Sugars, hypertriglyceridemia, and cardiovascular disease

Susan K Fried and Salome P Rao

ABSTRACT Short-term studies consistently show that raising the carbohydrate content of the diet increases serum triacylglycerol concentrations. As compared with starches, sugars (particularly sucrose and fructose) tend to increase serum triacylglycerol concentrations by ≈60%. The magnitude of the effect depends on other aspects of the diet, including the total amount of carbohydrate and the types of fat, carbohydrate, and fiber, but definitive studies to describe the dose-response relations are not available. Longer-term studies show that some high-carbohydrate diets are not associated with increased fasting serum triacylglycerol concentrations. However, sedentary subjects with upper-body and visceral obesity who have the metabolic syndrome tend to be at higher risk for hypertriglyceridemia in response to high-sucrose and high-carbohydrate diets; moderate weight loss mitigates the effect. Hyperinsulinemia or insulin resistance may play a role in promoting higher rates of VLDL synthesis and hypertriglyceridemia in obesity, but the mechanisms remain unclear. The effect of fructose in promoting triacylglycerol synthesis is independent of insulinemia, however. In terms of the long-term effects of diets high in sugars on the risk of cardiovascular disease, available epidemiologic evidence indicates no association of sugars or total carbohydrate intake per se, but high dietary glycemic load is associated with higher serum triacylglycerol concentrations and greater risk of coronary heart disease in women. Studies are needed to delineate the independent effects of dietary sugars and glycemic load on serum triacylglycerol concentrations in lean and obese men and women and to determine whether the elevations in fasting and fed concentrations of serum triacylglycerol with high-carbohydrate and high-sugars diets are associated with increased risk of cardiovascular disease.

INTRODUCTION

Epidemiologic evidence and tightly controlled clinical studies indicate that variations in the amounts and types of fats in the diet influence the risk of cardiovascular disease (CVD) by increasing serum LDL cholesterol (1, 2). Guidelines for reducing the risk of CVD in the general population or for treating high cholesterol concentrations are therefore focused both on restricting total fat to ≤30% of energy as a means of decreasing saturated fat consumption and on replacing fat energy with carbohydrate energy (3). Concerns about this approach have been raised on the basis of the results of numerous short-term (days to weeks) studies indicating that diets high in carbohydrates, particularly sugars and even more particularly sucrose and fructose, increase serum triacylglycerol concentrations and decrease serum HDL cholesterol and may therefore increase the risk of CVD (1, 4). However, it is unclear whether the moderate alterations in the lipid profile associated with higher-carbohydrate diets affect CVD risk (5).

Obesity, particularly abdominal obesity, represents an independent risk factor for the development of CVD in men and women (6–8). Abdominally obese individuals exhibit a cluster of metabolic abnormalities that are typical of the so-called metabolic syndrome (syndrome X), including insulin resistance, impaired glucose tolerance, high concentrations of circulating triacylglycerols, low concentrations of HDLs, and high concentrations of small, dense LDLs (9–12). Frayn and Kingman (13), Parks and Hellerstein (4), and Hellerstein (14) provided encyclopedic reviews of the determinants and mechanisms of carbohydrate-induced hypertriglyceridemia.

The focus here is on the effects of dietary sugars in the context of diets recommended for lowering CVD risk, specifically with regard to the following issues: 1) What is the independent effect of dietary sugars on fasting and fed concentrations of serum triacylglycerol? 2) Do other dietary factors (eg, amount and type of fat, composition of other dietary carbohydrates, fiber) modify the hypertriglyceridemic effects of high-sugars meals or diets, and what amount of sucrose can be incorporated into healthy diets without deleterious effects on the serum lipoprotein profile? 3) Does the rate of absorption of dietary carbohydrate [reflected in the glycemic index (GI)] affect circulating triacylglycerol? 4) Does abdominal obesity influence the metabolic effects of diets that are high in total carbohydrate or high in sugars? 5) What mechanisms underlie the apparently greater responsiveness of abdominally or viscerally obese individuals to the hypertriglyceridemic effects of high-carbohydrate and high-sugars diets? 6) Can exercise diminish the hypertriglyceridemic effects of diets that are high in sugars?
As shown in Figure 1, once absorbed, dietary fructose is mainly taken up by the liver, where it is phosphorylated to fructose-1-phosphate by fructokinase and can then be converted to glycerol-3-phosphate, which serves as a backbone for triacylglycerol synthesis (13). In contrast, glucose is metabolized via glucokinase and isomerized to fructose-6-phosphate; its progression through glycolysis then depends on the activity of phosphofructokinase, a highly regulated enzyme. Because fructose bypasses a major rate-determining step in glycolysis, a high influx of fructose to the liver promotes triacylglycerol synthesis and VLDL production.

The increased fasting triacylglycerol concentration associated with high dietary sucrose is accounted for by accumulation of atherogenic triacylglycerol-rich remnants. Sucrose may increase hepatic triacylglycerol synthesis and VLDL production and also decrease the catabolism of triacylglycerol-rich lipoproteins (14). Rates of hepatic triacylglycerol synthesis would be expected to be highest when the supply of fatty acids to the liver is also high. The likely sources of fatty acids are adipocyte lipolysis and the uptake of triacylglycerol-rich remnant particles. It is also possible that triacylglycerol stored within lipid droplets in hepatocytes can be used for VLDL synthesis. Moreover, the supply of fatty acids modulates the packaging of triacylglycerol into VLDL. The provision of fatty acids decreases apolipoprotein B degradation and therefore promotes VLDL synthesis and also hepatic triacylglycerol synthesis and VLDL production and also decreases the catabolism of triacylglycerol-rich lipoproteins (14).

Rates of hepatic triacylglycerol synthesis would be expected to be highest when the supply of fatty acids to the liver is also high. The likely sources of fatty acids are adipocyte lipolysis and the uptake of triacylglycerol-rich remnant particles. It is also possible that triacylglycerol stored within lipid droplets in hepatocytes can be used for VLDL synthesis. Moreover, the supply of fatty acids modulates the packaging of triacylglycerol into VLDL. The provision of fatty acids decreases apolipoprotein B degradation and therefore promotes VLDL synthesis (15). The role of insulin in determining hepatic triacylglycerol and VLDL production is controversial, appearing to be acutely inhibitory but chronically stimulatory (16–18). High-sugars diets also modify the rate of clearance of circulating triacylglycerol (13). Because the high-sugars diets increase concentrations of VLDL, these particles may compete for hydrolysis by lipoprotein lipase, which delays the clearance of chylomicrons and accounts for their presence in fasted serum (19). The higher affinity of lipoprotein lipase than of VLDL for chylomicrons may also be a factor in determining the relative rates of triacylglycerol clearance in these lipoprotein fractions (20). Although high-sugars diets increase de novo fatty acid synthesis by the liver, the absolute rate is too low to account for the elevated triacylglycerol production (21). Effects are similar in lean and obese subjects (22).

**DIETARY CONTEXT MAY MODIFY DOSE-RESPONSE CURVES FOR THE EFFECT OF SUGARS ON SERUM TRIACYLGLYCEROLS**

The effects of sugars on serum triacylglycerols have been studied in the context of diets that vary in the quantity of total carbohydrate (moderate to high, ie, 40–70%), fiber content, and types of fat. The extent to which dietary context influences the hypertriglyceridemic effects of sugars is not clear. For example, few studies address the question of whether the dose-response curves for the effect of sugars on serum triacylglycerol are affected by the total carbohydrate or the types or amounts of fats in the diet. Unsaturred fats lower triacylglycerol concentrations (23, 24), and some data indicate that high-saturated-fat diets may potentiate the sucrose effect (25).

**Very-low-fat (10–15% of energy), high-carbohydrate diets elevate fasting serum triacylglycerol whether the carbohydrate source is equal amounts of sugars and starches (4, 22, 26) or mainly starches (27).** Albrink and Ullrich (28) found a dose-dependent effect of the substituting sucrose for starch in the content of very-high-carbohydrate (70% of energy), very-low-fat (15% of energy) diets in healthy, young normolipidemic men. As compared with baseline concentrations with the men’s usual high-fat diet (40% of energy), the 0% sucrose diet tended to decrease serum triacylglycerol concentrations, and the 18% sucrose diet had no effect. The 36% and 52% sucrose diets led to a sustained increase in serum triacylglycerol concentrations over the 11-d test period; high amounts of dietary fiber (≥34 g/d) prevented the rise in serum triacylglycerol with the 36% sucrose diets but had no effect at 52% sucrose. These short-term dose-response studies indicate that ≤18% sucrose can be incorporated into a very-high-carbohydrate diet without increasing serum triacylglycerol concentrations and that high-fiber diets can attenuate the effects of higher-sucrose diets on serum triacylglycerol concentrations. However, it is unclear whether the dose-response relation for sucrose effects on serum triacylglycerol would be shifted in the context of a diet that is more moderate in total carbohydrates. Only limited data are available to address this important question, as reviewed below.

Several recent studies examined the independent effect of dietary sucrose on serum lipids in the context of diets that contain moderate quantities of total carbohydrate and fat. Markmann et al (29) and Raben et al (30) tested the effects of high sucrose (23% of energy) or low sucrose (2.5% of energy) in a diet with 29% of energy from fat and 59% of energy from carbohydrate for 2 wk in healthy, nonobese women. Diets were fed ad libitum, and the subjects were allowed to eat to satiety. Both diets increased serum triacylglycerol concentrations more than the control high-fat (46% of energy from fat, 21% of energy from saturated fats) diet did. However, the high-sucrose diet produced significantly higher concentrations of fasting and nonfasting triacylglycerol than did the low-sucrose diets (29). These data led Markmann et al to conclude that their short-term results indicated that high-carbohydrate diets in which a high amount of sucrose is substituted for saturated fat are not advisable. However, no information is available on whether more moderate
quantities of sucrose (>2.3% but <23% of energy) also increase serum triacylglycerol concentrations. Further studies of the dose-response for the effect of sucrose on serum triacylglycerols in the context of moderate carbohydrate diets are needed to guide policy recommendations.

Data from Hudgins et al (31) using liquid or solid diets show that sucrose increases serum triacylglycerol concentrations, but starch does not. Thus, the design of many studies of total carbohydrate and serum triacylglycerols are somewhat confounded by the covariation of sugars and total carbohydrate intake. Carbohydrate is increased whereas the ratio of sugars to total carbohydrate is kept constant (21). For example, Reaven’s group has consistently reported increased fasting and postprandial triacylglycerol concentrations with diets with 60% of energy from carbohydrate than with diets with 40% of energy from carbohydrate in which the ratio of sugars to starch was constant at one-third of the total (32). The intake of total sugars in the high-carbohydrate group was 18% of energy, compared with 12% of energy in the low-carbohydrate group, and the intake of sucrose was 8% of energy and 12% of energy, respectively. Although neither of these diets is considered high in sucrose (ie, ≥20% of energy), the increase in serum triacylglycerol concentrations may be due partly to the increase in sucrose rather than to the increase in total carbohydrate. In support of this possibility, an early study from Reaven’s laboratory showed that, when the sucrose content of diet was held constant at 13% of energy (20 g), but total carbohydrate was increased from 40% of energy to 60% of energy, the increase in fasting triacylglycerol was attenuated, and insulinemia was unchanged (33). Similarly, Vidon et al (34) found no effect on fasting serum triacylglycerol concentrations when the carbohydrate content of the diet was increased from 40% of energy to 55% of energy with fructose held constant at 18–20 g/d. Taken together, these studies suggest that, if the content of triacylglycerol-raising sugars (ie, sucrose and fructose) in the diet is kept in the moderate range, total dietary carbohydrate can be increased to 55% or 60% of energy without risking an increase in fasting serum triacylglycerol concentrations. Studies of fasting as well as postprandial triacylglycerol concentrations and kinetics are needed to fully evaluate the independent effects of dietary sugars and carbohydrate quality (30, 35, 36).

Knowledge is limited about the effect of high-carbohydrate or high-sugars diets on serum triacylglycerol concentrations in children. A recent report showed no significant effect of increasing dietary fructose from 6% of energy to 24% of energy in a diet with 60% of energy from total carbohydrate or of increasing total carbohydrate from 30% of energy to 60% of energy in children or adolescents (37). However, some persons did show exaggerated responses, and further research is needed to identify the underlying mechanisms and the prevalence of high-responders in these age groups.

### GENETIC FACTORS INFLUENCE SERUM TRIACYLGlycerol RESPONSES TO HIGH-SUGARS DIETS

The sudden introduction of very-high-carbohydrate diets (with dietary sucrose held constant at 25% of energy) appears to induce more profound increases in fasting serum triacylglycerol concentrations than does the introduction of progressively higher carbohydrate diets (38). However, some subjects show large increases in triacylglycerol concentrations even when the high-carbohydrate diet is introduced more slowly. One subject showed a clear dose-dependent increase (≤2-fold) in serum triacylglycerol and VLDL triacylglycerol concentrations, despite the slow transition from the low-carbohydrate (45% of energy) diet to the high-carbohydrate (65% of energy), high-sucrose diet, whereas several others showed a more modest increase. Thus, further studies of the tolerance of high and low responders to the graded introduction of high-carbohydrate and high-sugars diets and the genetic determinants of sucrose-induced hypertriglyceridemia are needed.

Nicklas et al (39) reported that the apolipoprotein E genotype determines the hypertriglyceridemic response to the step I American Heart Association diet that is high in carbohydrates and moderate in fat. In women with the APOE4+ genotype, triacylglycerol increased, whereas, in women with the APOE4+ genotype, it did not (40). An epidemiologic study showed that Finnish subjects with the E2 allele showed higher serum triacylglycerol concentrations when consuming a high-sucrose diets than did subjects with the E3 or E4 allele (41). The number of subjects examined in this study was small, as was the range of sucrose intakes (1–11% of energy). Studies are needed to define the genetic determinants of the hypertriglyceridemia response to high-carbohydrate and high-sucrose diets. It would be logical to focus studies on the influence of polymorphisms in genes involved in sucrose and fructose metabolism and hepatic VLDL production as well as on clearance mechanisms (42).

### The hypertriglyceridemic effects of high-sugars, high-carbohydrate diets may dissipate with time

The long-term effects of high-sucrose and high-starch diets were tested in the Carbohydrate Ration Management in European National diets (CARMEN) study (43). This 6-mo, multicenter, randomized controlled trial compared the effects of a 10% increase in each carbohydrate source (and a 10% decrease in total fat) in 398 moderately obese men and women [average body mass index (BMI; in kg/m²): 30]. This study was well-controlled, in that most foods were purchased in a special shop, which enhanced compliance while allowing for more of a real-life situation. The low-fat, high-sucrose group increased their intake of sucrose by 33 g (8%) to ≥29% of energy, and the starch group decreased their intake of sucrose by 44 g (−3.5%) to 19% of energy while increasing their starch intake by 8%. Both low-fat interventions resulted in a modest decline in food intake and body weight (−0.9 kg for the sucrose group and −1.8 kg for the starch group) after 6 mo, whereas the seasonal control group and high-fat groups tended to gain weight. Neither the high-sucrose diet nor the high-starch diet affected fasting serum triacylglycerol concentrations in these overweight subjects, but possible effects of the high-sucrose diet on postprandial triacylglycerol concentrations cannot be ruled out.

The importance of the small weight loss in preventing the expected increase in serum triacylglycerol concentrations in the CARMEN trial was supported by Schaefer et al (44) in a study of obese men. Similarly, Kasim-Karakas et al (45) reported that postmenopausal women consuming a high-carbohydrate diet with 15% of energy from fat that emphasized starchy foods were able to maintain a significant weight loss and did not have increased triacylglycerol concentrations. Taken together, these studies indicate that, in highly compliant and motivated patients, low-fat, high-carbohydrate diets containing low or high amounts of sucrose can be followed over the long term without detrimental effects on fasting serum triacylglycerol (or HDL) concentrations (43). Nevertheless, it will be important to investigate further the effects of long-term consumption of high carbohydrate with various contents.
of sugars on postprandial serum triacylglycerol concentrations and on the apolipoprotein composition and atherogenicity of the triacylglycerol-rich particles.

**Hypertriglyceridemic effects of high-sugars diets may be sex specific**

Fructose is considered the most hypertriglyceridemic sugar and is thought to account for the hypertriglyceridemic effect of sucrose (46). The addition of a large amount of fructose (17% of energy) to foods increased day-long plasma triacylglycerol concentrations by 32% in healthy lean men after 6 wk (47). However, there was no effect of this high-fructose diet in healthy lean women, which suggests that there is a pronounced sex difference in fructose metabolism, and this possibility should be considered in the design of all future studies.

**Metabolic effects of fructose depend on the dose**

In contrast to the effect of chronic consumption of high amounts of dietary fructose, low amounts of fructose added to a glucose load improved the area under the glucose curve during a tolerance test without affecting the triacylglycerol response (48). Most, if not all, studies to date used either sucrose or pure fructose. High-fructose corn syrups have replaced sucrose in many applications over the past 20 y. Despite the name, most of the high-fructose corn syrup used is similar in composition to sucrose, and thus its metabolic effects should also be similar (49). Future studies on the effects of fructose should consider the source and dietary form of fructose (solid food or beverage) and the sex-, genetics-, and obesity-related differences in responsiveness.

**ANALYSIS OF THE GLYCEMIC EFFECTS OF SUGARS AND STARCHES MAY BE IMPORTANT IN UNDERSTANDING THEIR ROLE IN CVD RISK**

Despite strong clinical data that sugars intake should be related to serum triacylglycerol concentrations, epidemiologic studies showed no independent relation between sugar intake and coronary heart disease (CHD) risk (50, 51). The classification of carbohydrates into simple and complex carbohydrates may not be the most helpful predictor of their metabolic properties. Rather, classification of dietary carbohydrates according to their glycemic effects appears to be a key determinant of their metabolic and long-term health effects. The GI assesses the glucose area under the curve after ingestion of a set amount of carbohydrate (eg, 50 or 100 g) from a food relative to the same amount of carbohydrate from a reference food (eg, 50 g glucose or 100 g white bread) (52). Certain starches are digested and absorbed more rapidly, which leads to higher peaks in blood glucose and insulin. In addition, early work by Jenkins et al (53) showed that low-GI diets decrease serum triacylglycerol concentrations in patients with hypertriglyceridemia. Thus, it is conceivable that different high-starch diets used in reported studies might have very different metabolic effects, which would lead to inconsistent results between laboratories attempting to delineate effects of dietary sugars. A limitation of the GI with respect to understanding the regulation of triacylglycerol concentrations is that it does not account for the unique metabolic effects of fructose that are independent of its effects on glycemia.

The glycemic load of a diet is calculated as the amount (in grams) of carbohydrate foods consumed multiplied by their GIs, summed across all foods. Liu et al (51) reported that the dietary glycemic load calculated from food-frequency questionnaire data best predicts the risk of CHD in the Nurses’ Health Study (relative risk =2 for subjects with a BMI > 23). The relation became even stronger when the data were adjusted for potential confounders such as dietary fatty acids. In contrast, total carbohydrate was weakly and nonsignificantly related to CHD risk, and sugars (eg, glucose, fructose, sucrose) or complex carbohydrate intake showed no relation. A problem with this analysis is that the fructose contained in dietary sucrose was not considered to contribute to the dietary fructose load. In addition, the GI of many foods depends on how the foods are prepared (52). Nevertheless, the utility of the glycemic load as a predictor of fasting serum triacylglycerol concentrations is supported by the finding that glycemic load was related to fasting triacylglycerol concentrations in postmenopausal women in the Nurses’ Health Study (54). Both total carbohydrate and glycemic load independently predicted fasting triacylglycerol concentrations. These data appear to provide a basis for the relation between glycemic load and CHD. In contrast, no relation among GI, metabolic risk factors, and incidence of CHD was observed in elderly men in the Zutphen Elderly Study (55).

The mechanism by which high-GI starches increase triacylglycerol concentrations appears to involve their effects on glycemia and insulinemia (51). In contrast, fructose has a very low GI and increases triacylglycerol concentrations even though it produces only a moderate increase in insulin concentrations. Thus, clinical studies are needed to determine the sensitivity to fructose-induced hypertriglyceridemia in the context of a low-glycemic-load diet. One study reported no difference in postprandial lipemia (area under the curve) in lean healthy men after the ingestion of fat loads mixed with carbohydrates with low or high GIs (17), despite different insulin responses. However, the time course differed, so that intestinally derived triacylglycerol-rich lipoproteins containing apolipoprotein B-48 peaked later after meals with higher GIs. The higher atherogenicity of these particles may contribute to the increased risk of CHD with diets containing a high glycemic load.

**ABDOMINAL OBESITY MAY EXACERBATE THE HYPERTRIGLYCERIDEMIC EFFECT OF HIGH-SUGARS DIETS**

As the public becomes fatter, it is important to determine whether subgroups of the obese, such as those with abdominal obesity, are more responsive to the effects of high-carbohydrate diets and high-sugars diets on the serum lipid profile (56). Upper-body, particularly visceral, obesity is associated with higher fasting serum triacylglycerol concentrations (57). Roust et al (58) first showed in a small clinical study that women with upper-body obesity significantly increased their fasting and post-evening-meal serum triacylglycerol concentrations after 4 wk of eating a relatively high-starch diet (27% of energy from fat, 53% of energy from carbohydrate with 20% of energy as sugars and 11–13 g of fiber). In contrast, lean women and lower-body-obese women showed no response (or a trend toward improvement). Given the results of Roust et al (58) that fat distribution may modify the hypertriglyceridemic effects of dietary carbohydrate, it will be important to better characterize fat distribution in the subjects in terms of their upper-body subcutaneous and visceral adiposity. It is likely that the higher
rates of fatty acid turnover (59) in viscerally obese women would render them more responsive to carbohydrate-induced hypertriglyceridemia, and this should be analyzed in future studies. A decrease in the rate of clearance of triacylglycerol-rich lipoproteins also contributes to hypertriglyceridemia in abdominally obese men (60).

Poppitt et al (61) specifically examined the effects of ad libitum consumption of a low-fat (20–25% of energy), high-carbohydrate (47–58% of energy) diet that contained large amounts of sucrose (29–34% of energy) or high starch (33–36% of energy) in overweight subjects who had >3 symptoms of the metabolic syndrome. The range of intakes reflects purchased food and reported intake. This study lasted 6 mo and used the same shop system as the CARMEN study (43), which produced a high rate of compliance with the intended macronutrient manipulations. The high-starch diet led to a small weight loss and improved lipid profile. However, in a subgroup analysis, subjects who did not lose weight also did not show improvements in their lipid profile. The high-sucrose diet did not significantly change body weight (when all subjects are considered together), and it increased triacylglycerol concentrations more than the high-fat (31–36% of energy), high-carbohydrate diet and the low-fat, high-starch diets did. Thus, high-sucrose diets may worsen hypertriglyceridemia when consumed by obese persons in quantities that maintain their body weight.

Metabolic ward studies indicate that sugars may cause acute effects on postprandial serum triacylglycerol excursions. In a test meal situation, the addition of sugars to a fat load leads to a higher area under the curve for triacylglycerols (62, 63). However, Brynes et al (64) showed that men at risk of CHD, as compared with age- and weight-matched control subjects, did not show exaggerated incremental serum triacylglycerol responses to the addition of 75 g sucrose or glucose to a moderate fat load. Longer-term studies are needed, but this result suggests that the occasional ingestion of sucrose may not be deleterious in high-risk subjects.

**ALtered fatty acid metabolism in abdominal obesity may underlie increased responsiveness to diets high in sugars**

Reesterification of fatty acids derived from adipose tissue lipolysis provides a substrate for VLDL synthesis in the fasted state. Basal lipolysis assessed after an overnight fast is increased in obesity, which inflicts high fatty acid concentrations on the liver. Fatty acid turnover is even higher in upper-body and visceral obesity. High rates of lipolysis in enlarged visceral fat depots that drain portally (Figure 1) may contribute to the hyperresponsiveness of obese individuals to high-sugar (fructose or sucrose) diets. Mittendorfer and Sidossis (18) found that maintaining the supply of fatty acids to the liver of normolipidemic, lean subjects by infusion of a fat emulsion plus heparin during a hyperinsulenic clamp increased VLDL production without affecting clearance (18). Thus, the resistance of viscerally obese persons to the antilipolytic effect of insulin (65, 66) may also contribute to elevated fed concentrations of hepatic VLDL secretion and high concentrations of circulating triacylglycerol in the fed state. In addition, the higher concentrations of serum nonesterified fatty acids in association with diets high in sugars rather than starch may also increase serum triacylglycerol concentrations over a period of 24 h (67).

The hyperinsulinemia associated with obesity may also play a role in promoting hepatic triacylglycerol production, but the mechanism is uncertain (17). It may involve resistance to insulin’s acute effect to depress VLDL production, or it may result from the chronic stimulatory effect of insulin on triacylglycerol synthesis (16).

A low rate of hepatic fatty acid oxidation that is typical of states of leptin deficiency or resistance may contribute to carbohydrate-induced hypertriglyceridemia (68). Mittendorfer and Sidossis (18) found that fatty acid oxidation was reduced when high-carbohydrate diets (with 35% of energy from sugars) are fed to lean persons, and they proposed that this effect may shunt glucose carbons toward glycerol-3-phosphate and therefore triacylglycerol synthesis. Zucker obese rats have impairments in hepatic fatty acid oxidation and hypertriglyceridemia and the specific effects of diets with low and high amounts of sucrose or fructose should be studied further in humans.

**Exercise attenuates hypertriglyceridemic effects of high-sugars and high-carbohydrate diets**

Most studies of dietary effects on lipid profile deliberately select sedentary subjects. Although this selection undoubtedly provides data that are relevant to most Americans, these studies beg the question of whether a chronic lack of exercise contributes to the effect observed. When exercise was incorporated into the Step I or II American Heart Association diet program, there was a more marked drop in fasting serum triacylglycerol concentrations (69).

Koutsari et al (70), in an interventional study, determined that moderate exercise (60 min of treadmill walking at 61% of VO_{2max}) influences the acute increase in serum triacylglycerol in response to a very-low-fat (15% of energy) diet. Subjects were overweight (BMI: 26) postmenopausal women, and the interventions lasted 3 d. Koutsari et al found that the exercise intervention attenuated the rise in fasting serum triacylglycerol and prevented triacylglycerol responses to a high-fat meal. However, the total energy intake was clamped, so that the exercise group was probably in negative energy balance. Future studies should examine the effect of exercise with ad libitum feeding. In a different study, Koutsari and Hardman (71) found that 30 min of moderate-intensity exercise (running or walking at 61% of VO_{2max}) did not prevent the increase in fasting triacylglycerol in response to 3 d of a high-carbohydrate (70% of energy), high-sugars (50% of total carbohydrate) diet in normolipidemic young men. However, exercise prevented the postprandial response to a high-fat test meal (71). Future studies should also examine the responses to low-fat meals, because exercise may specifically affect the metabolism of chylomicrons carrying dietary fat as opposed to VLDLs that carry endogenously generated triacylglycerols. The mechanism underlying the improved serum triacylglycerol concentrations with exercise appears to involve an increase in the clearance of triacylglycerol and apolipoprotein E–rich remnants as well as an attenuation of the carbohydrate-induced inhibition of fatty acid oxidation (70).

Exercise training (fitness as assessed by high VO_{2max}) is associated with lower serum triacylglycerol concentrations in older men, independent of less fatness (72). The lower serum triacylglycerol (and higher HDL) concentrations were associated with...
higher lipoprotein lipase activity, tested in plasma after a postheparin challenge, which suggested an improvement in triacylglycerol-rich lipoprotein clearance (72). Exercise training is known to increase both muscle and adipose tissue lipoprotein lipase activity and therefore would be expected to protect against the triacylglycerol-raising potential of high-carbohydrate, high-sugars diets.

CONCLUSION

A recent report from the American Heart Association on sugar and CVD concluded that, although no dietary trials link sugars consumption and CVD, there are several reasons that sugars consumption should be limited (73), among which was evidence that sucrose has a dose-dependent effect on serum triacylglycerol concentrations. Similarly, the Dietary Reference Intake report on macronutrients concluded that, although there was strong evidence that over the short term that sugars can be hypertri glyceridemic, the link to long-term CHD risk was not strong enough to set an upper limit for total or added sugars based on the serum lipoprotein profile as an endpoint (74). The Dietary Reference Intake report recommended increasing exercise to help maintain a healthy body weight. If this recommendation is followed, the deleterious effects of high-sugars, high-carbohydrate diets on serum triacylglycerol concentrations will likely be minimized. Nevertheless, dietary recommendations to patients with the metabolic syndrome prudently recommend limiting sugars consumption (3, 75).

Long-term, randomized clinical studies are needed to assess whether there is a threshold at which the fructose and sucrose content of recommended diets cause abnormalities in triacylglycerol metabolism. For example, the relatively high-carbohydrate, high-fiber, moderate-fat Dietary Approaches to Stop Hypertension diet did not produce the predicted increase in fasting serum triacylglycerol concentrations (76). Whether this is due to the low sugars content of this diet is not clear, and this question merits further study.

The design of studies of sugars and triacylglycerol metabolism is complex, and interactions with the type and amount of fat, the GI of starches, and subject factors such as exercise, sex, and genetics must be taken into consideration. Because the consumption of sugars appears to be on the rise, such studies are of increasing importance for constructing therapeutic diets and sound public health recommendations to prevent CVD.

REFERENCES

12. Reaven GM. Do high carbohydrate diets prevent the development or attenuate the manifestations (or both) of syndrome X? A viewpoint strongly against. Curr Opin Lipidol 1997;8:23–7.
SUGARS, HEPTERTRIGLYCERIDEMIA, AND CVD


