

Effect of dietary fructose on lipid metabolism, body weight and glucose tolerance in humans

Tommi J Vasankari^{1,2} and Tuula M Vasankari³

¹Department of Health and Exercise, University of Turku and Paavo Nurmi Center, Sports Medical Research Unit, Turku, Finland; ²Department of Exercise Medicine, Sport Institute of Finland, Vierumäki, Finland; ³Department of Respiratory Medicine, Turku University Hospital, Turku, Finland

Abstract

The prevalence of obesity is increasing worldwide. Increasing body weight together with decreasing physical activity is expected to increase the incidence of several diseases related to lifestyle, such as adult type diabetes and vascular atherosclerotic diseases. It has been postulated that increasing consumption of fructose may be a contributory factor in the development of obesity and the accompanying metabolic abnormalities. Most studies supporting these hypotheses, however, are animal studies, which suggest that consumption of high amounts of fructose may stimulate lipogenesis and thus alter lipid metabolism and increase body weight. This review explores the effects of dietary fructose on lipid metabolism in humans, with the conclusion that the data so far do not support any significant specific adverse effect of fructose apart from its energy content. A small amount of fructose may even improve glucose tolerance, and studies to date on diabetic subjects indicate that isocaloric replacement of some glucose-based carbohydrates with fructose may improve metabolic control.

Keywords: *cholesterol; diabetes; fructose; oral glucose tolerance; triglycerides*

Received: 14 Mar. 2006; Accepted: 3 May 2006

Introduction

The general overall view of physicians and nutritionists on fructose as a dietary component has changed during the past few decades. In the 1980s and early 1990s fructose instead of glucose was considered preferable for diabetic patients, because of the less pronounced acute glucose and insulin response (e.g. 1). Recently, however, the consumption of dietary fructose, which has increased in some countries, has been associated with the increasing prevalence of overweight and obesity, as expressed in recent reviews (2, 3). Compared with glucose, the hepatic metabolism of fructose in high doses favours lipogenesis, and this may be linked with both hyperlipidaemia and increased body fat stores.

The theoretical background for increased lipogenesis from fructose relates to the fact that fructose is taken up readily by body cells without the need for insulin. Fructose is absorbed primarily in the jejunum and transferred into the portal circulation (4). In the liver, fructose is phosphorylated to

fructose-1-phosphate, which may be converted to glycerol-3-phosphate or metabolized to acetyl-coenzyme A and incorporated into fatty acids through *de novo* lipogenesis (5). Through this pathway triglycerides can be formed. The primary phosphorylation of fructose in the liver by fructokinase to fructose-1-phosphate provides a route in addition to the one used by glucose with hexokinase phosphorylation as the primary step, increasing the capacity to metabolized fructose for various purposes including synthesis of lipids, i.e. lipogenesis. The primary difference between hepatic fructose and glucose metabolism is that fructose molecules bypass the main rate-controlling step in glycolysis, 6-phosphofructokinase. Whereas hepatic glucose metabolism is limited by the capacity to store glucose as glycogen and by the inhibition of glycolysis, fructose uptake is not inhibited and consumption of fructose may result in greater increases in circulating lactate than would a comparable amount of glucose (2).

However, most investigations in support of adverse effects of fructose are animal studies with very high dietary doses of fructose. The available data from human studies are explored and reviewed here.

Fructose and lipid metabolism

Human studies on fructose and plasma lipids show a diversity of results that may be caused by different study protocols and different study subjects (men versus women, healthy versus diabetic subjects). The amount of fructose consumed per day has also varied considerably, as well as the control diets, and the duration of intervention has varied from a few days to 2 years. All of these variations make it difficult to compare the studies, but some conclusions can be drawn.

Studies in healthy subjects

Some 1–2 week studies (6, 7) with 50–107 g fructose day⁻¹ did not show any changes in lipids, whereas other studies reported increases in either fasting serum triglycerides or serum cholesterol. Thus, Reiser et al. (8) reported minor increase in the concentration of serum fasting triglycerides (1.02 versus 0.85 mmol l⁻¹) and total cholesterol (5.38 versus 4.99 mmol l⁻¹) during a 5 week intervention in 11 men. Similarly, Swanson et al. (9) investigated 14 subjects during 4 weeks with fructose (20% of energy intake, E%) or with a high-starch diet. No change was seen in the fasting concentration of serum triglycerides, but serum cholesterol decreased with a high-starch diet, while no change was seen with the fructose diet.

Bantle et al. (10) studied 12 men and 12 women in a cross-over design with fructose and glucose (17E%) for 6 weeks. The concentration of serum triglycerides increased with fructose compared with glucose in men (1.25 versus 0.95 mmol l⁻¹), but not in women. No changes were seen either in serum total cholesterol or low-density lipoprotein (LDL) cholesterol. The gender difference in this study raises many unanswered questions: Did men have more difficulties in following the diet, which made them more susceptible to changes in triglycerides? Can sex hormones change the response to fructose between men and women? Importantly, the authors did not show the baseline values in either the glucose or the fructose trial. Therefore, baseline differences between the trials cannot be excluded (10).

To conclude, regarding the response of fasting serum lipids (triglycerides and cholesterol) to fructose diets in healthy subjects, the results are conflicting, and in all studies that reported increased concentrations of triglycerides or cholesterol, the mean increase was minor and the increased values usually remained within the normal range of serum triglycerides (<1.7 mmol l⁻¹) and total cholesterol (<5.0 mmol l⁻¹) (Table 1).

Postprandial metabolic changes have also been studied in diets containing fructose. In one study (11), 11 healthy volunteers were investigated twice during an oral fat load (40 g) with and without fructose (50 g). Addition of fructose to the fat load resulted in higher postprandial concentrations of triglyceride, and the higher the fasting plasma triglyceride concentration the greater the magnitude of the fructose effect. However, because the trial with fructose contained more energy than the trial without fructose, the results are not totally comparable. In some other studies, fat load with fructose/sucrose induced a greater postprandial response in serum triglyceride than fat load with glucose, which indicates fructose-induced postprandial lipaemia (12, 13). However, one study demonstrated the postprandial response to be attenuated within 7 days (9). Still, an increased acute postprandial lipaemia seems to be the most prominent response to a high amount of dietary fructose.

Studies in diabetic and hyperinsulinaemic subjects

Several studies have investigated the effect of fructose on plasma lipids in diabetic patients, which would be expected to be more sensitive due to their altered glucose and lipid metabolism. In one well-conducted study, 11 patients with type 2 (non-insulin-dependent) diabetes mellitus (112% of desirable body weight) and three patients with type 1 (insulin-dependent) diabetes mellitus were studied during 47 weeks: an 8 week control period, 23 weeks of fructose intervention (12E%), and a 16 week control period (14). In that study, no changes were seen in serum fasting lipids (triglycerides or cholesterol). Another study also reported no change in serum lipids in 5 obese patients with type 2 diabetes, with 13E% fructose during a 100 day intervention (15). Although this study was done with very few subjects, the duration of the study was longer than usual. In another study, 16 subjects with type 2 diabetes [body mass index (BMI) 21.2–28.5 kg m⁻²] were given three isocaloric diets for 28 days

Table 1. Effects of dietary fructose/sucrose on serum lipids in healthy humans

Subjects and study design	Amount consumed	Main results
Healthy subjects (normoglycaemic)		
11 subjects, 2 weeks of F feeding; sampling: 0, 3 and 14 days (6)	Range 63–99 g day ⁻¹	No changes in TG, minor decrease in TC and HDL
8 subjects, cross-over, F or sucrose (one-third of carbohydrates); sampling: 7 and 14 days (7)	Range 50–107 g day ⁻¹	No changes in TC, TG, LDL, HDL
11 healthy men, cross-over, 20E% from F or starch, 5 weeks (8)	183 g starch or 167 g F	Increased TG and TC higher after F
7 men and 7 women, cross-over, 4 weeks, 20E% from F or <3% from F (9)	20%: 100 g F + 132 g starch; <3%: 14 g F + 201 g starch	No differences in TG; TC and LDL decreased by 7% with starch but no change was seen with F
12 men and 12 women, cross-over, 17E% from F or glucose, 6 weeks both diet (10)	80 g F in F diet and 10 g in glucose diet	No differences in TC, LDL or HDL in men or women; TG did not differ in women but in men fasting and postprandial TG higher with fructose
11 volunteers, fat meal (40 g) with or without F, acute postprandial 10 h study (11)	50 g of F and 0 g of F	Increased postprandial TG with F; the higher the fasting TG the greater the response
9 men and 12 women, cross-over, fat meal with F, sucrose or glucose, acute postprandial study (12)	50 g of F, sucrose or glucose, or 100 g sucrose with the meal	Increased TG with 50 g F and 100 g sucrose, but not with 50 g sucrose or 50 g glucose
12 subjects, cross-over, 3 meals with 30E% as F or glucose in beverages, postprandial design (13)	45 g of F in each meal	Higher postprandial TG after F than after glucose

F: fructose; TC: total cholesterol; TG: triglyceride; HDL: high-density lipoprotein; LDL: low-density lipoprotein; E%: percentage of energy intake.

each: one with 20E% fructose, one with 19E% sucrose, and one control diet (16). No changes were observed in any lipid values.

However, there are also studies reporting increased serum lipids after fructose ingestion, especially in hyperinsulinaemic patients. In one study, 10 hyperinsulinaemic subjects (mean BMI 25.7 kg m⁻²) were studied for 5 weeks with fructose and 5 weeks with cornstarch (20E%) by a cross-over design (8). Sampling was performed before and after 5 weeks of intervention (fasting and after meals). A clear increase was seen in the concentration of serum triglycerides (2.41 versus 1.65 mmol l⁻¹) and also in serum cholesterol (5.82 versus 5.23 mmol l⁻¹). In another trial, 12 hyperinsulinaemic subjects (mean BMI 26.9 kg m⁻²) were studied with 0, 7.5 and 15E% fructose (17). Serum cholesterol increased with 7.5E% and 15E% fructose compared with 0E% (0E% 196.2 versus 7.5E% 204.3 versus 15E% 207.6 mg ml⁻¹). Similar changes were seen in serum triglycerides (0E% 101.6 versus 7.5E% 131.9 versus 15E% 163.4 mg ml⁻¹).

Some studies used interventions that lasted for several months. Osei and Bossetti (18) investigated 13 poorly controlled obese or overweight patients with type 2 diabetes during 6 months with fructose (60 g day⁻¹ of crystalline fructose) or 6

months with their ordinary diabetic diet. Although that study was not well controlled, it demonstrated

no change in serum lipids, lipoproteins or apolipoprotein A₁ and B₁₀₀ levels (18), and the authors reported clear beneficial changes in serum fasting glucose and glycosylated haemoglobin (HbA_{1c}). The long-term effects of fructose were investigated in another study by same group with 18 obese type 2 diabetic patients given either a fructose-enriched diet (60 g day⁻¹ crystalline fructose, *n* = 9) or a control diet (*n* = 9) during 12 weeks (19). Fasting serum triglycerides, total cholesterol, high-density lipoprotein (HDL) cholesterol and LDL cholesterol remained unchanged at week 12 compared with week 0 in the fructose group. However, the mean apolipoprotein A₁ concentration increased significantly at weeks 4 and 12 in the fructose group, whereas only transient changes occurred in apolipoprotein B₁₀₀ values. In contrast, fasting serum triglycerides increased at weeks 4 (15%) and 12 (38%) in the control group, but no significant changes occurred in lipids, lipoprotein or apolipoprotein A₁ and B₁₀₀ levels. Therefore, the results from long-lasting studies do not support the hypothesis that prolonged use of dietary fructose will increase levels of serum lipids (Table 2).

Table 2. Effects of dietary fructose/sucrose on serum lipids in hyperinsulinaemic and diabetic subjects

Subjects and study design	Amount consumed	Main results
<i>Subjects with hyperinsulinaemia</i>		
10 men with hyperinsulinaemia and 11 healthy men, cross-over, 20E% from F or starch, 5 weeks (8)	183 g starch or 167 g F	Increased TG and TC higher after F in both groups; in hyperinsulinaemic men VLDL also higher after F
12 men hyperinsulinaemia and 12 healthy men, cross-over, 0E%, 7.5E% and 15E% from F, 5 weeks (17)		TG increased by 30% and 60% with 7, 5% and 15% F in hyperinsulinaemic men, but not in normal men
12 men and 12 women, sucrose 5, 18 or 33E%, 6 weeks (20)	Amount of sucrose 33, 124 and 229 g day ⁻¹	Dose-dependent increase in fasting TG, TC, VLDL and LDL in men, but not in women
<i>Diabetic patients</i>		
14 diabetics (3 type 1 diabetes), 8 weeks of high-fibre high-carbohydrate, then 24 weeks supplemented with F and again high-fibre diet (14)	50–60 g of F	No differences in TG or TC with F
5 type 2 diabetic subjects, 13E% from F, 100 days (15)	Range of F 76–124 g	No differences in TC, TG, LDL or HDL with F
16 well-controlled type 2 diabetic subjects, cross-over, 3 isocaloric diets: 20E% from F, 19E% from sucrose, 5E% from sugars; each diet 4 weeks (16)	F diet: 63 g of F day ⁻¹ ; sucrose diet: 78 g of sucrose	No change in TG, TC, LDL, HDL with F or with sucrose
13 poorly controlled type 2 diabetic patients, cross-over 6 months with crystalline F (18)	60 g of F	No differences in TC, TG, LDL or HDL after 1, 3 or 6 months with F
9 type 2 diabetic patients, 12 weeks with crystalline F; another 9 type 2 diabetic patients without F (19)	60 g of F	No differences in TC, TG, LDL or HDL with F
7 type 2 diabetic subjects, 2 weeks with F (24E% of carbohydrates as either sucrose or F) (21)	F range 80–115 g day ⁻¹	No differences in TC, TG or HDL with F
12 type 2 and 6 type 1 diabetic subjects, cross-over, 20E% from either F or starch, 4 weeks (22)		TC and LDL increased by 9% and 11% in F compared with starch; no changes in fasting or postprandial TG
10 type 2 diabetic subjects, cross-over, 20E% from either F or starch, 4 weeks (23)	Range of F 45–65 g	No change in TG, TC, LDL, HDL with F
6 type 2 diabetic subjects and 6 healthy subjects, F or starch (0.75 g kg ⁻¹ body weight), 4 weeks + postprandial acute design (24)	F or starch 0.75 g kg ⁻¹ body weight	Increased postprandial TG response to F compared with starch

E%: percentage of energy intake; F: fructose; TG: triglyceride; TC: total cholesterol; VLDL: very low-density lipoprotein; LDL: low-density lipoprotein; HDL: high-density lipoprotein.

Confounding factors

The discrepancy between the results of the above studies may be caused by several factors. As mentioned above, the subject itself is a great cause of difference (healthy versus diabetic; diabetics with good balance versus uncontrolled diabetics, diabetic subjects with medication versus those without medication). The metabolic changes seen in healthy subjects may be different from those seen in diabetic subjects, with medicines also influencing lipid metabolism. Despite that, the main conclusions of studies with healthy and diabetic subjects are similar: most of the studies reported unchanged fasting serum lipids.

The study designs used in the papers mentioned earlier are usually unique and also contain several potential confounding factors. The duration of the study is of great importance. Any kind of acute change in diet can cause changes in lipid metabo-

lism and many of the fructose studies lasted for only days or a few weeks. Indeed, some long-lasting studies reported acute changes in serum lipids, which were thereafter normalized (9, 10). In the case of fasting serum lipids only long-lasting changes will influence cardiovascular risk. Hence, it may be concluded that the studies lasting for at least several weeks provide stronger scientific evidence on how dietary fructose will change serum lipids.

The amount of dietary fructose and the composition of control sugar or control diet will also greatly influence the results. During the 1970s and 1980s studies usually compared fructose with sucrose, which is not the best design because sucrose also contains fructose. The comparison between glucose and fructose may be scientifically more relevant, and the studies from the last decade usually evaluated this (e.g. references 10, 13). One potential

factor influencing the results is the baseline level of serum lipids. Most of the studies reported using only one baseline sample, which may not give adequate evidence of the baseline level, at least not regarding labile variables such as serum triglycerides. The most reliable study design is a double-blind randomized cross-over design (where subjects are their own controls) with clear washout periods, but unfortunately that design was used in few studies only. Seasons can also cause differences in the results, at least in long-term studies without blinded, randomized, cross-over design: serum lipids usually increase during winter to spring, and decrease during summer to autumn in countries with a cold winter (as in northern Europe) (25). Therefore, the seasonal variation may have had an influence in long-term, uncontrolled studies (e.g. 15).

In conclusion, most of the studies do not report any change in blood lipids after fructose. Even the latest critical reviews on fructose admit that despite studies demonstrating that fructose feeding leads to weight gain and hyperlipidaemia in animals, there is little direct evidence linking these phenomena in humans (3).

Fructose and body weight

In some animal studies, high-fructose diets are reported to increase body weight (26, 27), although not all studies confirm this (28). However, considerably less information is available from human studies. Some epidemiological studies have demonstrated an association between the consumption of larger amounts of sugar-sweetened beverages and greater weight gain (29). However, very few studies have compared diets containing fructose with control diets with the same amount of energy. Bantle et al. (10) reported decreases in body weight (74.1 versus 72.8 kg) after a 6 week diet containing 17% of energy from fructose in 24 healthy subjects, but a similar decrease was observed in the control diet (74.1 versus 72.7 kg). Another study demonstrated no difference in body weight between a diet containing 60 g of crystalline fructose (82.8 versus 83.8 kg) and a control diet without fructose (82.5 versus 83.0 kg) during a 12 week intervention in type 2 diabetic subjects (19). Body weight was measured as unchanged in three isocaloric diets containing 20E% fructose (65.9 versus 65.3 kg), 19E% sucrose (65.9 versus 66.0 kg) and only 5E% sugars (65.5 versus 65.3 kg) in 16 subjects with well-controlled type 2

diabetes (16). Similarly, fructose (60 g daily) incorporated in the normal diets of 13 poorly controlled type 2 diabetic patients did not change body weight compared with the normal diet (18). Therefore, the results from randomized controlled studies do not support the hypothesis that isocaloric consumption of dietary fructose would cause an increase in body weight.

Hormonal changes after fructose ingestion

Insulin and leptin, and possibly also ghrelin (an orexigenic gastroenteric hormone) are regarded as key signals to the central nervous system in the long-term regulation of energy balance (2). Fructose, unlike glucose, has a weak effect in stimulating insulin secretion (3). In a recent study, 12 women consumed three mixed macronutrient meals (carbohydrates 55E%, fats 30E%, proteins 15E%) accompanied by fructose-sweetened beverages on one day and glucose-sweetened beverages on another day (13). During the fructose day, the postprandial insulin response decreased by 65% compared with an isocaloric glucose day. In addition, circulating leptin concentrations over 24 h were reduced by 24% on the high fructose day compared with those of the high glucose day. The levels of ghrelin were suppressed by approximately 30% 1–2 h after ingestion of both the high fructose and the high glucose meal, while postprandial suppression of ghrelin was significantly less pronounced after the high fructose meal. The authors concluded that decreased circulating insulin and leptin and increased ghrelin concentrations could lead to increased caloric intake and ultimately contribute to weight gain. However, it is not fully understood how these hormonal changes after ingestion of different carbohydrates are linked to the energy intake and possible body weight changes.

Fructose and oral glucose tolerance

The glycaemic benefits of fructose as a substitute for other carbohydrates have been reported in several studies. Reiser et al. (8) studied 10 hyperinsulinaemic and 11 non-hyperinsulinaemic control men consuming a typical American diet containing 20E% either as fructose or as high-amylose cornstarch for 5 weeks in a cross-over design to determine their effects on indices of glucose tolerance. Glucose responses were significantly lower 60 and 120 min after the meals containing fructose (8). Similarly, the day-long glucose profile was lower

after meals containing fructose (8). Insulin response was also significantly lower 60 min after the meals containing fructose, as was the day-long insulin response on the fructose-containing diet (8).

The glycaemic benefits of fructose, together with results from animal studies, raised the hypothesis that a small catalytic dose of fructose administered with glucose may decrease the glycaemic response to the glucose load (30). Moore et al. (30) examined the effect of fructose on glucose tolerance by an oral glucose tolerance test (OGTT) in healthy human volunteers (five men and six women). Each subject underwent OGTT on two separate occasions, at least 1 week apart. Each OGTT consisted of 75 g glucose with or without 7.5 g fructose, in a random order. The area under the curve (AUC) of the change in plasma glucose was 19% less in the OGTT with fructose than in the OGTT without fructose ($p < 0.05$). The OGTT was improved by fructose in nine subjects and worsened in two. All subjects with the largest glucose AUC during OGTT without fructose had a decreased response during OGTT with fructose (mean decrease of 31%). There were no differences between the OGTTs in serum insulin AUC, glucagon, non-esterified fatty acid or triglyceride concentrations. The authors concluded that low-dose fructose improves the glycaemic response to an oral glucose load in normal adults without significantly enhancing the insulin or triglyceride response. Importantly, fructose appeared to be most effective in those normal individuals who had the poorest glucose tolerance (30).

The above-mentioned results inspired the same group to repeat the study with type 2 diabetic subjects. Five diabetic subjects underwent an OGTT on two occasions at least 1 week apart (31). As in the earlier study, OGTT consisted of 75 g glucose with or without the addition of 7.5 g fructose, in a random order. The AUC of the plasma glucose response was reduced by fructose administration in all subjects, and the mean AUC during the OGTT with fructose was 14% less than during the OGTT without fructose ($p < 0.05$). In contrast to the earlier study with normal adults, the insulin AUC was decreased by 21% with fructose administration. Neither non-esterified fatty acids nor triglyceride concentrations differed between the two trials, which is in line with the earlier study with healthy subjects (30).

Another group also studied the catalytic effect on postprandial glycaemic response of a small dose of

fructose administered before or simultaneously with a high glycaemic index starchy food (32). They gave 31 non-diabetic healthy adults a portion of instant mashed potato containing 50 g available carbohydrate alone or with 10 g fructose. The effect of timing of fructose ingestion was evaluated by asking the subjects to consume the 10 g fructose at 60 or 30 min before, or immediately (0 min) before the instant mashed potato meal. Compared with the control meal without fructose, the positive incremental AUC of blood glucose was reduced by 25% and 27% ($p < 0.01$) when fructose was fed 60 or 30 min before the meal, respectively. However, in contrast to the previous studies (30, 31), Heacock et al. (32) did not find any decreased glycaemic response when fructose was consumed simultaneously with instant mashed potato. The differences in the type and the amount of carbohydrate consumed in these three studies may explain that discrepancy. Moore et al. (30, 31) used glucose, which requires no hydrolysis for absorption, as opposed to the starch consumed in the other study (32). The greater amount of carbohydrate (75 versus 50 g) in the studies by Moore et al. (30, 31) compared with the study by Heacock et al. (32) may have enhanced the sensitivity for detecting changes in the glycaemic response when fructose was given simultaneously with the carbohydrate.

Another possible mechanism may be related to the absorption of fructose. It is known that the absorption of fructose from the intestine is greatly facilitated by the presence of free glucose (4), while the hydrolysis of starch by amylase will result in mainly disaccharides, trisaccharides and oligosaccharides in the lumen. Therefore, the absorption of fructose in the presence of disaccharides, trisaccharides and oligosaccharides from starch hydrolysis may have been slower than it would have been in the presence of free glucose.

Gannon et al. (33) compared the insulin responses to fructose alone and a combination of fructose and protein (cottage cheese, 147 g, grade A, dry and <0.5% milk fat). In that study, seven men with untreated type 2 diabetes were fed 25 g fructose, 25 g protein, 25 g fructose plus 25 g protein, 50 g glucose or water only (33). The insulin area response to protein was 2.5-fold greater than that to fructose, and the response to the two nutrients was additive and quantitatively similar to the response to 50 g glucose. In contrast, both the glucagon area response and the glucose area

response to fructose plus protein were less than the sum of the responses to the individual nutrients (33). The results indicate the complexity of the nutrient interactions, but also emphasize the importance of the protein component of the meal in affecting the postprandial plasma glucose concentrations. Because the glycaemic response to fructose plus protein was less than the sum of the responses to the individual nutrients, the catalytic effect of a small amount of fructose to the glycaemic response may also be the case for protein-rich foods.

Several potential mechanisms for the decreased glycaemic response caused by a catalytic small amount of fructose have been considered: fructose-induced malabsorption of carbohydrates, enhanced insulin secretion, and stimulation of hepatic glucose uptake secondary to hepatic glucokinase translocation (34). However, malabsorption should not be a problem with the small dose of fructose (7.5–10 g) used in the three studies (30–32), since in one recent study of 21 healthy subjects in whom malabsorption was demonstrated after ingestion of 50 g fructose, only four individuals experienced malabsorption when consuming 25 g fructose (35). Enhanced insulin secretion caused by fructose also seems not to be the case. Two of the three studies measured also the insulin AUC. In the study with healthy subjects no difference was seen between the OGTT with and without fructose, and in the study with type 2 diabetic patients, the insulin AUC decreased by 21% with fructose administration. Therefore, the most probable mechanism for the decreased glycaemic response may be fructose-induced stimulation of hepatic glucose uptake. It has been established that in hepatocytes, fructose is rapidly phosphorylated to fructose-1-phosphate, which competes with fructose-6-phosphate for binding on a glucokinase regulatory protein (GKRP). As a result of this competition, glucokinase is released from GKRP and the liberated glucokinase diffuses to the cytosol. The glucokinase translocation stimulates the hepatic glucose uptake by converting glucose to glycogen, and phosphorylation of glucose by glucokinase, which is a rate-determining step for hepatic glucose metabolism. Thus, the primary difference between hepatic fructose and glucose metabolism is that fructose molecules by-pass the main rate-controlling step in glycolysis, 6-phosphofructokinase. This hypothesis has been demonstrated in studies with dogs (36, 37). Although the fructose-induced stimulation of hepa-

tic glucose uptake seems to be the most obvious mechanism of catalytic effect of fructose, more studies are needed to confirm the mechanism in humans.

In summary, the addition of small catalytic amounts of fructose to a glucose load improves glucose tolerance in both healthy and diabetic subjects. Similarly, a small dose of fructose consumed 60 and 30 min before starchy food with a high glycaemic index decreased the glycaemic response compared with food without fructose. It seems that in physiological circumstances the fructose could be consumed before the carbohydrate load. Therefore, a snack containing a small amount of fructose, e.g. a piece of fruit, 30–60 min before a meal may be beneficial, especially for people with impaired glucose tolerance or type 2 diabetes. However, because of the small number of the studies dealing with the catalytic effect of fructose and the unknown mechanisms of the effect, more studies are needed before special recommendations can be made.

Effects of fructose on long-term glucose metabolism (glycosylated haemoglobin)

In type 2 diabetes more insulin is needed than the pancreas can produce. Therefore, foods that need lower secretion of insulin, i.e. foods that have a lower glycaemic index, are known to be beneficial for glucose metabolism. As reviewed above, short-term replacement of other carbohydrate sources in the diabetic diet with fructose is known to improve short-term glycaemic control (38), but there is also evidence of more prolonged improvement in glucose metabolism. For example, Koivisto and Yki-Jarvinen (23) studied the effects of 20% dietary fructose (45–65 g day⁻¹ for 4 weeks) on insulin concentration and HbA_{1c} in 10 type 2 diabetic patients. In that study, subjects were given, in a double-blind, randomized cross-over design, either crystalline fructose or an isocaloric amount of complex carbohydrate (control) diet evenly during four meals or snacks per day. Patients were hospitalized throughout the study period. The mean diurnal blood glucose concentration fell during both diets, but serum insulin concentration remained unchanged. Importantly, the HbA_{1c} as a marker of prolonged glucose balance improved only during the fructose diet (9.0% versus 8.0%, $p < 0.02$) (23). Even more long-term effects of a fructose diet on glycaemic control were studied by

Osei et al. (19). They performed an outpatient 12 week study with nine type 2 diabetic patients using crystalline fructose (60 g daily) and nine type 2 diabetic patients consuming their usual meals. The authors reported a progressive decrease in both serum glucose and HbA_{1c} values in the group treated with fructose, while in the other group, both parameters tended to increase during the study weeks. The authors concluded that a slight improvement in glycaemic control and alterations in the apolipoprotein compositions in favour of decreased risk for coronary artery disease may occur (19). Therefore, the available studies show some evidence that the replacement of other carbohydrate sources in the diabetic diet with fructose may improve the prolonged glycaemic control, although more research is needed to reach more precise conclusions.

Conclusion

Fructose has been regarded as an acceptable caloric sweetener for diabetic subjects for two decades, but recently some important mechanisms of the effects of fructose have been documented. Small, catalytic amounts of fructose seem to improve glucose tolerance in healthy and especially in diabetic patients. The replacement of other carbohydrate sources in the diabetic diet with fructose may also improve prolonged glycaemic control, measured by HbA_{1c}. All of these results were obtained with a small or moderate amount of fructose. High-fructose diets have been postulated to cause hypertension, insulin resistance, hyperlipidaemia and hyperinsulinaemia, at least in animal models (2), but small and moderate amounts of fructose seem to have a favourable effect on glucose metabolism. However, further studies are needed before any recommendations can be made.

References

1. Uusitupa MI. Fructose in the diabetic diet. *Am J Clin Nutr* 1994; 59: 753–75.
2. Elliott SS, Keim NL, Stern JS, Teff K, Havel PJ. Fructose, weight gain, and the insulin resistance syndrome. *Am J Clin Nutr* 2002; 76: 911–22.
3. Havel PJ. Dietary fructose: implications for dysregulation of energy homeostasis and lipid/carbohydrate metabolism. *Nutr Rev* 2005; 63: 133–57.
4. Riby JE, Fujisawa T, Kretchmar N. Fructose absorption. *Am J Clin Nutr* 1993; 58: 748–53S.
5. Frayn KN, Kingman SM. Dietary sugars and lipid metabolism in humans. *Am J Clin Nutr* 1995; 62: 250–61S.
6. Crapo PA, Kolterman OG. The metabolic effects of 2-week fructose feeding in normal subjects. *Am J Clin Nutr* 1984; 39: 525–34.
7. Bossetti BM, Kocher LM, Moranz JF, Falko JM. The effects of physiologic amounts of simple sugars on lipoprotein, glucose and insulin levels in normal subjects. *Diabetes Care* 1984; 7: 309–12.
8. Reiser S, Powell AS, Scholfield DJ, Panda P, Ellwood KC, Canary JJ. Blood lipids, lipoproteins, apolipoproteins, and uric acid in men fed diets containing fructose or high-amylose cornstarch. *Am J Clin Nutr* 1989; 49: 832–9.
9. Swanson JE, Laine DC, Thomas W, Bantle JP. Metabolic effects of dietary fructose in healthy subjects. *Am J Clin Nutr* 1992; 55: 851–6.
10. Bantle JP, Raatz SK, Thomas W, Georgopoulos A. Effects of dietary fructose on plasma lipids in healthy subjects. *Am J Clin Nutr* 2000; 72: 1128–34.
11. Jeppesen J, Chen YI, Zhou MY, Schaaf P, Coulston A, Raeven GM. Postprandial triglyceride and retinyl ester responses to oral fat: effects of fructose. *Am J Clin Nutr* 1995; 61: 787–91.
12. Cohen JC, Schall R. Reassessing the effects of simple carbohydrates on the serum triglyceride responses to fat meals. *Am J Clin Nutr* 1988; 48: 1031–4.
13. Teff KL, Elliott SS, Tschop M, Kieffer TJ, Rader D, Heiman M, et al. Dietary fructose reduces circulating insulin and leptin, attenuates postprandial suppression of ghrelin, and increases triglycerides in women. *J Clin Endocrinol Metab* 2004; 89: 2963–72.
14. Anderson JW, Story LJ, Zettwoch NC, Gustafson NJ, Jefferson BS. Metabolic effects of fructose supplementation in diabetic individuals. *Diabetes Care* 1989; 12: 337–44.
15. Thorburn AW, Crapo PA, Beltz WF, Wallace P, Witztum JL, Henry RR. Lipid metabolism in non-insulin-dependent diabetes: effects of long-term treatment with fructose-supplemented mixed meals. *Am J Clin Nutr* 1989; 50: 1015–22.
16. Malerbi DA, Paiva ESA, Duarte AN, Wajchenberg BL. Metabolic effects of dietary sucrose and fructose in type II diabetic subjects. *Diabetes Care* 1996; 19: 1249–56.
17. Hallfrisch J, Reiser S, Prather ES. Blood lipids distribution of hyperinsulinemic men consuming three levels of fructose. *Am J Clin Nutr* 1983; 37: 740–8.
18. Osei K, Bossetti B. Dietary fructose as a natural sweetener in poorly controlled type 2 diabetes: a 12-month crossover study of effects on glucose, lipoprotein and apolipoprotein metabolism. *Diabet Med* 1989; 6: 506–11.
19. Osei K, Falko J, Bossetti BM, Holland GC. Metabolic effects of fructose as a natural sweetener in the physiologic meals of ambulatory obese patients with type II diabetes. *Am J Med* 1987; 83: 249–55.
20. Reiser S, Bohn E, Hallfrisch J, Michaelis OE, Keeney M, Prather ES, et al. Serum insulin and glucose in

- hyperinsulinemic subjects fed three different levels of sucrose. *Am J Clin Nutr* 1981; 34: 2348–58.
21. Crapo PA, Kolterman OG, Henry RR. Metabolic consequences of two-week fructose feeding in diabetic subjects. *Diabetes Care* 1986; 9: 111–9.
 22. Bantle JP, Swanson JE, Thomas W, Laine DC. Metabolic effects of dietary fructose in diabetic subjects. *Diabetes Care* 1992; 15: 1468–76.
 23. Koivisto VA, Yki-Jarvinen H. Fructose and insulin sensitivity in patient with type 2 diabetes. *J Intern Med* 1993; 233: 145–53.
 24. Abraha A, Humphreys SM, Clark ML, Matthews DR, Frayn KN. Acute effect of fructose on postprandial lipaemia in diabetic and non-diabetic subjects. *Br J Nutr* 1998; 80: 169–75.
 25. Robinson D, Bevan EA, Hinohara S, Takahashi T. Seasonal variation in serum cholesterol levels: evidence from UK and Japan. *Atherosclerosis* 1992; 95: 15–24.
 26. Kanarek RB, Orthen-Gambill N. Differential effects of sucrose, fructose and glucose on carbohydrate-induced obesity in rats. *J Nutr* 1982; 112: 1546–54.
 27. Kasim-Karakas SE, Vriend H, Almario R, Chow LC, Goodman MN. Effects of dietary carbohydrates on glucose and lipid metabolism in golden Syrian hamsters. *J Lab Clin Med* 1996; 128: 208–13.
 28. Suga A, Hirano T, Kageyama H, Osaka T, Namba Y, Tsuji M, et al. Effects of fructose and glucose on plasma leptin, insulin, and insulin resistance in lean and VMH-lesioned obese rats. *Am J Physiol Endocrinol Metab* 2000; 278: E677–83.
 29. Schulze MB, Manson JE, Ludwig DS. Sugar-sweetened beverages, weight gain, and incidence of type 2 diabetes in young and middle-aged women. *JAMA* 2004; 292: 927–34.
 30. Moore MC, Cherrington AD, Mann SL, Davis SN. Acute fructose administration decreases the glycemic response to an oral glucose tolerance test in normal adults. *J Clin Endocrinol Metab* 2000; 85: 4515–9.
 31. Moore MC, Mann SL, Davis SN, Cherrington AD. Acute fructose administration improves oral glucose tolerance in adults with type 2 diabetes. *Diabetes Care* 2001; 24: 1882–7.
 32. Heacock PM, Hertzler SR, Wolf BW. Fructose prefeeding reduces the glycemic response to a high-glycemic index, starchy food in humans. *J Nutr* 2002; 132: 2601–4.
 33. Gannon MC, Nuttall FQ, Grant CT, Ercan-Fang S, Ercan-Fang N. Stimulation of insulin secretion by fructose ingested with protein in people with untreated type 2 diabetes. *Diabetes Care* 1998; 21: 16–22.
 34. McGuinness OP, Cherrington AD. Effects of fructose on hepatic glucose metabolism. *Curr Opin Clin Nutr Metab Care* 2003; 6: 441–8.
 35. Truswell AS, Seach JM, Thorburn AW. Incomplete absorption of pure fructose in healthy subjects and the facilitating effects of glucose. *Am J Clin Nutr* 1998; 48: 1424–30.
 36. Shiota M, Moore MC, Galassetti P, Monohan M, Neal DW, Shulman GI, Cherrington AD. Inclusion of low amounts of fructose with an intraduodenal glucose load markedly reduces postprandial hyperglycemia and hyperinsulinemia in the conscious dogs. *Diabetes* 2002; 51: 469–78.
 37. Shiota M, Galassetti P, Monohan M, Neal DW, Cherrington AD. Small amounts of fructose markedly augment hepatic glucose uptake in the conscious dogs. *Diabetes* 1998; 47: 867–73.
 38. Bantle JP, Laine DC, Thomas JW. Metabolic effects of dietary fructose and sucrose in types I and II diabetic subjects. *JAMA* 1986; 256: 3241–6.

Professor Tommi Vasankari

Department of Health and Exercise
 University of Turku
 Paavo Nurmi Center
 Kiinamyllynkatu 10
 FI-20540 Turku
 Finland
 Tel: +358 40 5059157
 Fax: +358 2 2502610
 E-mail: tommi.vasankari@vierumaki.fi