Sugars in Nutrition, edited by M. Gracey,
N. Kretchmer, and E. Rossi,
Nestlé Nutrition Workshop Series, Vol. 25.
Nestec Ltd., Vevey/Raven Press, Ltd., New York © 1991.

The Effects of Increased Sucrose Consumption on Carbohydrate and Lipoprotein Metabolism in Individuals with Insulin Resistance

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Resistance to insulin-stimulated glucose uptake is a relatively common phenomenon that occurs not only in individuals with non-insulin-dependent diabetes mellitus (NIDDM) (1,2) but also has been characterized in individuals with other metabolic disorders (3–5). For example, individuals with impaired glucose tolerance, obesity, endogenous hypertriglyceridemia, and hypertension have been shown to be more resistant to insulin-stimulated glucose uptake than control populations. In addition, there is evidence that insulin resistance is present in as much as 20–25% of the normal glucose-tolerant population (6). The normal compensatory response in insulin-resistant individuals is an increase in insulin secretion and increased day-long insulin concentrations. Normal glucose tolerance appears to be maintained to the extent that the β-cell is capable of maintaining increased levels of plasma insulin (6,7). Although this compensatory hyperinsulinemia may mask glucose intolerance in individuals with insulin resistance, the hyperinsulinemia present may not be totally benign. Indeed, it has been suggested that the presence of insulin resistance, and the resultant hyperinsulinemia, may play a central role in the pathogenesis and clinical course of several important metabolic diseases (8). For example, hyperinsulinemia has been strongly correlated to increased very low density lipoprotein (VLDL) triglyceride secretion rates, as well as leading to increased plasma total triglyceride concentrations (9–11). It is believed that elevated total plasma and VLDL triglyceride concentrations may predispose otherwise healthy individuals to coronary artery disease (CAD), and there is evidence that high plasma triglyceride concentrations are involved in the pathogenesis of CAD in diabetes (12,13). Low levels of high density lipoprotein (HDL) cholesterol concentrations also are associated with insulin resistance, hyperinsulinemia, and hypertriglyceridemia. Since HDL cholesterol concentrations have been shown to be inversely correlated to the incidence and prevalence

of CAD (12,14,15), a reduction of HDL cholesterol concentrations in these individuals presumably would lead to an increased risk of CAD.

Thus, resistance to insulin-stimulated glucose uptake is associated with glucose intolerance, hyperinsulinemia, hypertriglyceridemia, and decreased HDL cholesterol concentrations. All of these factors have shown to increase the risk of CAD. Of particular importance are the observations (16–25) that increases in dietary sucrose have been shown to lead to hyperglycemia, hyperinsulinemia, hypertriglyceridemia, and decreases in HDL cholesterol concentrations. Given these considerations, it would seem reasonable to examine more closely the role that dietary sucrose may play in the dietary management of individuals with insulin resistance. In this presentation, we discuss the evidence from our group and others designed to assess the metabolic impact of moderate sucrose consumption on carbohydrate and lipid metabolism in individuals with varying metabolic abnormalities associated with insulin resistance.

HYPERINSULINEMIA

As previously discussed, hyperinsulinemia is a normal compensatory response in individuals with insulin resistance. This phenomenon can exist in individuals without the loss of glucose tolerance. These individuals usually have a significantly greater insulin concentration than generally observed in response to variations in the amount and type of dietary carbohydrate. For example, Reiser et al. (16,17) have demonstrated in 19 normoglycemic hyperinsulinemic individuals that the isocaloric addition of sucrose in the diet for 6 weeks increased fasting plasma glucose and insulin as well as total and VLDL triglyceride and total cholesterol concentrations. Plasma glucose concentrations to a sucrose tolerance test did not differ following the sucrose diet. However, peak insulin concentrations to the sucrose challenge were significantly greater when compared to starch diet. In addition, mean fasting triglyceride concentrations were 33% higher following the sucrose diet, with significant differences being observed as early as week 2 on the diet. In a subgroup of 9 individuals with fasting plasma triglyceride concentrations greater than 150 mg/dl, the hypertriglyceridemic effect of added sucrose was even greater. Mean fasting plasma triglyceride concentrations in this subgroup of individuals were 45% greater following the sucrose diet than the starch diet. Fasting total plasma cholesterol levels also were significantly greater following the sucrose diet. Unlike plasma triglyceride, the magnitude of the sucrose effect on plasma cholesterol concentrations increased with the duration of the study. During the last 2 weeks of the 6-week study, mean plasma cholesterol concentrations were approximately 11% greater following the sucrose diet when compared to the starch diet.

In another series of studies, Reiser et al. (18,19) demonstrated that increasing levels of dietary sucrose significantly increased both fasting and postprandial plasma glucose and insulin concentrations in individuals classified as carbohydrate-sensitive on the basis of a hyperinsulinemic response to a standard sucrose challenge. In these

studies, 24 individuals were fed diets containing 5, 18, and 33% of total calories as sucrose for periods of 6 weeks on each of the diets. At the end of each 6-week period, subjects were administered a sucrose challenge (2 mg/kg). Both glucose and insulin responses to this challenge increased in proportion to the amount of sucrose consumed during the preceding diet period, with the greatest increases occurring between 5% and 18% of total daily calories as sucrose. Since 18% of the total calories approximates the typical dietary intake of sucrose in the United States (26), these data suggest that sucrose restriction might benefit a portion of the normal glucose-tolerant population with exaggerated insulin response to dietary carbohydrate.

HYPERTRIGLYCERIDEMIA

Highly significant correlations have been shown to exist between resistance to insulin-stimulated glucose disposal and hyperinsulinemia, increased VLDL triglyceride production, and triglyceride concentrations in both normal lipemic and hypertriglyceridemic individuals. It would seem quite possible that much of the hypertriglyceridemia observed in individuals with insulin resistance is secondary to the compensatory hyperinsulinemia that develops as a result of insulin resistance. The notion that hyperinsulinemia is an important etiological factor in this cascade of events leading to hypertriglyceridemia is supported by studies in perfused rat livers (27), which suggest that hepatic VLDL triglyceride secretion is strongly related to ambient insulin concentrations. Therefore, it seems reasonable to conclude that any dietary perturbation that leads to an increase in ambient insulin concentrations would lead to increased hepatic VLDL triglyceride secretion and, in turn, to increased plasma triglyceride concentrations. It is not surprising that clinical studies assessing sucrose consumption in individuals with insulin resistance have reported both increased ambient insulin concentrations and increased plasma triglyceride concentrations (16–25).

There are several studies that have assessed the metabolic impact of increased dietary sucrose in individuals with endogenous hypertriglyceridemia (20–23). Although the experimental approaches differed from study to study, the data are quite consistent. For example, Kuo and Bassett (20) reported significantly increased total plasma triglyceride, cholesterol, and phospholipid concentrations in patients with endogenous hypertriglyceridemia when they were switched from starch- to sucrose-containing diets. Comparative studies made of the fatty acid composition of plasma lipids suggested that the sucrose-induced hypertriglyceridemia resulted primarily from active endogenous lipogenesis. Further evidence that increased dietary sucrose results in increased triglyceride synthesis is provided by Nikkila (21), who demonstrated increased fasting triglyceride concentrations in a group of individuals with primary endogenous hypertrigyceridemia when a sucrose-containing diet was compared with either starch- or fructose-containing diets. The increase in triglyceride concentrations in these individuals appears to result from an increase in the pro-

duction rate of triglyceride rather than from a change in total triglyceride turnover rates.

Using a somewhat different approach, Liu et al. (22) demonstrated that the magnitude of dietary-induced hypertriglyceridemia varied as a function of the sucrose content of the diet. Specifically, fasting and postprandial total plasma and VLDL triglyceride concentrations were significantly increased following high carbohydrate diets when dietary sucrose was allowed to increase as compared to when sucrose content was held constant. These data are very similar to those previously discussed in individuals with hyperinsulinemia (18,19).

In a population of individuals whose fasting plasma triglyceride concentrations varied, Roberts (23) pointed out that plasma triglyceride levels fell when nondiabetic individuals were switched from a normal to a sucrose-free diet, but only in those individuals in whom triglyceride concentrations were greater than 120 mg/dl during the normal diet. Thus, it appears from these observations that an increase in dietary sucrose would result in an increase in triglyceride concentrations in individuals with normal glucose tolerance who demonstrate fasting hypertriglyceridemia.

NON-INSULIN-DEPENDENT DIABETES MELLITUS

Much of the research conducted in individuals with NIDDM has focused primarily on the acute effects of added sucrose on the control of plasma glucose and insulin concentrations (28–30). The data from these studies are consistent with earlier observations of the acute effects of sucrose in normal individuals and individuals with impaired glucose tolerance (31–33). However, these data should not be taken to support the notion that moderate amounts of sucrose may be safely added to the diets of individuals with NIDDM over longer periods of time. For example, the data suggest that substitution of a moderate amount of sucrose to a single meal does not result in an exaggerated plasma glucose or insulin response. The substitution of sucrose for other carbohydrate occurred for only a single meal, and these studies assessed only the metabolic changes to the acute effects of added sucrose on plasma glucose and insulin concentrations. However, previous studies have demonstrated that long-term sucrose feedings have been associated with alterations in both carbohydrate and lipoprotein metabolism (16–25). For example, we have published the results of two studies that assessed the effects of added sucrose to the diets of individuals with NIDDM for from 2 (24) to 4 weeks (25). In one study (24), the only variable was the amount of total calories presented as added sucrose. After 2 weeks of diets containing 16% of the total calories as added sucrose, there were no significant changes to fasting plasma glucose or insulin concentrations. On the other hand, there was a significant increase in day-long glucose and triglyceride concentrations. In addition, there were significant elevations in fasting total plasma and VLDL triglyceride and cholesterol concentrations compared to the sucrose-free diet. Further evidence of a deterioration of glycemic control was documented by a significant increase in 24-hour urinary glucose excretion when sucrose was substituted

for starch in the diet, despite the fact that there was no change in the total carbohydrate content. Thus, substituting sucrose for starch in the diet for 2 weeks in individuals with NIDDM led to the deterioration of both carbohydrate and lipoprotein metabolism.

Since current recommendations (34) include an increase in dietary carbohydrate and allow the use of moderate amounts of sucrose, we were interested in the effects of parallel changes in carbohydrate and sucrose in patients with NIDDM. Diets containing 40% of the total calories as carbohydrate and 3% as sucrose were contrasted with diets containing 60% of total calories as carbohydrate and 10% as sucrose (25). The combination of these two dietary manipulations appeared to exacerbate the metabolic effects observed with increased sucrose alone. Specifically, day-long plasma glucose, insulin, and triglyceride concentrations were elevated significantly as a result of the increase in dietary carbohydrate and sucrose. Further evidence that the high-carbohydrate, moderate-sucrose diet resulted in a deterioration in day-long glycemic control is supported by the observation that mean 24-hour urinary glucose excretion more than doubled (25 versus 56 g/24 hour). In addition, fasting total plasma and VLDL triglyceride and VLDL cholesterol concentrations increased significantly, and HDL cholesterol concentrations decreased significantly as a result of the high-carbohydrate, moderate-sucrose diet. Consequently, the addition of moderate amounts of sucrose to the diets of individuals with NIDDM, in amounts comparable to those typically consumed by the general population (26), resulted in significant day-long hyperglycemia, hyperinsulinemia, fasting and postprandial hypertriglyceridemia, fasting hypercholesterolemia, and decreased fasting HDL cholesterol concentrations.

Although these data are consistent with similar well-controlled studies in individuals with normal glucose tolerance, hyperinsulinemia (16–19), and hypertriglyceridemia (20–23), they are in contrast to a number of reports in individuals with NIDDM (35–39). Several studies report no significant metabolic effects of replacing complex carbohydrate with an equal amount of sucrose (35,36). However, dietary sucrose content generally has not been controlled in these studies. Individuals were given dietary advice and asked to alter their consumption of sucrose. Without control of dietary intake, the experimental variable, it is difficult to accept these results as proof that increased dietary sucrose has no adverse metabolic effects. In other studies, dietary sucrose intake has been quite low, providing as little as 4% of total daily calories as sucrose (36). Since this is roughly equivalent to the amount of sucrose contained naturally in fruits and vegetables in diets of individuals on sucrose-restricted diets, this level of sucrose ingestion hardly constitutes an adequate test of the effects of an increase in the consumption of sucrose.

Finally, in two other studies, the experimental design used made comparisons between the sucrose-added and sucrose-restricted diets difficult (37,38). For example, in one of these studies, the two dietary periods used were approximately 11 months apart, and the degree of metabolic control in these individuals at the start of the experimental diets differed (38). Specifically, mean ± SEM fasting plasma glucose concentration was 187 ± 25 mg/dl before the low-sucrose diet and 237 ±

26 mg/dl before the high-sucrose diet. As a result, the investigators could not make direct comparisons between the two dietary periods and reported changes in glucose, insulin, and triglyceride concentrations from two separate baseline periods. The effect of these differences in baseline values on the estimates of glycemic response is difficult to evaluate. Parenthetically, fasting hypertriglyceridemia was noted in both of these studies after the high-sucrose diet (37,38).

At this point, there appears to be only a single, well-controlled metabolic study conducted over an 8-day period in individuals with diabetes in which the authors report no significant differences in metabolic control as a result of increased dietary sucrose (39). In this study, fasting, 1-hour and 2-hour postprandial, and overall mean plasma glucose concentrations were higher after the sucrose diets in both individuals with IDDM and NIDDM. Moreover, fasting and postprandial peak triglyceride concentrations were increased in the sucrose-containing diets in both groups. The fact that differences reported did not reach levels of significance may be a result of the specific statistical analysis used or the length of time over which the studies were conducted. This study lasted only 8 days, and it is possible that the magnitude of these metabolic changes may have increased with duration of the diet.

CONCLUSION

There is evidence that increased dietary sucrose consumption can significantly increase postprandial plasma glucose, insulin, and triglyceride concentrations, as well as fasting total and VLDL triglyceride and cholesterol concentrations, and significantly decrease HDL cholesterol concentrations. Since similar changes have been shown to occur in individuals with normal glucose metabolism, hyperinsulinemia (16–19), hypertriglyceridemia (20–23), and NIDDM (24,25), we believe that these findings should be viewed as the expected sequelae of such diets. Furthermore, these deleterious effects on carbohydrate and lipid metabolism have been shown to occur at levels of dietary sucrose comparable to those consumed by the average American adult (17% of total calories) (26). Although it could be argued that many of these changes may be modest in magnitude, the changes that have been shown to occur may be of great clinical significance. This may be particularly true given the multiplicity of the deleterious metabolic effects that have been described to occur when dietary sucrose consumption is increased. The fact that all studies do not show these deleterious effects does not negate the positive data. It is likely that the magnitude of the deleterious effects will vary from individual to individual, depending on such factors as baseline plasma glucose, insulin and lipid concentrations, degree of insulin resistance, and amount of dietary sucrose. Because current data do not permit the prediction of which individuals may be adversely affected, perhaps the best advice is to limit sucrose consumption, be aware of the potential deleterious effect, monitor individuals closely, and modify sucrose consumption appropriately in accordance with any changes in the individual's metabolic status.

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DISCUSSION

Dr. Wahlqvist: How might sucrose influence the variables under consideration? How confident are you about the steps in the sequence of your initial hypothesis, which was that insulin resistance might itself be induced by sucrose? If that were the case, do you have any ideas about the mechanisms involved? One particular confounding variable may be saturated fat. When we deliberately alter sucrose in the diet, other dietary changes occur. In the several studies that you referred to, including the 2-week crossover study where you examined 16% sucrose against 2%, could you say something about the changes in, for example, plant food intake in the diet and the possible impact that may have had, independent or together with sucrose? There may have been food and nutrient interactions.

Dr. Hollenbeck: The point of the presentation was that increased consumption of sucrose has been shown to lead to a deterioration of carbohydrate and lipid metabolism in individuals already insulin resistant, not that it causes insulin resistance *per se*. On the other hand, there certainly are data in animal models that clearly demonstrate that increased dietary sucrose and fructose consumption results in the development of an insulin-resistant state, so I would not exclude that possibility. In fact, that is an interesting question that, I believe, has not been adequately addressed in humans. Some of our more recent work, however, suggests that increased sucrose or fructose results in increased resistance of insulin-stimulated glucose disposal in peripheral tissue. In response to your question regarding differences in dietary

composition other than sucrose, in almost all of the studies cited, the amounts of fat, carbohydrate, and protein were held constant, as was the P/S ratio of the fat, dietary cholesterol, and dietary fiber. However, your question about the type of fat is quite relevant, and there are data in the literature that suggest that the degree of saturation may influence the response to sucrose.

Dr. Wahlqvist: Would you comment on the relevance of the observations in those with insulin resistance to the population at large who might not be insulin resistant?

Dr. Hollenbeck: Virtually all individuals with NIDDM are profoundly insulin resistant. In addition, individuals with obesity, hypertension, and hypertriglyceridemia have been shown to be insulin resistant when compared to control populations. Recently, several studies, including one of our own, have suggested that as much as 20 to 25% of the normal glucose-tolerant population may be classified as having insulin resistance. Therefore, I feel that my comments may be very relevant to the general population.

Dr. O'Dea: Would you agree with the suggestion that insulin resistance or hyperinsulinemia is a marker of diabetes susceptibility? If that is so, would you then agree that in subpopulations of those at risk for diabetes, sucrose is a particular problem?

Dr. Hollenbeck: Yes, I think so. But more importantly, what I have tried to point out is that sucrose may be a particular problem even in those individuals with insulin resistance who may never go on to develop frank diabetes.

Dr. Truswell: How do you explain the numerous studies (1–3) that have given sucrose to diabetics and not seen any change in the diabetic control?

Dr. Hollenbeck: Some of those were short-term studies, single meal studies, or outpatient studies where dietary advice was given in lieu of defined metabolic diets. The studies that I tried to highlight in my presentation were ones that used defined diets provided under controlled metabolic conditions in research units. I believe that there is a big difference between those two experimental approaches. The Petersen study is a good example of a lot of research done in the area of nutrition and diabetes in which dietary advice is given to an individual, who then is essentially unsupervised during the rest of the study. Personally, I do not believe that there is sufficient control of the experimental variable (i.e., diet) to allow statements regarding the effect of a given diet with any degree of confidence.

Dr. Truswell: Was the study by Roberts *et al.* in Antarctica well controlled?

Dr. Hollenbeck: Yes, absolutely. All of the food that was consumed was brought to Antarctica and prepared for the individuals. There are not many opportunities to run to the store in Antarctica.

Dr. Zimmet: I was interested in your statement that approximately 20% of the population may have insulin resistance. Should we look at insulin sensitivity as a spectrum and the far edge of it as insulin resistance? Alternatively, is insulin resistance like plasma glucose and plasma cholesterol and has a unimodal distribution in the population? Population data in the Pima Indians have shown bimodality of insulin sensitivity. Is this analogous to the situation of plasma glucose being bimodal in that population and in the Nauruan population? We are talking a lot now about insulin resistance in hypertension, in diabetes, and in chronic disease. Perhaps we need to better define what we are talking about.

Dr. Hollenbeck: There are several studies that have demonstrated that resistance to insulin-stimulated glucose disposal is present in approximately 20 to 25% of the normal glucose-tolerant population, and ours was one. In our study, we used the euglycemic insulin clamp technique to determine insulin resistance, which is a fairly defined procedure. We did not see a bimodal distribution in our population. However, we studied only 100 individuals, and perhaps if we studied a greater number of subjects, a bimodal distribution may have emerged.

On the other hand, one must also wonder whether the Pimas and/or Nauruans are representative of the general population. Finally, I totally agree with you that we need to be careful in how to define and use terms, such as insulin resistance.

Dr. Shafrir: Your results are of interest because they show that even at a moderate intake of sucrose you can demonstrate increases in VLDL triglycerides and LDL cholesterol. This is similar to what occurs in our animals on a higher sucrose intake. A question was raised before whether there was increased triglyceride production without obligatory insulin intervention in the enhanced triglyceride production. You have to realize that sucrose-derived fructose suppresses gluconeogenesis. On a fructose-rich diet, some precursors of gluconeogenesis may be rerouted to lipogenesis because the enzymes converting 3-carbon units into glucose may be reduced in activity. I am not convinced that insulin is really necessary to produce VLDL and LDL cholesterol increases in this condition—just the lipogenic potential of fructose may be expressed in this way. Reiser *et al.* have shown that on 20% substitution of starch by fructose, even the noninsulin-sensitive controls had significant increases in serum triglycerides and cholesterol (4).

Dr. Schiffman: When you gave additional sucrose, was it in liquid or in solid form in the food?

Dr. Hollenbeck: It was a solid form. We have our own dietary kitchen, and sucrose and fructose are added to the diet. It is incorporated into breads and other baked products.

Dr. Schiffman: So the tastes of the two diets were definitely different, is that correct? A high-sucrose diet tastes different from a low-sucrose diet. Tastes and odors in and of themselves can produce biological responses. For example, we recently found that sniffing peanut odor significantly increased blood levels of histamine in a patient allergic to peanuts. Likewise, the taste of a high-sucrose diet could conceivably alter blood lipids simply because sugar was presented with fat in a previous diet.

Dr. Hollenbeck: I find it hard to believe that it is going to cause a difference in the metabolism.

Dr. Schiffman: I think you will have to investigate that by a well-controlled experiment.

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