

## CURRENT SURVEY

### Fructose in medicine

A review with particular reference to diabetes mellitus

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#### Summary

A review is given of the metabolism of fructose in the mammalian organism, and its significance in medicine. Emphasis is laid upon the absorption and assimilation of fructose through pathways not identical with those of glucose. The metabolism of fructose is largely insulin-independent, although the ultimate fate of fructose carbons is determined by the presence or the absence of insulin.

Clinical and experimental work has suggested that fructose may exert beneficial effects as a component of the diet for patients with mild and well-balanced diabetes. Fructose is absorbed slowly from the gut, and does not induce drastic changes in blood sugar levels. Secondly, fructose is metabolized by insulin-independent pathways in the liver, intestinal wall, kidney and adipose tissue.

As a consequence of the rapid and efficient utilization of fructose, it has been used widely for intravenous feeding in medicine and surgery. However, it has been shown that the rapid infusion of large amounts of fructose may cause accumulation of lactic acid in the extracellular fluid. The possibility of lactate acidosis, with concomitant impairment of the acid-base balance, already disturbed, constitutes a relative contraindication to the use of intravenous fructose in the treatment of diabetic ketoacidosis.

Fructose is known to accelerate ethanol metabolism in the liver. No well-documented reports on the use of fructose in the treatment of ethanol intoxication have been published, although it has recently been suggested that fructose might be of value in the treatment of delirium tremens.

Fructose may be less cariogenic than sucrose, at least in short-term experiments. Long-term trials are lacking, and thus the potential advantages of fructose in preventive odontology have not been determined.

Fructose does not seem to have any side-effects when used in reasonable amounts. However, it has been reported that the administration of fructose in large amounts induces hyperlipidemia both in man

and in experimental animals. Earlier suggestions concerned with the atherogenic properties of fructose have recently been challenged. The apparent increase in the incidence of coronary disease among sucrose users seems to be a statistical artefact, caused by the increased ingestion of coffee and soft drinks by cigarette smokers.

#### Introduction

The metabolism of fructose has engaged the attention of clinicians since 1874, when Kulz suggested that diabetic patients can assimilate fructose better than glucose. These observations have been confirmed in a number of experimental and clinical studies (Minkowski, 1893; Naunyn, 1906; Joslin, 1923), it being further shown that in some patients fructose feeding brings a reduction in glucosuria and the respiratory quotient. However, contradictory reports, together with the discovery of insulin in 1922, made the use of fructose in the treatment of diabetes less fashionable; it was virtually forgotten for the next thirty years. Reports on the beneficial effects of fructose in diabetic ketoacidosis (Darragh *et al.*, 1953; Miller *et al.*, 1953), and its accelerating effect upon ethanol oxidation (Stuhlfauth & Neumaier, 1951; Pletscher *et al.*, 1952) gave rise to intense research after 1953, resulting in several reports on the various aspects of fructose metabolism and its potential use in the treatment of diabetes. Early positive experience with fructose in the management of ketoacidosis was challenged in studies with more rigorous control, but the other potential indication for fructose, its employment as a sweetening agent, and as a carbohydrate source in mild, controlled diabetes, has not been disputed. The lack of further experience in this respect is attributable to the unavailability of commercial fructose preparations, which has made it difficult to engage in long-term trials. The purpose of this paper is to provide a critical survey of the metabolism of fructose in the normal and diabetic organism, along with clinical studies concerned with the effects of fructose upon the diabetic state. It is felt that a survey of this type is of value because of the need for a harmless sweetening agent and

carbohydrate source for diabetics. This is especially important in the light of the emphasis recently laid upon the dietary management of diabetes and the potential hazards involved in the use of artificial sweeteners.

### Biochemistry and metabolism of fructose

The absorption of fructose from the duodenum occurs by passive diffusion, in contrast to the active transport mechanism of glucose (Wilson & Vincent, 1955). For this reason, and possibly others as well, the rate of absorption of fructose is slower than that of glucose. Slow absorption and rapid metabolism in the liver (*vide infra*) effectively prevent rapid changes in the serum levels of fructose after peroral administration, and it is difficult to attain concentrations of fructose exceeding 30–40 mg/100 ml after the ingestion of fructose or sucrose. Some metabolism of fructose occurs in the intestinal wall, which contains an active fructose-metabolizing pathway. The extent of intestinal metabolism appears to vary from one species to another. Estimations in human subjects have suggested that 10–20% of the fructose consumed is metabolized in the gut wall (Miller *et al.*, 1956). Fructose is utilized at the same rate as glucose in the intact organism (Smith, Ettinger & Seligson, 1953). As an indicator of fructose assimilation, the blood levels of lactate, pyruvate,  $\alpha$ -ketoglutarate and citrate rise more rapidly after a fructose than a glucose load (Craig *et al.*, 1957). A rapid fall in serum phosphate occurs after the injection of fructose, indicating that fructose is phosphorylated by the intracellular kinases (Smith, Ettinger & Seligson, 1953; Miller, Craig & Drucker, 1956).

Approximately one half of the fructose administered intravenously is utilized by the liver (Mendeloff & Weichelsbaum, 1953) through the specific fructose-1-phosphate pathway (Cori *et al.*, 1951). The same metabolic pathway, which is not dependent upon insulin, is also operative in the kidney and the intestinal wall. The first reaction of this pathway is the conversion of fructose to fructose-1-phosphate by a specific kinase, fructokinase. In contrast to the corresponding enzyme of glucose metabolism, the activity of fructokinase is not regulated by insulin. The fructose-1-phosphate is split by aldolase into equal parts of dihydroxyacetone-phosphate and glyceraldehyde.

Dihydroxyacetone-phosphate enters the triose-phosphate pool, and is metabolized either to pyruvate or to glucose and glycogen, depending upon whether glycolysis or gluconeogenesis is dominant. Glyceraldehyde appears to have the choice of at least three pathways: (1) phosphorylation to glyceraldehyde phosphate by triokinase, (2) reduction to glycerol by alcohol dehydrogenase, and (3) oxida-

tion to glycerate by aldehyde dehydrogenase. Glycerol may either be further oxidized in mitochondria, or used as the substrate for triglyceride synthesis in the cytoplasm. The two other metabolites of glyceraldehyde, glycerate and glyceraldehyde phosphate, are incorporated into the Embden-Meyerhof pathway, and metabolized to glucose or pyruvate. Currently, it is unknown which of these pathways is quantitatively most important. In any case, it is clear that the ultimate fate of triose fragments is determined by the same factors as those that determine the direction of metabolite flow in glycolysis and gluconeogenesis. Thus, when gluconeogenesis dominates, as during fasting, or with a high fat diet, or severe diabetes, triose phosphates generated from fructose are converted to glucose. However, after feeding with a high carbohydrate diet and in the presence of insulin, trioses are oxidized to pyruvate, and finally to citric acid cycle intermediates.

Two inborn errors of fructose metabolism have been described (Schapira *et al.*, 1961; Froesch *et al.*, 1963). The first enzyme of the fructokinase pathway is lacking in essential fructosuria, whereas in hereditary fructose intolerance the block is caused by the absence of fructose-1-phosphate aldolase. Despite the virtual absence of fructose metabolism in the liver, more than 80% of the fructose given is assimilated by patients with these two defects. Alternative routes for fructose utilization must consequently exist in the body. The metabolism of fructose is also known to occur in muscle and adipose tissue, whereas little or no utilization takes place in the brain. This results at least partially from the blood-brain barrier, which prevents the effective uptake of fructose by brain cells (Park *et al.*, 1957).

The metabolism of fructose in muscle proceeds through the same metabolic pathways as that of glucose. Fructose is phosphorylated by the same kinase as glucose, and is rapidly metabolized when present in the interstitial fluid in sufficiently high concentrations. High concentrations of glucose (> 200 mg/100 ml) inhibit fructose assimilation, but the inhibition is not augmented by insulin (Froesch, 1965). At low concentrations (< 50 mg/100 ml), fructose is not utilized under *in vitro* conditions, which suggests that, at the low concentrations obtaining after oral fructose administration, muscle plays only a minor role in fructose metabolism. Nevertheless, results obtained from *in vivo* studies with a perfusion technique suggest that significant amounts of fructose are taken up by muscle even at low concentrations (Butterfield *et al.*, 1964; Bergström & Hultman, 1967).

Adipose tissue is capable of metabolizing fructose at a relatively rapid rate (Froesch, 1965). Fructose appears to have a different transport mechanism

from that of glucose, and is taken up by an insulin-independent mechanism. The two monosaccharides share the same kinase, but do not compete with each other, by reason of the low intracellular concentrations of free monosaccharides. By supplying glycerol for triglyceride synthesis, fructose increases the re-esterification of fatty acids, and diminishes fatty acid mobilization and the influx of fatty acids into the liver. Thus, at least theoretically, fructose should oppose the development of ketosis in the diabetic situation.

Fructose is capable of stimulating insulin release in the  $\beta$ -cells of the islets of Langerhans (Grodsky *et al.*, 1963; Aitken & Dunnigan, 1969). However, the stimulatory effect of fructose is weak as compared with glucose and mannose, and virtually no stimulation of insulin release is observed after the oral administration of fructose to experimental animals (Nijjar & Perry, 1970).

#### Metabolism of fructose in diabetes mellitus

Fructose administered both orally and intravenously is rapidly metabolized by the diabetic organism, even when the cellular utilization of glucose is impaired (Darragh *et al.*, 1953; Smith *et al.*, 1953; Miller *et al.*, 1956). As in the normal, the liver is the main site for fructose metabolism in the diabetic. The fate of triose units obtained from fructose depends upon the severity of insulin deficiency. In mild diabetes, and in well-balanced insulin-dependent diabetes, the fructose is mainly converted to pyruvate and Krebs cycle intermediates, as is shown by the increment in the serum levels of pyruvate, lactate,  $\alpha$ -ketoglutarate and citrate after fructose injection (Smith *et al.*, 1953; Metz *et al.*, 1967). Furthermore, pyruvate is effectively utilized by the peripheral tissues, and no more than a slight impairment in the assimilation of pyruvate is observable in diabetes (Takanami *et al.*, 1960).

Two controlled clinical studies have been published on the effect of fructose-feeding upon diabetes. Hiller (1955) examined 160 patients on isocaloric glucose and fructose diets, and found a significant decrease in both hyperglycemia and glycosuria during the fructose period. The tendency to ketosis was diminished in the group maintained on a fructose diet. Corresponding findings were published by Moorhouse & Kark (1957), although their series comprised only nine patients. In their experimental plan fructose or glucose was fed continuously through a tube to the gastrointestinal tract. In three patients with mild or moderately severe diabetes, a clear improvement was visible in the clinical picture during fructose feeding, as compared with the situation during the isocaloric mixed carbohydrate or sucrose diet. Thus the blood glucose was restored to the fasting level,

and a sharp reduction in glycosuria and blood acetone was discernible. As against this, in the three patients with severe insulin deficiency no change in the clinical picture was observed during the fructose period. A report of a similar experience with the use of fructose in the treatment of mild diabetes has also been published by Voss (1957) and by Mehnert *et al.* (1964).

The use of intravenous fructose infusions in the treatment of diabetic ketoacidosis has been suggested by Darragh *et al.* (1953), Miller *et al.* (1956) and Mehnert *et al.* (1970). Theoretically this should not offer any advantages in the management of ketoacidosis. In the absence of insulin, most of the fructose is converted to glucose in the liver, and its administration consequently has no advantages over conventional fluid therapy (Nabarro *et al.*, 1955). In fact, the administration of fructose may in some cases lead to the accumulation of lactic acid, and further deterioration of the acidosis already existing (Bergström *et al.*, 1969).

#### Effect of fructose on ethanol oxidation

The effect of fructose upon ethanol oxidation was first reported by Stuhlfauth and Neumaier in 1951, and their observations were confirmed by Pletscher *et al.* (1952), who found an average increase of 80% in the elimination rate of ethanol after the intravenous administration of 1–2 g of fructose/kg/hr. The mechanism of the effect of fructose upon ethanol metabolism has not finally been settled, but it appears to arise from a number of different reactions. Tygstrup *et al.* (1965) suggest that the most important factor from a quantitative aspect is the formation of glyceraldehyde from fructose. Glyceraldehyde, which is normally oxidized to glycerate, is reduced to glycerol by alcohol dehydrogenase in the presence of ethanol breakdown. Consequently the limiting step in the oxidation of ethanol, the dissociation of the complex of alcohol dehydrogenases and reduced NADH, is circumvented. The oral administration of fructose results in the same stimulatory effect on ethanol oxidation (Lundquist & Wolthers, 1958), indicating that the fructose concentrations attained in the splanchnic system after peroral administration are sufficiently high to modify ethanol metabolism.<sup>1,2</sup>

The effect of fructose feeding upon the improvement in performance tests after alcohol consumption has been studied by Merry & Marks (1967). Although a better performance was observable in the fructose group throughout the experiment, the difference from the control group was not statistically significant. A recent claim has been made for the potential advantages of fructose in the treatment of delirium tremens (Dalton & Duncan, 1970). However, no controlled studies are available, and further clinical trials should be carried out

before fructose can be recommended for the treatment of alcohol delirium.

### Fructose and dental caries

Preliminary results have suggested that fructose might be less cariogenic than sucrose (Frostell *et al.*, 1967; Scheinin & Mäkinen, 1971). In these studies, it was shown that dental plaque formation was significantly less in the fructose group than in the sucrose consumers. However, no long-term studies have been published, and accordingly the role of fructose in caries prevention is still highly speculative.

### Use of fructose in parenteral nutrition

In view of its rapid and efficient utilization, fructose has been used widely for parenteral feeding in medicine and surgery. For a recent review, reference should be made to the paper of Mehnert's group (Mehnert *et al.*, 1970).

### Precautions in fructose utilization

Epidemiological studies made in the early sixties gave some indication that the excessive consumption of sucrose (and of fructose) might lead to premature atherosclerosis (Yudkin & Roddy, 1964; Yudkin & Morland, 1967). It was thought that a possible biochemical mechanism for this lay in the increased levels of plasma triglycerides induced by dietary fructose (Nikkilä & Ojala, 1965). Nonetheless, although the increment in serum levels of triglycerides after fructose administration is discernible in experimental animals (Nikkilä & Ojala, 1965; Zakim *et al.*, 1967), the results obtained in human experiments have been contradictory (Macdonald, 1965; Nikkilä & Pelkonen, 1966; Lees, 1965; for a review, see Nikkilä, 1969). Furthermore, a careful analysis of epidemiological studies has shown that the high prevalence of coronary disease in sucrose consumers is probably an artefact, induced by the coincidence of cigarette smoking and the excessive consumption of coffee and soft drinks in the high risk group (Paul *et al.*, 1968). When the risk resulting from cigarette smoking is subtracted, no correlation is observable between sugar consumption and coronary disease (Medical Research Council Working Party, 1970).

The occurrence of lactic acid acidosis during intravenous fructose administration has recently been reported in normal subjects and in diabetics (Bergström *et al.*, 1969). However, the amounts of fructose administered were relatively large (1–3 g/kg/hr), and the concentrations of fructose reported in this study far exceed the serum levels attained after peroral administration. In any case, the possibility of lactate acidosis should be borne in mind when large amounts of fructose or invert sugar are given parenterally. This is of especial im-

portance in the treatment of diabetic ketoacidosis, where the pH is already low.

It has been reported that fructose administered parenterally increases the hepatic catabolism of purines, possibly by stimulation of the enzyme deadenylate deaminase (Mäenpää *et al.*, 1968). Changes in the hepatic levels of adenine nucleotides in the rat after the administration of fructose may be induced by the same mechanism (Mäenpää *et al.*, 1968; Woods *et al.*, 1970). Although the results in human studies have been somewhat contradictory (Perheentupa & Raivio, 1967; Curreri & Pruitt, 1970), it is theoretically possible that the ingestion of large amounts of fructose might induce attacks of gout in susceptible patients.

### Conclusions

It has been demonstrated in both experimental and clinical work that fructose administered orally and intravenously is effectively utilized by normal and diabetic organisms. The ordinary cellular uptake of fructose is not dependent upon insulin, although the ultimate fate of fructose metabolites is determined, at least partially, by the presence or the absence of insulin. Thus, in mild diabetes and controlled insulin-dependent diabetes, fructose is metabolized to pyruvate and Krebs cycle intermediates, mostly in the liver but also in the intestinal wall, muscle and adipose tissue. The liver appears to consume 40–60% of the fructose administered orally whereas the distribution of fructose to other tissues is not known precisely. In severe insulin deficiency, the bulk of fructose is converted to glucose, and contributes to serum and urinary glucose.

Theoretically, fructose possesses a number of advantages as a component of the diabetic diet. Fructose is an excellent sweetening agent, and is non-toxic, at least when used in reasonable amounts. Secondly, fructose is absorbed slowly from the intestine, and thus does not cause abrupt changes in the serum levels of carbohydrates. In this respect, fructose shares the advantages of starch and glycogen, which are absorbed relatively slowly because of the necessary hydrolysis to glucose, the rate-limiting step in the uptake process. Thirdly, fructose is only a weak stimulant of insulin secretion, and no change in the insulin level is discernible after the peroral use of fructose. The cellular utilization of fructose in normal and diabetic organisms is rapid, and mainly occurs through insulin-independent pathways. Finally, fructose is utilized by adipose tissue cells, and is potentially capable of diminishing fatty acid mobilization, even in the absence of insulin.

Two controlled studies on the effects of fructose feeding in diabetes suggest that, in mild and well-controlled diabetics, fructose diminishes hyper-

glycemia and glycosuria, and also the tendency to ketosis. However, the author feels that if it is employed as a component of the diabetic diet, fructose should be taken within the caloric restrictions applied in conventional dietary treatment. This is important, as it has been shown convincingly that obesity impairs glucose tolerance, and increases the insulin resistance of peripheral tissues (Perley & Kipnis, 1966). It has been suggested by both clinical and theoretical work that the use of fructose in the treatment of diabetic ketoacidosis does not offer any advantages over routine fluid therapy, and may in fact be dangerous on account of the risk of lactic acidosis.

The acceleration of ethanol oxidation after intravenous and oral fructose administration is a well-documented phenomenon. However, no clinical trials on the use of fructose in the treatment of ethanol intoxication have come to my notice. A report on the application of fructose infusion in the management of delirium tremens has recently been published, but is difficult to evaluate because of the lack of adequate control material.

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