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# CURRENT ISSUES IN FRUCTOSE METABOLISM[1]

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## INTRODUCTION

Fructose is the sweetest of the simple sugars and is found in high concentrations in honey, fruit, and some vegetables. Until recently, ingestion of foods naturally containing fructose accounted for most of its intake. Over the

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last two decades, however, fructose consumption has increased significantly as many manufacturers now use high-fructose corn syrups in place of sucrose to sweeten processed foods and beverages. The use of fructose has also attracted a great deal of attention recently because of its unique metabolic properties. Some studies claim that fructose may be beneficial to individuals who are overweight, have non-insulin dependent (Type II) diabetes mellitus (NIDDM), or participate in endurance exercise activities. On the other hand, considerable scientific evidence indicates that dietary fructose may have adverse effects on lipid, copper, and uric acid metabolism, particularly in certain susceptible individuals. The current status of each of these issues, as well as their perceived importance and implications, is reviewed in this report.



## METABOLIC ASPECTS OF FRUCTOSE

### *Fructose Absorption and Metabolism*

The absorption of fructose across the small intestine in man is still poorly understood. Absorption appears to take place via an oxygen-dependent transport system at a slower rate than absorption of galactose and glucose, but more efficiently than in the case of passively transported sugars (e.g. sorbitol and xylitol). Interest in the mechanism by which fructose is absorbed has increased because of the finding that the absorption capacity of fructose is limited in 60% of adults. In the last six years, several published reports have documented symptoms of malabsorption after fructose ingestion (12, 60, 77, 82–84, 92, 100). However, this effect is largely abolished when glucose is given with fructose (12, 60, 82, 83, 100), possibly owing to activation of the fructose carrier by glucose (60). The cellular mechanisms by which glucose alleviates fructose malabsorption in man remain unknown, but further investigation is warranted because such work may have practical application for the dietary composition of foodstuff and possibly in the treatment of certain types of irritable colon.

Although fructose is absorbed more slowly than glucose, it is more readily metabolized by the liver because cellular uptake and the early steps of glucose and fructose metabolism differ markedly. Unlike glucose, fructose has only a modest effect on the stimulation of insulin secretion and does not require the presence of insulin to gain access to the intracellular compartment. This is one of the reasons fructose has been recommended as a dietary sweetener for non-insulin dependent (Type II) diabetes mellitus (NIDDM). It also explains why fructose is often used in research studies to separate the specific effects of hyperinsulinemia from those of increased cellular glucose utilization (93).

Once inside the cell, fructose is very rapidly converted to fructose-1-phosphate (FIP) (50). This phosphorylation step bypasses the early rate-

limiting steps of insulin-stimulated transport, which glucose must undergo. By this process, an oral fructose load will cause ATP to be converted to ADP and the liver to be depleted of inorganic phosphate (Pi) (87). This low Pi level allows the degradation of AMP to uric acid, which is then excreted from the cell. The high FIP concentration inhibits the degradation of glycogen and facilitates the production of lactate from fructose. About two thirds of fructose is converted to glucose, which may accumulate as glycogen or be released as glucose. The rest of the metabolized fructose is released from the liver as lactate. Under normal circumstances, small amounts of fructose are oxidized to carbon dioxide or metabolized to lipid. Fructose can inhibit ketone body production and may exert a protein-sparing action by replacing endogenous amino acids as gluconeogenic substrate (42). Therefore, fructose is absorbed and metabolized in a unique manner producing mainly glucose, glycogen, and lactate, and enhancing the formation of uric acid.



### *Effect of Fructose on Appetite*

The suggestion has been made that fructose may aid weight control in obese subjects by decreasing appetite. A limited number of studies have addressed the effect of fructose on appetite; these studies are all short term in nature (80, 81, 90, 99). While the ingestion of a single oral load of fructose alone appears to suppress subsequent food intake in both lean and obese subjects (80, 81, 90), this effect does not seem to be present when fructose is incorporated into mixed meals (81). Currently, the mechanism for fructose suppression of appetite is unknown. Possible modes of action include reduced insulin stimulation, slower gastric emptying, or increased fructose oxidation (80). Further studies in this area are needed. Long-term studies with mixed meals containing fructose will also be necessary to determine whether fructose has any potential as a weight loss agent.

## NUTRITIONAL ASPECTS OF FRUCTOSE

### *Use of Fructose in the Diet of Non-Insulin Dependent Diabetic Subjects*

EFFECT OF FRUCTOSE ON BLOOD GLUCOSE AND INSULIN Compared to most other carbohydrates, fructose, when given acutely as a sole nutrient, produces low postprandial glucose responses (25). This effect is still present when fructose is incorporated into mixed meals with other carbohydrates, fat, and protein (2). These observations have been responsible for raising the possibility that fructose may be beneficial in diabetic diets. Several long-term studies have been conducted to determine the potential usefulness of fructose as an alternative sweetener and as a therapeutic tool for diabetes mellitus. A summary of the effects of physiologic doses of fructose on plasma glucose

and insulin levels in studies conducted over the past 6 years is given in Table 1. Unfortunately, these studies have not yielded consistent results and can be almost equally divided into those reporting beneficial effects, no effect, or adverse effects after fructose ingestion. Conflicting results may be explained, at least partly, by differences in experimental conditions, e.g. animal versus human studies, the duration of feeding, the background diet, the degree of metabolic control of the subjects, or the type of carbohydrate replaced by fructose in the diet (3, 4, 9, 13, 23, 24, 44, 45, 61, 68, 73, 96, 97, 105, 110).

However, it is important to note that no adverse effects on blood glucose and insulin were observed in any of the seven studies conducted in non-insulin dependent diabetic subjects. Therefore, recent data indicates that long-term moderate fructose ingestion (10–21% of calories) has no apparent adverse effects on mean blood glucose and insulin levels in NIDDM subjects. However, in some susceptible NIDDM subjects, particularly those with accelerated hepatic very-low-density-lipoprotein (VLDL) triglyceride synthesis and secretion, fructose can cause insulin levels to increase dramatically (95), thus indicating that fructose may be potentially harmful in the presence of preexisting marked hypertriglyceridemia. This potential for adverse effects on serum



**Table 1** Effect of long-term (>1 week) fructose ingestion on plasma glucose and insulin in studies conducted over the past 6 years

| Subject | Length of feeding | Fructose (% of calories) | Effect on glucose | Effect on insulin | Compared to | Ref. |
|---|---|---|---|---|---|---|
| NIDD | 24 weeks | 12 | No change | | Starch | 3 |
| IDD & NIDD | 8 days | 21 | Decrease | — | Sucrose or starch | 4 |
| Rat | 11 weeks | 27 (wt/wt) | Increase | Decrease | Glucose | 9 |
| Normal | 2 weeks | 12–16 | No change | No change | Sucrose | 13 |
| Normal | 2 weeks | 13 | Decrease | Decrease | Sucrose | 23 |
| NIDD | 2 weeks | 13 | Decrease | No change | Sucrose | 24 |
| NIDD | 9 weeks | 8 | No change | No change | Starch | 44 |
| Normal & hyperinsulinemic | 5 weeks | 15 | Increase | Increase | Starch | 45 |
| IGT & normal | 4 weeks | 15 | Decrease | Decrease | Glucose | 61 |
| NIDD | 4 weeks | 12 | Decrease | — | Low fructose diet | 68 |
| NIDD | 12 weeks | 10 | Decrease | — | Low fructose diet | 73 |
| NIDD | 14 weeks | 13 | No change | No change | Sucrose | 96 |
| Rat | 4 weeks | 35 | No change | No change | Glucose | 97 |
| Sow | 3 weeks | 17 | Increase | No change | Glucose or starch | 105 |
| Rat | 2 weeks | 66 | No change | Increase | Starch | 110 |

triglyceride levels has been shown in rats (97, 109) and humans (95) and requires further investigation before fructose can be recommended as a safe sweetener for all NIDDM subjects.

HEPATIC AND WHOLE-BODY INSULIN SENSITIVITY Very few studies have delineated the underlying mechanisms for the beneficial or adverse effects on plasma glucose and insulin sometimes found after fructose feeding. Recently, it has been shown that despite lower acute postprandial plasma glucose responses to a fructose diet, insulin sensitivity does not improve after three months of fructose feeding (as measured by the euglycemic clamp technique) (96). In fact, both hepatic and whole-body insulin action remained unchanged after fructose feeding. In rats, however, fructose has been demonstrated to increase hepatic glucose output (98) and to reduce rates of glucose disposal (56, 97). These differing results may be explained by species differences or the larger amounts of fructose fed to the rats (35–66% versus 13% of calories). In man, large doses of fructose (1000 kcal/day for 1 week) have been shown to reduce insulin binding and insulin sensitivity in monocytes (5). However, more physiologic studies using moderate doses of fructose over longer periods of time (120 kcal/day for 2 months) have shown no increase in insulin binding to erythrocytes (44). Therefore, the small amount of data collected so far suggests that moderate doses of fructose produce no adverse effects on insulin sensitivity in man.

EFFECT OF FRUCTOSE ON CARBOHYDRATE OXIDATION AND THERMOGENESIS Fructose induces a larger increase in thermogenesis and carbohydrate oxidation than glucose when given as an oral dose (39, 87, 88) or as part of a mixed meal (86). This increased thermic effect does not depend on an increase in the plasma insulin concentration per se but rather depends on an augmentation of cellular metabolism, perhaps mediated in part by the $\beta$-adrenergic nervous system (87) or via futile cycling of metabolic pathways (86). Increased carbohydrate oxidation after fructose consumption without a corresponding decrease in fat oxidation (86), together with the demonstration that storage of fructose as glycogen utilizes more energy than glucose, could be responsible for the greater increase in energy expenditure after fructose compared to glucose consumption. Increased thermogenesis after an oral fructose dose has been shown to occur in insulin-resistant states (e.g. aging, obesity, and diabetes) as well as in normal individuals (88). However, rats fed fructose for extended periods of time show reduced glucose oxidation in muscle (104) and liver (101) and reduced thermogenesis (43) compared to rats fed glucose. It is not known whether these conflicting results are due to species differences, the larger amount of fructose given to the rats (70% of

calories), or differences in the duration of fructose feeding. Therefore, further long-term studies on the diet-induced thermic effect of fructose (with an account of the intracellular distribution of fructose into its oxidative and nonoxidative components) seem warranted.

EFFECT OF FRUCTOSE ON NONENZYMATIC GLYCOSYLATION OF PROTEIN Increased glycosylation of proteins is believed to be a major health risk for diabetic individuals. In general, the extent of nonenzymatic glycosylation is directly related to the degree of hyperglycemia and is measured in the A1c fragment of hemoglobin (HbA1c). There is evidence that fructose causes more rapid nonenzymatic modification of hemoglobin than does glucose (14) and therefore fructose may be detrimental even though plasma glucose levels are lower following its ingestion than with other sugars (59). However, all the long-term studies conducted in impaired glucose tolerant and NIDDM subjects so far have reported no change in HbA1c even after 4 weeks (61), 9 weeks (44), 12 weeks (73), 14 weeks (96), and 23 weeks (3) of fructose feeding.

Some evidence indicates that lens proteins react with endogenous fructose, thereby causing nonenzymatic fructosylation and inducing protein cross-linking (69). The effect of fructose in the diabetic diet therefore requires a closer examination of the overall biological effects of fructose (i.e. examining the possible deleterious effects of changes in blood fructose as well as looking at changes in blood glucose after fructose feeding).

EFFECT OF FRUCTOSE ON LACTATE No differences have been reported between lactate levels in normal (23) or NIDDM subjects after a sucrose or fructose meal (24) or in NIDDM subjects after 12 weeks of fructose feeding (73), although compared to starch meals fructose feeding has been shown to raise lactate levels after 8 days (4) and 23 weeks of fructose feeding (3). Therefore, a greater proportion of fructose compared to starch appears to be transported from the liver as lactate. Lactate can inhibit the supply of free fatty acids to the liver from adipose tissue, but whether this benefits NIDDM subjects is unknown. The source of the increase in plasma lactate after fructose consumption is uncertain but seems most likely to be a consequence of its unique peripheral (muscle, adipose tissue, etc) or hepatic metabolism (24).

EFFECT OF FRUCTOSE ON GLYCOGEN SYNTHESIS Fructose can promote glycogen synthesis because of its gluconeogenic efficiency, its ability to inactivate synthase phosphorylase, and its capacity to activate glycogen synthase (70–72).

Fructose appears to be more efficient than glucose in promoting glycogen synthesis. Despite lower rates of intestinal absorption compared to glucose, glycogen synthesis has been reported to be greater following an oral load of fructose than following an equivalent oral load of glucose (72). The dose of fructose has been reported to affect glycogen synthase; small doses increase glycogen synthase activity, whereas larger doses can decrease glycogen synthase (70). There is also a time factor involved. Fructose may initially lead to an increase in fructose-1-phosphate with lowering of inorganic phosphate and therefore an increase in glycogen after 4–5 h. After longer exposure to fructose, however, enhanced hepatic inorganic phosphate and glycogenolytic responses to fructose may decrease glycogen stores and antagonize insulin-induced suppression of hepatic glucose output (94). These three variables are probably responsible for a great deal of the variability observed between different studies. From the studies conducted so far, it is difficult to draw any conclusions about the effect of fructose on glycogen synthesis. Well-controlled studies need to be conducted in human subjects to determine the effect of long-term physiologic doses of fructose (incorporated into mixed meals) on tissue glycogen storage. It would also be interesting to know whether glucose and fructose act synergistically on glycogen synthesis in human tissue as they have been reported to do in rat liver (15, 71, 74, 107, 108).

## *Fructose as an Energy Source During Exercise*

It is well recognized that during prolonged exercise blood glucose levels fall and muscle glycogen depletion occurs, which may limit athletic exercise intensity and endurance (6, 20, 76). To prevent or delay the onset of these adverse events and improve athletic performance, a number of dietary manipulations have been tried, the most notable of which has been the ingestion of oral glucose. While the ingestion of oral glucose has beneficial effects under certain conditions, its use has been perceived as less than optimal overall since it also stimulates insulin and suppresses glucagon secretion (11). Fructose, on the other hand, because of its unique metabolic properties, results in minimal change in blood glucose, insulin, and glucagon levels following ingestion and has been advocated as a more ideal energy source during prolonged exercise. Because the potential adverse effects of glucose and the potential beneficial effects of fructose with exercise vary according to the time of ingestion, the current status of fructose as an energy source during exercise will be reviewed in relation to when it is ingested (i.e. timing of ingestion).

FRUCTOSE INGESTION BEFORE EXERCISE A number of studies in humans compare the metabolic effects of fructose, glucose (50–75 grams orally), or

placebo given up to an hour before vigorous exercise (55–75% $V_{02}$ MAX for 30–120 min) (27, 29, 49, 62–64). The results of these studies are generally quite consistent and can be summarized as follows:

1. Fructose administration before exercise stimulates plasma glucose, insulin, and gastrointestinal polypeptide (GIP) levels much less than does glucose and is more similar to placebo administration. The exercise-induced fall in blood glucose after fructose is similar to the effect produced by placebo and is much less than after glucose administration.
2. During exercise blood lactate levels are only transiently higher after fructose compared to glucose or placebo administration.
3. Free fatty acids fall by 40–50% after both glucose and fructose administration and remain suppressed by 30–40% during exercise compared to levels found after placebo administration. Following exercise, changes in uric acid, glycerol, and glucagon are similar after fructose and glucose administration.
4. No difference in exercise performance (time until exhaustion) or maximum voluntary work occurs following fructose, glucose, or placebo administration.
5. Following ingestion and exercise, comparable amounts of fructose and glucose are oxidized.
6. Muscle glycogen levels decline with exercise. In one study, after 30 min of vigorous exercise, muscle glycogen usage was greater after glucose than after placebo administration. In another study of identical exercise duration, muscle glycogen depletion was less following fructose than after either glucose or placebo administration. In yet another study, after 120 min of vigorous exercise, muscle glycogen declined by 60–65% after all feedings. Therefore, it is unclear whether fructose exerts a significant glycogen-sparing effect compared to glucose when either is taken before exercise.



FRUCTOSE INGESTION DURING EXERCISE Considerable evidence indicates that glucose intake during prolonged exercise can postpone exhaustion by preventing the blood glucose level from falling, reducing muscle glycogen depletion, and maintaining adequate fluid balance (21, 22, 28, 48). However, when glucose is given in large amounts during exercise it has the potential disadvantage of stimulating insulin release, which in turn inhibits lipolysis and lipid oxidation (1, 41). This metabolic response not only reduces free fatty acids as an available energy source but also favors increased glycogen utilization, which may limit benefits on exercise performance. To optimize the benefits of carbohydrate ingestion during exercise, some researchers

propose that fructose may be preferable to glucose ingestion since the rise in insulin is much less, consequently favoring fat utilization (11, 63) and possibly the sparing of muscle glycogen (18). The articles evaluating the use of fructose during exercise are limited in number (8, 66, 67, 85) and have shown the following:

1. The fall in plasma glucose during vigorous exercise can be prevented and normoglycemia maintained by equivalent amounts of either glucose or fructose. The fall in plasma insulin with exercise is similar with glucose or fructose ingestion.
2. Serum lactate levels rise 2–3 fold with exercise and are similar with glucose, fructose, or placebo (water). The rise in glycerol is less with glucose than with fructose or placebo. The rise in free fatty acids with exercise is less with glucose, intermediate with fructose, and greatest with placebo. The rise in epinephrine and norepinephrine is similar during glucose, fructose, or placebo administration.
3. During vigorous exercise, fructose is less available than glucose for oxidation. Fat oxidation is the same or greater following fructose ingestion than after glucose ingestion, and both are lower than after placebo.
4. Muscle glycogen sparing during exercise is either the same or greater with glucose than with fructose or placebo ingestion. Fructose does not spare muscle glycogen more than does glucose.
5. The total exercise time to exhaustion is longer with glucose than with either fructose or placebo. There is no difference between fructose and placebo in time to exhaustion.

FRUCTOSE INGESTION AFTER EXERCISE Only a few studies (16, 19) (none in humans) compare the effects of fructose versus glucose administration on glycogen repletion following exercise. This data can be summarized as follows:

1. Within two hours following vigorous or exhaustive exercise in rats, rates of liver glycogen repletion were similar after ingestion of either fructose or glucose. By four hours after exercise, fructose-fed exercised animals had higher glycogen repletion than glucose-fed animals.
2. By 2–3 hours after vigorous or exhaustive exercise, muscle glycogen repletion is the same or less after fructose compared to glucose ingestion.

In summary, although fructose has potential advantages over glucose as an energy source in exercise owing to its unique metabolic properties, no evidence demonstrates that fructose ingestion is more advantageous than glucose

ingestion in promoting exercise endurance. If anything, the literature indicates that for some aspects of exercise metabolism, fructose may be less advantageous.

## POTENTIAL ADVERSE EFFECTS OF FRUCTOSE

### *Effect of Fructose on Lipid Metabolism*

One of the most controversial areas in the dietary fructose literature is the effect of fructose on serum lipids and, in particular, on triglyceride levels. This issue has arisen because of fructose's unique hepatic metabolism, which may favor the formation of VLDL-triglyceride.

Studies on the effects of fructose ingestion on triglyceride metabolism may be divided into four different categories: (*a*) normal (nondiabetic) subjects, (*b*) hyperinsulinemic normal (nondiabetic) subjects, (*c*) normotriglyceridemic diabetics, and (*d*) hypertriglyceridemic diabetics. Whether or not fructose can cause hypertriglyceridemia has particular relevance in diabetes because fructose has been advocated as an alternative sweetener in this disease owing to its potential benefits in regard to carbohydrate metabolism. It is also important because increased triglyceride levels may exacerbate the risk of coronary artery disease in a group that is already at high risk for this complication. To assist in the review of this complex research area, an accompanying Table details the recent studies that have addressed the issue of long-term (>1 week) fructose ingestion and serum triglyceride levels in humans (Table 2).

From Table 2 it is apparent that the majority of studies in both normal (nondiabetic) and diabetic subjects demonstrate no effect of fructose ingestion on serum triglyceride levels. In one study that lasted only eight days (4), a rising trend (nonsignificant) in serum triglyceride was noted. In 4 other studies done over the last 10 years, definite increases in serum triglyceride levels have been documented following fructose ingestion. In only one of these studies (47) have normal (nondiabetic) subjects developed increased triglyceride levels; these subjects were hyperinsulinemic men consuming 7.5 and 15% of total calories as fructose in standard mixed meals over 5-week periods. The triglyceride level increased significantly in these subjects as the amount of fructose in the diet increased. It is notable that no changes in serum triglyceride occurred in the normoinsulinemic men in this study. This study may have particular relevance, since insulin is believed to play a pivotal role in accelerating VLDL-triglyceride synthesis. It seems feasible that hyperinsulinemic subjects may be a group that is particularly prone to triglyceride increases following fructose ingestion.

Three other studies have shown increases in serum triglyceride levels in Type II diabetic subjects. In one of these studies (24), triglyceride levels

**Table 2** Effect of fructose ingestion on human serum triglyceride levels in studies conducted over the past 10 years

| Subjects (number) | Length of feeding | Fructose (% of calories) | Effect on triglyceride | Compared to | Ref. |
|---|---|---|---|---|---|
| Diabetic (14) | 24 weeks | 12 | No change | Starch | 3 |
| Diabetic (24) | 1 week | 21 | No change | Sucrose<br>Starch | 4 |
| Normal (8) | 2 weeks | 12–16 | No change | Sucrose | 13 |
| Normal (11) | 2 weeks | 13 | No change | Sucrose | 23 |
| Diabetic (7) | 2 weeks | 13 | No change | Sucrose | 24 |
| Hypertriglyceridemic (5) | | | Increase | Sucrose | |
| Diabetic (8) | 8 weeks | ~8 | Increase | Starch | 44 |
| Normoinsulinemic Normal (12) | 5 weeks | 7.5, 15 | No change | Starch | 47 |
| Hyperinsulinemic Normal (12) | 5 weeks | 7.5, 15 | Increase | Starch | 47 |
| Normal (9) | 4 weeks | 15 | No change | Glucose | 61 |
| Diabetic (9) | 4 weeks | 15 | No change | Glucose | 61 |
| Diabetic (10) | 4 weeks | 25 | No change | ?Sucrose | 68 |
| Diabetic (9) | 12 weeks | 10 | No change | No sugar | 73 |
| Diabetic (5) | 14 weeks | 13 | No change | Sucrose | 95 |
| Hypertriglyceridemic (1) | | | Increase | Sucrose | |
| Hypertriglyceridemic | 2 weeks | 9–17 | | | |
| Normal (4) | | | No change | Dextromaltose | 102 |
| Diabetic (2) | | | No change | Dextromaltose | 102 |



increased 13% after 14 days of fructose in the diet only in diabetic subjects with initial fasting triglycerides over 150 mg/dl. In another study (44), the mean triglyceride level after the fructose diet period, although still in the normal range, was significantly higher than baseline. This study lasted for 8 weeks, and fructose (30 g per day) was substituted in a mixed diet for starch. In the last study (95) that has shown changes in triglyceride levels, 6 NIDDM subjects consumed 13% of total calories in mixed meals as added fructose for 14 weeks. In 5 of the 6 subjects, several of whom had mild hypertriglyceridemia (>150 mg/dl but < 500 mg/dl), no changes in triglyceride levels occurred after 6 weeks. In one subject with marked preexisting hypertriglyceridemia (800 mg/dl) a dramatic rise in triglyceride levels occurred along with a marked rise in serum insulin levels. These studies suggest that while fructose does not appear to have significant effects on triglycerides in most normal and diabetic subjects, there may be a subpopulation(s) that is particularly susceptible to added fructose intake. This aspect of fructose metabolism is probably one of the major issues that needs to be resolved in the scientific literature before fructose can be advocated in the diet, particularly in NIDDM subjects.

The effect of increased fructose consumption on lipids other than triglycerides is less contentious, with very little evidence of adverse or beneficial effects on total cholesterol, LDL cholesterol, HDL cholesterol, or apoproteins. However, two studies have shown effects of fructose on these lipid parameters. In the study by Hallfrisch et al (47), both total and LDL cholesterol rose after 5 weeks when fructose constituted 7.5 and 15% of the total calorie intake. In the study by Osei et al (73), apoprotein $A_1$ levels rose significantly on the high fructose diet, consistent with a reduced risk of coronary artery disease.

## *Effect of Fructose on Copper Metabolism*

Recent studies have evaluated the effect of the type of carbohydrate on the severity and consequences of copper deficiency (32–38, 78). These studies have suggested that either fructose or sucrose (as compared to starch or, to a lesser extent, glucose), when used as the sole carbohydrate in the diet of young, male rats, exacerbates the severity of the symptoms of copper deficiency (anemia, hypercholesterolemia, hypertrophy of the heart and liver, and histopathological features of the myocardium leading to sudden death). Female rats appear to be protected from the lethal consequences of copper deficiency and a fructose diet (37, 39). Fructose has been thought to be the component in sucrose that is responsible for the effect, and the most recent research has focused on the effects of fructose alone. It has been suggested that the amount of dietary copper required for optimal tissue function is greater when rats are fed diets that are high in sucrose or fructose than when they are fed starch. Data to support this conclusion are lacking. However, a recent study of the immunoresponsiveness of rats has demonstrated that the amount of dietary copper required for optimal function of the humoral immune system, thymic growth, and maintenance of normal tissue levels of copper is greater when young rats are fed diets with fructose than with starch (31). In addition, a study reports that feeding fructose as compared with starch, prior to and during pregnancy and lactation, results in a reduced copper status of suckling pups (106).

The greater incidence of anatomical and physiological abnormalities and the higher rate of mortality of rats fed copper-deficient diets containing fructose or sucrose (31) may likely be due to a more severe copper deficiency in the animals fed sucrose or fructose. While copper absorption may be lower in copper-deficient male rats fed sucrose or fructose than in those fed starch (32, 51, 52, 57, 58), these alterations may only be temporary (32) and it is possible that in some way fructose metabolism increases copper utilization. Additional studies are needed to clarify the mechanisms by which the type of

dietary carbohydrate affects tissue levels of copper in copper-deficient rats. The presence of fructose or sucrose in the diet as the sole carbohydrate does not appear to adversely affect the metabolism and/or dietary requirement of all essential trace elements (89).

The results of the above studies suggest that a high intake of sucrose or fructose in the human diet may lower copper levels further in individuals who have marginal copper status due to inadequate copper intake (78). Limited studies support this conclusion in humans. Evaluation of a diet comparatively low in copper and containing either 20% fructose or starch in male subjects found that fructose ingestion reduced cuprozinc superoxide dismutase activity of erythrocytes. However, the study had to be terminated after 4 of 24 subjects exhibited heart-related abnormalities. There was no apparent relationship between the occurrence of the heart-related abnormalities and the type of dietary carbohydrate (fructose or starch) that was being consumed (79). The possibility of common marginal copper deficiency in humans warrants continued evaluation of the effect of dietary fructose on copper status. However, based on current information, there is no reason to recommend that any population eliminate or restrict sources of fructose from the diet beyond that required for the provision of an overall well-balanced diet.



## *Fructose and Gout*

A number of studies in both man (10, 54) and animals (14a, 65) have demonstrated that large loads of fructose deplete intrahepatic concentrations of ATP. The resultant utilization of inorganic phosphate with ADP decreases physiologic inhibition of AMP deaminase and results in loss of adenine nucleotides in the form of uric acid (103). For the most part, these effects (hyperuricemia/hyperuricosuria) occur when large amounts of fructose are given, especially when infused at rapid rates. These effects, can occur, however, when fructose is used in parenteral nutrition (10) and have been reported when fructose is infused intravenously at rates of 1–1.5 g/kg/h in healthy volunteers (53). Hyperuricemia resulting from lower infusion rates has been inconsistent, however, and has been reported by some (40) but not by other authors (17, 26, 53). On the basis of these studies plus numerous others not cited, it appears that there is a large degree of individual variation in the hyperuricemic response to intravenous fructose administration. Based on this information, however, it seems prudent to avoid the use of fructose in parenteral nutrition and intravenous infusions particularly in individuals with a known history of hyperuricemia or overt gout.

With regard to the oral administration of fructose, large doses of fructose (>1 g/kg body weight) have been reported to induce hyperuricemia in man

(30), and this effect may be more pronounced in individuals with preexisting abnormalities of uric acid metabolism (91).

In a large number of studies when fructose was added as part of mixed meals (<20% of total calories) over weeks to months in both nondiabetic (23, 55, 102) and diabetic (3, 24, 44, 73) subjects, no increases in serum uric acid were noted. In other studies, however, fructose has been found to increase uric acid levels particularly in children with hereditary fructose intolerance (75) and in hyperinsulinemic men (46), which suggests that certain individuals are uniquely predisposed to the hyperuricemic effect of fructose. It should be noted that in those studies in which uric acid levels did rise, the elevations were modest at best and not associated with acute attacks of gout.



## SUMMARY

The ingestion of fructose, particularly in refined form, has significantly increased in the North American diet over the last two decades. The unique way in which fructose is metabolized has given rise to much research examining whether fructose is advantageous in appetite control, exercise endurance, and disease states such as diabetes. Overall, there is very little evidence that modest amounts of fructose have detrimental effects on carbohydrate and lipid metabolism in nondiabetic or NIDDM subjects or that its use is particularly advantageous compared to that of other sugars. However, fructose can cause insulin and triglyceride levels to rise dramatically, and hence be potentially harmful, in a subgroup of NIDDM subjects who have concomitant pronounced hypertriglyceridemia. Large doses of fructose should also be avoided by subjects with gout because of the hyperuricemia which may result. No evidence exists that fructose has any clear advantages over glucose in regard to exercise endurance. Similarly there is no conclusive evidence that physiologic amounts of dietary fructose exacerbate copper deficiency or aid in weight control.

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