Symposium: Carbohydrates—Friend or Foe

Effect of Dietary Carbohydrate on Triglyceride Metabolism in Humans

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ABSTRACT When the content of dietary carbohydrate is elevated above the level typically consumed (>55% of energy), blood concentrations of triglycerides rise. This phenomenon, known as carbohydrate-induced hypertriglyceridemia, is paradoxical because the increase in dietary carbohydrate usually comes at the expense of dietary fat. Thus, when the content of the carbohydrate in the diet is increased, fat in the diet is reduced, but the content of fat (triglycerides) in the blood rises. The present article will review studies of carbohydrate-induced hypertriglyceridemia, highlighting data obtained in fasted subjects habituated to high carbohydrate diets, data obtained from subjects in the fed state, and metabolic studies investigating fatty acid and triglyceride synthesis in subjects consuming diets of different carbohydrate content. The available data have been recently expanded by new methodologies, such as the use of stable isotopes, to investigate the metabolism of sugars in humans in vivo. Given the significant increase in body weight observed in the American population over the past decade and the changing availability of carbohydrate in the food supply, future studies of carbohydrate-induced hypertriglyceridemia promise to provide important information of how the macronutrient composition of the diet can influence health.


KEY WORDS: dietary carbohydrate, triglycerides, lipogenesis, human subjects, feeding study

When individuals reduce their intake of dietary fat, they frequently increase their intake of carbohydrate, and a common observation is that their blood concentration of triglycerides (TG) rises. This phenomenon, known as carbohydrate-induced hypertriglyceridemia (HPTG), has been observed in research subjects consuming high carbohydrate, low fat diets for as few as 5 d. This article reviews how the phenomenon has been studied previously, in both the fasted and fed states; what is currently known about the metabolic mechanisms that cause blood TG elevation; and the clinical implications of these diet-induced changes in blood lipids.

Increases in dietary carbohydrates lead to elevations in both fasting and postprandial lipemia

Numerous studies have investigated the effects of alterations in dietary carbohydrate on fasting blood TG concentrations (1). One example of data is from 34 patients with coronary artery disease who were switched to a diet very high in dietary carbohydrate (76%) with almost no fat (8% of energy). For the group as a whole, the average plasma TG concentration did not increase significantly from the baseline diets, although a highly variable response was noted in the data of individual subjects (2). Those with a body mass index (BMI; expressed as kg/m²) ≥ 28 kg/m² experienced a 30% increase in TG concentration, whereas those with a BMI < 28 kg/m² experienced no change ($P$ < 0.05 for the interaction between treatment and BMI group). These data demonstrate that certain characteristics (e.g., BMI) can make some individuals more sensitive to lipid and lipoprotein changes when dietary carbohydrate is increased. Such characteristics that have been identified from previous work in this field and include BMI, insulin sensitivity, concentration of TG before the dietary change is made (4), hormone replacement therapy (5) and genetic factors (6).

A carbohydrate-induced effect on fasting TG concentration has been established over the past four decades, and it is now clear that the concentrations of both very low density lipoprotein (VLDL) and chylomicrons are elevated in the fasting state. The effect of carbohydrate feeding to increase TG concentrations in the postprandial state has become more evident recently. A postprandial study of eight postmenopausal women making graded changes to reduce dietary fat intake and increase carbohydrate intake showed sequential elevations in fasting TG concentration as dietary carbohydrate was increased from 50% to 67% of energy (7,8). Fasting TG concentration rose from 1.8 mmol/L on the ad libitum 50% carbohydrate diet to 2.3 mmol/L on the 67% carbohydrate diet. The incremental area under the curve (AUC) of postprandial TG concentrations was similar across all diets. Higher absolute concentrations of circulating TG from VLDL and chylomicrons in the postprandial period were observed on higher carbohydrate diets, and these concentrations were strongly correlated to the elevations in fasting plasma TG.
concentration. Thus, against this higher load of TG in the blood in the fasting state, further addition of TG after absorption of a fatty meal lead to significantly higher postprandial TG concentrations. In this study, the subjects were fed high carbohydrate diets for 4 wk and the HPTG ensued gradually over that time.

By contrast, the effects of elevated TG during high carbohydrate feeding can be observed even after a single meal. Harbis et al. (9) fed four test meals varying in glycemic index to 10 healthy men. Mixed meals with a high glycemic index contained either white bread or spaghetti and those with a low glycemic index contained kidney beans or no carbohydrate at all (i.e., protein and fat only). Neither the amplitudes of the chylomicron TG responses nor the total chylomicron-TG AUC were different between the various meals. The similar shape of the chylomicron-TG curves suggests that neither chylomicron-TG production (release from the intestine) nor TG clearance rates (from the plasma via lipases) were affected by a higher glycemic index. In contrast to the chylomicron-TG data, chylomicron apolipoprotein (apo) B48 concentrations were significantly elevated after meals with a high glycemic index meals compared with those with a low glycemic index. For the low glycemic index meals, apoB48 peaked at 3 h and fell as would be expected during the latter phases (3–6 h) of the test to return to baseline values. This fall in apoB48 concentration between 3 and 6 h was delayed after the high glycemic index meals (9). One interpretation of these data is that higher postprandial glucose and insulin concentrations may act directly on the liver to slow chylomicron particle clearance via receptor-mediated events. Indeed, in the study by Harbis et al. (9), incremental 1–6-h AUC data for apoB48 were positively and significantly correlated with higher insulin AUC.

Because changes occur in the flux of metabolites after the ingestion of a mixed meal, the body is not in a steady state. Therefore, postprandial changes in concentrations of apoB48 or TGs can only be used as a starting point to hypothesize how lipoprotein particle and TG production and clearance rates may be affected by differences in glycemic index. In studies using stable isotopes, actual measurements of particle turnover has allowed for the identification of the metabolic mechanisms that cause carbohydrate-induced HPTG.

Studies of TG turnover and lipogenesis

Numerous studies of TG production and clearance rate have been performed to investigate the effect of high carbohydrate diets on the concentration of VLDL particles (apoB100) and VLDL-TG (1). Feeding a high carbohydrate diet increases the production rate and reduces the clearance rate of VLDL particles. Similar effects have been observed for VLDL-TG production and clearance. Delineating whether the elevation in blood TG is due to production or clearance is important because these two situations can have very different ramifications with respect to cardiovascular risk. If carbohydrate-induced HPTG results from increased production of VLDL particles, this mechanism also has the potential to increase the blood cholesterol load because hepatic cholesterol secretion rate is proportional to the VLDL particle secretion rate. A greater number of particles secreted per hour can also increase the LDL particle concentration because VLDL particles are the precursors of LDL in the blood. Alternatively, the cholesterol load of the blood is less likely to increase if carbohydrate-induced HPTG results from reduced clearance of TG rather than from overproduction. A reduced clearance effect can be targeted by therapeutic strategies that stimulate TG clearance, such as exercise and energy restriction.

In addition to turnover measurements, the sources of fatty acids that are used for hepatic VLDL-TG synthesis are important variables to consider. Four potential sources are: 1) fatty acids derived from the plasma free fatty acid pool, which in the fasting state primarily originate from adipose tissue; 2) fatty acids derived from the de novo lipogenesis pathway in the liver; 3) fatty acids originally derived from the diet that enter the liver via chylomicron remnant clearance; and 4) fatty acids that are stored in the liver in TG droplets. Two candidate sources have been investigated: the free fatty acid pool (source 1) and de novo fatty acids (source 2).

The contribution of free fatty acids to VLDL-TG synthesis during carbohydrate-induced HPTG is an important variable to measure because endogenous HPTG has been shown to result from a greater flow of free fatty acids to the liver (10). Endogenous HPTG is genetically controlled; manifests as elevated blood TG, cholesterol concentrations or both on higher fat diets; and significantly increases the risk of coronary heart disease development (11). If the consumption of a high carbohydrate diet increases the VLDL-TG production rate through a mechanism similar to that of endogenous HPTG, similar increases in coronary heart disease risk might be attributed to the two HPTG.

The second source of fatty acids for VLDL-TG synthesis, de novo lipogenesis, could be stimulated by an excess flow of glucose through the glycolysis pathway and into the hepatic acetyl coenzyme A pool. We measured the contribution of both free fatty acids and de novo lipogenesis to VLDL-TG synthesis in healthy men before and after 5 wk of isoenergetic, high carbohydrate feeding in which the diet was rich in polysaccharides (complex carbohydrates) and high in fiber. We found no evidence that carbohydrate-induced HPTG resulted from elevated free fatty acid flow or de novo lipogenesis (12). The primary phenomenon of carbohydrate-induced HPTG could be explained by a 37% reduction in TG clearance from the blood.

By contrast, an increase in de novo lipogenesis was observed by Hudgins et al. (13) who fed healthy subjects high carbohydrate diets rich in monosaccharides and disaccharides (simple sugars). Aside from pointing out that this diet stimulated de novo lipogenesis, the reader is referred to that publication to appreciate the large variability among subjects in the amount of de novo lipogenesis. A particularly striking observation was that two general patterns of de novo lipogenesis were observed throughout the day: a constant and a diurnal pattern (13). For subjects exhibiting a carbohydrate-stimulated increase in de novo lipogenesis of the constant pattern, the percentage of VLDL-TG fatty acids derived from the de novo pathway was steady throughout the 24 h of data collection. Lipogenesis was the same during all meals and even when the subjects were sleeping. For subjects exhibiting a diurnal pattern, the percentage of VLDL-TG fatty acids derived from de novo synthesis was very low in the morning. Levels rose with every meal, peaked at ~ 10 PM, fell through the night and were low again in the morning. No clinical characteristics were found that would distinguish the subjects in the constant or diurnal groups. That is to say, the two groups had the same number of obese and lean subjects, percentages of men and women and young and older subjects. The two groups did not differ by blood concentrations of metabolites (insulin, glucose, fatty acids, etc.) or by hormone concentrations.

These observations illustrate that extremely little is known about the stimulation of fatty acid synthesis in humans. Now that accurate methods are available to measure this process in
vivo (14–16), efforts should be made to study children, a population for which we have no data and one that may be very susceptible to obesity as a result of the overconsumption of simple sugars. Studies are also needed to assess the contribution of de novo lipogenesis to HPTG in adults with insulin resistance.

**Lipogenesis and the glycemic index**

It might be assumed by some individuals that the higher the blood glucose concentration after a meal, the more likely that fatty acids will be synthesized from that glucose because of an oversupply of carbon units in the liver. If elevated concentrations of insulin and glucose occur after higher carbohydrate meals (i.e., meals with a higher glycemic index) and stimulate de novo lipogenesis, a statistical relationship might be observed between these variables. However, an analysis of data from four studies showed no such positive relationship between fractional de novo lipogenesis and either blood insulin or glucose concentrations in subjects on high carbohydrate diets (17). In contrast, a positive association was found between fasting insulin concentration and de novo lipogenesis in subjects on a high fat diet. These data suggest that in healthy subjects, some other variable besides glucose or insulin concentration is directly related to increased lipogenesis, or, if higher postprandial glucose or insulin concentrations are the root cause of increased lipogenesis, there exists an intermediary effect translating this signal in the liver. Further study is needed to elucidate the relationship between the glycemic index of a meal and its ability to stimulate lipogenesis.

**Summary and future research priorities**

The influence of lowering dietary fat and increasing dietary carbohydrate goes beyond the elevation in plasma TG concentration. The concurrent reduction in low density lipoprotein cholesterol concentration makes it difficult to predict whether the phenomenon of carbohydrate-induced HPTG will have dramatically negative health consequences. A number of key research questions remain to be addressed (Table 1). Which subject characteristics are related to elevations in lipogenesis and which hormones or genes control the diurnal pattern of fatty acid synthesis? Preliminary data suggest that the state of insulin resistance at the level of the liver may be associated with increased lipogenesis. Do different sugars (glucose, lactose and maltose) have different effects on lipogenesis, TG clearance and VLDL-particle production rate and what about the structure of the polysaccharide? Is the absorption rate of the carbohydrate important in the lipogenic potential of the sugar? Further method development will be necessary to quantify de novo lipogenesis in human adipose tissue in vivo and to determine whether this amount of lipogenesis can contribute substantially to obesity. Finally, given the shift in the distribution toward elevated body weights in the population, the metabolic effects of overconsumption of dietary carbohydrate will be a critical focus of future research.

**LITERATURE CITED**