Diabetes and fructose metabolism[1,2]

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ABSTRACT The clinical aspects of fructose supplementation in the diets of individuals with diabetes should focus on the balance between beneficial effects and possible side effects. Fructose supplementation in diabetes mellitus was advocated before insulin was discovered. Fructose elicits a lower glucose and insulin response in healthy individuals and in individuals with diabetes. The use of fructose as a sweetener in the diets of diabetics has been debated repeatedly. Short-term studies have now shown that substitution of fructose for sucrose in the diets of individuals with diabetes improves glycemic control and does not appear to have substantial side effects. In balanced diets, reasonable amounts of fructose supplementation do not affect lipoprotein metabolism or result in gastrointestinal symptoms. Long-term studies are still needed to ascertain that long-term fructose supplementation has a sustained beneficial effect in diabetes and is devoid of deleterious side effects. *Am J Clin Nutr* 1993;58(suppl):796S–799S.

KEY WORDS Fructose, fructose metabolism, fructose supplementation, non-insulin-dependent diabetes mellitus, dietary management, glycemic control, sweetener, hypertriglyceridemia

Introduction

Fructose supplementation in diabetes mellitus was advocated before the advent of insulin discovery. Fructose in comparison with other carbohydrates and specifically sucrose, the most commonly used simple sugar, elicits a lower glucose and insulin response in healthy individuals and in individuals with diabetes. Fructose in the diet of patients with diabetes can play a dual role: both as part of the carbohydrate content and as a sweetening agent. The use of fructose as a sweetener in the diets of diabetics has been debated repeatedly. Fructose is sweeter than glucose and provides the same sweetness effect for less energy. Therefore, fructose used as a sweetening agent in the diet of patients with diabetes may have a definite advantage.

In recent years multiple short- and long-term studies have evaluated the effect fructose substitution may have on glycemic control in non-insulin-dependent diabetes mellitus (NIDDM). In general, these studies have shown no adverse effect on glycemic control but the degree of glycemic control improvement and the possible side effects on other aspects of metabolism have been debated. A recent article (1), by authors who have extensively worked in the field, comprehensively reviews issues in fructose metabolism. In this section we review the research studies that specifically address the effect of fructose supplementation on glycemic control in patients with NIDDM. (For a critical review of the studies addressing the possible side effects fructose supplementation may have on lipid metabolism, *see* 2.) Finally, we offer an estimate of the research needed to evaluate the risk-to-benefit ratio of any potential increased use of fructose by healthy, diabetic individuals.

Role of fructose in the dietary management of diabetes

The recommended carbohydrate content of the diets of individuals with diabetes has varied over the years. The American Diabetes Association has recommended that 55–60% of total energy should derive from carbohydrates (3). This larger proportion of carbohydrate energy does not seem to result in less desirable blood glucose control (4). Simple sugars in these diets are recommended in moderation, whereas complex carbohydrates should constitute the highest proportion of the carbohydrate energy. The use of sweetening agents in the diets of diabetic patients has been debated. The use of fructose as a sweetening agent and/or as carbohydrate replacement in the dietary management of diabetes has been extensively investigated.

Studies by Crapo et al (5) in the early 1980s demonstrated that acute administration of fructose results in lower glycemic and insulin responses in normal subjects, individuals with impaired glucose tolerance, and patients with NIDDM, compared with dextrose or sucrose given in similar formulations. Furthermore, when fructose was incorporated as a sweetener in foods such as cakes and ice creams (6) or was mixed with other carbohydrates, fats, and protein (7, 8), a lower glycemic response was observed in normal and diabetic individuals. This desirable effect in acute fructose administration encouraged the notion that fructose could be widely used in the diets of NIDDM patients. Nevertheless, fructose supplementation would only be widely accepted if a long-term beneficial effect of fructose on carbohydrate metabolism could be ascertained. Fructose substitution for sucrose in the diet of normal subjects for 2 wk resulted in an improvement of glucose and insulin response to an oral glucose load and to meals at 3 and 14 d after the start of this regimen (9). In a similar study comparing the effects of fructose substitution for 2 wk in normal subjects, Bossetti et al (10) observed no difference in the serum glucose and insulin concentrations. In two different studies in patients with NIDDM, 1 or 2 wk of fructose supplementation

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resulted in a desirable decrease of serum glucose response to meals at the end of the experimental period (11, 12). In longer studies, in NIDDM patients, fructose substitution of ≈8–12% of the total energy for 1 (13), 2 (14), or 3 mo (15) again had no deleterious effect on glucose metabolism. These encouraging results were not consistently observed in animal studies (16–18), because a greater extent of fructose substitution did not improve glucose metabolism.

In the past few years it became obvious that additional prolonged studies were needed to answer the question of the effect of fructose supplementation in diabetes. Two studies in NIDDM patients attempted to address this question. In a 100-d study by Thorburn et al (19), six subjects were fed diets supplemented with fructose for ≈13% of the total daily energy. Patients were monitored closely and the diets were accordingly adjusted to maintain constant weight. Meal, glucose, and fructose tolerances were studied at days 1, 50, and 100. Furthermore, glucose-turnover studies were performed after infusion of labeled glucose for determination of the rates of glucose appearance and disappearance at baseline and during a 3-h, hyperinsulinemic euglycemic clamp at days 0 and 100. Results of this study indicated no change in serum baseline glucose and glucose and insulin responses to meals at the beginning and end of the 3-mo study. Likewise, no change was noted in the rates of basal hepatic glucose output and stimulated glucose disposal as indicated by the glucose turnover studies after 100 d of fructose supplementation. Five of the six subjects completed the study, but one of the patients had to discontinue because of very high triglyceride concentrations. Investigators in this study concluded that fructose supplementation in diabetes is not detrimental to glucose control but does not have a clear demonstrable beneficial effect, and cautioned on the effect fructose supplementation may have on lipid metabolism in susceptible individuals.

In a recent large study by Anderson et al (20), fructose was added to a high-fiber, high-carbohydrate, low-fat diet for 24 wk in 14 NIDDM patients. Fasting blood glucose, glycosylated hemoglobin, and indexes of lipid metabolism, as well as body weight, were monitored 8 wk before the start of fructose supplementation and 16 wk after the end of the fructose diet for a total of 48 wk. Patients were hospitalized the last week on the control diet and the first week of the fructose-supplemented diet. The remainder of the study took place in an outpatient setting. Fasting blood glucose decreased significantly during the week-long hospital stay on the fructose-supplemented diet, compared with the preceding week on the control diet in the hospital. The same fructose-supplemented diet that was associated with a beneficial effect in the hospital did not seem to affect glycemic control or glycosylated hemoglobin concentrations when followed subsequently in the outpatient setting. Furthermore, cholesterol and triglyceride concentrations did not seem to be affected compared with the pre- and postfructose diet control period. Despite the identical content of nutrients prescribed in both diets, energy intake was higher and subjects, on average, gained weight on the fructose-supplemented diet. These findings led the investigators to conclude that a fructose-supplemented diet for a substantially long period of time would have favorably affected glycemic control had the energy intake been kept constant (20).

In an effort to evaluate the effect of fructose feeding on carbohydrate-induced thermogenesis and energy expenditure, Simonson et al (21) performed calorimetric studies in NIDDM patients as well as in obese and older individuals, in all states of insulin resistance. It was hypothesized that because fructose entry into the cells is independent of insulin action, fructose may have a metabolic advantage in these patients. Results indicated a significant increase in carbohydrate oxidation and energy expenditure after fructose ingestion compared with glucose, supporting the authors' original hypothesis. Lipid oxidation did not seem to be affected by fructose ingestion. Of particular interest in this study is the finding that fructose ingestion increased carbohydrate-induced thermogenesis compared with glucose, even in the healthy young individuals used as control subjects. This observation has substantial implications in the management of weight control in healthy individuals as well as in patients with diabetes. Thermogenic effects of dietary fructose are reviewed elsewhere (22).

In summary, detrimental effects of fructose on carbohydrate metabolism were not reported in any of these studies, and there may be a beneficial effect short-term. This beneficial effect was not sustained during long-term use of fructose in diabetes although only a limited number of studies have been conducted. Although total fructose availability in the US diet has not changed appreciably (23), it is important to establish the safety and efficacy of special dietary uses of fructose by individuals with diabetes.

Side effects of fructose supplementation

Studies in rats (18, 24) had implied that high-dose fructose supplementation results in hypertriglyceridemia. This obviously would be an adverse effect of particular importance in diabetes, because lipid metabolism is impaired by the lack of or resistance to insulin. Most of the studies described above evaluating the effect of fructose supplementation on carbohydrate metabolism in NIDDM invariably monitored indexes of lipid metabolism. Their results had been inconclusive (12, 20) and the methods used did not provide for the appropriate dietary controls. For a comprehensive and critical review of two well-controlled recently published studies in diabetics and healthy subjects that have examined the effect of fructose supplementation on lipid metabolism, see the study by Hollenbeck (2).

Using elegant techniques with radioactively labeled glycerol, Thorburn et al (25) studied six volunteers with NIDDM on a fructose substituted diet for 3 mo. In these subjects dietary sucrose, 25% of total carbohydrate, was substituted with fructose in mixed meals. There was no adverse effect on glycemic control. The specific activity of triglycerides was identical before and at the end of the 3-mo period, indicating that triglyceride production and catabolism were not changed. Other indexes of lipid metabolism monitored in the same study were likewise not affected in these individuals with NIDDM. These observations were not in accordance with findings of earlier studies in which fructose-supplemented diets were shown to increase serum triglyceride concentrations in normal and diabetic individuals (14, 26). The only data presented in these earlier studies are exclusively on the basis of serum measurements whereas in the study by Thorburn dynamic metabolic indexes are examined albeit in a limited number of subjects.

In a well-controlled study recently published by Swanson et al, (27) a crossover design was used in 14 healthy subjects who consumed a fructose-supplemented (100 g) diet and a high-starch (201 g) diet for 28 d. Total energy content 8791 kJ (2100 kcal) and nutrient composition were identical in the two diets. Indexes

of carbohydrate and lipid metabolism were monitored weekly in all subjects. There were no changes noted in any of the indexes of carbohydrate metabolism. Fasting serum total cholesterol and low-density-lipoprotein (LDL) cholesterol concentrations between the two groups were significantly different at 28 d. A small rise in fasting serum cholesterol concentrations was observed during the fructose-supplemented diet but it was not statistically significant, a finding consistent with the findings of previous investigators (26). However, in this study it was obvious that a decline in cholesterol concentrations in the starch-fed subjects during the study period was the reason for the significant difference in the two groups.

Other side effects of fructose supplementation occasionally reported are gastrointestinal disturbances such as flatulence and diarrhea (28). Most of the gastrointestinal side effects observed were related to excessive amounts of fructose administered. Accordingly, most investigators who have worked extensively with fructose supplemented diets believe that balanced diets with moderate amounts of fructose do not cause these side effects (29). For a review of fructose absorption, *see* the study by Riby et al (30).

Finally, fructose-related glycation of proteins was studied (31). For a comprehensive review of this topic see the study by Dills (32). Although fructose supplementation does not seem to affect the concentrations of hemoglobin A_{1c} as shown in several studies (19, 20, 27), the direct effect of fructose on protein glycation is only now being examined. Very early evidence from a published study indicated that lens protein may react with circulating fructose to cause fructosylation of this protein (33). Results are still preliminary and inconclusive but this could be a very important issue with widespread implications.

In summary, the side effects of fructose supplementation do not seem at this time to be of particular concern when fructose is ingested in modest amounts. Considering the potential for increased exposure to free fructose, continuous surveillance for side effects in healthy and diabetic individuals is of utmost importance.

Research in progress

A few studies to date have shown that short-term fructose supplementation has a beneficial effect on metabolic control in diabetes. Long-term studies have failed to show that this effect is sustained. Nevertheless, available studies indicate no detrimental effect of modest intake by diabetics. Despite the overall reassuring findings of a lack of significant side effects, further long-term detailed studies on cholesterol and lipid metabolism will need to be performed to evaluate the possible atherogenic effect of fructose in patients with diabetes. Diabetes frequently is associated with metabolic disorders such as obesity, hypertension, and dyslipidemia. The effect of fructose supplementation in diabetes complicated by these disorders will need to be evaluated in long-term studies. The effect of fructose ingestion on long-term complications in diabetic individuals and the association of fructose-related glycation will need to be studied very carefully. Finally, well-controlled study designs need to be developed, with particular attention focused on the risk-to-benefit ratio of fructose supplementation so that while taking advantage of all the benefits, side effects can be avoided.

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