Continuing Medical Education

Fructose Consumption—Free Sugars and Their Health Effects

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Summary

Background: The excessive consumption of free sugars, including fructose, is considered a cause of overweight and metabolic syndrome throughout the Western world. In Germany, the prevalence of overweight and obesity among adults (54%, 18%) and children (15%, 6%) has risen in the past few decades and has now become stable at a high level. The causative role of fructose is unclear.

Methods: This review is based on publications retrieved by a selective search in PubMed and the Cochrane Library, with special attention to international guidelines and expert recommendations.

Results: The hepatic metabolism of fructose is insulin-independent; because of the lack of a feedback mechanism, it leads to substrate accumulation, with *de novo* lipogenesis and gluconeogenesis. Recent meta-analyses with observation periods of one to ten weeks have shown that the consumption of fructose in large amounts leads to weight gain (+ 0.5 kg [0.26; 0.79]), elevated triglyceride levels (+ 0.3 mmol/L [0.11; 0.41]), and steatosis hepatis (intrahepatocellular fat content: + 54% [29; 79%]) when it is associated with a positive energy balance (fructose dose + 25–40% of the total caloric requirement). Meta-analyses in the isocaloric setting have not shown any comparable effects. Children, with their preference for sweet foods and drinks, are prone to excessive sugar consumption. Toddlers under age two are especially vulnerable.

Conclusion: The effects that have been observed with the consumption of large amounts of fructose cannot be reliably distinguished from the effects of a generally excessive caloric intake. Further randomized and controlled intervention trials of high quality are needed in order to determine the metabolic effects of fructose consumed under isocaloric conditions. To lessen individual consumption of sugar, sugary dietary items such as sweetened soft drinks, fruit juice, and smoothies should be avoided in favor of water as a beverage and fresh fruit.

Cite this as:
Stricker S, Rudloff S, Geier A, Steveling A, Roeb E, Zimmer KP:
Fructose consumption—free sugars and their health effects. Dtsch Arztebl Int 2021; 118: 71–80. DOI: 10.3238/arztebl.m2021.0010

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Cardiovascular diseases are still among the main causes of death in the Western world, despite a recent decline in incidence (1). They are usually due to the metabolic syndrome, whose main manifestations are predominantly truncal obesity, dyslipidemia, arterial hypertension, and impaired glucose tolerance or type 2 diabetes mellitus (2–4).

The prevalence of overweight and obesity in the Western world has risen sharply in the past few decades and has now become stable at a high level (3, 5). According to current data, 47% of all women and 62% of all men in Germany are overweight (body mass index >25 kg/m^2), while 18% of all adults are obese (BMI >30 kg/m^2) (6, e1, e2). Among children aged 3 to 17, 15% are overweight (above the 90th Kromeyer–Hauschild percentile), while 6% are obese (above the 97th Kromeyer-Hauschild percentile) (7, e3). Positive caloric balance and the consumption of free sugars are important contributory causes of overweight and the metabolic syndrome. The term "free sugars" refers to monosaccharides (glucose, fructose) and disaccharides (saccharose, i.e., household sugar; lactose) that are either naturally present in food and beverages or are added to them during processing. Unlike oligosaccharides and polysaccharides, free sugars are essentially a rapidly mobilizable energy source that provides little or no physiological nutritional benefit. It is recommended in the current WHO guideline that the amount of free sugars consumed should be less than 10% of the recommended daily calorie intake (RDCI) of adults and children. With an RDCI of 2000 kcal, this corresponds to 50 g of sugar (17 sugar cubes ≈ 12 teaspoons of household sugar ≈ 500 ml of orange juice) per day *(Table 1)*. This recommendation pertains both to sugars that have been added to foods and beverages during their production and to free sugars contained naturally in honey, syrup, fruit juices, and fruit juice concentrates (8, 9). The sugar intake of children is particularly important, as they have an inborn, evolutionarily

Free sugars

Free sugars are mono- and disaccharides that are either naturally present in food and beverages or are added to them during processing. They are essentially a rapidly mobilizable energy source that provides little or no physiological nutritional benefit.

TABLE 1

Quantitative recommendations for free sugar intake in adults and children*

Recommending body	Region	Target group	Quantitative recommendation
WHO, 2015 (8)	global	general population	< 10% of RDCI (strong)
			< 5% of RDCI (conditional)
DAG/DDG/DGE, 2018 (9)	Germany	general population	< 10% of RDCI
ESPGHAN, 2017 (13)	Europe	children, adolescents (2 to 18 years old)	< 5% of RDCI
		infants, toddlers (<2 years old)	less

*The WHO recommendation for further reduction of free sugar intake to less than 5% of the recommended daily caloric intake, in order to lower the risk of dental caries, is of conditional applicability.

DAG, German Obesity Society *(Deutsche Adipositas-Gesellschaft)*; DDG, German Diabetes Society *(Deutsche Diabetes Gesellschaft)*; DGE,German Society for Nutrition *(Deutsche Gesellschaft für Ernährung)*; ESPGHAN, European Society for Pediatric Gastroenterology, Hepatology, and Nutrition; RDCI, recommended daily caloric intake; WHO, World Health Organization

advantageous preference for sweet foods and drinks, and their nutritional requirement undergoes major shifts during infancy and the pubertal growth spurt (10). Children are more sensitive to sugar and prefer a higher sugar content in water and soft drinks than adults do (11, 12, e4, e5). Pre- and postnatal exposure to certain types of taste via the amniotic fluid and breast milk affects future taste preferences (e6, e7). Breast milk, compared to formula, offers the infant a wider variety of taste sensations and seems to promote children's acceptance of a more diverse range of foods (13). Taste preferences and dietary habits develop largely in the first two years of life and persist throughout childhood. Children who regularly drink sweet beverages at a young age continue to prefer them when they are older. Because of this so-called flavor learning, children under age 2, whose taste preferences can still be influenced, are a vulnerable group for excessive sugar intake (10). Because of this, the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommends that children and adolescents aged 2–18 years should consume no more than 5% of their recommended daily caloric intake in the form of sugar, corresponding to 16 g of sugar (4 teaspoons) for a 4-year-old boy. Children under age 2 should consume even less sugar *(Table 1)* (13). At present, the actual amount of free sugars consumed as a percentage of overall caloric intake is 13–14% in adults and 15–17.5% in children, which is far above the recommended upper limit (9, 14, e8). Most of the free sugar intake in childhood is accounted for by sweets (34%) and fruit juices (22%), but sugar-sweetened beverages (SSB) play a role as well, as they have little satiating effect despite their high energy density (14, 15, e9). The individual sugar intake can be reduced by replacing sugary products such as SSB, fruit juices, and smoothies with water as a beverage and fresh fruit *(Box)*.

In the past, emphasis was laid on the adverse metabolic effects of glucose, including elevated blood sugar levels and hyperinsulinism. In this review article, we will devote particular attention to the special metabolism of fructose and its association with the metabolic syndrome and with steatosis hepatis, and we will discuss the preventive measures that can be taken.

Methods

This review is based on pertinent publications retrieved by a selective search in PubMed and the Cochrane Library, with special attention to international guidelines and expert recommendations. The following search terms were used: "fructose AND weight gain AND obesity," "fructose AND hypertension AND uric acid," "fructose AND metabolism AND triglycerides AND insulin," and "fructose AND non-alcoholic fatty liver disease." Clinical trials and meta-analyses from countries with a Western lifestyle, published in either English or German in the period 1987–2020, were considered.

Chemical properties and metabolism

Fructose is a ketohexose found naturally in fruits and vegetables. It plays a major role in industrial food production, e.g., as a component of saccharose or high-fructose corn syrup (HFCS). Sugared soft drinks account for much of the fructose intake. In Europe, such drinks are sweetened with household sugar (saccharose), which consists of equal portions of fructose and glucose

Obesity prevalence and sugar consumption

Sugar consumption and the prevalence of obesity rose in parallel from 1980 to 2005; in the past decade, the prevalence of obesity in Germany has stabilized, while sugar consumption has declined

Recommended sugar intake for adults

The amount of free sugars consumed should be less than 10% of the recommended daily calorie intake (RDCI). With an RDCI of 2000 kcal, this corresponds to 50 g of sugar.

connected by a glycoside bond. In the USA, saccharose has been replaced to an increasing extent in recent decades by HFCS, which is less expensive. HFCS is a mixture of free fructose and free glucose, with the fructose contribution varying from 42% to 55%. Fructose alone is a more powerful sweetener than saccharose (× 1.17 in comparison to saccharose) or glucose alone (× 0.67 in comparison to saccharose). Fructose also has a lower glycemic index than glucose, i.e., it elevates blood sugar to a lesser extent than glucose does (fructose: 19 vs. glucose: 100) (e10–e12) *(Figure 1)*.

Fructose, obesity, and lipid metabolism

The increasing prevalence of obesity in the Western world since the 1980s and the parallel increase in the consumption of free sugars suggest that sugar, and fructose in particular, may be playing a harmful role. This suspicion remains even though, in the past decade, the prevalence of obesity in Germany has stabilized, while sugar consumption has declined, mainly among children (4, 7, 9, 14, 16, e13).

It must be asked, however, whether fructose poses a particular danger because of its special metabolism, or whether the observed adverse effects are due merely to increased caloric intake by way of fructose. There is no question that a high caloric intake, exceeding the individual's energy requirement over a long period of time, will lead to weight gain (17), and excessive calorie intake via fructose is certainly a major part of this. In a retrospective cohort study involving 628 children, Disse et al. found that primary fructose malabsorption, a phylogenetically impaired capacity to absorb fructose, is negatively associated with obesity (odds ratio: 0.35, 95% confidence interval [0.13; 0.97]) (18). Experiments in rats have shown weight gain with high fructose intake (20% of the total caloric requirement) under isocaloric conditions, but meta-analyses to date have not revealed any such effect on human body weight (e14, e15). In human trials, the consumption of large quantities of fructose (40% of the RDCI) in addition to the subjects' usual diet for periods of 1 to 10 (median: 3) weeks resulted in significant weight gain (+ 0.53 kg, [0.26; 0.79]) (17, 19) *(Table 2)*.

Aside from the adverse effect of fructose on body weight, it is also thought to adversely affect metabolism via substrate accumulation in the liver, leading to lipo- and gluconeogenesis through the activation of SREBP-1c (sterol regulatory element binding protein 1c) and ChREBP (carbohydrate responsive element binding protein) (20, e16) *(eBox)*. Randomized trials have shown that fructose administration (20% of RDCI) leads to a mild elevation of postprandial triglyceride levels (+ 0.09 mmol/L, [0.01; 0.18 mmol/L]), while meta-analyses have shown that the intake of large amounts of fructose (median daily dose, 175 g and 193 g) significantly raises triglyceride levels (+ 0.26 mmol/L, [0.11; 0.41]) (20, 21, e17– e20). Recent meta-analyses have not revealed any adverse effects on triglyceride or HDL- and LDL-cholesterol concentrations after the consumption of fructose for seven days or longer under isocaloric conditions (22). Nonetheless, in a 10-week intervention trial involving 32 subjects, Stanhope et al. found that the long-term consumption of soft drinks containing fructose (25% of RDCI), compared to soft drinks containing glucose, led to an increase in visceral fat deposits (+ 14.0 ± 5.5 % versus 3.2 ± 4.4 %), in agreement with the animal data (e20–e22).

Fructose, uric acid, and insulin metabolism

Adenosine diphosphate (ADP) is produced in the first step of fructose metabolism in the liver and is then broken down into uric acid *(Figure 1, eBox)*. Because uric acid inhibits endothelial nitric oxide synthase, an elevated uric acid level may lead to diminished release

BOX

Practical recommendations for lowering free sugar intake

The individual intake of free sugars can be lowered by replacing dietary items that contain sugar by alternatives that do not. The drinking of water, rather than sugary soft drinks and fruit juices, is recommended. A further possible alternative is unsweetened tea; however, as the consumption of large amounts of tea over the long term poses a health risk for children, pregnant women, and nursing mothers because of a potentially high pyrrolizidine alkaloid content (mainly in herbal teas), these persons should drink tea only in alternation with other beverages (e30). Fruit purees and smoothies are particularly popular among toddlers and contain large amounts of free sugar, yet, unlike fresh fruit, they yield hardly any dietary fiber. In the selection of dairy products and cereals, unsweetened alternatives should be chosen preferentially; these can be sweetened with fresh fruit if necessary. Replacing sugary soft drinks with soft drinks that have been sweetened with non-caloric substances (aspartame, acesulfam K) has a beneficial effect on weight development in children (e31, e32). Nonetheless, the long-term effects of these sweeteners, particularly in children, have not been adequately studied, and their consumption can therefore not be recommended. Special so-called children's foods often contain large amounts of free sugars and cannot be recommended (13).

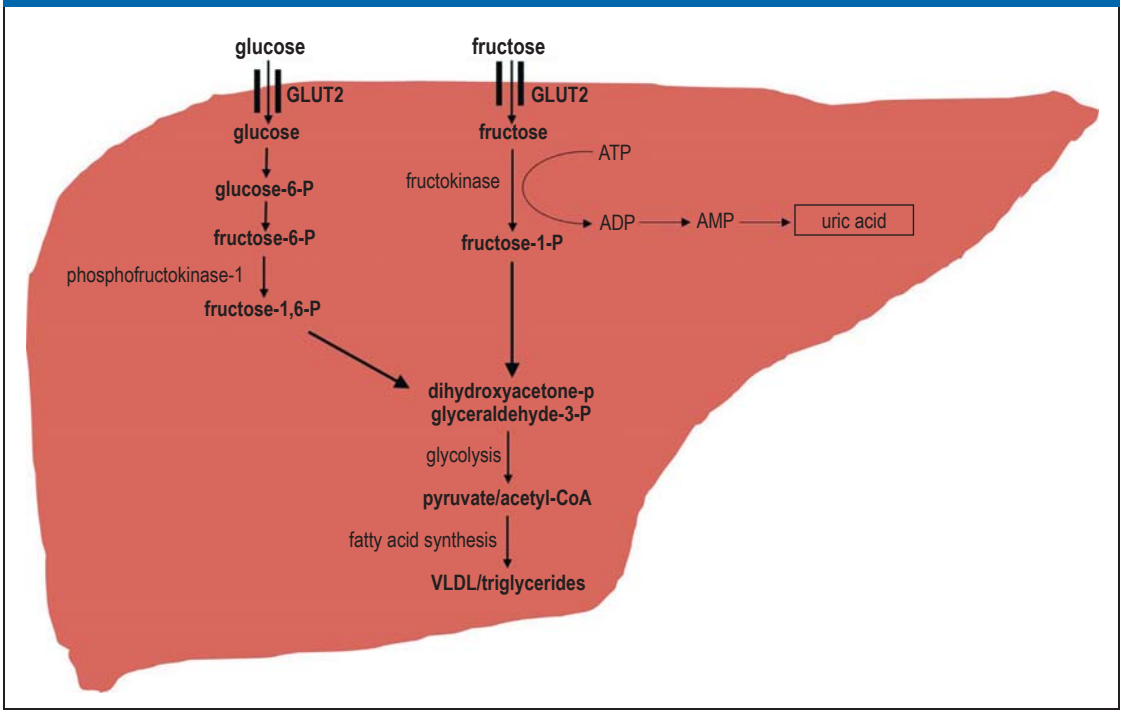
The special situation in children

Children are more sensitive to sugar and prefer sweeter food and beverages compared to adults.

Taste preferences in childhood

Taste preferences and dietary habits develop largely in the first two years of life and persist throughout childhood and are influenced by multiple pre- and postnatal factors.

FIGURE 1



The hepatic metabolism of fructose and glucose

The uptake of fructose in the intestinal epithelium and its transport into the portal venous circulation take place independently of insulin by means of the highly specific fructose transporter GLUT5. In the liver, hepatocellular uptake of fructose and glucose is facilitated by the insulin-independet transporter GLUT2. Degradation of glucose to fructose-1,6-phosphate occurs with the aid of the key enzyme of glycolisis phosphofructokinase-1, whereas degradation of fructose circumvents this regulatory mechanism. The metabolism of both monosaccharides leads to the generation of dihydroxyacetone phosphate and glyceraldehyde-3-phosphate, which are degraded to pyruvate in glycolysis. As there is no feedback mechanism regulating fructose metabolism, acetyl-CoA substrate accumulation ensues, exceeding the capacity of the citrate cycle. Excess citrate serves as a substrate for *de novo* lipogenesis. Fructose is converted to fructose-1-phosphate with the consumption of ATP. The resulting ADP is degraded to uric acid, which inhibits endothelial NO synthase, thereby contributing to arterial hypertension. ADP, adenosine diphosphate; AMP, adenosine monophosphate; ATP, adenosine triphosphate; GLUT, glucose transporter; P, phosphate; VLDL, very low density lipoproteins. Adapted from (e25).

of the vasodilator NO, resulting in arterial hypertension (23). Prospective cohort studies suggest an association between elevated uric acid levels and essential hypertension, particularly in adolescents (23, 24). In a randomized trial, the daily consumption of 200 g of fructose (32% of RDCI) in addition to the subjects' usual diet raised the uric acid level by 65 ± 6 µmol/L, while also leading to a rise in blood pressure values in 24-hour measurements (systolic, + 6.9 ± 2.3 mm Hg; diastolic, + 4.7 ± 1.6 mm Hg). These effects were significantly counteracted in an intervention group by the administration of allopurinol at a daily dose of 300 mg (uric acid level, − 113 ± 12 µmol/L; systolic blood pressure, + 2.1 ± 1.2 mm Hg; diastolic blood pressure, + 1.0 ± 0.8 mm Hg), in accordance with the findings of animal experiments involving a high fructose intake (60% of overall caloric intake) (25, e23). In a review article, elevation of the uric acid level (+ 31 µmol/l, [15.4; 46.5]) was demonstrated only after the consumption of very large amounts of fructose (> 200 g per day) (26). A meta-analysis of three prospective cohort studies involving more than 200,000 subjects did not reveal any correlation between fructose intake and arterial hypertension; in contrast, Kelishadi et al., in another meta-analysis, found an association between fructose consumption and elevated systolic blood pressure,

Sugar consumption in children

At present, children in Germany consume roughly three times as much sugar as the recommended upper limit (5% of daily caloric intake). Children consume sugar mainly in sweets and fruit juices, as well as in soft drinks.

Reducing sugar consumption

Individual sugar consumption can be lowered by replacing sugary items such as sugared soft drinks, fruit juices, and smoothies with water as a beverage and fresh fruit

TABLE 2

Overview of recent meta-analyses on fructose and metabolic parameters *

Design	Source	Studies analyzed	RCT	N	Follow-up (weeks)	Fructose dose	Control	Remarks
Fructose and obesity								
i	Sievenpiper et al. (17)	31	18/31	637	8 (1–52)	69 g/d, 17% RDCI (22.5–300 g/d)	fructose vs. starch, glucose, saccharose, HFCS	no effect of fructose on body weight
i	Te Morenga et al. (19)	12	12/12	135	4 (4–24)	–	high-fructose diet vs. low-fructose, isocaloric diet	no weight gain with isocaloric exchange of free sugars
h	Sievenpiper et al. (17)	10	6/10	119	3 (1–10)	+ 182 g/d, 37.5% RDCI (104–250 g/d)	normal diet + fructose vs. normal diet	no weight gain with hypercaloric fructose intake
h	Te Morenga et al. (19)	10	10/10	382	4 (4–24)	+ 19% RDCI (80–132 g/d)	increased vs. decreased intake of free sugars	0.75 kg weight gain with increased free sugar intake
x	Te Morenga et al. (19)	5	5/5	1285	24 (10–32)	− 8% RDCI (44–71 g/d)	decreased free sugar intake vs. normal diet	0.8 kg weight loss with decreased free sugar intake
Fructose and lipid metabolism								
i	Wang et al. (20)	14	8/14	290	13 (1–95)	120 g/d, 20% RDCI (22.5–168 g/d)	fructose vs. starch, glucose, saccharose, HFCS	no difference in postprandial triglycerides
i	Chiavaroli et al. (21)	51	24/51	943	4 (1–95)	97 g/d, 20% RDCI (25–300 g/d)	fructose vs. starch, glucose/saccharose/HFCS	no effect on LDL, HDL, triglycerides, or apolipoprotein B
i/h	Kelishadi et al. (28)	15	–	452	2 (0.3–10)	150 g/d, 25% RDCI (40–250 g/d)	–	increased triglycerides, decreased HDL-cholesterol
h	Wang et al. (20)	2	0/2	33	5 (2–8)	+ 175 g/d, 25% RDCI (168–182 g/d)	normal diet + fructose vs. normal diet	increased postprandial triglycerides
h	Chiavaroli et al. (21)	8	4/8	125	2 (1–10)	+ 193 g/d, 25% RDCI (150–213 g/d)	normal diet + fructose vs. normal diet	increased apolipoprotein B and triglycerides
Fructose and arterial hypertension/uric acid level								
i	Wang et al. (26)	18	8/18	390	16 (1–52)	94 g/d, 5–33% RDCI (25–213 g/d)	fructose vs. starch/glucose/saccharose	hepatic insulin resistance, no systemic insulin resistance
y	Jayalath et al. (27)	3	–	223,330	14–20 years	5.7–14.3% RDCI	–	no association between fructose intake and arterial hypertension
i/h	Kelishadi et al. (28)	15	–	452	2 (0.3–10)	150 g/d, 25% RDCI (40–250 g/d)	–	increased systolic blood pressure
h	Wang et al. (26)	3	3/3	35	1 (1)	+ 215 g/d, 35% RDCI (213–219 g/d)	normal diet + fructose vs. normal diet	increased uric acid level (+ 0.5 mg/dL)
Fructose and insulin metabolism								
i	Ter Horst et al. (33)	32	17/32	826	4 (1–95)	98 g/d, 18% RDCI (26–250 g/d)	fructose vs. starch, glucose, saccharose, HFCS	hepatic insulin resistance, no systemic insulin resistance
i/h	Kelishadi et al. (28)	15	–	452	2 (0.3–10)	150 g/d, 25% RDCI (40–250 gld)	–	increased fasting blood sugar
h	Ter Horst et al. (33)	14	7/14	168	1 (1–6)	+ 184 g/d, 25% RDCI (36–293 g/d)	normal diet + fructose vs. normal diet	increased plasma insulin level, hepatic insulin resistance
Fructose and NAFLD								
i	Chiu et al. (38)	7	6/7	184	4 (1–10)	182 g/d, 22% RDCI	fructose vs. starch, glucose, saccharose	no effect

Children's foods

So-called children's foods, such as tea for children or fruit purees, often contain large amounts of free sugar.

Fructose metabolism

Fructose is a more powerful sweetener than glucose and saccharose and also has a lower glycemic index than they do.

Design	Source	Studies analyzed	RCT	N	Follow-up (weeks)	Fructose dose	Control	Remarks
h	Chiu et al. (38)	6	1/6	76	3 (1–10)	+ 193 g/d, 25% RDCI (150–220 g/d)	normal diet + fructose vs. normal diet	increased hepatic fat deposition increased ALT(+ 5 U/L)
h	Chung et al. (39)	6	4/5	54	2 (1–4)	+ 3.5 g/kg/BW/d (35% RDCI)	normal diet + fructose vs. normal diet	ca. 50% increase in intrahepatic lipids
h	Chung et al. (39)	3	3/3	51	1 (1)	+ 3.5 g/kg/BW/d (35% RDCI)	normal diet + fructose vs. normal diet	mild rise of ALT (+ 5 U/L)
h	Chung et al. (39)	3	3/3	53	2 (1–4)	≈ + 30% RDCI	fructose vs. glucose	increase in intrahepatic lipids, no difference between fructose and glucose
h	Chung et al. (39)	4	4/4	98	4 (1–10)	+ 40 g/d ± 3.5 g/kg/BW/d	fructose vs. glucose	rise in AST(+ 1.15 U/l) and ALT (+ 2.06 U/L) in both groups; no difference between fructose and glucose

*Meta-analyses of trials conducted in an isocaloric setting display wide variation in fructose intake and yield no more than low-level evidence. These meta-analyses have failed to show any adverse effects. In trials conducted in a hypercaloric setting, i.e., those involving fructose intake in addition to the subjects' otherwise usual diet, adverse metabolic effects have been demonstrated. Because of the way these trials are designed, however, there is no way to determine whether the demonstrated effects are due to fructose *per se,* or rather to the associated caloric surplus. There is an overall lack of methodologically sound randomized and controlled trials under isocaloric conditions. In this table, the median fructose dose is given both in absolute terms and in relation to the RDCI, and its range is indicated in square brackets. Follow-up = median length of follow-up in weeks (range); ALT, alanine aminotransferase; AST, aspartate aminotransferase; BW, body weight; g/d, grams per day; HDL, high density lipoprotein; HFCS, high fructose corn syrup; h, hypercaloric; i, isocaloric; LDL, low density lipoprotein; n, number of subjects; NAFLD, non-alcoholic fatty liver disease; RCT, number of randomized, controlled trials included in each meta-analysis; RDCI, recommended daily caloric intake; studies included, number of studies included in each meta-analysis; x, hypocaloric trial design; y, prospective cohort studies.

although they did not evaluate the mean fructose dose (27, 28) *(Table 2)*. Finally, a Cochrane Library study found insufficient evidence for the efficacy of blood pressure reduction by drugs that lower the uric acid level (29).

In summary, there is no clear evidence that fructose adversely affects uric acid levels and arterial blood pressure under isocaloric conditions, but very large amounts of fructose can indeed affect both of these parameters adversely.

Fructose has a low glycemic index and thus does not affect the blood glucose level or the insulin level to any substantial extent. For this reason, fructose was long held to be an ideal sweetener, especially for patients with impaired glucose tolerance (30, e24). Epidemiologic data suggest an association of fructose consumption with type 2 diabetes. For example, a meta-analysis of prospective cohort studies showed that persons who drink sugary beverages several times a day are more likely to develop type 2 diabetes mellitus (relative risk: 1.26 [1.12; 1.41]) (31). Romaguera et al. found a positive association between soft drink consumption and the incidence of type 2 diabetes mellitus, even after adjusting for caloric intake and BMI (hazard ratio: 1.18 [1.06;1.32]) (32). Ter Horst et al., in a meta-analysis of trials of at least six days' duration, found that fructose consumption under isocaloric conditions led to hepatic insulin resistance (standardized mean difference [SMD]: 0.47, [0.03; 0.91]), while the consumption of fructose in a median dose of 184 g per day under hypercaloric conditions led not only to hepatic insulin resistance (SMD: 0.77, [0.28; 1.26]), but also to mildly elevated fasting insulin levels (+ 3.38 pmol/L, [0.03; 6.73 pmol/L]) (33).

There are as yet no reliable clinical data showing a clear correlation between fructose consumption and the development of type 2 diabetes mellitus, because fructose consumption in the available studies was always coupled with glucose consumption, in the form of either saccharose or high-fructose corn syrup.

Fructose and non-alcoholic fatty liver diseases

Fructose, which is metabolized mainly in the liver, is thought to be a contributing factor in the development of non-alcoholic fatty liver diseases (NAFLD). The overall category of NAFLD can be further broken down into potentially reversible non-alcoholic fatty liver (NAFL), defined by a fat concentration of more than 5% of the weight of the hepatic parenchyma, and non-alcoholic steatohepatitis (NASH), where mixed-cell inflammatory infiltrates and ballooned hepatocytes

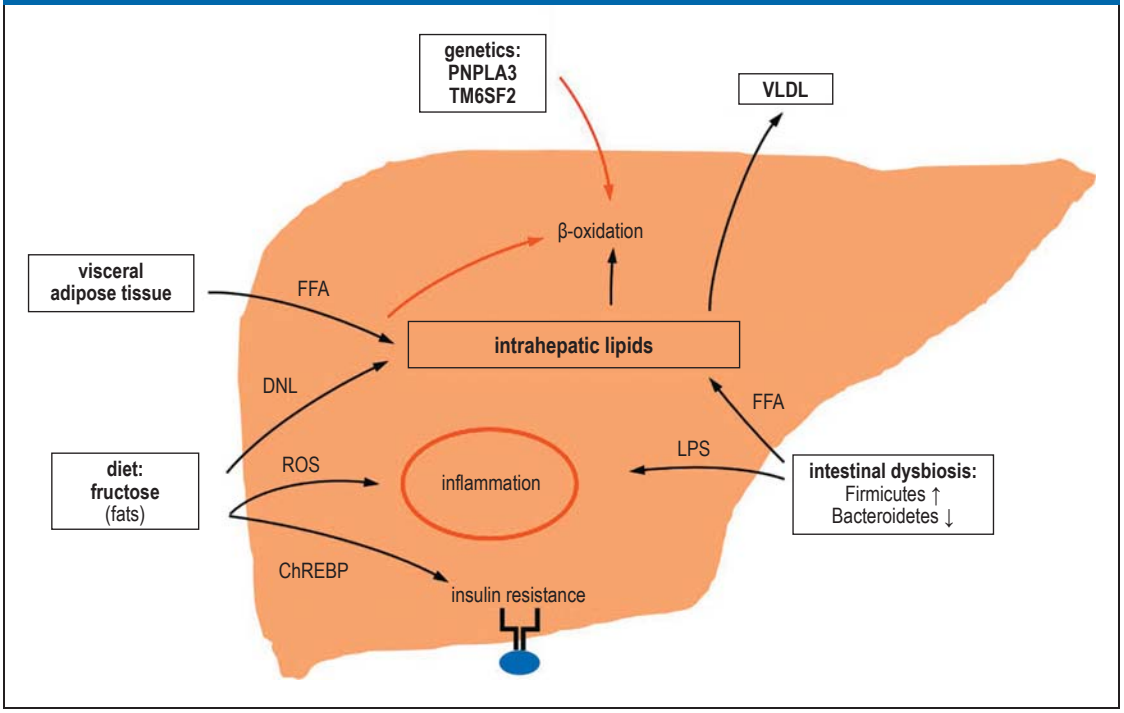
The hepatic metabolism of fructose

Most of the resorbed fructose is taken up into hepatocytes via GLUT2. The further metabolism of fructose is not subject to any negative feedback mechanism.

Fructose and obesity

Hypercaloric fructose intake with a positive caloric balance leads to overweight.

FIGURE 2



The multifactorial pathogenesis of NAFLD

Hepatic lipid accumulation due to the arrival of increased amounts of lipids in the liver is sustained by intestinal dysbiosis (dysequilibrium of the intestinal microbiota), free fatty acids from the diet, and visceral fat deposits, as well as by fructose-induced *de novo* lipogenesis. Lipid degradation via β-oxidation is inhibited by fructose metabolites and genetic predisposition. The transition from NAFLD to NASH is promoted by inflammation, which is triggered by endotoxins (LPS and others) released by the altered microbiome, as well as by reactive oxygen species (ROS) arising as by-products of fructose metabolism.
ChREBP, carbohydrate-responsive element binding protein; DNL, *de novo* lipogenesis; FFA, free fatty acids; LPS, lipopolysaccharide; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; ROS, reactive oxygen species; PNPLA3, papatin-like phospholipase domain-containing 3; TM6SF2, transmembrane 6 superfamily member 2; VLDL, very low density lipoproteins.
Figure modified from (e25).

are seen in addition (34). The prevalence of NAFLD in industrialized countries around the world is estimated at 20–30%; it is positively correlated with the metabolic syndrome and with hyperalimentation (abdominal girth, body mass index, triglyceride levels), and it can progress to cirrhosis or hepatocellular carcinoma (35, 36). Fructose is held to be a contributing factor in the development of steatosis hepatis that can itself lead to hepatic energy overload and thus also to increased amounts of fat in the hepatocytes *(Figure 2)* (e25). Retrospective data, some of which are controversial, show higher fructose consumption among patients with NAFLD, as well as an effect on the degree of fibrosis of the liver (e26–e29). In a case-control study, Abid et al. showed that 80% of the NAFLD patients consumed more than 500 mL of soft drinks per day, compared to only 17% of the normal control subjects. Soft-drink consumption was found to be a good predictor of NAFLD in their regression model (odds ratio: 2.0) (37). Two meta-analyses have dealt with the relation between fructose consumption and steatosis hepatis. Chiu et al. and Chung et al., analyzing reported trials in which fructose was given in isocaloric exchange with other carbohydrates, found no effect of fructose on intrahepatocellular fat content or on the alanine aminotransferase (ALT) level; but, in contrast, hypercaloric fructose intake (+ 25–35% of RDCI) affected both parameters adversely compared to an isocaloric diet (intrahepatocellular fat content: + 54% [29; 79%], ALT: + 4.94 U/L [0.03; 9.85]) (38, 39) *(Table 2)*. Such effects were found with the hypercaloric administration of either fructose or glucose, implying that the excessive

Fructose and lipid metabolism

Hypercaloric fructose intake leads to elevated triglyceride and uric acid levels.

Meta-analyses concerning fructose consumption

Meta-analyses of randomized controlled trials (which are heterogeneous and provide low-level evidence) have not revealed any metabolic effect of isocaloric fructose consumption with an appropriate, unchanged caloric balance.

caloric intake accounts for the observed effects (38). The informative value of meta-analyses is limited, however, by the heterogeneity of the constituent trials, the controversial state of the evidence, and the often short follow-up intervals. It cannot be stated with certainty whether fructose itself affects human metabolism adversely, or whether such effects are due solely to the excessive caloric intake when large amounts of fructose are consumed. The latter hypothesis is supported by the fact that meta-analyses have revealed adverse metabolic effects mainly in trials with a hypercaloric design.

Overview

The high prevalence of overweight and obesity associated with the metabolic syndrome is a problem around the world. In addition to lack of exercise, an important contributing cause is the consumption of large amounts of free sugars, which should be avoided in small children in particular, as their taste preferences can still be influenced. Fructose, either by itself or as a component of common household sugar, plays a special role, as it is mainly metabolized in the liver. Current evidence indicates that very high fructose consumption has adverse metabolic effects, but it remains unclear whether these are due to fructose itself or to the associated increase in caloric intake. Meta-analyses of trials conducted in an isocaloric setting have not confirmed any such effects, or any effect on steatosis hepatis and hepatocellular damage *(Table 2)*. There is a general lack of methodologically sound, prospective, randomized, and controlled clinical trials, with adequate patient numbers and a sufficient follow-up duration, with which the possible adverse effects of fructose consumption could be studied. Individual sugar consumption can be lowered by replacing sugary items such as sugared soft drinks, fruit juices, and smoothies with water as a beverage and fresh fruit *(Box)*. On the population level, health-promoting behavior can be reinforced with public information, food quality ratings, and taxes placed on products with added sugar.

Conflict of interest statement
The authors state that they have no conflict of interest.

Manuscript received on 29 April 2020 and accepted after revision on 3 October 2020.

Translated from the original German by Ethan Taub, M.D.

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The effects of large amounts of fructose

High doses of fructose are associated with adverse metabolic effects. The current state of the evidence does not allow any conclusion as to whether these effects are due to a positive caloric balance or to fructose *per se*.

The current state of the evidence

Because of the heterogeneity of the available studies and the low level of evidence that they provide, current RCTs and meta-analyses are of limited informative value. There is a lack of methodologically sound randomized and controlled clinical trials with sufficient follow-up under isocaloric conditions.

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Cite this as:
Stricker S, Rudloff S, Geier A, Steveling A, Roeb E, Zimmer KP: Fructose consumption—free sugars and their health effects. Dtsch Arztebl Int 2021; 118: 71–80. DOI: 10.3238/arztebl.m2021.0010

▶ **Supplementary material**

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Only one answer is possible per question. Please select the answer that is most appropriate.

Question 1

What does the expression "free sugars" refer to in this article?

a) all mono- and disaccharides in the diet, regardless of source
b) all monosaccharides in the diet, regardless of source
c) all mono- and disaccharides that are found naturally in dietary items or are added to processed foods
d) all mono- and disaccharides that are added to foods
e) only mono- and disaccharides found naturally in dietary items

Question 2

At present, what percentage of women and men in Germany are overweight?

a) 7% of women, 22% of men
b) 17% of women, 32% of men
c) 27% of women, 42% of men
d) 37% of women, 52% of men
e) 47% of women, 62% of men

Question 3

What type of dietary item accounts for the largest amount of free sugar intake in children?

a) beverages with added sugar
b) sweets
c) fruit juices
d) dairy products
e) raw fruit

Question 4

How does fructose differ from glucose?

a) Fructose is a less powerful sweetener.
b) Fructose has a higher glycemic index.
c) Fructose has less of an effect on the insulin level.
d) Fructose is consumed exclusively via fruit and fruit juice.
e) Fructose is not used as an additive in industrial food production.

Question 5

By means of what transporter is fructose taken up by enterocytes?

a) glucose transporter 1
b) glucose transporter 2
c) glucose transporter 3
d) glucose transporter 4
e) glucose transporter 5

Question 6

What is the key enzyme of glucose metabolism?

a) aldolase B
b) triokinase
c) fructokinase
d) phosphofructokinase
e) hexokinase

Question 7

According to recent meta-analyses, what is the consequence of high fructose intake with a positive caloric balance?

a) a lower uric acid level
b) a higher triglyceride level
c) a lower fasting blood sugar level
d) a lower intrahepatocellular fat content
e) a lower ALT level

Question 8

According to the recent meta-analyses of Chung et al. (2014) und Chiu et al. (2014), what effect does fructose consumption have with respect to NASH?

a) elevated intrahepatocellular fat content with isocaloric fructose intake
b) elevated ALT level with isocaloric fructose intake
c) elevated intrahepatocellular fat content with hypercaloric fructose intake
d) reduced ALT level with hypercaloric glucose intake
e) improved insulin sensitivity with hypercaloric fructose intake

Question 9

What is a practical way to lessen the intake of free sugars?

a) drinking water instead of sugary soft drinks and fruit juices
b) replacing sugary soft drinks with fruit juices, as these contain less sugar
c) replacing sugar with non-caloric sweeteners, as the long-term consequences of their use have been thoroughly studied and are well known
d) preferentially consuming fruit purees and smoothies, which are low in sugar
e) giving children so-called children's foods such as children's tea or fruit purees, as these contain less sugar than the usual dietary items do

Question 10

What disease is linked to high fructose consumption?

a) non-alcoholic fatty liver disease
b) type 1 diabetes mellitus
c) peripheral arterial occlusive disease
d) ischemic stroke
e) gestational diabetes

► **Participation is possible only over the internet: cme.aerzteblatt.de**

Supplementary material to:

Fructose Consumption—Free Sugars and Their Health Effects

by Sebastian Stricker, Silvia Rudloff, Andreas Geier, Antje Steveling, Elke Roeb, and Klaus-Peter Zimmer

Dtsch Arztebl Int 2021; 118: 71–80. DOI: 10.3238/arztebl.m2021.0010

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eBOX

A comparison of fructose and glucose metabolism

Fructose, unlike glucose, is taken up into enterocytes by an insulin-independent mechanism via the highly specific fructose transporter GLUT5 and then passes into the portal venous circulation. Most of the fructose resorbed in the gut is taken up by hepatocytes via GLUT2 and metabolized. The blood sugar level rises only by a small amount compared to glucose, and there is neither a compensatory insulin secretion nor a negative feedback effect on gluconeogenesis. While glucose in the liver and other peripheral tissues primarily becomes a substrate for glycolysis and thus serves as a direct energy carrier, the intermediate products of fructose metabolism are mainly used for the synthesis of triglycerides. Glycolysis, under aerobic or anaerobic conditions, is the first step of the degradation of glucose to pyruvate and is subject to a feedback mechanism involving the key enzyme phosphofructokinase-1, which impedes glycolysis in the setting of a high concentration of ATP (adenosine triphosphate) or citrate. Because fructose metabolism takes place independently of phosphofructokinase-1, there is no feedback mechanism, and there may be an accumulation of acetyl-CoA, which serves as a substrate for fatty acid synthesis. In addition, the first step of fructose metabolism consumes ATP, which, in its further catabolism, is degraded to uric acid as an end product.