterozygous ($n = 2$) and homozygous ($n = 1$) for LDL receptor defects.

important to discern not only because they may distinctly affect the LDL production rate, but also because each of these defects can be targeted by different therapeutic strategies. If increased synthesis and secretion of VLDL particles is the metabolic cause of HPTG, then the problem is driven by the actions of the liver and pharmaceutical strategies could be used to reduce the VLDL particle secretion rate. Alternatively, reduced clearance of VLDL triacylglycerol from the plasma can be ameliorated by nontherapeutic regimens such as exercise training.

More triacylglycerol per particle

Using ultracentrifugation to subfractionate the TRL fraction, Mancini et al (48) found that the average ratio of VLDL triacylglycerol to protein increased 230% when subjects were switched from their ad libitum diet to a HC diet (20:0:80) composed of bread, fruit, and liquid formula, suggesting that carbohydrate induction resulted in larger VLDL particles. This evidence of compositional change in VLDL is compatible with electron microscopic observation of increased size of VLDL during carbohydrate induction (49) and with the analytic data of Schonfeld (100) and Ruderman et al (49) (Table 3). Schonfeld (100) concluded that more triacylglycerol was secreted per VLDL particle during carbohydrate-induced HPTG.

Increases in particle number

Both Schonfeld (100) and Ruderman et al (49) observed increases in the quantity of protein within the VLDL fraction during carbohydrate induction (Table 3). Although VLDL contains only one apo B-100 molecule per particle, variable quantities of other small apolipoproteins are present. Thus, an increase in the protein content of the fraction could be due to an increase in the quantities of these smaller apolipoproteins in the particle. In this case, an increased protein content within the fraction would not necessarily equate to increased particle number. Indeed, Huff and Nestel (101) observed that carbohydrate feeding was associated with an increase in the content of apo C-III in

VLDL and Weisweiler et al (44) documented a shift in the type of apo E isoforms present.

To clearly document changes in particle number, Ginsberg et al (102) and Huff and Nestel (101) isolated the apo B-100 content of the VLDL fraction and confirmed absolute increases in particle number with carbohydrate feeding (Table 3). In the studies of Melish et al (103), Abbott et al (76), and Stacpoole et al (104), a large variability among subjects was observed with respect to change in VLDL particle number such that the mean changes for the study groups were not significant (Table 3). Static measurements showing increases in the number of triacylglycerols per particle or VLDL particle number provide specific information about the characteristics of carbohydrate-induced HPTG. To understand the underlying metabolic causes of this form of HPTG, kinetic measurements must be made to assess rates of VLDL triacylglycerol and particle production.

Changes in the production rates of VLDL triacylglycerol or apo B

In 1965 Reaven et al (87) proposed that carbohydrate-induced HPTG, like most endogenous HPTG, results primarily from overproduction and not from decreased efficiency of clearance. Their data were generated by the infusion of a bolus of radiolabeled glycerol to pulse label triacylglycerol. One important observation in this study was that a positive relation was established between the fasting triacylglycerol concentration and the turnover rate of plasma triacylglycerol with an $S_r > 20$ (TRL) in humans. The V_{max} for clearance was calculated to be 26.5 mg triacylglycerol·kg⁻¹·h⁻¹ (0.299 mmol·kg⁻¹·h⁻¹). These findings provided new in vivo information suggesting saturability for lipoprotein lipase, the enzyme primarily responsible for the clearance of triacylglycerol from plasma. Brunzell et al (105) found a similar V_{max} for triacylglycerol clearance (32.7 mg triacylglycerol·kg⁻¹·h⁻¹, or 0.369 mmol·kg⁻¹·h⁻¹) in nondiabetic subjects with endogenous HPTG. Since it was published, the study by Reaven et al (87) and a comparison of 3 mathematical models developed by this group (41) have been cited fre-

TABLE 4

Studies of VLDL apolipoprotein B and triacylglycerol (TG) production and clearance during carbohydrate feeding¹

Author (reference)	Subject description (prestudy or HF diet TG concentration in mmol/L)	Diets (protein:fat:carbohydrate)	Production rate of VLDL apo B or TG	FCR of VLDL apo B or TG
Reaven et al (87)	4 control subjects (0.7), 2 HPTG patients (4.4)	HF liquid formula: 14:69:15, HC liquid formula: 14:1:85	4/6 subjects ↑ TG PR with HC diet	ND
Quarfordt et al (111)	2 control subjects (0.6), 2 HPTG patients (3.1)	HF liquid formula: 20:40:40, HC liquid formula: 20:0:80	3/4 subjects ↑ TG PR	2/4 subjects ↓ TG FCR
Melish et al (103)	3 control patients (1.82), 3 HPTG patients (2.8)	HF liquid formula: 15:40:45, HC liquid dextrin: 20:0:80	No change in apo B PR, ↑ 60% in TG PR	apo B FCR, no change in TG FCR
Ginsberg et al (102)	3 HPTG patients (3.3)	HF liquid formula: 15:40:45, HC liquid dextrin: 20:0:80	No change in apo B PR	↓ apo B FCR ²
Huff and Nestel (101)	6 control subjects (1.2)	HF whole food: 14:47:39, HC type not stated: 14:18:68	↑ 49% in apo B PR	↓ 23% in apo B FCR
Abbott et al (76)	7 nondiabetic subjects (1.5) ³ , 7 diabetic subjects (2.0) ³	HF whole food: 15:42:43, HC whole food: 15:21:65	No change in apo B or TG PR	No change in apo B or TG FCR
Stacpoole et al (104)	2 control subjects (1.2), 3 FH subjects (1.5) ⁴	HF whole food: 15:40:45, HC liquid glucose: 9:1:90	↑ 58% in apo B PR	↑ apo B FCR
Parks et al (50)	7 control subjects (0.7) 6 HPTG patients (1.7)	HF whole food: 16:35:50 HC whole food: 17:15:68	↑ 33% in apo B PR in HPTG patients No change in TG PR	No change in apo B FCR ↓ 37% in TG FCR

¹apo B, apolipoprotein B; FCR, fractional catabolic rate, the percentage of the pool cleared per day; FH, familial hyperlipidemic; HC, high-carbohydrate; HF, high-fat; HPTG, hypertriglycerolemia; ND, not determined; PR, production rate (mg·kg⁻¹·d⁻¹).

²Percentage of VLDL cleared directly by receptor processes increased from 38–50% with the HF diet to 58–66% with the HC diet; the rest of the VLDL fraction cleared more slowly.

³Nondiabetic Pima Indians and Pima Indians with type 2 diabetes.

⁴Hyperlipidemic subjects were heterozygous ($n = 2$) and homozygous ($n = 1$) for LDL receptor defects.

quently as providing evidence that carbohydrate-induced HPTG results primarily from overproduction of triacylglycerol (49, 102, 106–109). In extending their studies (110), these investigators found several subjects with very high VLDL triacylglycerol concentrations (>3.39 mmol/L, or 300 mg/dL) in whom net VLDL triacylglycerol transport (production) was no higher than in subjects with triacylglycerol concentrations of 2.26 mmol/L (200 mg/dL) when both groups were studied under the same conditions of carbohydrate feeding.

Not all studies of the effect of carbohydrate feeding on the triacylglycerol production rate since these early observations found the production rate to be significantly increased (Table 4). Five studies measured the VLDL apo B production rate through the injection of labeled apolipoproteins and continuous ingestion of a low-energy, fat-free diet, resulting in a relatively constant, although nonphysiologic, insulinemic state. In all these studies body weight was kept constant between the dietary phases. Huff and Nestel (101) and Stacpoole et al (104) reported significant increases of ≈50% in the VLDL apo B production rate, whereas the data of Melish et al (103), Ginsberg et al (102), and Abbott et al (76) did not support a change in the VLDL particle production rate.

In summary, HC diets are associated with elevations in both the amounts of triacylglycerol per particle and the number of VLDL particles in the plasma. Significant increases in the production rates of both triacylglycerol and apo B (particles) were observed in some but not all studies when the HC diets were composed of fat-free, liquid formulas.

Decreased triacylglycerol clearance

In 1964 Knittle and Ahrens (30) postulated that carbohydrate-induced HPTG reflected a peripheral clearance defect in which insulin played a role. They hypothesized that a defect in the action of insulin on adipose and muscle tissue leads to a block in the

peripheral utilization of triacylglycerol. This block would then result in a “damming back of triacylglycerol-rich β-lipoproteins originating in the liver” (30). In essence, this hypothesis suggested that the decreased clearance of triacylglycerol from plasma was part of the mechanism for HPTG. Mancini et al (48) tested this mechanism using an intravenous fat-tolerance test in 4 healthy subjects fed nonfat diets for 4–10 wk. The half-life of triacylglycerol before HC feeding averaged 6.6 mg·dL⁻¹·min⁻¹ (0.078 mmol·L⁻¹·min⁻¹). After 5 d of HC feeding, the half-life rose significantly (turnover slowed) and after 6 wk it fell again slightly [averaging 17 and 14 mg·dL⁻¹·min⁻¹ (0.20 and 0.16 mmol·L⁻¹·min⁻¹), respectively]. The authors concluded that peripheral uptake of triacylglycerol was decreased by HC diets in normal subjects.

Melish et al (103) found that the higher triacylglycerol concentrations of patients with type IV lipoproteinemia fed a HF diet than of control subjects were not due to an abnormally high rate of VLDL production but rather to a “defect in the rate of VLDL removal.” A HC diet in these patients, as in normal subjects, increased VLDL production, but the increase was not any greater in patients with elevated baseline triacylglycerols and cholesterol than in healthy control subjects. The difference in triacylglycerol concentrations between these 2 groups appeared to lie in the inability of the patients to cope with the increased VLDL production. Thus, the limit of the system was clearance, as Quarfordt et al (111) had hypothesized earlier. The mathematical model of Quarfordt et al (111) also supported an increase in triacylglycerol synthesis from nonesterified fatty acid uptake by the liver, rather than increased nonesterified fatty acid flow to the liver. The model could not, however, discern the following hypothetical mechanisms: increased channeling of nonesterified fatty acids to triacylglycerol synthesis with a HC diet and increased fractional rate of release of VLDL triacylglycerol concurrent with a decrease in the fractional clearance of triacylglycerol from the plasma.

In a similar study, Huff and Nestel (101) found that the decay of radioactivity from labeled lipoproteins injected into subjects reflected higher fractional clearance rates of VLDL after HC feeding than after HF feeding (0.26 and 0.19 h⁻¹ for HC and HF feeding, respectively). Flux through the pool was also higher for all subjects during carbohydrate feeding. These results indicate that although more triacylglycerol was secreted during HC feeding, more was also being cleared. In this study, the cause of the HPTG was postulated to be the failure of clearance to keep up with production. The enzyme primarily responsible for triacylglycerol clearance from the plasma is lipoprotein lipase. Because of its role in triacylglycerol clearance, the activity of lipoprotein lipase during HC feeding has been the subject of recent investigation.

Lipoprotein lipase

Lipoprotein lipase is located on the surface of capillary endothelial cells and is readily released into the circulation by intravenous administration of heparin, thus allowing detection of lipolytic activity in plasma. Lipoprotein lipase hydrolyzes the core triacylglycerol of circulating chylomicrons and VLDL; its activity in subjects with HPTG fed standard HF diets was shown to be inversely correlated with VLDL-cholesterol concentrations (112), VLDL triacylglycerol (113), and total plasma triacylglycerol (114, 115). Kasim et al (116) showed that lipoprotein lipase activity was inversely correlated with fasting plasma triacylglycerol in subjects fed either HF ($r = -0.31$) or HC ($r = -0.47$) diets.

One as yet unconfirmed hypothesis is that elevations in postprandial insulin during HC feeding decrease lipoprotein lipase activity in muscle, leading to decreased triacylglycerol clearance. In support of this, Lithell et al (117) found lower lipoprotein lipase activity in a short-term feeding study in which 7 healthy men consumed a HC diet (70% carbohydrate; fat and protein content not reported) for 3 d. Both Fredrickson et al (114) and Jackson et al (118) reported similar results; furthermore, Campos et al (119) found that the level of plasma lipoprotein lipase activity was significantly lower after 6 wk of HC (17:24:59) consumption than after HF (16:45:39) consumption in 43 free-living, healthy men.

In contrast, a recent report did not support decreased skeletal muscle lipoprotein lipase activity with feeding HC diets (120). Yost et al (120) found that both adipose tissue and skeletal muscle lipoprotein lipase activity were higher postprandially whether the subjects ate a whole-food diet that was HF (20:50:30) or HC (20:25:55). The change in lipoprotein lipase activity between the fasting and fed states was greater than the effect of the background diet. HC feeding did increase the responsiveness of adipose tissue lipoprotein lipase to a HC meal. Although the duration of each feeding condition was not long (15 d), 6-h postprandial lipoprotein lipase activity was clearly elevated in both tissues. Although lipoprotein lipase has been shown to be inversely regulated in skeletal muscle and in adipose tissue (117, 121) (down-regulated by insulin in the former tissue and up-regulated in the latter), it appears to be up-regulated in both tissues postprandially (122, 123). More research will be needed to determine whether carbohydrate-induced HPTG results from decreased clearance of TRL from plasma through lower lipoprotein lipase activity or through some other mechanism. Furthermore, the individual contributions of adipose and muscle lipoprotein lipase to whole-body triacylglycerol clearance have not yet been clarified. There is currently no way to assess lipoprotein lipase activity in vivo without the use of heparin, which may not provide physiologically relevant results.

In summary, from a kinetic perspective, elevated triacylglycerol concentrations must result from an alteration in triacylglycerol synthesis or utilization, which presumably develops during the transitional period after the replacement of fat by carbohydrate. Triacylglycerols then stabilize at a new but higher concentration at a new steady state. During this new steady state, if triacylglycerol production is elevated, there must also be a greater absolute utilization (or clearance) of synthesized triacylglycerol. Thus, it is reasonable in principle to conclude that in some subjects both elevated triacylglycerol synthesis and inadequate or reduced triacylglycerol clearance could contribute to carbohydrate-induced HPTG. The increased synthesis of triacylglycerol results primarily from both increases in the particle secretion rate by the liver and in VLDL particle size (with more triacylglycerol per particle), although most of these data were generated when subjects consumed liquid diets that were high in monosaccharides. Reductions in triacylglycerol clearance were also present in some but not all subjects. Evidence suggests that reduced triacylglycerol clearance may be due in some part to reductions in lipoprotein lipase activity. However, the exact contribution of lipoprotein lipase remains unclear at this time.

Does de novo lipogenesis contribute to carbohydrate-induced HPTG?

The most obvious metabolic explanation for carbohydrate-induced HPTG would be increased conversion of carbohydrate to fat in the liver through the de novo lipogenesis pathway, resulting in increased production of VLDL triacylglycerol. Two testable kinetic predictions are implied by this metabolic model: first, that VLDL triacylglycerol production is elevated when HC diets are fed (which, as described above, can occur), and second, that hepatic de novo lipogenesis makes a major contribution to VLDL triacylglycerol.

Recent evidence indicates that increasing dietary carbohydrate can increase the de novo lipogenesis contribution to VLDL triacylglycerol only under certain conditions. The fractional contribution from hepatic de novo lipogenesis to fatty acids (ie, the percentage of VLDL fatty acids made new), contributes <5% of VLDL triacylglycerol (or <2 g/d) in healthy subjects consuming HF diets (124–126). Obese, hyperinsulinemic humans exhibit a de novo lipogenesis contribution of ≤ 3 -fold higher, but this still represents <10% of VLDL triacylglycerol (125). Oral administration of fructose (at 10 mg·kg lean body mass⁻¹·min⁻¹) for 6 h in subjects who fasted overnight increased the fractional de novo lipogenesis contribution substantially (to >30%), whereas isoenergetic glucose administration failed to increase de novo lipogenesis above 2–4% (127). In this study, absolute de novo lipogenesis flux was still quantitatively minor, however, representing <5% of the total hepatic fructose disposal rate, and serum triacylglycerol concentrations did not change acutely. Massive carbohydrate overfeeding while under metabolic ward conditions also increased the fractional contribution from de novo lipogenesis to VLDL triacylglycerol (128). Indeed, under such conditions of gross overfeeding, it was calculated that significant adipose tissue de novo lipogenesis occurred.

Schwarz et al (129) fed controlled diets of different total carbohydrate content for 5 d each; the carbohydrate content ranged from a 50% surplus of carbohydrate energy (added to a mixed diet) to a 50% deficit of carbohydrate energy (subtracted from a mixed diet). Fractional hepatic de novo lipogenesis correlated closely with recent carbohydrate energy intake. Even with the



TABLE 5
VLDL triacylglycerol production and lipid source after consumption of a high-fat and a high-carbohydrate diet¹

	Normolipidemic subjects (n = 6)		Hypertriacylglycerolemic subjects (n = 5)	
	HF	HC	HF	HC
Plasma TG				
(mmol/L)	0.69 ± 0.08 ^a	1.13 ± 0.15 ^b	1.73 ± 0.16 ^c	2.57 ± 0.25 ^d
(mg/dL)	61 ± 7 ^a	100 ± 13 ^b	153 ± 14 ^c	228 ± 22 ^d
VLDL cholesterol				
(mmol/L)	0.28 ± 0.03 ^a	0.70 ± 0.20 ^b	0.88 ± 0.13 ^b	1.14 ± 0.10 ^c
(mg/dL)	11 ± 1 ^a	27 ± 8 ^b	34 ± 5 ^b	44 ± 4 ^c
VLDL TG PR (mg · kg ⁻¹ · h ⁻¹)	24 ± 3 ^a	29 ± 6 ^a	62 ± 3 ^b	41 ± 8 ^a
VLDL clearance (mL/min)	23 ± 3 ^a	19 ± 3 ^b	29 ± 10 ^a	12 ± 4 ^b
VLDL TG from NEFA (%) ²	94 ± 3 ^c	92 ± 4 ^c	80 ± 3 ^b	67 ± 3 ^a
VLDL TG from DNL (%) ²	2.5 ± 1.5 ^a	2.5 ± 1.5 ^a	1.7 ± 1.4 ^a	3.4 ± 1.5 ^b

¹ $\bar{x} \pm$ SEM. DNL, de novo lipogenesis; HC, high-carbohydrate diet (protein:fat:carbohydrate = 16:15:69) fed for 5 wk; HF, high-fat diet (15:30:50) fed for 1 wk; NEFA, nonesterified fatty acids; PR, production rate; TG, triacylglycerol. Values in a row with different superscript letters are significantly different, $P < 0.05$. Adapted from Parks et al (50).

²Percentage of VLDL TG palmitic acid derived from NEFA or DNL.

diet containing a 50% surplus of carbohydrate energy [>700 g carbohydrate and 4500 kcal (≈ 19 MJ) total energy], absolute hepatic de novo lipogenesis represented the synthesis of only 3 g lipid/d (<10 g glucose converted directly to VLDL triacylglycerol). Neese et al (130) reported similar results during ad libitum carbohydrate overfeeding [up to 1000 g carbohydrate and 5500 kcal (≈ 23 MJ) total energy intake/d]. Fractional de novo lipogenesis increased to $>30\%$ of VLDL palmitate, although only a few grams of total fat were synthesized. These results were confirmed in other studies of intravenous and nasogastric overfeeding (128). Thus, under the conditions of surplus carbohydrate intake and rapid weight gain, HPTG is commonly observed and de novo lipogenesis may contribute to VLDL triacylglycerol, despite contributing only modestly to whole-body fat accrual. This nevertheless represents an atypical dietary setting, in that most persons with HPTG have relatively stable body weights or even lose weight when fed HC diets.

More relevant to carbohydrate-induced HPTG is the isoenergetic, HC dietary setting. In this setting, the contribution from de novo lipogenesis to HPTG appears to be controlled in a complex manner. Hudgins et al (131) studied healthy, lean subjects (fasting triacylglycerol: 0.86 mmol/L, or 76 mg/dL; total cholesterol: 4.09 mmol/L, or 158 mg/dL) fed a liquid-formula HC diet (15:10:75; carbohydrate was short-chain glucose polymers) for 4 wk while in a metabolic ward. Hepatic de novo lipogenesis was measured by mass isotopomer distribution analysis from [¹³C]acetate infusions and also by the dilution of linoleate (18:2) in VLDL triacylglycerol relative to dietary 18:2 and adipose tissue 18:2. Both indexes showed that stimulation of de novo lipogenesis contributed to VLDL triacylglycerol: 30–40% of VLDL palmitate came from de novo lipogenesis, as measured by mass isotopomer distribution analysis, with a slightly higher estimate by 18:2 dilution. The contribution from other sources (eg, nonesterified fatty acids or chylomicron remnants) was not assessed for comparison, but a significant proportion of circulating triacylglycerol clearly came from de novo lipogenesis.

In a subsequent study, Hudgins et al (132) compared the effects of the form of carbohydrate (solid food as opposed to liquid-formula diets), the presence of starch, and the type of carbohydrate (mono-, di-, or polysaccharides). All diets contained 75% of energy as carbohydrate. The results obtained with solid food were different from those obtained with the control, liquid formula that con-

tained short-chain glucose polymers. During the ingestion of the control formula, the de novo lipogenesis contribution was 40%, as determined by the 18:2 dilution technique. The addition of purified beet fiber to the control formula did not reduce de novo lipogenesis. By contrast, a liquid diet containing equal quantities of starch and sugar or a solid food diet (15:15:70; starch-to-sugar ratio of 60:40) showed no stimulation of de novo lipogenesis. Although the results of the beet fiber experiment did not support an antilipogenic effect of fiber, the results of the whole-food diet experiment did. The hypolipidemic effect of fiber added to HF diets was well demonstrated previously (60).

We performed a study that further addressed the concept of the antilipogenic effects of fiber and unprocessed carbohydrate (50). Normolipidemic subjects (fasting triacylglycerol: 0.69 mmol/L, or 61 mg/dL; total cholesterol: 3.39 mmol/L, or 131 mg/dL) and HPTG subjects (fasting triacylglycerol: 1.73 mmol/L, or 153 mg/dL; total cholesterol: 4.94 mmol/L, or 191 mg/dL) were fed a controlled HC diet for 5 wk. The LF-HC diet (16:15:69) was composed of whole foods, was high in fiber (0.004 g · kJ⁻¹ · d⁻¹, or 16 g · 1000 kcal⁻¹ · d⁻¹), and contained 44% of carbohydrate as mono- and disaccharides. The percentage increase in triacylglycerol during carbohydrate feeding was not significantly different between the 2 groups of subjects (Table 5). Of interest, however, de novo lipogenesis was not stimulated in the postabsorptive state even though fasting triacylglycerol concentrations were significantly elevated. In both groups fed the HC diet, the percentage of triacylglycerol fatty acids derived from de novo lipogenesis after an overnight fast was $<4\%$. Furthermore, in the fasting state, the percentage of VLDL triacylglycerol derived from plasma nonesterified fatty acids (usually the primary source of fatty acids for VLDL triacylglycerol synthesis) was significantly different between groups. This discrepancy was even greater after consumption of the HC diet, when only 67% of the palmitate in VLDL triacylglycerol of subjects with HPTG was derived from plasma nonesterified fatty acids compared with 92% in the normolipidemic subjects. No previous studies attempted to account for the sources of the fatty acids that form triacylglycerol during carbohydrate induction. Clearly, in the subjects with HPTG, other sources of fatty acids besides nonesterified fatty acids and de novo lipogenesis (perhaps chylomicron remnants or



stored hepatic triacylglycerol) were also used for triacylglycerol synthesis. These sources contributed even more during carbohydrate feeding.

The combined studies by Hudgins et al (131, 132) confirm that de novo lipogenesis can be elevated during carbohydrate-induced HPTG when the starch-to-sugar ratio of carbohydrate energy is <50:50. We (50) too showed that hepatic de novo lipogenesis is minimal when subjects consume LF-HC diets in which the carbohydrate is derived from whole foods, contains both fiber and starch, and has a starch-to-sugar ratio of $\geq 50:50$.

In summary, not only the total carbohydrate content (hyperenergetic as opposed to isoenergetic) and the proportion of carbohydrate present (percentage of total energy), but also the type of carbohydrate (starch compared with simple sugars) affects de novo lipogenesis and possibly the plasma triacylglycerol response to dietary carbohydrate. Whether de novo lipogenesis correlates with the HPTG response when highly processed foods that are high in sugar are fed will be of interest to establish. One might speculate that certain types of HC diets (eg, those containing predominantly simple sugars or taken in mostly liquid form) are more lipogenic and HPTG inducing than others, and that the effects of increased de novo lipogenesis and HPTG are mechanistically linked. Results in a small number of subjects ($n = 4$) fed HC sugar or starch diets suggested that the link between these 2 effects is not statistically significant (132). The studies cited above show that during chronic overfeeding or during the consumption of HC diets high in sugar, hepatic de novo lipogenesis is increased, although most of the fatty acids in VLDL are not derived from this source. Increases in de novo lipogenesis induced by carbohydrate feeding may contribute to triacylglycerol overproduction through several mechanisms. Hepatic de novo lipogenesis might either contribute directly to the VLDL triacylglycerol fatty acid pool destined to be secreted or contribute indirectly by increasing the efficiency of reesterification of nonesterified fatty acids. The latter mechanism has yet to be explored.

Characteristics of carbohydrate-sensitive individuals

Several subject characteristics may be useful in predicting sensitivity to carbohydrate feeding. Potentially important characteristics include sex, ethnicity, indexes of insulin resistance, glucose intolerance, the concentration of triacylglycerol in the fasting state when HF diets are fed, and measures of obesity.

Effects due to sex and ethnicity

The effects of subject sex were highlighted by Beveridge et al (31), who studied 25 university students who were switched from their self-selected diets to a fat-free (15:0:85), homogenized, formula diet in which the carbohydrate was 90% dextrimaltose and 10% sucrose. The average triacylglycerol response of men ($n = 11$) was a more than 2-fold increase after 9 d, whereas in the women ($n = 14$), the average response was a minimal, nonsignificant increase. Similarly, a difference in response between young women and men was noted by MacDonald (55). One explanation for why young women fail to respond at all or even experience reductions in serum triacylglycerol could be their higher levels of postheparin lipoprotein lipase in serum (133) and possibly adipose tissue (134). A beneficial role for steroid hormones is suggested by these data; however, the effect of estrogen is complex. Women who take estrogen (for birth control or at the onset of menopause) experience elevations in plasma triacylglycerol concentrations con-

current with significant reductions in lipoprotein lipase activity (135). More research is needed to determine whether an interaction exists between the fat content of the diet and the effect of estrogen in modulating triacylglycerol elevations in response to carbohydrate feeding. In addition, the effect of changing estrogen concentrations during menopause on lipoprotein lipase activity and dietary responsiveness will be an important future area of research.

Within the past decade, more effort has been devoted to characterizing how risk factors for coronary artery disease may differ across ethnic groups (136, 137). Few LF diet intervention studies have been designed to look at race a priori, although there are notable exceptions (138). The effect of ethnicity was highlighted in a series of studies of diet and insulin resistance in diabetic and nondiabetic Pima Indians, a population with a higher incidence of obesity and diabetes than whites but without the characteristic lipoprotein patterns seen in whites (76, 97, 109).

Recent research has reemphasized that we must avoid making generalizations across ethnic groups. For example, elevated body weight and triacylglycerol concentrations do not always go hand-in-hand. Gerhard et al (139) showed that in healthy, premenopausal women, blacks had significantly higher BMIs (in kg/m^2) but lower ($P < 0.0001$) fasting triacylglycerol concentrations (0.9 mmol/L, or 80 mg/dL) than whites (1.2 mmol/L, or 108 mg/dL). Yet, within an ethnic group, BMI and triacylglycerol concentration may still be associated (140, 141). More data are becoming available on the effects of race-related issues on coronary artery disease risk factors. The specific effect of HPTG may be difficult to ascertain given the wide variability in triacylglycerol concentrations within populations. Because obesity and insulin resistance are increasing dramatically among African Americans and Mexican Americans, future studies should focus on how changes in the macronutrient intakes of specific populations interact with these and other risk factors to increase overall risk.

Measures of insulin resistance

Hyperinsulinemia (68, 88, 142) and glucose intolerance (26, 88, 142) can correlate with the degree of triacylglycerol elevation during carbohydrate feeding. Glueck et al (37) found no significant correlations between change in triacylglycerol and insulinogenic indexes in a heterogeneous group of patients with type II a/b, III, and IV lipoproteinemia ($n = 52$) and in normolipidemic subjects ($n = 23$; Table 1). Jeppesen et al (143) studied 10 healthy, postmenopausal women consuming a relatively high-sucrose (12% of energy), LF-HC diet (15:25:60) for 3 wk. They found that the degree of insulin resistance (as assessed by a fasting insulin suppression test) was significantly correlated with postprandial incremental increases in insulin and plasma triacylglycerol in the TRL fraction.

Much has been written about the effects of LF-HC diets in persons with type 2 diabetes (18, 74, 84, 93). The sensitivity of subjects with type 2 diabetes to carbohydrate feeding may represent very different metabolic mechanisms in these persons than in healthy persons. In the prediabetic state, fasting glucose may be normal whereas fasting insulin concentrations are frequently at the upper range of normal. Over years as the disease progresses, glucose increases and insulin decreases, such that by the time the syndrome has advanced to frank diabetes, hyperglycemia is present in both the fasting and postprandial states. With HF diets, diabetic HPTG is related directly to the degree

of glucose control (144). Whether LF-HC diets hasten the progression of prediabetes to type 2 diabetes is controversial and will not be discussed here.

Obesity and baseline triacylglycerol concentrations

Elevated body weight exaggerates carbohydrate inducibility and carbohydrate intolerance (36, 68, 145, 146). In a well-controlled, 5-mo study, Cole et al (147) found that compared with women with a BMI <24, obese women experienced greater increases in VLDL triacylglycerol when all subjects were switched from whole-food, isoenergetic diets that were HF (19:37:43) to HC isoenergetic diets (19:21:59).

The question may be asked whether, among persons without evidence of lipid abnormalities, there is a corresponding tendency for large triacylglycerol responses to occur in those who have higher initial triacylglycerol concentrations. Ginsberg et al (43) considered this relation and found that triacylglycerol concentrations in normolipidemic subjects whose basal concentrations were 0.97 mmol/L (86 mg/dL) increased to 1.43 mmol/L (127 mg/dL) with HC feeding; concentrations in those with basal concentrations of 1.45 mmol/L (128 mg/dL) increased to 2.18 mmol/L (193 mg/dL) and those in subjects with basal concentrations of 2.85 mmol/L (252 mg/dL) increased to 3.82 mmol/L (338 mg/dL). The authors concluded that the relative rise in triacylglycerol was not a function of basal concentration, but that the greater the basal triacylglycerol concentration the greater the absolute increase. However, others found no such correlation (23, 148). It may be possible that there are 2 types of normolipidemic persons: those who are highly responsive to dietary carbohydrate and those who are nonresponsive. No convincing evidence to support this possibility was found in the distributions of the responses analyzed by Anderson (148).

Retzlaff and colleagues (45, 149) published a comprehensive analysis of the predictors of carbohydrate-induced HPTG in healthy hypercholesterolemic subjects (fasting triacylglycerol: 1.13 mmol/L, or 100 mg/dL; total cholesterol: 6.59 mmol/L, or 255 mg/dL) and in subjects with combined hyperlipidemia (fasting triacylglycerol: 2.25 mmol/L, or 200 mg/dL; total cholesterol: 7.01 mmol/L, or 271 mg/dL). Univariate analysis showed that the log of the baseline plasma triacylglycerol concentration was the only variable (among baseline triacylglycerol, body weight, log of BMI, age, and insulin) that predicted the magnitude of the triacylglycerol change (Pearson correlation coefficients ranged from $r = -0.49$ to -0.59 , $P = 0.01$). Note that the sign of the coefficients was negative, indicating that those with the highest triacylglycerol concentrations were most likely to experience reductions in triacylglycerol when dietary fat was decreased. Thus, in different studies, baseline triacylglycerol concentrations were positively and negatively correlated with triacylglycerol change. Adaptation to dietary change is a complex metabolic response; therefore, it is not surprising that a single characteristic fails to reliably identify carbohydrate-sensitive individuals. However, the proportion of change that can be explained by the baseline triacylglycerol concentration appears to be substantial.

Inspection of individual subject data from a clinical study shows how the interactions between factors (BMI, insulin, and triacylglycerol concentration before triacylglycerol induction) might be used to predict the direction of triacylglycerol change among individuals. We (EJ Parks, BO Schneeman, PA Davis, unpublished observations, 1994) studied a group of coronary artery disease patients switched from a LF diet (15:20:65) to a

very LF (10%), vegetarian diet that was one therapeutic component, along with exercise and stress-reduction therapy, of an intensive atherosclerosis treatment program. Univariate analysis showed that the higher the baseline triacylglycerol concentration, the greater the decrease in triacylglycerol during carbohydrate feeding ($r = -0.404$, $P < 0.01$). Retzlaff et al (45), Knopp et al (149), and Nicklas et al (150) studied postmenopausal women and described similar carbohydrate-induced reductions in triacylglycerol in subjects with very high lipid concentrations.

We also found a significant interaction between the patients' baseline BMI and the change in triacylglycerol, indicating that those with a BMI >27 experienced the largest increases in triacylglycerol. However, a complex relation existed between the baseline plasma triacylglycerol concentration and change in triacylglycerol during carbohydrate feeding. The individual subject data are shown in **Figure 1**. For each subject (denoted on the x axis by their baseline BMI), 2 triacylglycerol values are plotted on the y axis: the subject's triacylglycerol concentration when he or she was consuming the 20%-fat diet (pre) and the triacylglycerol concentration after 3 mo of the very-LF-HC diet (post). Three conclusions are of note. First, subjects with higher BMIs experienced larger increases in triacylglycerol concentrations; second, subjects with the highest triacylglycerol concentrations at baseline (above the horizontal line) were persons within the midrange of BMI (values of 24–27); and third, it was these latter persons who experienced the greatest reductions in triacylglycerol with carbohydrate feeding.

The sum of these observations would seem counterintuitive given the well-recognized positive association between BMI and fasting triacylglycerol concentration. Clearly, elevations in BMI explain only a portion of the variability in fasting triacylglycerol. As can be appreciated from Figure 1, persons with baseline triacylglycerol concentrations >1.58 mmol/L (140 mg/dL) were heterogeneous. The simplest analysis divides the subjects into 2 groups. The first group was made up of persons whose extremely high triacylglycerol concentrations were driven by some factor other than BMI, such that when these persons reduced their fat intake, their triacylglycerol concentrations fell dramatically. The second group consisted of those subjects with higher BMIs (>27) and only moderately elevated baseline triacylglycerol concentrations (>1.58 mmol/L, or 140 mg/dL). This group was most likely to experience the greatest increases in triacylglycerol concentration during dietary fat restriction.

Discriminant function analysis (151) is one statistical strategy that can be used to identify factors that might predict the triacylglycerol response of patients. Within our data set, the baseline factors found to be predictive were prediet BMI and plasma triacylglycerol and insulin concentrations. The jackknife procedure was applied to this analysis, and with use of all 3 clinical characteristics, the algorithm predicted 90.5% of those who showed an increase in their triacylglycerol concentration and 66.7% of those who did not. The overall predictive accuracy was 80.6% ($P < 0.01$).

In summary, subject characteristics such as sex, triacylglycerol concentration when fed a HF diet, BMI, and insulin concentration have been variably shown to individually predict changes in fasting triacylglycerol when research subjects consume LF-HC diets. No single characteristic reliably predicts the response of subjects. Described above are examples of preliminary strategies used to determine which subjects will experience carbohydrate-induced HPTG. Application of these methods to larger data sets

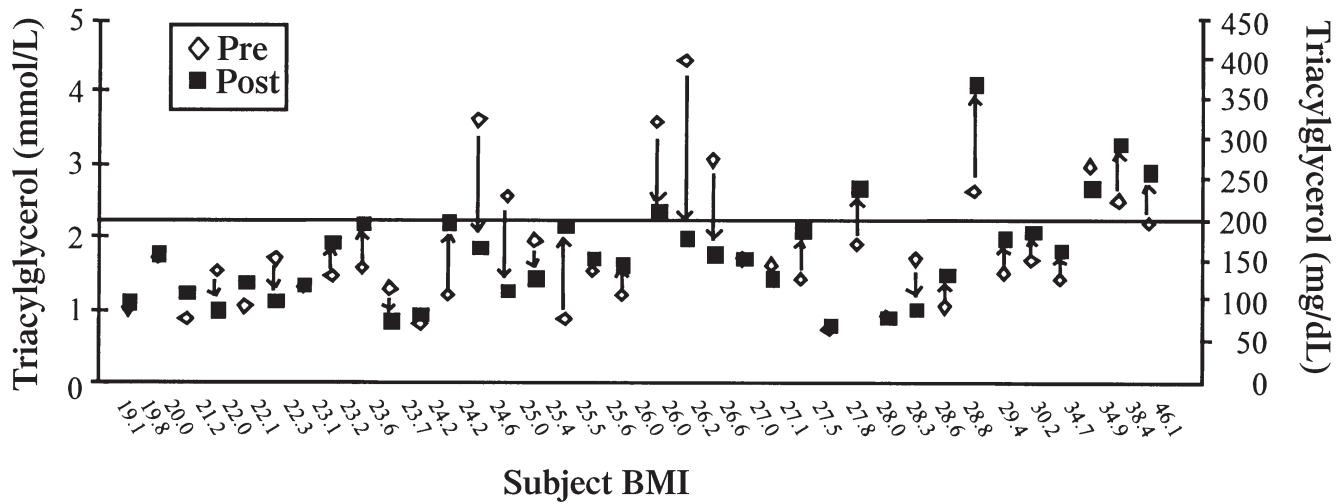


FIGURE 1. Variability in plasma triacylglycerol concentration in response to dietary fat reduction. Shown are individual data for 36 coronary artery disease patients consuming a low-fat, high-carbohydrate diet. The BMI values for each subject are on the x axis. On the y axis, the triacylglycerol concentration of each subject is represented by 2 points: pre, the concentration with consumption of a low-fat diet (protein:fat:carbohydrate = 18:22:60), and post, the concentration after consumption of a very-low-fat, vegetarian diet (17:9:74). The arrow indicates an absolute change in triacylglycerol concentration of >0.34 mmol/L (>30 mg/dL). Data are from EJ Parks, DA Hyson, BO Schneeman, and PA Davis, unpublished observations, 1994.

and independent data sets will be required to further refine these strategies. The results suggest that obesity might increase the likelihood of triacylglycerol induction. Persons who are not obese and have the highest triacylglycerol concentrations while consuming higher-fat diets (>2.26 mmol/L, or 200 mg/dL) may benefit most from LF-HC feeding by experiencing significant reductions in their triacylglycerol concentrations.

Avoiding carbohydrate-induced HPTG

Gradual changes in carbohydrate intake

Ullmann et al (152) postulated that carbohydrate-induced HPTG may be avoidable altogether if the percentages of dietary fat and carbohydrate are changed gradually rather than in a single large step (such as when subjects are switched directly from diets containing 35% of energy as fat to those containing 10% of energy as fat). In their study, 8 mildly overweight, healthy persons were fed a HF, whole-food diet (15:40:45) and then fed diets in which the exchange of fat for carbohydrate was made in increments of 5% of total energy. Each phase was isoenergetic and lasted 10 d (Table 6). Total and VLDL triacylglycerol during all dietary phases were not significantly different, although visual inspection of the individual subject data reveals a large variability among the subjects. At least 3 subjects experienced elevations in triacylglycerol concentrations when fed the final HC diet (15:20:65). The strength of this study was its unique design of gradual changes in dietary carbohydrate intake and the constant content of simple sugars across the dietary phases. Furthermore, the results reemphasize the potential beneficial effects of carbohydrates derived from whole foods and the presence of fiber in preventing carbohydrate-induced HPTG.

Although the study of Ullmann et al (152) has been cited frequently to show that carbohydrate-induced HPTG may be avoidable, the results should be viewed with caution. The sam-

ple size was small, which brings into question the generalizability of the findings. In many larger data sets, one finds that in roughly 10% of subjects, triacylglycerol concentrations do not increase dramatically with carbohydrate feeding (23, 37, 45, 61, 116, 147, 153, 154). As the individual data reveal, some subjects experience reductions in fasting triacylglycerol concentrations with carbohydrate feeding, even when body weight is kept constant (23, 147, 154).

In 1997 Kasim-Karakas et al (155) published the results of a 4-mo, controlled dietary study of 54 postmenopausal women in which dietary fat was decreased stepwise from a habitual intake of 35% to 25% and then to 15% of daily energy (Figure 2). During the initial isoenergetic dietary phases, study personnel prepared all foods and the goal was for the subjects to maintain their body weights. The subjects' mean triacylglycerol concentration rose from 1.70 to 2.30 mmol/L (151 to 204 mg/dL) with increasing dietary carbohydrate ($P < 0.05$). The results are interesting in that the increase in triacylglycerol concentration occurred even though efforts were made to keep the sugar content of the diet low and the subjects were given longer to acclimate to the dietary change (eg, ≥ 1 mo per dietary phase) than the 10 d in the study by Ullmann et al (152). Clearly, even with gradual changes in carbohydrate intake and even when HC diets are isoenergetic, some individuals will experience elevations in triacylglycerol concentrations for several months or longer. The effects over an even longer period were also studied by Kasim et al (discussed in the next section).

Weight loss and decreased food intake

Studies of the metabolic effects of carbohydrate feeding were designed to be isoenergetic so that changes in variables (glucose or lipid concentrations) could be attributed to the change in the diet and not to the loss of body weight. The consumption of HC diets ad libitum, however, is consistently associated with reductions in body weight ranging from 1 to 5 kg (94, 123–126). Results of the Multiple Risk Factor Intervention Trial showed no

TABLE 6
Effect of stepwise reductions in dietary fat on carbohydrate-induced hypertriacylglycerolemia¹

	AAD	Phase 1	Phase 2	Phase 3	Phase 4
Diet composition					
Protein (% of energy)	15	15	15	15	15
Total fat (% of energy)	40	35	30	25	20
Saturated fat (% of energy)	15	11	8	6	5
PUFA (% of energy)	6	8	8	8	8
P:S	0.4	0.7	1.0	1.3	1.6
Total carbohydrate (% of energy)	45	50	55	60	65
Complex carbohydrate (% of energy)	17	25	30	35	40
Simple carbohydrate (% of energy)	28	25	25	25	25
Plasma lipids					
LDL cholesterol (mmol/L) ²	4.32 ± 0.44 ³	3.72 ± 0.41	3.65 ± 0.41	3.46 ± 0.36	3.26 ± 0.39
Triacylglycerol (mmol/L) ²	2.40 ± 0.43	2.62 ± 0.42	2.68 ± 0.34	2.60 ± 0.42	2.60 ± 0.40

¹*n* = 8 subjects with average BMI (29.5; in kg/m²). AAD, Average American diet (control period); PUFA, polyunsaturated fatty acids; P:S, ratio of polyunsaturated to saturated fatty acids. The dietary treatments (AAD, Phase 1, Phase 2, etc) were successive phases of 10 d each. Adapted from Ullmann et al (152).

²To convert LDL cholesterol to mg/dL, multiply by 38.7; to convert triacylglycerol to mg/dL, multiply by 88.6.

³ $\bar{x} \pm$ SEM.

evidence that intake of dietary carbohydrate, sucrose, or other simple carbohydrates affected plasma triacylglycerol concentrations, and this lack of association between carbohydrate intake and triacylglycerol was suggested by the authors to be due to the gradual changes in diet and the loss of body weight by the participants (156). Weight loss could result from significant increases in energy expenditure with consumption of HC diets (157), but more likely results from reduced food intake (158, 159).

Lichtenstein and colleagues (160, 161) studied the effects of a HC diet on lipid and lipoprotein concentrations under 2 conditions: 1) when the subjects' food intake was controlled to maintain body weight and 2) when subjects ate to satiety. Eleven hypercholesterolemic subjects were tested while consuming their baseline diets and then after consuming 2 isoenergetic diets, each for 5 wk (Table 7). The subjects then continued to consume the lowest-fat diet ad libitum another 10 wk, with testing after weeks 5 and 10. As summarized in Table 7, triacylglycerol concentrations were significantly elevated during consumption of the isoenergetic HC diet but were lowered when the HC diet was fed ad libitum for 5 wk, during which time the subjects lost an average of 3.6 kg (8 lb) body weight. No statistics were reported for the analysis of the second 5-wk ad libitum phase, but triacylglycerol concentrations dropped a further 0.11 mmol/L (10 mg/dL: from 130 to 120 mg/dL) after 10 wk of feeding the HC diet ad libitum.

In the study by Kasim-Karakas et al (155) discussed in the previous section, 54 postmenopausal women consumed isoenergetic diets for 4 mo. After this controlled feeding period, 48 of the women continued to consume the 15%-fat diet ad libitum on an outpatient basis (Figure 2). After 8 mo of consuming their HC, self-selected diets, the subjects lost roughly 2 kg body weight and their triacylglycerol concentrations returned to baseline values. Data from 7-d food records indicated continued adherence to the HC diet during the outpatient phase. Thus, carbohydrate-induced HPTG was shown to be transient under these conditions of ad libitum intake.

Strong evidence suggests that diets high in carbohydrate will not automatically result in HPTG if subjects are allowed to eat to satiety, if carbohydrate is derived from whole foods, and if the ratio of starch to sugar is $\geq 50:50$ (both carbohydrate sources represented as per-

centage of total carbohydrate). The restriction of sugars may lessen HPTG for several reasons. First, meeting carbohydrate needs by focusing primarily on increased intake of legumes and vegetables significantly increases dietary fiber intake to ≥ 0.002 g/kJ (8 g/1000 kcal) (162) and as high as 0.006 g/kJ (25 g/1000 kcal) (109). Increased fiber intake lowers plasma triacylglycerol concentrations. Second, the consumption of fiber-rich carbohydrate is associated with body weight losses of 0.5–5 kg as a result of decreased food intake (155, 161, 163). This is because foods rich in fiber are bulky and decrease the subjective feeling of hunger (164, 165). Third, if the intake of mono- and disaccharides does not exceed 30% of energy, elevations in triacylglycerol are much less likely to occur. This last requirement is more difficult to achieve, although not as prohibitive as was asserted by some reviewers (51). However, if the ratio of starch to sugars is maintained at 50:50 or higher, the intake of the latter should not exceed 30% of total energy (assuming that dietary fat represents $\geq 10\%$ of total energy) because a consistent result of replacing fat with fiber-rich carbohydrate is that the percentage of energy from protein increases to 18–20%. The higher protein intake is derived from vegetables, grains, and legumes (155, 162).

In conclusion, the incidence of carbohydrate-induced HPTG may be decreased when large reductions in dietary fat are made more gradually over a period of weeks, instead of abruptly. Fewer persons will experience HPTG when the intake of the LF-HC diet is ad libitum, when weight loss occurs, and when the fat is replaced by carbohydrate from whole foods in which the ratio of starch to sugars is $\geq 50:50$. The combination of such HC, high-fiber diets with a consistent exercise regimen can also be expected to result in sustained low concentrations of total and LDL cholesterol against a background of constant triacylglycerol concentrations.

POSITIVE AND NEGATIVE CONSEQUENCES OF HIGH-CARBOHYDRATE DIETS: FUTURE RESEARCH

Effects on other dietary components

In healthy populations, the benefits of lowering plasma cholesterol concentrations through dietary fat reduction have been well documented (12). Yet, the effect of LF-HC diets on vari-

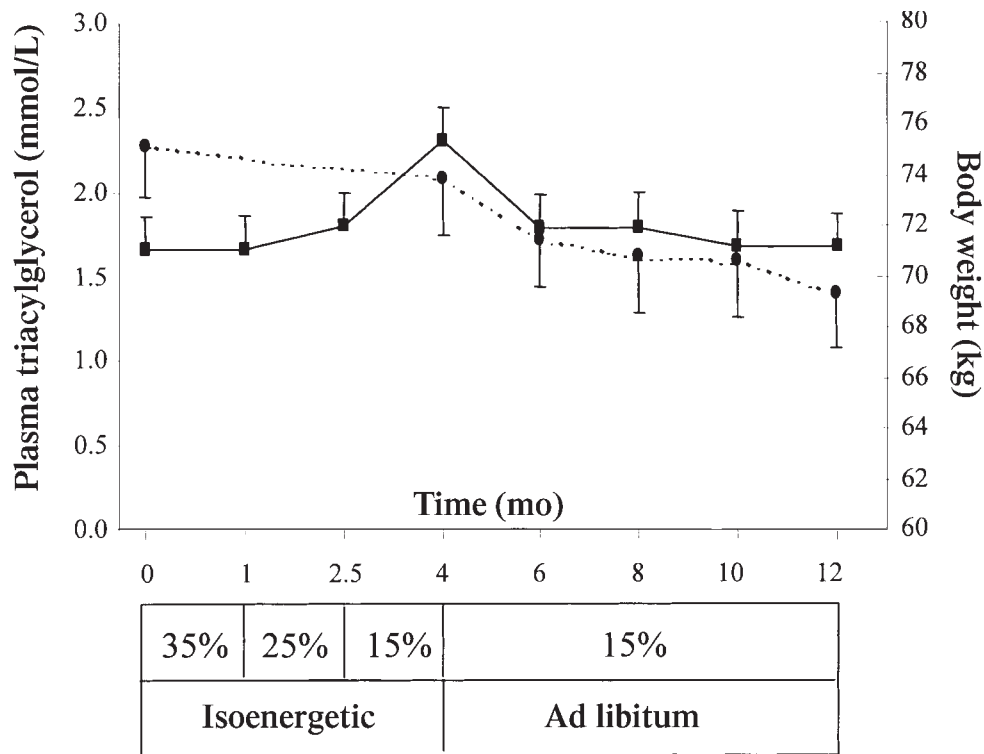


FIGURE 2. Mean (\pm SD) effects on body weight (●) and plasma triacylglycerol (■) of long-term adherence to a 15%-fat diet in postmenopausal women. The 3 diets fed consisted of whole foods in which the percentages of energy from protein, fat, and carbohydrate were 18:35:47 with 71 g sugar/d, 18:25:57 with 92 g sugar/d, and 18:15:67 with 105 g sugar/d, respectively. Forty-eight women completed 1 y of participation.

ables other than cholesterol is less certain. Numerous studies have compared the dietary micronutrient intakes of omnivores consuming higher-fat diets with those of vegetarians and persons who eat LF diets for religious reasons (eg, Seventh-day Adventists) (166–170). Millet et al (166) showed that vegetarians eating a 34%-fat diet consumed on average 14 mg α -tocopherol/d and 8 mg β -carotene/d. These persons had higher serum concentrations of α -tocopherol than did omnivores and equivalent concentrations of carotenoids (166). The intake of α -tocopherol by some subjects was below the recommended dietary allowance (10 α -tocopherol equivalents) for this nutrient (171). We observed the same or slightly lower plasma concentrations of fat-soluble vitamins in persons switched to very-LF diets (172). When patients with coronary artery disease were switched from a 20%-fat diet (18:22:60) to an 8%-fat, whole-food, high-fiber, HC diet (17:9:74), no significant change in intake of α -tocopherol was observed although β -carotene intake increased 2.2-fold as a result of an increase in the consumption of fruit and vegetables (172). Occasionally, lower concentrations have not been viewed as cause for concern because the recommended dietary allowance for α -tocopherol is based on polyunsaturated fat intake. When the ratio of serum concentrations of α -tocopherol to blood lipids is compared in those consuming HF and HC diets, the ratios are similar (173).

Although the literature points to numerous analyses showing that LF, vegetarian diets can contain adequate quantities of carotenoids and vitamin C (167–170, 174), the data on intake of both α -tocopherol and β -carotene reported may not be accurate because the contents of these compounds in many foods are miss-

ing from the databases designed to analyze food intake. In addition to potential reductions in micronutrient intake, the consumption of LF-HC diets, in which protein derived from animal sources is low, could lead to suboptimal intakes of vitamin B-12 and calcium. There is currently an increasing interest in the inverse relation between dietary micronutrient intake (α -tocopherol, vitamin C, and folate), plasma concentrations of homocysteine, and coronary atherosclerosis (175, 176). Therefore, an important goal of future research will be to understand how dietary modification aimed at reducing fat intake affects the intake of these micronutrients.

Effects on other lipoproteins besides VLDL

The consumption of LF-HC diets is consistently associated with higher intakes of dietary fiber and significant losses of body weight, 2 events clearly beneficial to health. Furthermore, numerous studies have successfully incorporated LF diets into therapeutic regimens designed to intensively treat patients with coronary artery disease (177–180). The reductions in clinical events documented in these studies support the health benefits of LF diets. However, it could be argued that the significant reductions in clinical events occurred despite the potentially negative changes in blood lipids observed (elevations in triacylglycerol and reductions in HDL cholesterol). Reductions in HDL cholesterol have been a compelling reason to discourage the consumption of these diets (181, 182) and this effect of LF-HC diets has been the subject of numerous research studies; the results of 3 are described below.

Dreon et al (153) reported that a switch from a HF (16:46:38) to a LF-HC diet (16:24:60) caused a 14% reduction in HDL cho-



TABLE 7
Effect of body weight loss during high-carbohydrate feeding on lipid concentrations¹

Measurement	Baseline or HF (17:36:48) ²	Reduced fat (17:29:53) ²	Isoenergetic HC (17:15:68) ²	HC ad libitum (first 5-wk phase)	HC ad libitum (second 5-wk phase)
Triacylglycerol (mmol/L)	1.24 ± 0.36 ^a	1.30 ± 0.35 ^a	2.12 ± 0.86 ^b	1.47 ± 0.36 ^a	1.35 ± 0.36
VLDL cholesterol (mmol/L)	0.54 ± 0.16 ^a	0.65 ± 0.08 ^{a,b}	1.01 ± 0.39 ^c	0.83 ± 0.23 ^{b,c}	0.80 ± 0.18
Total cholesterol (mmol/L)	5.84 ± 0.85 ^c	5.04 ± 0.49 ^{b,c}	5.38 ± 0.57 ^b	4.91 ± 0.49 ^a	4.91 ± 0.44
LDL cholesterol (mmol/L)	4.09 ± 0.7 ^c	3.31 ± 0.41 ^{a,b}	3.47 ± 0.44 ^b	3.07 ± 0.39 ^a	3.13 ± 0.39
Change in body weight (kg/wk)	—	-0.06 ± 0.27	-0.14 ± 0.20	-0.62 ± 0.47	-0.43 ± 0.43

¹ $\bar{x} \pm SD$. HF, high-fat; HC, high-carbohydrate. The first 3 dietary phases were 5 wk each, the HC ad libitum intake was split into two 5-wk phases. Statistics were reported for analyses between the first 4 phases, but not for the analysis of the second HC ad libitum phase. Statistics for change in body weight were not reported. To convert LDL cholesterol to mg/dL, multiply by 38.7; to convert triacylglycerol to mg/dL, multiply by 88.6. Values within a row with different superscript letters are significantly different, $P < 0.05$.

²Percentage of energy from protein, fat, and carbohydrate.

lesterol in healthy male subjects. This percentage reduction in HDL cholesterol is common when healthy persons switch from diets containing >35% of energy as fat to diets containing <25% of energy as fat. Knopp et al (149) studied 7 groups of subjects with various forms of hyperlipidemia (a total of 444 subjects) switched from HF diets (that averaged 16:37:47) to various LF-HC diets. Although the different groups were targeted to consume different amounts of fat (ranging from 30% to 18% of energy), after 1 y, all groups were consuming similar diets (averaging 17:26:57). Mean triacylglycerol concentrations were significantly elevated (12–28%) and HDL-cholesterol concentrations reduced (3–4%) compared with baseline in hypercholesterolemic subjects consuming diets that contained 22–25% of energy as fat. These authors concluded that aggressive restriction of fat to <26% of energy offers no further benefit to risk than does moderate fat restriction. However, reductions in both LDL and HDL with these diets can result in an improvement in the ratio of LDL to HDL, as shown recently by Turley et al (183). In this study, healthy, free-living men ($n = 38$) consumed an ad libitum LF-HC diet (6:22:59) and a HF diet (18:36:43) for 6 wk each. LF-HC consumption was associated with significant reductions in both LDL (18.4%) and HDL cholesterol (11.5%) compared with HF values. The subjects lost 1.5 kg (3.3 lb) and fasting triacylglycerol concentrations were not significantly different between the dietary phases.

Effects on LDL particle size

Another important consequence of lowering dietary fat is the effect on LDL particle size. Two patterns of LDL size were identified by Austin et al (184). Persons with pattern A have predominantly larger, buoyant LDL, whereas those with pattern B have a major peak size of smaller, more dense LDL particles. In population studies, smaller LDL particle sizes are statistically correlated with other risk factors for coronary artery disease. These risk factors include abdominal adiposity, elevated triacylglycerol concentrations, increased concentrations of apo B, and decreased concentrations of HDL. Because LDL particle size is inversely related to triacylglycerol concentration, an important question to address is whether elevations in triacylglycerol induced by HC diets are associated with reductions in LDL particle size (153, 181).

Dreon et al (153) analyzed changes in LDL particle size in 105 healthy men consuming HF (16:46:38) and HC (16:24:60) diets for 6 wk each. Fifty-one men with pattern A (larger LDL particles) while consuming the HF diet did not experience reductions in LDL particle size during carbohydrate feeding (the HC

diet). Eighteen subjects with pattern B (the smaller, potentially more atherogenic LDL) while consuming the HF diet remained pattern B while consuming the HC diet, whereas 36 men with pattern A while consuming the HF diet became pattern B while consuming the HC diet. Reductions in plasma concentrations of apo B, a measure of the number of potentially atherogenic particles, were observed in subjects with pattern B but not in the subjects with pattern A. The authors concluded that for the 2 groups (those with pattern A and those who switched from pattern A to pattern B), a substantial portion of the carbohydrate-induced reduction in LDL cholesterol resulted from a shift of more buoyant LDL to more dense LDL particles. This phenomenon may not be beneficial. The authors concluded that whereas persons with pattern B while consuming HF diets are at higher coronary artery disease risk than those with pattern A, persons with pattern B while consuming HC diets may experience a greater relative improvement in risk by virtue of significant reductions in the number of smaller, more dense LDL particles. Whether greater risk is assigned to those who switched from pattern A to pattern B during carbohydrate feeding is currently unknown.

Conclusions regarding the increased atherogenicity of lipid changes induced by carbohydrate feeding have been made based on risk factor analysis of epidemiologic data derived from populations consuming high-fat diets (14, 149, 161, 185). These LF-diet-induced changes that are potentially atherogenic have been given much media attention (186). To date, however, no long-term HC feeding studies have been performed in which the endpoints assessed were specific, clinical outcomes. Therefore, the only long-term data available are from the secondary prevention trials mentioned above (177, 178, 180), which indicate a net benefit to those with preexisting coronary artery disease. Whether LF-HC diets provide a net benefit with respect to new disease risk is currently a key and unresolved public health issue.

FUTURE RESEARCH

Study design constraints

Over the past 4 decades, the results of studies of carbohydrate-induced HPTG have been inconsistent. Human studies are expensive, time consuming, and have design constraints. The following is a summary of some investigational shortcomings and how these may account in large part for the controversy over whether LF-HC diets provide net benefit to health. First, the studies conducted have been observational in nature. A good portion of our under-



standing of carbohydrate-induced HPTG is based on observed phenomenon, rather than on results of studies designed to determine the mechanism. In addition, many of the metabolic studies conducted so far have had small sample sizes (<30 subjects). Efforts should be made to improve our ability to quantify metabolic flux in studies with larger numbers of subjects. Second, to decrease the variability in dietary intake data, many investigators have used liquid-formula diets. Therefore, it is difficult to extrapolate study findings to the metabolic changes associated with more regular patterns of eating. This was more of a problem in earlier published studies. In recent years, the use of whole-food diets has become common, although the preparation of such diets requires increased personnel time and expense. Third, the duration of most dietary studies has been too short to extrapolate the findings to the long-term dietary consumption of individuals over a life span. In this respect, the question of the transitory nature of carbohydrate-induced HPTG is still not completely answered. Longer studies in which all food intake is controlled are not feasible; thus, increasing the duration of feeding studies will require an outpatient feeding regimen, ie, one in which dietary compliance is no longer assured. Nonetheless, understanding the adaptability of persons to LF-HC diets will be key for predicting the long-term benefits and risks of these diets. Fourth, kinetic studies required to understand metabolic differences elicited by different diets are optimally performed when the subjects are in a metabolic steady state throughout the data collection period. To accomplish this, studies have frequently been conducted in the fasting state, or when subjects were continually consuming small amounts of energy (liquid or solid) frequently (every half-hour) throughout the day, causing measurements of triacylglycerol production to be conducted in nonphysiologic states. Again, this design makes it difficult to generalize the findings to normal meal-eating patterns. Fifth, many studies of carbohydrate feeding have not shown a statistically significant change in triacylglycerol concentrations, which may be due to the fact that the subject population consisted of persons with different lipoprotein phenotypes. Future studies should include characterization of the lipoprotein phenotype of the subjects and assessment of the changes in the various lipoprotein classes (chylomicrons, VLDL, IDL, etc). Large variability in triacylglycerol measurements may also be due to a lack of standardized measurement. Concentrations of blood triacylglycerols vary more than the concentrations of most other metabolites and can be affected by previous ethanol consumption, dehydration, and other factors. This large daily variability can be decreased if subjects are instructed to fast for ≥ 12 h, abstain from ethanol for ≥ 2 d, and consume ≥ 473 mL (2 cups) of water ≈ 1 h before the collection of blood. In particular, the importance of the 2-d abstinence from ethanol is based on significant alterations in the plasma fatty acid pattern that persist 24 h after the consumption of alcohol (187) and elevations in triacylglycerols observed as late as 9 h after the consumption of ethanol with dinner (188).

Future research and overall conclusions

The following is a summary of some of the key questions regarding carbohydrate-induced HPTG. Some of them have been resolved; most, however, will require more research.

Is the phenomenon real? At what fat concentration does it occur?

Initially, carbohydrate-induced HPTG was thought to be a rare phenomenon, but it is now clear that most persons experience

elevations in triacylglycerol when dietary fat is replaced by carbohydrate. There appears to be no threshold for the effect. The replacement of dietary fat with as little as 5% carbohydrate can elevate triacylglycerol concentrations.

Is carbohydrate-induced HPTG transient? Can it be avoided?

Without weight loss, there appears to be only a partial normalization of triacylglycerol concentrations, which can remain 10% above baseline as long as the diet is consumed. In many persons, the effect of carbohydrate feeding can be significantly diminished by weight loss, exercise, and dietary restriction of a high percentage of monosaccharides. Postmenopausal women may be more sensitive to triacylglycerol induction and carbohydrate-induced HPTG may be further exacerbated by hormone replacement therapy. Because endogenous HPTG is a particularly strong risk factor for coronary artery disease in women, efforts should be made to determine whether a further elevation in triacylglycerols as a result of LF-HC feeding adds to this risk substantially.

Is there a difference between the effects of monosaccharides and polysaccharides?

Carbohydrate-induced HPTG is more extreme when it results from the consumption of a diet fed in liquid form in which the ratio of starch to sugar is <50:50 (when each is represented as a percentage of carbohydrate energy). Clearly, the presence of fiber is beneficial. Other components of whole-food diets in addition to fiber are likely to be beneficial as well.

Is VLDL overproduced?

Carbohydrate-induced HPTG appears to result from the overproduction of both VLDL triacylglycerol and VLDL particles; clearance of VLDL is also impaired. Because the concentration of other TRLs (eg, chylomicrons or IDL) may become elevated in carbohydrate-induced HPTG, efforts should be made to identify which lipoprotein particles are present in the blood. Research has shown that endogenous HPTG results from an overproduction of TG. By contrast, carbohydrate-induced HPTG is more related to reduced clearance of TG from plasma. Therefore, because the 2 HPTGs have different mechanisms, they do not necessarily pose the same health risks. More research is needed to sort out the differences between these 2 forms of HPTG. Carbohydrate-induced overproduction and reduced clearance of VLDL were measured in studies in which the HC diet was composed of a high percentage of sugars. Response among research subjects is highly variable and may be related to individual characteristics such as abdominal obesity, hypertension, or high fasting insulin, baseline glucose, or triacylglycerol concentrations. Why some persons are more sensitive to carbohydrate feeding will be an important question for future studies to answer.

Does de novo lipogenesis contribute to carbohydrate-induced HPTG?

De novo lipogenesis is not likely to be a primary factor in carbohydrate-induced HPTG because these fatty acids represent a small portion of total VLDL fatty acids unless diets high in sugars are fed. However, the relation between the glycemic index of food carbohydrates and their ability to stimulate de novo lipogenesis is of interest. De novo lipogenesis from carbohydrate could provide a signal within the hepatocyte to shift more plasma-derived fatty acids toward reesterification and triacylglycerol



synthesis. In this case, carbohydrate oxidation would be increased, fat oxidation would be decreased, and more fatty acids would be shunted toward VLDL production. Whether this actually occurs is unknown.

How does the potentially negative effect of triacylglycerol elevation interact with other risk factors for coronary artery disease?


Sequential meals that are higher in simple carbohydrate content have been shown to cause greater swings in insulin concentrations throughout the day than meals higher in fat. Does this repeated pattern lead to insulin resistance in the long term? The answer to this important question is not known. Clearly, overconsumption of carbohydrates will lead to weight gain, which precedes insulin resistance. Insulin resistance appears to contribute more to risk in some ethnic populations than in others. Understanding how changes in the dietary intake of specific populations interact with body weight, blood pressure, and other risk factors is of enormous importance. Does the reduction in HDL cholesterol that has been observed during carbohydrate-induced HPTG confer increased risk? Last, because endogenous HPTG is associated with increased blood clotting and reduced fibrinolysis, does the carbohydrate-induced form also alter the coagulation pathway?

What magnitude of triacylglycerol elevation represents an increase in risk?

Is a 0.68-mmol/L (60-mg/dL) increase in triacylglycerol detrimental if it raises triacylglycerol from 0.79 mmol/L (70 mg/dL) with consumption of a HF diet to 1.47 mmol/L (130 mg/dL) with consumption of a HC diet? If so, is it as detrimental as a 0.68-mmol/L (60-mg/dL) increase from 1.81 mmol/L (160 mg/dL) to 2.49 mmol/L (220 mg/dL)? Whether the same risks are incurred at every concentration of baseline triacylglycerol is not clear. More importantly, the clinical significance of carbohydrate-induced HPTG when blood cholesterol concentrations are at the same time significantly decreased remains to be determined.

What magnitude of triacylglycerol elevation represents a significant change?

Some advocates of LF-HC diets have argued that elevations in triacylglycerol in subjects consuming very LF diets should be tolerated unless the increase in triacylglycerol is significant. An important question to answer then is, what increment represents a significant increase? One definition of a significant increase in triacylglycerol might be a change that is greater than would be expected as a result of day-to-day variation, which can average $\approx 10\%$ (189). A change of this size may be statistically significant but not necessarily physiologically or clinically significant. A second definition of a significant triacylglycerol change might be determined in light of epidemiologic data demonstrating an association between higher triacylglycerol concentration and increased disease risk. Thus, the risk of carbohydrate-induced HPTG is based on the risk associated with endogenous HPTG. This reasoning may not be sound if a similar metabolic basis for the 2 forms of HPTG (endogenous HPTG present while consuming a HF diet and the carbohydrate-induced form of HPTG) does not exist. Moreover, no studies conducted so far have been of sufficient duration and sample size to determine the influence of carbohydrate feeding on actual clinical outcomes (hard endpoints).

In conclusion, the American public has increased its consumption of carbohydrate, either through the consumption of more food per day or through replacement of fats with carbohydrates (190). At the same time, the incidence of obesity in this country is rising. Whether these 2 trends are linked is unknown. However, if they continue, health professionals will observe the phenomenon of carbohydrate-induced HPTG more often. Understanding the causes of carbohydrate-induced HPTG and its ramifications in terms of health will be important research goals for the future. 

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