

Sugars, insulin sensitivity, and the postprandial state¹⁻⁴

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ABSTRACT Since insulin resistance was first associated with type 2 diabetes and later with cardiovascular disease and hypertension, there has been considerable interest in the role of dietary and environmental factors. Sucrose and fructose have been a particular research focus. Research on animals, particularly rodents, has shown a clear and consistent effect of high-sucrose and high-fructose diets in decreasing insulin sensitivity. Experiments in humans have produced very conflicting results, with limited evidence for a negative effect on insulin sensitivity at higher intakes of fructose or sucrose (generally >30% of daily energy from sucrose and >15% of daily energy from fructose). Observation studies in humans have not shown a link between sucrose consumption and insulin sensitivity independent of other dietary factors. This is in contrast with several small studies that showed an improvement in insulin sensitivity after subjects followed dietary advice to lower the glycemic index of their food choices (where sugars were not a target for change). However, the pattern of postprandial glucose and insulin responses elicited by sucrose and fructose differs substantially from that elicited by starches, with lower troughs elicited by sucrose and fructose 2–3 h after eating. These differences in the pattern of postprandial responses offer a potential explanation for the conflicting results on insulin sensitivity, with the possibility that increases in insulin exposure may affect insulin sensitivity through down-regulation of insulin action. *Am J Clin Nutr* 2003;78(suppl):865S–72S.

KEY WORDS Sucrose, fructose, sugars, insulin sensitivity, postprandial response

INTRODUCTION

The effect of diet on glucose metabolism has remained an active subject of research for many decades. Since Himsworth's early work (1), insulin resistance has been recognized as having a role in type 2 diabetes. This was a major stimulus for looking at environmental factors affecting insulin sensitivity; an additional stimulus was provided by recognition of the association with hypertension and ischemic heart disease (2, 3).

Examining the effect of diet is difficult because many other environmental influences affect insulin action. Obesity is a major negative factor (4), and weight loss improves insulin sensitivity. Visceral obesity has a particularly strong negative correlation (5). In contrast, physical activity has a strong positive effect (6, 7). Any effect of diet has to be seen in the context of such strong associations and separated from their effects where possible. This means that any literature review has to give particular weight to experimental studies that are tightly controlled for such influences.

There are problems in assessing insulin action. Measurement of fasting insulin concentrations is a basic approach, suitable

mainly for large numbers of subjects. It is less suitable for small intervention studies. However, fasting insulin has been shown to correlate with the euglycemic clamp technique, one of the most widely accepted methods (8). Homeostatic model assessment (9), derived from the ratio of fasting insulin and glucose concentrations, has been shown to be an improvement on fasting insulin alone, but again only in large studies (10). Apart from the criticism that such fasting tests are best suited to large studies, a further problem is that these tests reflect insulin action in an unstimulated or basal state, whereas in life much of insulin action is postprandial.

Various attempts have been made to overcome these problems. The frequently sampled intravenous-glucose-tolerance test developed by Bergman et al (11) uses physiologic models of glucose use and insulin kinetics together with computer analysis to derive a measurement of insulin sensitivity. This test is often known as the minimal model, and its measurements correlate strongly with euglycemic clamp measurements (12). The modified insulin tolerance test is based on the measurement of the rate of decrease in plasma glucose concentration over 15 min in response to a bolus of intravenous insulin and has similarly been shown to correlate well with euglycemic clamp measurements (13).

The euglycemic clamp technique is perhaps the most sophisticated method of assessing insulin sensitivity (14). Insulin is infused at a fixed rate, and a variable glucose infusion rate is used to maintain euglycemia. This glucose infusion rate provides an index of whole-body insulin sensitivity.

The various influences on insulin action and the different methods of assessing insulin sensitivity need to be considered when approaching the literature. A final point relates to the design of dietary studies themselves. Dietary interventions that manipulate total carbohydrate content cannot reflect effects of sugars independent of other dietary factors. For example, comparing a high-fat, high-sugars diet with a high-fiber, low-fat diet does not allow separation of the effects of a high-sugars diet from the effects of a high-fat diet. Therefore, the present review is concerned with intervention studies that control for all other dietary components.

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TABLE 1
Animal studies: effects of sucrose and fructose on insulin sensitivity¹

Dietary intervention ²	Results and comments	Reference
Starch compared with sucrose (68%)	Sucrose decreased sensitivity as assessed by clamp	25
Starch compared with sucrose (69%)	Sucrose decreased sensitivity as assessed by clamp	26
Sucrose (66%) compared with starch and sucrose (47 or 19%)	Sucrose decreased sensitivity as assessed by clamp	27
Starch compared with sucrose (62–63%)	Sucrose decreased sensitivity as assessed by clamp	28
Starch (69%) compared with fructose (34%) and glucose (34%)	Fructose decreased sensitivity as assessed by clamp	29
Starch (70%) compared with fructose (35%)	Fructose decreased sensitivity as assessed by clamp (lower weight gain with fructose)	30
Fructose compared with glucose (60%)	Fructose decreased sensitivity as assessed by clamp	31
Fructose compared with glucose (60%)	Fructose decreased sensitivity as assessed by hyperinsulinemic, euglycemic clamp	32

¹ Abridged from Daly et al (24).

² Dietary content is given in parentheses as a percentage of total dietary energy.

ANIMAL STUDIES

Most of the work in this area has been conducted in rodents and with high intakes of sucrose (>60% of energy) or fructose (>35% of energy). Such diets have consistently been shown to be capable of reducing insulin sensitivity, and such models (particularly with fructose feeding) are used to induce insulin resistance for the testing of therapeutic agents (15–23). Because of the large number of rodent studies concerning sugars and insulin sensitivity, it is possible to be selective and examine only tightly controlled studies in which the experimental design is least open to criticism. Some of these studies, in which the design was optimal and the euglycemic clamp was used, are summarized in **Table 1**. A key feature of these animal studies is the very high percentage of energy from carbohydrates; therefore, the percentage of energy from fat in these studies was low. However, the only studies that were included in Table 1 were those that controlled for subtypes of dietary fat (eg, saturated fat) as a constant between the 2 experimental diets.

There has been a concern that the effects of such diets may be related to copper deficiency. Both fructose and sucrose are known to decrease the bioavailability of copper and exacerbate copper deficiency in rats (33–35). Although fructose can exacerbate copper deficiency, no firm evidence exists that copper deficiency per se causes insulin resistance. Therefore, in the absence of such evidence, it is difficult to maintain that induced copper deficiency is a major mechanism by which fructose or sucrose mediates its effects on insulin sensitivity. Therefore, the literature supports a negative effect of high fructose or sucrose on insulin sensitivity in animals, particularly rodents.

HUMAN STUDIES

Assessing the role of diet in humans is more difficult, partly because of the other factors affecting insulin sensitivity. Observation and intervention studies, in which the design allows specific consideration of carbohydrate type independent of other dietary factors, are considered in the present review.

Observation studies have looked at the relations between diet and insulin sensitivity. Comparatively few studies are suitable for examination because the dynamic assessment of insulin sensitivity is time consuming and expensive and does not lend itself to large-scale studies. One study, by Sevak et al (36), assessed postprandial insulin concentrations in response to a glucose load in 173 subjects and had the advantage of using 7-d weighed intakes. This study

found that carbohydrate intake (as a percentage of total energy) was inversely correlated with insulin sensitivity (ie, total carbohydrate and sucrose were positively correlated with insulin resistance), with a stronger correlation for sucrose than for starch. The same pattern was seen for fasting insulin, but the correlation was weaker. Conversely, another study found an inverse correlation with fat intake (37). The sample size in this study was smaller (45 subjects) than that in the study by Sevak et al, and the assessment of insulin sensitivity was more sophisticated (the frequently sampled intravenous-glucose-tolerance test); however, the assessment of dietary intake was weaker (a retrospective food-frequency questionnaire).

Large studies have looked at diet and the development of diabetes but have not involved measurement of insulin sensitivity. Because resistance to insulin is a major factor in the development of type 2 diabetes, a significant proportion of those diagnosed can be assumed to have been insulin resistant. van Dam et al (38) looked at food-frequency questionnaires in 42 504 male healthcare professionals in a prospective cohort study in which diabetes was reported as absent at baseline. They found that men who had a high intake of foods associated with a Western-style diet had an increased risk of the subsequent development of diabetes. The definition of a Western-style diet included frequent consumption of sweets and desserts. However, the definition also included factors associated with a high saturated fat intake (red meat, processed meat, French fries, high-fat dairy products), which is known to be associated with decreased insulin sensitivity (39) and a high glycemic load (refined grains). Other similar articles showed that the glycemic load of the diet is associated with the development of diabetes (40, 41) and that lipid abnormalities are associated with the insulin resistance syndrome (42–44) and ischemic heart disease (45). However, in these articles, sugars were not the major contributors to the mean glycemic load of the diet in the populations studied (fructose has a low glycemic index (GI), and sucrose has a lower GI than do potatoes or white bread); the major determinants of glycemic load in one of these studies were potatoes and breakfast cereal. However, if a person has a high intake of sugars, the contribution to that person's diet may be more significant.

Some controlled studies of the intake of specific carbohydrates showed a negative effect (increased fasting or postprandial insulin concentrations) of sucrose or fructose at high intakes (>15% of dietary energy from fructose and >33% of dietary energy from sucrose) (46–48). Other studies showed a positive effect of fructose (increased sensitivity with euglycemic clamp) (49) or a high-sucrose diet (increased sensitivity with euglycemic clamp) (50), whereas still others showed no effect (clamp or basal insulin concentrations) (51–53). One factor that singled out the positive



TABLE 2

Human studies: effects on insulin sensitivity of sugars compared with those of starch¹

Dietary intervention ²	Design	Time	Subject group	Change in basal insulin concentrations	Insulin sensitivity	Reference
Iso-caloric exchange of sucrose for starch at 30%	Crossover	6 wk	Healthy subjects, subgroup with hypertriglyceridemia, <i>n</i> = 19	Greater in sucrose group	—	46
Sucrose at 5%, 18%, and 33%	Crossover	6 wk	Subjects with hyperinsulinemia, <i>n</i> = 24	Increased as sucrose content rose	—	47
Fructose at 0%, 7%, and 15%	Crossover	5 wk	Healthy subjects with subgroup with hyperinsulinemia, <i>n</i> = 23	No significant differences but increased postprandial insulin	—	54
Addition of 250 g fructose or glucose	Case-control	1 wk	Healthy subjects, <i>n</i> = 7	None	25% decrease in sensitivity in fructose group by IVITT	55
Fructose substituted for 24% of carbohydrates, ie, 13.2%	Single factor	2 wk	Subjects with type 2 diabetes, <i>n</i> = 7	No significant change	—	56
Fructose substituted for 20% of carbohydrates in a 45% or 85% carbohydrate diet	Crossover	>2 wk	Subjects with hypertriglyceridemia with or without type 2 diabetes, <i>n</i> = 6	No significant changes	—	57
Fructose substituted for 20% starch	Crossover	4 wk	Subjects with type 2 diabetes, <i>n</i> = 10	—	Increased sensitivity in fructose group by euglycemic clamp	49
Fructose at 13%	Single factor	3 mo	Subjects with type 2 diabetes, <i>n</i> = 6	No significant change	No change on euglycemic clamp	53
Sucrose at 32%, starch at 70%	Crossover	4 wk	Healthy subjects, <i>n</i> = 9	No significant change	—	51
Replacement of 45 g starch with sucrose	Crossover	6 wk	Subjects with type 1 or type 2 diabetes, <i>n</i> = 24	No significant change	—	58
Exchange of starch and sucrose at 23%	Crossover	14 d	Healthy subjects, <i>n</i> = 9	No significant change	—	52
Low glycemic diet compared with high glycemic diet (but 25% compared with 1% sucrose)	Crossover	28 d	Healthy males, <i>n</i> = 7	No significant changes	Decreased sensitivity with low glycemic diet	50
High-sucrose diet (33.1%) compared with low-sucrose diet (5.5%)	Crossover	28 d	Overweight subjects, <i>n</i> = 7	—	Both diets increased sensitivity with clamp	59
High-fructose diet (40%) compared with moderate-fructose diet (10%)	Crossover	7 d	Adolescents, <i>n</i> = 12	—	No change with IVGTT	60

¹Revised and updated from Daly et al (24). IVITT, intravenous insulin tolerance test; IVGTT, intravenous glucose tolerance test.²Dietary content is given as a percentage of total dietary energy, except where stated.

studies from those of the Beltsville group (46, 47, 54) was the use of subjects who were more insulin resistant or who had hypertriglyceridemia. The researchers hypothesized that such persons may be more sensitive to the negative effects of diet on insulin sensitivity. However, these earlier studies used fasting or postprandial insulin concentrations to assess insulin sensitivity. After a review of the literature (Table 2) (24), our own group sought to design a study to see whether overweight persons (who are likely to be less insulin sensitive) are susceptible to such dietary intervention (33.1% of total energy from sucrose compared with 5.5% of total energy from sucrose, isocaloric for total carbohydrates). Using a hyperinsulinemic, euglycemic clamp, we found that the diets did not differ in their effects on insulin sensitivity (59).

Other studies concentrated on GI (61–63) and showed the ability of a low-GI diet to improve insulin sensitivity. Another study showed the ability of similar diets to improve glycemic control in diabetic patients (64). However, in those studies, sugars did not have a major effect in determining the difference in GIs between the experimental diets.

No studies have shown a negative effect of sucrose on insulin sensitivity through the use of a sophisticated assessment method. Some research suggests that increasing intakes of sucrose [as high as 33% of total energy (47)] may alter insulin sensitivity as assessed by fasting and postprandial insulin concentrations, but the results were most convincing in identified subgroups (insulin-resistant subjects and hypertriglyceridemic subjects). There was evidence of a dose-response effect in the 3 studies (46, 47, 54) that were larger than most of the other studies and that used a higher fat intake than that used in most of the other studies. No research center has repeated such studies in the same subject groups. Overall, there is no conclusive or consensual evidence to show that humans respond similarly to rodents to sucrose- or fructose-rich diets at the doses used in human studies. The use of higher dietary doses of sucrose or fructose would be unfeasible in terms of palatability in the human population. Furthermore, such research would have little clinical application because so few people consume sugars in

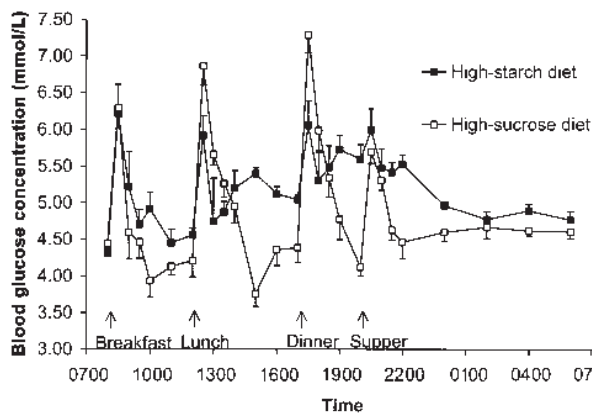


FIGURE 1. Glucose responses to high-sucrose and high-starch diets. Reprinted with permission from reference 70.

the quantities used in typical human studies, much less than the even higher quantities used in animal studies.

RESOLVING THE CONFLICTS IN THE HUMAN LITERATURE—A DISCUSSION OF POTENTIAL MECHANISMS

Why should the human studies have such conflicting results? Within Table 2, every outcome is covered—no change and increased and decreased insulin sensitivity with fructose or sucrose. This is in contrast to the animal studies, in which very high intakes of fructose or sucrose produced consistent results. Although differences in the absolute quantities of sugars used may contribute to the differences in results between the animal and human studies, the key remaining question is why there is such disparity within the human literature.

One possible explanation is that the control diets may differ between studies (ie, although matched in terms of carbohydrate content, high-starch diets used as controls may differ between studies in other ways and thus give what would appear to be conflicting results). This prospect is best addressed by looking in more detail at the postprandial state, and I have taken the opportunity here to revisit some of the classification issues regarding postprandial glycemia before discussing this point further.

The GI, which is used as a common measure to quantify postprandial glucose response, was introduced by Jenkins et al (65). The GI is defined as the incremental area under the blood glucose response curve of a 50-g carbohydrate portion of a test food expressed as a percentage of the response to the same amount of carbohydrate from a standard food taken by the same subject for a 2-h period. For the purposes of standard GI tables, subjects have normal glucose tolerance. The glycemic load of a meal or diet is defined as the GI of the meal's or diet's carbohydrate constituents multiplied by the total carbohydrate content of the meal or diet. The 50-g carbohydrate content of the test meal is usually defined by available carbohydrate, where available carbohydrate usually means starch and digestible sugars, as opposed to unavailable carbohydrates (undigestible sugars, oligosaccharides, and nonstarch polysaccharides). However, a criticism of this definition is that it does not acknowledge the role of colonic fermentation in the metabolism of other carbohydrate sources. Attempts have been made to

modernize the term *available carbohydrate*, and the term *glycemic carbohydrate*, which is defined as carbohydrates provided for metabolism (including non-glucose-containing sugars, such as fructose, that are capable of providing glucose for metabolism but not sugars available for colonic fermentation), has been proposed. The use of the word *glycemic* is possibly suboptimal because many metabolizable sugars do not contribute to glycemia; nor does colonic fermentation of carbohydrate (66).

Jenkins argued that physiologic data would be more valuable in advising people with diabetes than would simple chemical analysis alone. At that time the classification of carbohydrates into simple and complex carbohydrates was associated with the assumption that simple carbohydrates produced a greater glycemic response than did starches. Subsequent research has shown that this is not always the case and that glycemic response is more dependent on the type of carbohydrate chosen than on the simple-complex classification. Unfortunately, this classification has persisted. Even in a review published in 2000, Frost and Dornhorst (67) felt it necessary to comment that this is a misconception still held by many health professionals. For instance, authors have found that white bread and potatoes produce a higher GI than that produced by sucrose, and fructose was found to have a GI far lower than that of most of the starches in the early work by Wolever et al (68). Longer postprandial studies (3 h instead of the 2-h GI test) show similar patterns, but sucrose shows a more rapid decline in the later postprandial phase (which becomes more obvious when considering ≥ 3 h), with glucose producing the highest initial responses (69–73).

Glycemic response can also be affected by other factors in the meal, especially the fat content, because fat retards the glycemic response of the meal's carbohydrates. Meal timing can affect glycemic response because the metabolic response to sucrose may differ between the fed and fasting states (70, 74). This may be related to altered metabolism of the fructose component of sucrose in the fed and fasted states. Longer postprandial studies show the pitfalls of concentrating on the first 2 h. For example, 24-h glucose profiles after consumption of high-starch and high-sucrose diets are shown in **Figure 1** (70). Total carbohydrate was maintained at 55% of energy; the high-sucrose diet contained 50% of total dietary energy from sucrose and 5% from starch, and the high-starch diet contained 50% of total dietary energy from starch and 5% from sucrose. All meals within the 24-h period were derived from readily available foods commonly consumed in the United Kingdom. Eight healthy volunteers (4 men, 4 women) took part. (This was a short-term study—subjects consumed their habitual diet before each 24-h test period.) Lower troughs in insulin concentrations were seen with high-sucrose meals than with high-starch meals in the later postprandial period until the next meal. As expected, the insulin and glucose concentrations were closely related (**Figure 2**). How could such differences explain the inconsistencies in the human literature?

One answer may be in the insulin responses to different foods that follow differences in glucose response. An important principle in endocrinology is receptor down-regulation. If concentrations of a hormone increase and become chronically high, receptor numbers or function down-regulate to maintain the status quo. Any diet that persistently alters insulin concentrations may be expected to also alter insulin sensitivity. High- and low-GI starches can produce different postprandial insulin responses [in terms of area under the curve (AUC) for insulin concentration]. However, when

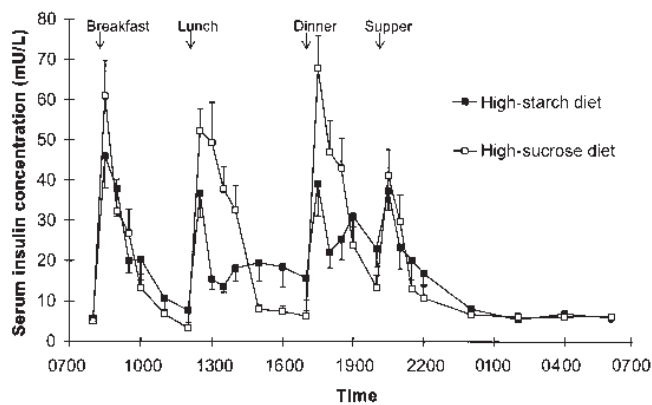


FIGURE 2. Insulin responses to high-sucrose and high-starch diets. Adapted from reference 70.

the 24-h insulin profiles seen in Figure 2 were analyzed, a high-sucrose diet was found to produce an AUC for insulin similar to that produced by a high-starch diet, despite differing patterns of response (70). It is possible that some resistant starch in the high-starch diets was not absorbed; however, had it been possible to correct for this factor, this would only have exaggerated the differences between the diets for the later postprandial period.

In a separate, randomized crossover study, postprandial metabolic profiles (insulin and glucose) were carried out after 2 high-starch, potato-based meals were consumed by 8 healthy subjects (75). These 2 meals were isocaloric for total carbohydrate content, but the potatoes were prepared differently: freshly cooked and hot for one meal, but cooked the night before the study and chilled overnight for the other meal. Despite marked differences in initial postprandial insulinemia (with the freshly cooked potatoes producing greater incremental rises in insulin), the insulin curves returned to the same baseline (ie, not overshooting as with sucrose in Figures 1 and 2), showing that overall insulin exposure is much greater for the higher-GI meal. Therefore, the mean (\pm SEM) postprandial insulin AUCs were markedly different ($8677 \pm 1269 \text{ mL}^{-1}$ for the freshly cooked meal compared with $6527 \pm 759 \text{ mL}^{-1}$; $P = 0.01$), whereas with the sucrose and starch, overall AUCs for insulin were comparable despite their different patterns.

If extended postprandial AUCs for insulin reflect 24-h exposure of the body to insulin, high-sucrose and high-starch diets of the type fed in the acute (24-h) study are unlikely to differ in terms of insulin exposure. However, starch-based meals differing in glycemic response and producing different AUCs for insulin may make a greater difference to 24-h insulin exposure and potentially to insulin sensitivity. However, there is no evidence to determine whether patterns of insulin secretion or 24-h exposure to insulin has more influence on insulin sensitivity, which may affect the usefulness of the GI regarding insulin sensitivity.

Alterations in the starch content of diets (ie, higher- or lower-GI starches) affect insulin sensitivity, with lower-GI starch diets apparently having a positive effect. If sucrose differs substantially from most starches in affecting late postprandial insulin concentrations, the GI may not be useful with respect to sucrose in this regard. Certainly, one study using sucrose as a higher-GI food showed a positive effect of the higher-GI diet on insulin sensitivity (50), whereas only studies concentrating on using starches to change the GI of the diet showed a beneficial effect of a low-GI

diet (62, 63). This hypothesis may partially explain why simple comparisons of sucrose and starch do not show any differences in insulin sensitivity and why types of starch within the diet may be more important than the presence of simple carbohydrates.

Several other hypotheses are linked to a mechanism for the effects of dietary carbohydrates on insulin sensitivity. Elevated triacylglycerol concentrations are a regular finding in the sucrose and fructose rodent studies and correlate with changes in insulin sensitivity. It has been argued that elevated triacylglycerol concentrations directly affect insulin action, as muscle (a major glucose disposal site) preferentially uses nonesterified fatty acids and triacylglycerols as fuel over glucose, thus affecting insulin action. Altered insulin sensitivity with sucrose was shown in rodents without hyperlipidemia (76). Boivin and Deshaies (77) also showed in a rodent model that the effects of dietarily induced hypertriglyceridemia and altered insulin sensitivity can be dissociated. Interestingly, these effects were noted with a high-glucose, high-starch diet when it was compared with a high-fat diet. Therefore, decreased insulin sensitivity is not an inevitable consequence of elevated lipid concentrations; nor is the reverse true.

Because few studies in humans have shown a negative effect of sucrose on insulin sensitivity, few studies have explored the mechanisms. However, there has been a wealth of research on the effects of carbohydrate-induced hypertriglyceridemia, and this research was reviewed extensively by Parks and Hellerstein (78). The effects appear to be caused by a combination of increased production and decreased clearance of VLDL. The inconsistency of a link between decreased insulin sensitivity and hypertriglyceridemia precludes further investigation of mechanisms in humans.

Another explanation for the abundance of negative studies is that recruitment of volunteers for nutrition studies is notoriously difficult, and many studies have a young or a highly health-oriented population. Both groups are likely to be physically active. Given the strength of the positive influence of physical exertion on insulin sensitivity, such persons are likely to be resistant to the negative effects of diet. However, this does suggest that the promotion of physical activity may have a greater influence on insulin sensitivity than does diet.

The negative results in the human studies may be true negative findings. Major species differences in metabolic capacity between rodents and humans may affect sensitivity to dietary sugars, and an effect may be shown in rodent studies only because they use such extreme diets.

DEFINING CARBOHYDRATE INTAKE BY GLYCEMIC INDEX OR GLYCEMIC LOAD—RELEVANCE TO HEALTH EFFECTS

The terms *GI* and *glycemic load* have relevance to nutritional research (both concepts have been associated with disease or markers of health and disease), but the terms have particular limitations with respect to sugars and health. The GI concerns only the first 2 h of the postprandial period. As shown in Figures 1 and 2, there are major differences between starches and sucrose in the later postprandial period.

However in the potato-meal-based study discussed earlier, the postprandial insulin curves returned to similar baseline values despite a difference in digestibility between the starch meals. The possibility cannot be ignored that a ranking of foods by GI may be a more useful tool for starches than for sugars. At the very least,

a GI defined by a 4–6-h postprandial period would alter the ranking of sucrose in a GI table.

The term *glycemic load* is misleading; it is often used in the phrase “the glycemic load of a diet” and as such is mistakenly taken to represent the overall 24-h glucose supply. Because *glycemic load* is defined by the 2-h postprandial definition of *GI*, this may not always be the case. The values for the calculated glycemic load of the 2 diets in Figure 1 were within 1% of each other [154 for the high-sucrose diet compared with 155 for the high-starch diet, as per Foster-Powell et al (79)]. Yet the 24-h AUC for glucose was significantly higher for the high-starch diet than for the high-sucrose diet (6780 compared with 6290 mmol/L; $P < 0.001$), although it could be argued that this difference is not significant clinically. Evidence for negative health effects of high-glycemic-load diets comes from studies in which starches rather than sugars provided the major component of the overall glycemic load.

FUTURE RESEARCH DIRECTIONS

Although the metabolic effects of sucrose have been studied extensively and persistently over many decades, fundamental questions still remain with regard to effects on insulin sensitivity. Does the rat model of altered insulin sensitivity with high fructose (>30% of dietary energy) or high sucrose (>60% of dietary energy) have a meaningful parallel in humans? No group of researchers has yet shown a convincing negative or positive effect of sucrose on insulin sensitivity by using dynamic insulin sensitivity assessment (eg, euglycemic clamp). In young healthy adults or sedentary overweight adults and in the setting of controlled experimental high-carbohydrate diets, no negative effects of sucrose on insulin sensitivity were seen (50, 59). Therefore, the following type of study is needed: a comparison between ad libitum high-sucrose diets (>25% of energy) and ad libitum high-starch diets in the context of high-carbohydrate (>55% of energy) and moderate-carbohydrate (≈40% of energy) intakes with insulin sensitivity assessed by using a gold-standard assessment of insulin sensitivity (such as the euglycemic clamp) at baseline and after treatment.


Frayn and coworkers (80–83) showed reproducible effects of fructose on postprandial hypertriglyceridemia only in the context of a significant fat load. We should not ignore the possibility that sucrose may affect insulin sensitivity only with a high fat intake, particularly given the high fat intake in the positive studies by the Beltsville group (46, 47, 54). Furthermore, these studies should be done in different subject groups [patients with a body mass index >25 but without diabetes, patients with hypertriglyceridemia, and patients with diabetes (type 1 and type 2 separately)]. Results should be interpreted not only as results of the dietary intervention itself but also as changes from the subjects' habitual diet.

Such research is very expensive and time consuming. It may be wise to first consider its potential benefits. In the United Kingdom, a very small proportion of persons consume sucrose at the intakes prescribed in the experimental human studies (84). If a defined subject group was found to be sensitive to the effects of sucrose in a way that was comparable with that observed in the mouse model, then the work would be informative.

Dose-response studies looking at changes both in dynamic insulin sensitivity and in fasting and postprandial triacylglycerol concentrations in the susceptible group across a range of sucrose intakes in an ad libitum design are also needed. Such research should also be tempered by the effects of public health information. Further research is needed to define how different population

groups change their dietary intake when advised on sucrose intake. For example, how do other dietary constituents change if subjects reduce their sucrose intake? The effects that arise when sucrose is replaced by saturated fat may be very different from those that arise when sucrose is replaced by whole grains and fruit.

CONCLUSION

Overall, despite the wealth of interest that sucrose has attracted, research has failed to show a consistent effect of dietary sucrose or fructose on insulin sensitivity. 

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