

Is Fructose the Optimal Low Glycemic Index Sweetener?

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Abstract

Fructose is a monosaccharide which is abundant in nature. It is the sweetest naturally occurring carbohydrate. The availability of fructose increased substantially when it became possible in the 1960s to economically produce high fructose syrups from corn starch and other starches. Such high fructose syrups are now used to sweeten soft drinks, fruit drinks, baked goods, jams, syrups and candies. The most recent data available suggest that fructose consumption is increasing worldwide. Fructose presently accounts for about 10% of average total energy intake in the United States. Studies in both healthy and diabetic subjects demonstrated that fructose produced a smaller postprandial rise in plasma glucose and serum insulin than other common carbohydrates. Substitution of dietary fructose for other carbohydrates produced a 13% reduction in mean plasma glucose in a study of type-1 and type-2 diabetic subjects. However, there is concern that fructose may aggravate lipemia, particularly in men. In one study, daylong plasma triglycerides (estimated by determining the area under response curves) in healthy men was 32% greater during a high fructose diet than during a high glucose diet. There is also concern that fructose may be a factor contributing to the growing worldwide prevalence of obesity. Increasing fructose consumption is temporally associated with the increase in obesity. Moreover, on theoretical grounds, dietary fructose might increase energy intake. Fructose stimulates insulin secretion less than does glucose and glucose-containing carbohydrates. Since insulin increases leptin release, lower circulating insulin and leptin after fructose ingestion might inhibit appetite less than consumption of other carbohydrates and lead to increased energy intake. However, there is not yet any convincing experimental evidence that dietary fructose does increase energy intake. Although evidence that fructose has adverse effects is limited, adding fructose in large amounts to the diet may be undesirable, particularly for men. Fructose that occurs naturally in fruits and vegetables is a modest component of energy intake and should not be of concern.

Fructose is a six-carbon monosaccharide which is abundant in nature. Free fructose is present in honey, dates, figs, apples, grapes and most berries. An additional, important quantitative natural source of fructose is the disaccharide sucrose which is composed of equimolar quantities of fructose and glucose. When ingested by humans, fructose is absorbed by an active transport system but at a slower rate than is glucose [1]. Co-ingestion of glucose increases intestinal absorptive capacity for fructose. In the absence of glucose, human intestinal capacity to absorb fructose appears to be quite variable with some people unable to completely absorb 30- to 40-gram quantities [1]. Those individuals unable to completely absorb ingested fructose are at risk for diarrhea and other gastrointestinal side effects.

The first several steps in fructose and glucose metabolism differ significantly. Fructose stimulates only modest insulin secretion and does not require the presence of insulin to enter cells [2]. Avidly taken up by hepatic cells, fructose is rapidly converted to fructose-1-phosphate and bypasses the early rate-limiting steps of glucose metabolism. Fructose-1-phosphate is mainly converted to lactate, glucose and glycogen [3]. Gluconeogenesis from fructose is increased by starvation and poorly controlled diabetes. Fructose may also form acetyl CoA which is used in fatty acid synthesis. Enhanced activity of lipogenic enzymes with chronic fructose feeding may promote hepatic triglyceride production and output of VLDL particles. Presumably, energy intake must be excessive for fructose to stimulate lipogenesis.

Fructose is the sweetest tasting naturally occurring carbohydrate (table 1). Advances in technology in the 1960s made possible the production of inexpensive high fructose syrups from corn starch [4]. Corn is an abundant worldwide source of starch. To make high fructose syrups, corn starch is first separated from other corn by-products by wet milling. Next the starch is digested with mineral acid and amylase to form glucose. The enzyme glucose isomerase is then used to convert glucose to fructose. A syrup containing 42% fructose is the first product of this process. Through chromatographic enrichment, 55 and 90% high fructose syrups can then be produced. The 55% high fructose syrup has taste and sweetness equivalent to sucrose. Because of sweetness and low cost, high fructose syrups found commercial application. In the mid 1980s, 55% high fructose syrup was adopted by the carbonated-beverage industry and became the predominant sweetener in soft drinks.

The United States has from the beginning been the world's largest producer of high fructose corn syrups but Japan, Canada, South Korea, China, Argentina, and other countries are also significant producers [5]. In Asia, tapioca starch and broken rice are used in production of high fructose syrups. High fructose syrups are widely used in soft drinks, fruit drinks, baked goods, jams, syrups and candies. In 1977-1978, average fructose intake was estimated to be 37 g per day, accounting for ~8% of total energy intake in the

Table 1. Sweetness relative to sucrose [4]

Substance	Relative sweetness
Fructose	117
High fructose syrup – 90%	106
Sucrose	100
High fructose syrup – 55%	99
High fructose syrup – 42%	92
Glucose	67

United States [6]. In 1987–1988, fructose intake had increased to 39 g per day, accounting for ~9% of energy intake [7] and in 1988–1994, it had further increased to 55 g per day, accounting for ~10% of energy intake [8]. Approximately one third of fructose came from fruits, vegetables and other natural sources and two thirds were added to beverages and foods in the diet. A similar trend toward substantial caloric sweetener and fructose consumption is occurring worldwide [9].

There has long been interest in the metabolic effects of fructose, particularly in people with diabetes. Studies in diabetic subjects done in the 1970s and 1980s demonstrated that fructose-containing test meals produced smaller postprandial increases in plasma glucose than test meals containing isocaloric amounts of sucrose, glucose and starch [10–12]. Jenkins et al. [13] greatly expanded our knowledge about the differences in response to dietary carbohydrates with the development of the glycemic index of foods. Glycemic index was defined as the increase in plasma glucose area from 0 to 120 min after ingestion of 50 g of available carbohydrate from a test food compared to 50 g of carbohydrate from a reference food such as glucose. The glycemic indices of carbohydrate-containing foods vary substantially, with fructose having a particularly low glycemic index (table 2).

In an effort to further evaluate the potential for fructose to lower postprandial plasma glucose, we developed five test meals containing different carbohydrates and fed the meals to healthy and diabetic volunteers [14]. The meals contained nearly identical amounts of carbohydrate, protein and fat but a different test carbohydrate which accounted for 24 or 25% of total calories. The test carbohydrates were glucose, fructose, sucrose, potato starch and wheat starch. Plasma glucose and serum insulin were measured before and at intervals for 240 min after the meals. In healthy volunteers, type-1 diabetic volunteers and type-2 diabetic volunteers, the fructose meal produced the smallest postprandial increment in plasma glucose and the smallest increment in postprandial glucose area (fig. 1). The fructose meals also produced the smallest increment in serum insulin in healthy and type-2 diabetic volunteers but the differences among meals were not significant.

Table 2. Glycemic indices of selected carbohydrate-containing foods [from 13]

Food	Glycemic index	Food	Glycemic index
Instant potato	80	Banana	62
White rice	72	Apple	39
White bread	69	Orange juice	46
Frozen peas	51	Glucose	100
Sweet corn	59	Sucrose	59
Carrots	92	Fructose	20
Lentils	29	Skim milk	32
Kidney beans	29	Ice cream	36

Reference food was 50 g glucose.

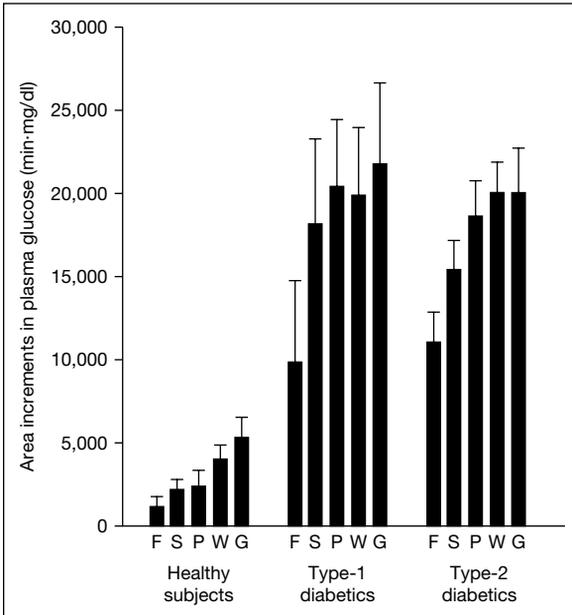


Fig. 1. Area increments in plasma glucose (mean \pm SEM) after test meals indicated as follows: fructose (F), sucrose (S), potato (P), wheat (W) and glucose (G) [from 14].

Since fructose has an agreeable taste similar to that of sucrose and since fructose produces a smaller postprandial rise in plasma glucose than other common carbohydrates, fructose seemed to be an excellent candidate for a sweetening agent in the diabetic diet. To test this possibility, we studied 12 type-1 and 12 type-2 diabetic subjects who were fed three isocaloric diets for 8 days each using a randomized, crossover design [15]. The three diets provided,

respectively, 21% of energy as fructose, 23% of energy as sucrose, and almost all carbohydrate energy as starch with less than 5% of energy derived from fructose and sucrose. All meals were prepared in a metabolic kitchen and provided to subjects. The fructose diet resulted in significantly lower 1- and 2-hour postprandial plasma glucose levels, overall mean plasma glucose, and urinary glucose excretion than did the starch diet. The reductions in mean plasma glucose with the fructose diet were 24% in type-1 diabetic subjects and 7% in type-2 diabetic subjects. Of note, the fructose diet increased postprandial lactate. There were no differences between the sucrose and starch diets in any of the measure of glycemic control in either subject group.

It next seemed important to extend the period of dietary intervention with fructose to see if beneficial effects on glycemia persisted and to look for potential adverse effects. Accordingly, we compared isocaloric high fructose (20% of energy derived from fructose) and high starch diets (less than 3% of energy derived from fructose) in 6 type-1 and 12 type-2 diabetic subjects using a crossover design [16]. Both study diets were composed of common foods. All meals were prepared in a metabolic kitchen and provided to subjects for 28 days. The diets were well received by all subjects. Mean plasma glucose, urine glucose and serum glycosylated albumin were all lower during the fructose diet than during the starch diet. On day 28 of the fructose diet, mean plasma glucose was 13% lower than on day 28 of the starch diet. However, of concern, fasting serum LDL cholesterol on day 28 of the fructose diet was 11% higher than the corresponding value for LDL cholesterol on day 28 of the starch diet.

Thus, a diet in which fructose was substituted for other carbohydrates was pleasant to eat and resulted in reduced glycemia in people with diabetes but appeared to have an adverse effect on serum LDL cholesterol. This raised concern about fructose as a sweetening agent in the diabetic diet. This finding also raised concern about the potential effects of dietary fructose in the general population since, in the United States and many other countries, fructose is a significant source of dietary energy [9]. Several studies did not find adverse effects of dietary fructose on serum lipids in healthy subjects [17–19]. However, these studies either compared fructose to sucrose or were outpatient studies that did not provide meals to subjects. Since sucrose is composed of 50% fructose, it is not an optimal reference. Moreover, rigorous control of nutrient intake requires the provision of meals. Thus, these studies may not be reliable in assessing the effects of dietary fructose on serum lipids.

Two studies which compared a high fructose diet to a diet nearly devoid of fructose and established rigorous control of nutrient intake by providing all food to subjects both reported adverse effects of fructose on serum lipids [20, 21]. Hallfrisch et al. [20] reported that high fructose diets consumed for 5 weeks increased fasting plasma LDL cholesterol in healthy and hyperinsulinemic men and increased fasting plasma triglycerides in hyperinsulinemic men. Reiser et al. [21] found that a high fructose diet consumed for 5 weeks increased fasting plasma LDL cholesterol in healthy men and fasting plasma

triglycerides in both healthy and hyperinsulinemic men. These two well-done studies suggested that dietary fructose does adversely affect serum lipids, at least in men. Women were not included in either study.

In an effort to gain additional insight into the effects of fructose on plasma lipids, we compared high and low fructose diets in 24 healthy volunteers (12 men and 12 women; 6 of each gender age <40 years and 6 of each gender age >40 years) [22]. All subjects consumed two isocaloric diets for 6 weeks. One diet provided 17% of energy as fructose. The other diet was sweetened with glucose and was nearly devoid of fructose. Diet order was assigned randomly using a balanced, crossover design. Both diets were composed of common foods and contained nearly identical amounts of carbohydrate, protein, fat, fiber, cholesterol and saturated, monounsaturated and polyunsaturated fatty acids. All meals were prepared in the metabolic kitchen of the University of Minnesota General Clinical Research Center. The fructose diet resulted in higher fasting total and LDL plasma cholesterol at day 28 but this effect did not persist at day 42 (table 3). The plasma triglyceride responses to the diets differed by gender. The fructose diet had no significant effect on fasting or postprandial plasma triglycerides in women (table 3, fig. 2). However, in men, the fructose diet produced significantly higher fasting and postprandial plasma triglycerides. This effect persisted through day 42. On day 42 of the fructose diet, daylong plasma triglycerides (estimated by determining the area under the response curves) in men was 32% greater than during the glucose diet. We concluded that diets high in added fructose may be undesirable, particularly for men. Glucose may be a suitable replacement sugar.

Another potential concern about fructose is its association with increased energy intake and obesity. Worldwide trends in per capita consumption of caloric sweeteners (of which high fructose syrups are a major component) demonstrated an increase from 232 kcal/day in the year 1962 to 306 kcal/day in the year 2000 [9]. In the United States, caloric sweeteners accounted for 16% of energy intake in the year 1996 [9]. About 43% of the caloric sweeteners came from soft drinks and fruit drinks.

Several authors have suggested that dietary fructose may play a role in the worldwide increase in obesity prevalence [23, 24]. Their reasons for implicating fructose are principally two. The first is the association, mentioned above, between increasing consumption of fructose and increasing obesity. The second is the theoretical possibility that dietary fructose increases energy intake. Clearly dietary fructose stimulates insulin secretion less than glucose and glucose-containing carbohydrates. Insulin stimulates leptin release from adipocytes [25] and circulating insulin and leptin concentrations were thus lower after ingestion of fructose-containing meals than after ingestion of glucose-containing meals in healthy women [26]. However, energy intake by the women was not greater during the fructose-containing meals. Nevertheless, lower circulating insulin and leptin after fructose consumption might inhibit appetite less than consumption of other carbohydrates and lead to an increase in food intake.

Table 3. Effects of the two study diets on mean fasting plasma lipids [22]

	Day		
	14	28	42
Plasma cholesterol, mmol/l			
Fructose diet	4.53	4.61	4.30
Glucose diet	4.43	4.30	4.22
p ^a	0.154	<0.001	0.169
Plasma LDL cholesterol, mmol/l			
Fructose diet	2.67	2.69	2.49
Glucose diet	2.59	2.49	2.49
p ^a	0.256	<0.001	0.756
Plasma HDL cholesterol, mmol/l			
Fructose diet	1.35	1.37	1.30
Glucose diet	1.40	1.37	1.30
p ^a	0.077	0.897	0.965
Plasma triglycerides, mmol/l			
Women			
Fructose diet	0.97	1.02	0.93
Glucose diet	0.88	0.99	0.97
p ^a	0.298	0.810	0.631
Men			
Fructose diet	1.32	1.30	1.25
Glucose diet	1.12	1.03	0.95
p ^a	0.018	0.001	<0.001

The means for each endpoint have a common SE based on the appropriate repeated-measures ANOVA error term; to convert cholesterol to mg/dl, multiply by 38.6; to convert triglycerides to mg/dl, multiply by 88.5.

^aBecause 6 paired comparisons of this endpoint were made (all data not shown), only $p < 0.008$ (0.05/6) should be considered significant at the 0.05 level.

Consistent with the idea that dietary fructose might increase energy intake are data from Ludwig et al. [27] which demonstrated an association between consumption of sugar-sweetened drinks and obesity in children. Further evidence is provided by Raben et al. [28] who fed overweight subjects supplements of either sucrose or artificial sweeteners for 10 weeks. The subjects who consumed sucrose demonstrated increases in energy intake, body weight, fat mass and blood pressure. However, it is important to point out that subjects in the sucrose group were ‘instructed’ to consume 2 g sucrose/kg body weight daily (~23% of energy intake) and were provided with the necessary sucrose-sweetened beverages and foods to do so. Thus, the increased sucrose intake was not spontaneous. These two studies were the main evidence cited by the World Health Organization when implicating sugars as a cause of obesity and to justify their recommendation that free sugar consumption be less than 10% of total daily energy intake [29].

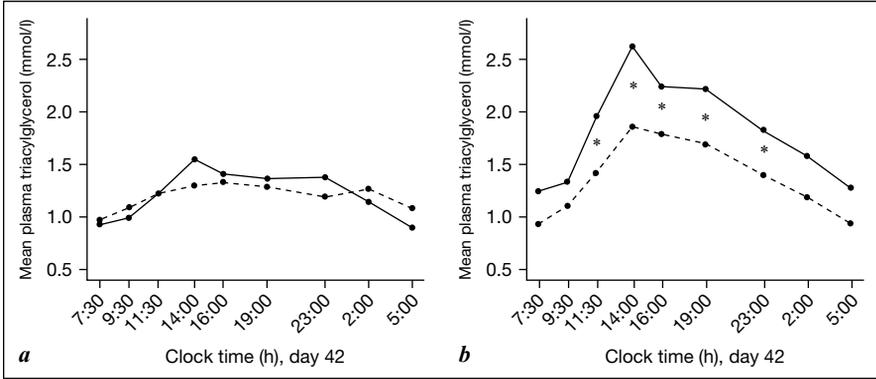


Fig. 2. Mean plasma triacylglycerol (triglyceride) concentrations in women (a) and men (b) during the 24-hour metabolic profiles on day 42 of the fructose (—) and glucose (-----) diets. Significant difference (*) between the two points is shown, $p < 0.006$ (0.05/9, Bonferroni adjustment for multiple comparisons). To convert triglycerides to mg/dl, multiply by 88.5 [from 22].

Although increasing fructose consumption is temporally associated with the increasing worldwide prevalence of obesity, there is little or no evidence proving cause and effect. In the US, increasing energy intake was associated with increased restaurant and fast-food meals and increased consumption of salty snacks and pizza as well as soft drinks [30]. Decreased physical activity is also almost certainly a factor in the increasing prevalence of obesity. To demonstrate that dietary fructose is important in causing obesity, it would be necessary to conduct a clinical trial demonstrating that fructose caused a spontaneous increase in energy intake. Given fructose’s availability, low cost and pleasant taste, such a clinical trial might provide important new information.

In summary, fructose is a naturally occurring sugar with a pleasant taste. It produces a smaller postprandial rise in plasma glucose than other common carbohydrates and thus may be a useful sweetening agent in the diabetic diet. However, dietary fructose appears to have adverse effects on plasma lipids. Moreover, there is concern that dietary fructose may stimulate energy intake and promote weight gain and obesity. Thus, adding large amounts of fructose to the diet may be undesirable. Nevertheless, concern about fructose should not extend to the naturally occurring fructose in fruits and vegetables. These are healthy foods which provide only a modest amount of fructose in most diets.

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Discussion

Dr. Katsilambros: A long time ago I learned personally from Prof. Alexander Margot that when patients come in at the beginning in a state of uncontrolled diabetes, it is quite undesirable and contraindicated to provide fructose because it is much more readily converted to glucose in uncontrolled diabetes. Is this also your opinion? The second comment refers to personal studies done many years ago when I was an assistant. Patients with hepatitis B were given fructose orally, once in the acute stage and again in the recovery stage. Glucose and fructose were measured separately. In the first acute phase there was fructose intolerance; the curve was high and delayed. Then in the recovery phase a considerable improvement in this curve was observed. This means that fructose intolerance was due to the diminished capacity of the liver to transform fructose to glucose. The related question now refers to your observation that men and women have large differences with regard to the triglyceride increase; that in men triglycerides were much higher than in women. Are you sure that these men were not drinkers?

Dr. Bantle: Let me answer the first question which is about the effect of fructose in poorly controlled diabetes. I think you are absolutely correct. If fructose is fed to someone with poorly controlled diabetes, there is a greater rise in plasma glucose than in people who have well-controlled diabetes. But I think if you look at the response of such a person to ingested glucose, it is also greatly increased and in fact the glycemic response to fructose is somewhat less than glycemic response to glucose in that situation. It is true, however, that more fructose is converted to glucose in poorly controlled diabetes. Your second point about the use of fructose as a test for liver disease, I cannot answer. I don't have experience with that. Please, what was the last question?

Dr. Katsilambros: The fact that triglycerides were higher in men. Usually these men are volunteers and in many countries including yours these volunteers are paid, and certainly some of them are drinkers. With women this is not the case and it might possibly make a difference.

Dr. Bantle: This might make a difference but we screened subjects carefully for a history of alcohol consumption. They were to avoid alcohol during the period of study but I cannot guarantee they did. We were quite certain they ate what we asked them to eat, but whether or not they used alcohol I can't say for certain. They were solid Minnesotan citizens who pretty much do what you ask them to if they say they will. I will tell you a story about our study. One day I was called by one of the nurses to come and talk to one of the subjects. When I came into the room, the woman was crying. She said she had to tell me that she had eaten something that wasn't in the study diet. She confessed to have eaten 2 Cheros, and then she started crying again. I was fairly confident the data from that woman were reliable. But I can't verify that some of our subjects didn't consume alcohol. One would hope that any effect of alcohol was evenly distributed between both treatments so that the randomization process would have reduced or eliminated any effect.

Dr. T. Wilkin: If I recall a review I read some months ago now, the average American child is consuming something between 60 and 80 g of fructose from soda drinks alone in the course of the day, whereas if left to the natural sources of fruit and vegetables it might be between 10 and 15 g. Even if your evidence is such that you observe nothing special about the action of fructose, there was a huge increase in the number of calories that have been consumed as a result of fructose ingestion and the link between obesity and fructose can surely be argued still to be there.

Dr. Bantle: Yes, and perhaps the problem with fructose is it tastes good and is pleasant to consume. The overall problem may be that we are victims of our own success with abundant food that tastes good and is inexpensive. Several years ago

McDonalds was implicated in the outbreak of obesity and they may have a similar sort of problem. They make food that tastes good and is inexpensive. That may be as much the problem as the specific food type. I would not implicate fructose until we have better evidence. For instance, sucrose might do the same thing, and if we decided to sweeten drinks with glucose, it would potentially do the same thing.

Dr. T. Wilkin: In your data of the 42-day study you showed us I think 14, 28 and 42 days, but I don't think you showed us the time zero, and I wondered if the levels of time zero or levels of day 42 had returned to what they were at time zero.

Dr. Bantle: The lipid values?

Dr. T. Wilkin: Cholesterol values.

Dr. Bantle: There were baseline values obtained. The main thing that happened was that lipids got better on the glucose diet which would suggest that the baseline diet was high in fructose.

Dr. Golay: Do you have more details concerning the group of women: age, hormone replacement, etc.?

Dr. Bantle: The women were picked so that 6 were under 40 and 6 were over 40. We looked at age in both men and women and could find no effect, although the subject sample size was small. Both in younger men and older men, the triglyceride values were higher on the fructose diet. In older and younger women there was no effect of the fructose diet on triglycerides. I don't recall the hormonal status but I think most of the older women were postmenopausal. We did not stop any replacement therapy they were receiving so we cannot speak much on the effect of estrogens based on this study.

Dr. Metzger: I am also interested in the differences between the men and women. Is there any difference in the handling of fructose between men and women?

Dr. Bantle: Not that I know of and I am not sure there was a real difference in our study. In the study from Elliott et al. [1] that I showed, the women did have a rise in triglycerides when given a high fructose diet. However, there was more fructose, 30% of energy for 1 day, and I think that is an important issue.

Dr. Slama: I had a similar experience as you many years ago and I came to the same conclusion. But for women I have not looked at that carefully; perhaps I missed something but I could go back to my data. Having a large experience with animal models I can say that when you feed rats large amounts of sucrose or fructose then a massive infiltration of fat is seen everywhere. What is striking is that the liver is twice the size of that of the control rat, and this liver is half fat and half glycogen. The same but less striking observation can be made in the muscle; there is a lot of fat in the muscle and a lot of glycogen which could be utilized by sportsmen. This is so true that not only we but also others are routinely using an insulin-resistant rat model: fructose fat rats.

Dr. Bantle: I think you made a good point. Fructose is very lipogenic in animal models although many of the animal studies have employed very high fructose intakes, between 30 and 70% of energy. I think a key point that is not commonly reported is the energy balance of the animals. That is, with excess energy, fructose is much more lipogenic and there are more adverse effects on lipids than with an energy-deficient diet where most of the fructose is burned as it is consumed. But that hasn't been studied.

Dr. Slama: I can add that we observed this even pair-fed rats; they have the same body weight but much more fat and glycogen in the liver than control rats. So it is not only a question of energy and free access to palatable food, it is a question of metabolism and you have shown that the fructose is prone to conduct rather to glycogen and/or to lipids rather than going back to glucose.

Dr. Bantle: I don't doubt the observation but I have difficulty to explain how, if they are truly pair-fed and getting isocaloric diets, they would produce and store more

fat on one diet than on the other, no matter what the source of energy. Perhaps there is something about fructose that affects metabolism.

Dr. Hill: I have a comment and a question. First I think it is very dangerous to correlate specific things in the environment with changes in obesity rates. There are so many things that correlate. Along those lines, it is disturbing to hear everybody blaming the obesity epidemic on fructose with such little data. My question relates to Dr. Slama's question. One of the concerns is that fructose may be producing insulin resistance in the liver and that could lead to weight gain and obesity. Are there data available that this may be a pathway to link fructose with obesity?

Dr. Bantle: This is a good question and I am afraid I am not aware of any data. Perhaps someone in the audience is. Is anyone aware of such data?

Dr. Slama: No, because really in animals you can feed them with 70% calories coming from fructose.

Dr. Bantle: Regarding your comment Dr. Hill, I think that the liquid sweeteners may in fact be more a problem than solid sweeteners. That is, all the calories that we get through soft drinks may in fact be highly undesirable.

Dr. Chiasson: I remember that Dr. Reaven was using that specific animal model to create hypertension and also insulin resistance. I was just wondering whether in your experience the subjects did develop any change in the blood pressure?

Dr. Bantle: We did monitor blood pressure carefully and could not demonstrate any difference between the two diets in blood pressure. I too read Dr. Reaven's studies with interest. I think he used 70% fructose in his rat models.

Dr. Halimi: As Dr. Slama's group with the same animal model, we found the same things: a huge amount of visceral fat, a large liver with steatosis, and hypertension. Fructose increases plasma triglycerides in men but not in women, and not to the same extent in all populations, more subjects with metabolic syndrome. When plasma triglyceride increases, what happens to the low-density lipoprotein particle size in the studies mentioned?

Dr. Bantle: We did not measure the particle size in our studies and I am not aware of anyone who has. So again, I am afraid I can't answer the question based on any experience or data.

Dr. Slama: I find Dr. Halimi's comment very interesting. Could you not apply the definition of metabolic syndrome to both populations in your population and see if there is a trend towards more frequent metabolic syndrome in men than in women?

Dr. Bantle: You mean retrospectively go back and look at the data and define those in the groups who had metabolic syndrome. This is an interesting idea. I think we did have a range of body mass indexes. So it may be possible for us to do that and see if it was those with higher body mass indexes and metabolic syndrome who had the more significant response to fructose. It is a good idea, thank you.

Dr. T. Wilkin: Given the data on hepatic infiltration in the animals, did you have the opportunity to look at inflammatory markers?

Dr. Bantle: We had the opportunity but we didn't take it. In retrospect, I wish we had.

Dr. Mooradian: Just a caution to those of us who do a lot of cell culture studies: fructose is a very nasty substance and it has a lot of cell toxicity. I have concerns about this fructose intake even though the effect on glycemia and lipids seems to be modest within the range of fructose consumed day to day. But at least in the cell culture field fructose is by far a much more toxic substrate than glucose is. I wonder if we are missing some additional effects of fructose when we just focus on glucose and the lipid effect of this sugar.

Dr. Bantle: That is a good point and there may be other effects of fructose, as yet not defined, that are adverse. I would use the opportunity to point out that we were looking at 17% of energy as fructose which is something like the 90th percentile of intakes in the United States. It was quite a high fructose intake but 10% of the people

in the United States consume that much or more. I am of the opinion that putting this much fructose into the energy stream is perhaps not a good idea. We suggested glucose would be a suitable replacement but it turns out that glucose is much less sweet than fructose. The amount you have to put in to make a soft drink taste like it does now would give 50% more calories. Recipes that employ sucrose or high fructose corn syrup would have to be changed in terms of preparation, amounts, baking time, caramelization and all sorts of factors. These would become problems that would need to be solved.

Dr. Halimi: Just another comment about the high fructose diet in rats. It is not confirmed in human studies but in rats there is also a huge increase in many oxidative stress parameters and this parallels insulin resistance [2, 3]. It would be very interesting to examine the situation in humans, with a high fructose intake as the current intake in the US, to measure the oxidative stress in these populations.

Dr. Bantle: I agree, more study in fructose is clearly needed to see if what happens in animals also happens in humans.

Dr. Mooradian: Just to follow up on Dr. Halimi's point: tomorrow I am going to show data specifically on the effect of fructose in oxidation. Fructose is 7- to 8-fold more pro-oxidant compared to glucose.

Dr. Slama: Have you seen convincing data that 50:50% mixing of glucose and fructose is the same as sucrose in terms of the metabolic effect?

Dr. Bantle: No, I don't know of any such data. My assumption is that, since 55% fructose corn syrup contains nearly equal amounts of glucose and fructose, it would have the same effect as sucrose.

Dr. Slama: I am not sure really but there might be some data proving the reverse. I think that the problem comes from your country because you are not producing sucrose or only very small amounts, and so you are producing your natural sweeteners, corn syrup, whereas in other countries sucrose is widely used.

Dr. Bantle: I agree, we are part of the problem. Where I come from, as soon as you leave the city, there is corn as far as the eye can see in all directions.

Dr. Slama: So you may have some trouble in your country to pick up all.

Dr. Bantle: Corn is a good thing in most respects.

Dr. Halimi: Just some information, very interesting in my opinion. In cooperation with a center specialized in animal feeding, we have confirmed that a high fructose diet is able to induce insulin resistance in male rats. But this diet does not induce insulin resistance in females [4]. Second, when the same diet, very rich in fructose, is reproduced using honey, then there is no insulin resistance. This could be due to antioxidative substances in the honey [5].

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