REVIEW

Fructose drives *de novo* lipogenesis affecting metabolic health

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Abstract

Despite the existence of numerous studies supporting a pathological link between fructose consumption and the development of the metabolic syndrome and its sequelae, such as non-alcoholic fatty liver disease (NAFLD), this link remains a contentious issue. With this article, we shed a light on the impact of sugar/fructose intake on hepatic *de novo* lipogenesis (DNL), an outcome parameter known to be dysregulated in subjects with type 2 diabetes and/or NAFLD. In this review, we present findings from human intervention studies using physiological doses of sugar as well as mechanistic animal studies. There is evidence from both human and animal studies that fructose is a more potent inducer of hepatic lipogenesis than glucose. This is most likely due to the liver's prominent physiological role in fructose metabolism, which may be disrupted under pathological conditions by increased hepatic expression of fructolytic and lipogenic enzymes. Increased DNL may not only contribute to ectopic fat deposition (i.e. in the liver), but it may also impair several metabolic processes through DNL-related fatty acids (e.g. beta-cell function, insulin secretion, or insulin sensitivity).

Key Words

- sugar
- glucose
- fructose
- *de novo* lipogenesis
- fatty acids

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Introduction

Metabolic health is at risk in societies with an excess supply of energy-dense palatable food and drinks and an everyday life with low physical activity. There is a global epidemic of metabolic syndrome (Saklayen 2018), which includes obesity (particularly visceral adipose tissue accumulation), dyslipidemia, impaired glucose tolerance, and hypertension. Importantly, this syndrome not only affects adults but also children and adolescents, in particular in developing countries (Noubiap *et al.* 2022). Similarly, the prevalence of non-alcoholic fatty liver disease (NAFLD), the hepatic manifestation of the metabolic syndrome, is increasing (Moore 2010, Sahota *et al.* 2020, Riazi *et al.* 2022). The metabolic syndrome, with all of its associated comorbidities, not only burdens the affected individual but also the public health care system (Boudreau *et al.* 2009).

It is commonly acknowledged that an increased body weight, associated with a positive energy balance, is a major trigger for the development of metabolic diseases. It is assumed, however, that factors other than an imbalanced energy intake and expenditure can influence metabolic health. A well-balanced macronutrient intake, characterized by a moderate fat and carbohydrate intake, with a focus on sugar restriction, is regarded as an important component of a healthy diet. A high intake of added sugars, and in particular of fructose – which is often present in a typical western diet – is considered to be a principal factor promoting metabolic derangements

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(Lim *et al.* 2010, Jensen *et al.* 2018). Despite numerous studies, it is still debated whether the metabolic effects of added sugars are mediated by excess energy intake/weight gain or whether fructose and glucose affect metabolism differently and independently of excess caloric intake. This review aims to shed a light on the current literature regarding this question.

Sugar consumption and its effects

Current recommendations

To reduce the risk of developing obesity and metabolic diseases, the World Health Organization recommends that adults and children consume less than 10% (preferably less than 5%) of their energy needs from free sugar (WHO 2015). Importantly, free sugars include monosaccharides and disaccharides added to food and beverages as well as sugars naturally present in honey, syrups, fruit juices, and fruit juice concentrates. Recent studies on sugar intake in Europe, Latin America, and the USA found that mean sugar intakes in most countries were higher than the recommended intake (Fisberg *et al.* 2018, Löwik 2021, DiFrancesco *et al.* 2022). As a consequence, measures to reduce sugar intakes such as better food labeling or taxes on sweetened food are discussed or already implemented in many countries.

Dietary glucose and fructose

Glucose and fructose are stereoisomers. Fructose displays a higher sweetening power compared to glucose (Moskowitz 1970). Fructose and glucose occur naturally as monosaccharides in fruits and honey but also as sucrose (a disaccharide consisting of glucose and fructose). Other sugar sources include table sugar (sucrose) or high-fructose corn syrup (HFCS) (a mixture of fructose and glucose), concentrated fruit juices, agave or maple syrup, and so on. Sugar added to food and beverages as sweeteners are termed 'added sugars'. Importantly, the digestion/absorption of sugar from fruits is much slower than that of beverages and thus is unlikely to be associated with any negative effects. Unfavorable metabolic effects are particularly induced by beverages containing high amounts of free sugar that are rapidly absorbed, as detailed below. HFCS is manufactured industrially from corn starch through the isomerization of glucose to fructose. The proportion of fructose varies between 42 and 90% in HFCS (Serna-Saldivar 2016). HFCS with 42% fructose is widely used as a sweetener in processed foods, whereas HFCS with 55% fructose is commonly used in beverage production (Kay Parker 2010). HFCS was first introduced to the market in the USA in the 1970s, and it is now a significant US export product, particularly to developing countries. The average fructose intake increased since the 1970s in the USA (Tappy & Lê 2010). HFCS is a cheap sweetener used in the food and beverage industries, and its consumption is linked to the occurrence of type 2 diabetes (Kmietowicz 2012) and other metabolic diseases, as described below.

Sugar-sweetened beverage consumption is a risk factor for cardiometabolic diseases

A major source of added sugars are sugar-sweetened beverages (SSBs) (Johnson *et al.* 2009, Malik & Hu 2022). Their consumption has been linked not only to the development of obesity but also to its complications such as type 2 diabetes, NAFLD, and cardiovascular disease (Malik & Hu 2022). Prospective cohort studies from the USA and the UK found an association between high SSB consumption and an increased risk of type 2 diabetes independently of obesity (Imamura *et al.* 2015). Similarly, studies confirmed that habitual SSB consumption is associated with a dose-dependent increase in the risk of dyslipidemia and coronary heart disease (Te Morenga *et al.* 2014, Yin *et al.* 2021). Importantly, studies showed that habitual SSB consumption has a dose-dependent effect on the risk of NAFLD (Ouyang *et al.* 2008, Chen *et al.* 2019) and that SSB intake in early childhood is associated with the later development of hepatic steatosis in adulthood (Sekkarie *et al.* 2021). In addition to metabolic abnormalities, there is evidence of a link between SSB consumption and breast cancer, pancreatic and prostate cancer, and colorectal cancer (Malik & Hu 2022).

Worldwide, SSB intake is still rising (Singh *et al.* 2015, Malik & Hu 2022). However, regional differences regarding SSB consumption are striking. Overall, SSB intake is highest in men and women in Latin America and the Caribbean (average SSB intake about 325 g/day), where it has been rising for decades. In contrast, SSB intake in western high-income countries has stabilized since the 1990s at around 150–200 g/day (Malik & Hu 2022). In Asian countries, SSB consumption is remarkably low (the average intake of SSB is about 30 g/day). Given these data on global SSB consumption, the global burden of obesity and chronic diseases for societies is likely to rise further, particularly in developing countries.

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A specific role for fructose in the etiology of cardiometabolic diseases?

Differences between fructose and glucose metabolism

Although high sugar consumption is recognized as a risk factor for cardiometabolic diseases, the debate over whether the fructose component of consumed sugar plays a specific role in the etiology of such diseases is still ongoing. This question cannot be easily assessed by epidemiologic studies as fructose is rarely ingested in a pure form but mostly co-ingested with glucose.

There are important differences regarding the cellular absorption and distribution of glucose and fructose (Maruhama & Macdonald 1973). Fructose is primarily absorbed via facilitated diffusion via glucose transporter 5 (GLUT5) (Burant *et al.* 1992), which is expressed on epithelial intestinal cells, whereas glucose is absorbed via sodium-glucose-cotransporter 1, an active transporter (Gorboulev *et al.* 2012). A proportion of fructose is directly metabolized into glucose in enterocytes. However, when large amounts of fructose are consumed (e.g. when consuming SSB), fructose spills over to the liver and large intestine (Jang *et al.* 2018) (Fig. 1). Fructose and glucose enter the circulation via GLUT5 and GLUT2, respectively (Koepsell 2020). Following that, the liver, which is the primary site of fructose metabolism, extracts a large portion of it (Mendeloff & Weichselbaum 1953). However, it can also be metabolized by the kidney, skeletal muscle, and adipose tissue. Hesley *et al.* (2020) provided a thorough review of tissue-specific fructose metabolism. In contrast, glucose is taken up and metabolized by most

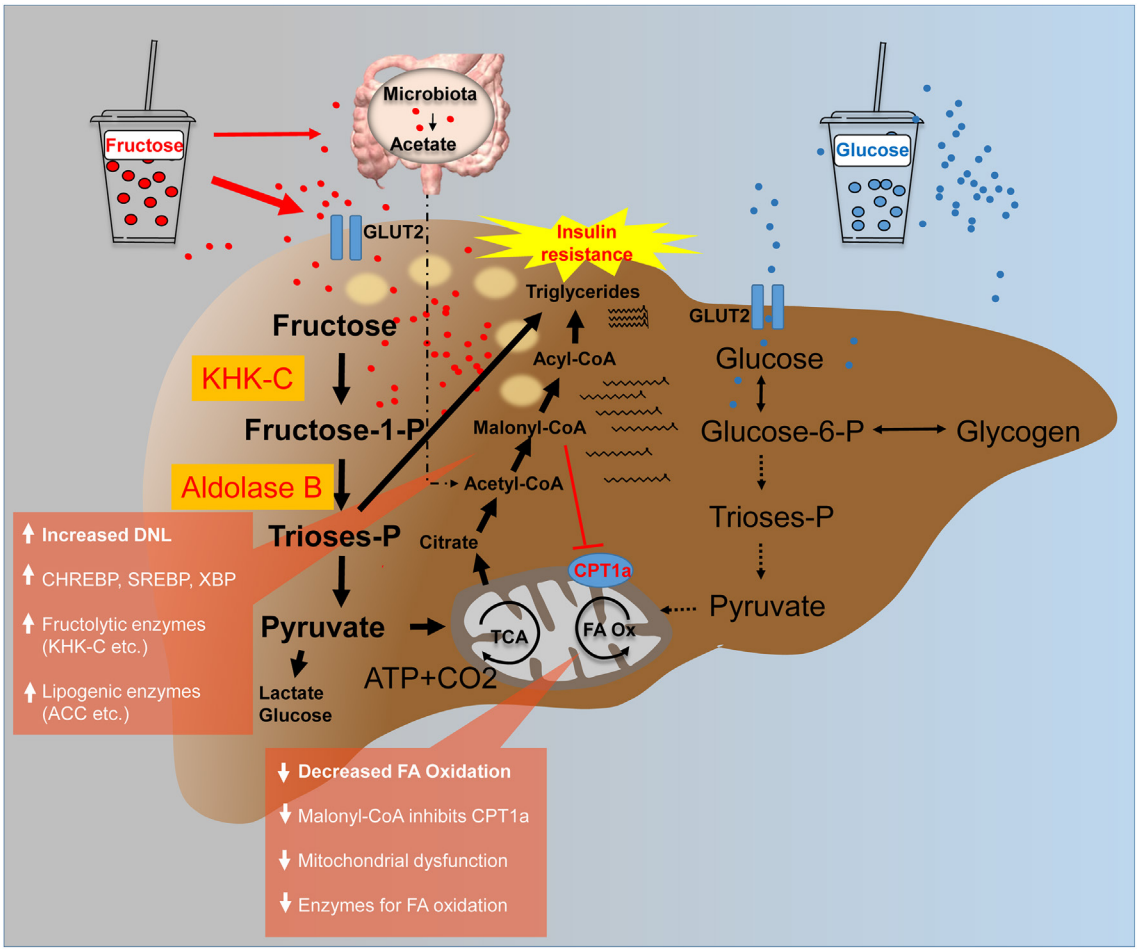

Figure 1
A comparison of the hepatic fructose (left) and glucose (right) metabolism after consumption of high loads of sugar in the form of SSB. It is hypothesized that an increased *de novo* lipogenesis after fructose intake in parallel with a decreased fatty acid oxidation leads to hepatic fat deposition. ACC, acetyl-CoA-carboxylase; ATP, adenosine triphosphate; CPT1a, carnitine palmitoyltransferase 1A; FA, fatty acid; GLUT, glucose transporter; KHK-C, ketohexokinase-C; Ox, oxidation; P, phosphate; SSB, sugar-sweetened beverage; TCA, tricarboxylic acid cycle.

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mammalian tissues (Thorens & Mueckler 2010). The majority of glucose is taken up by the liver and muscle and stored as glycogen – processes that require insulin. Further amounts of glucose are metabolized by the brain, adipose tissue, and the kidney (Gerich 2000). Following cellular uptake, fructose and glucose are phosphorylated at different rates by specific kinases. Fructokinase is expressed as the two isoforms ketohexokinase-A (KHK-A) and KHK-C. KHK-C is primarily expressed in the liver, but it is also found in the kidney and intestines, whereas KHK-A is more widely expressed (Diggle *et al.* 2009). KHK-C drives hepatic fructose uptake by phosphorylating fructose at a very high rate without feedback inhibition, resulting in a flux of fructose toward the liver (Ishimoto *et al.* 2012) (Fig. 1). Glucose is phosphorylated by glucokinase (GK). Importantly, the phosphorylation rate of KHK is 10 times higher than that of GK. Phosphorylated fructose is cleaved into trioses and enters the glycolytic pathway. Fructose is mainly metabolized into lactic acid and converted to glucose or hepatic glycogen and lipids (Chong *et al.* 2007, Parks *et al.* 2008). Notably, fructose absorption is increased when it is co-ingested with glucose (Rumessen & Gudmand-Høyer 1986). Furthermore, animal studies have shown that consuming high amounts of fructose increases the expression of fructolytic and gluconeogenic enzymes and expands the intestinal cell surface, which improves nutrient absorption (Patel *et al.* 2015*a*, Taylor *et al.* 2021).

Metabolic effects of regular sugar/fructose intake

Traditionally, easily measurable outcome parameters of known clinical significance (cardiovascular risk markers), such as fasting glucose, insulin, c-peptide, insulin sensitivity/resistance, or serum lipids, are measured for the risk assessment of dietary products regarding metabolic health. However, when metabolic health is defined just as the presence of ideal levels of these markers, fine metabolic changes may be missed. As a result, studies used more subtle outcome parameters to investigate how moderate sugar intake affects the metabolism of healthy men. Indeed, they provide evidence that consumption of SSB containing fructose in moderate amounts leads to metabolic derangements such as decreased hepatic insulin sensitivity (reflected by impaired suppression of glucose production during euglycemic–hyperinsulinemic clamps) (Aeberli *et al.* 2013), induces a shift toward a more atherogenic low-density lipoprotein (LDL) subclass distribution (Aeberli *et al.* 2011) in healthy men, or increases hepatic lipogenic activity (Geidl-Flueck *et al.* 2021).

The latter, an increased *de novo* lipogenesis (DNL), is supposed to be linked to various metabolic complications/perturbations. As a result, the following section focuses on metabolic interactions between dietary sugars, specifically fructose and DNL.

De novo lipogenesis in health and disease

De novo lipogenesis (DNL) converts excess dietary carbohydrates (CHO) into fatty acids (FAs). FAs are formed during this process from acetyl-CoA molecules generated directly from CHO catabolism (i.e. glycolysis or fructolysis) or acetate generated by microbiota fructose fermentation (Zhao *et al.* 2020). DNL necessitates the expression of lipogenic pathway enzymes by various cell types, particularly white adipocytes and hepatocytes. DNL contributes to the maintenance of glucose homeostasis. A healthy balance of hepatocyte and adipocyte DNL is essential for maintaining systemic insulin sensitivity (Song *et al.* 2018). The master transcription factors sterol-responsive element-binding protein-1 (SREBP-1) induced by CHO intake/insulin signaling and carbohydrate responsive element-binding protein (ChREBP) stimulated by CHO intake regulate the expression of lipogenic enzymes. DNL provides FA for the structural maintenance of the cells, allows storage of energy from CHO beyond the glycogen store (thus contributing to glucose homeostasis), and regulates FA oxidation.

The process of FA synthesis in the liver has been identified as being of particular interest in the etiology of the metabolic syndrome as well as a specific feature of NAFLD (Donnelly *et al.* 2005, Lambert *et al.* 2014, Imamura *et al.* 2020). Clinical studies showed that DNL is increased in subjects with increased hepatic fat content (isotope approaches) (Diraison *et al.* 2003, Lambert *et al.* 2014). Furthermore, DNL was found to be positively related to intrahepatic triglyceride (TAG) levels (Diraison *et al.* 2003, Lambert *et al.* 2014) and negatively related to hepatic and whole-body insulin sensitivity (Smith *et al.* 2020). DNL is supposed to increase intrahepatic fat both by providing FA for TAG synthesis and by inhibiting FA oxidation promoting the re-esterification process. Importantly, accumulating intermediates (i.e. malonyl-CoA) inhibit FA import into the mitochondria and thus FA oxidation (McGarry *et al.* 1977, Cox *et al.* 2012). Furthermore, a clinical study (crossover) showed that an increase in DNL induced by a diet high in simple sugars correlates with triglyceridemia both in lean and in obese subjects (Hudgins *et al.* 2000). In addition, increased concentrations of DNL-related FAs (i.e. palmitate 16:0) have been linked to the

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metabolic syndrome in observational and interventional studies (Vessby 2003). Mechanistic *in vitro* studies suggest that palmitate impairs beta-cell function via ceramide formation, causing endoplasmic reticulum stress, and induces the apoptotic mitochondrial pathway (Maedler *et al.* 2001, Maedler *et al.* 2003, Cunha *et al.* 2008). Other studies revealed that palmitate stimulates interleukin-6 expression, a mechanism involved in the pathogenesis of insulin resistance and vascular inflammation (Rotter *et al.* 2003, Staiger *et al.* 2004, Weigert *et al.* 2004, Testa *et al.* 2006, Korbecki & Bajdak-Rusinek 2019). Therefore, from a clinical perspective, DNL may serve as a valuable marker for the development of cardiometabolic disease beyond hepatic lipid accumulation/NAFLD.

The impact of macronutrients on DNL – insights from human intervention studies

Regarding the question of how different macronutrients impact metabolic health, early human studies compared the effects of diets with different carbohydrate and fat intake on metabolic outcomes. Later, the effects of different forms of carbohydrates were compared (e.g. simple sugars vs complex carbohydrates or different types of sugar) in studies with children or adults, with or without obesity/metabolic disease. Interventions aimed at increasing sugar/fructose consumption, e.g. by SSB intake or decreasing sugar/fructose intake by prescription of sugar/fructose restriction (Donnelly *et al.* 2005, Lambert *et al.* 2014). Finally, they all contribute to the understanding of the relationship between CHO intake and metabolic complications in general as well as the relative importance of fructose and glucose. Importantly, studies on the effects of sugar consumption on DNL are rarely comparable due to significant differences in the study populations, interventions, and/or methods used. (Studies discussed below are summarized in Table 1).

Of note, the process of hepatic DNL is assessed by applying different methods that all analyze FA bound to very low-density lipoproteins (VLDL). They range from calculating FA desaturation indices to calculating the percentage of surrogate FA for newly formed FA (i.e. palmitate) in total FA to labeling newly formed FA with isotopes to calculate fractional DNL or fractional secretion rates of *de novo* synthesized FAs (Hellerstein *et al.* 1991). Measurement of DNL by isotope labeling methodology is considered the gold standard. However, it is costly and thus only appropriate for studies with small sample sizes.

Initially, it was assessed by Hudgins *et al.* how the fat and CHO content of a diet impacts hepatic DNL in healthy men. Subjects were randomly assigned to either an eucaloric liquid high-fat diet (40% of calories as fat and 45% as glucose polymers, $n=3$) or a high-CHO diet (10% of calories as fat and 75% as glucose polymers, $n=7$) for 25 days. DNL was increased in men on a high-CHO diet after 10 days, reflected as palmitate-enriched, linoleate-deficient VLDL triglycerides, and palmitate synthesis (mass isotopomer distribution analysis (MIDA) of palmitate labeled with 13C-acetate) was increased after 25 days compared to the high-fat diet (Hudgins *et al.* 1996).

In a later study, Schwarz *et al.* (2015) compared the effects of a high-fructose (25% energy content), weight-maintenance diet to those of an isocaloric diet with the same macronutrient distribution but complex carbohydrates (CCHO) substituted for fructose (crossover design, $n=8$). Importantly, fructose was provided as beverages, whereas complex carbohydrates were provided as solid food. After 9 days of intervention, high-fructose intake was associated with higher fractional hepatic DNL (MIDA of palmitate labeled with 13C-acetate) compared to the diet in which fructose was replaced by CCHO (Schwarz *et al.* 2015). Stanhope *et al.* (2009) investigated the effects of glucose and fructose consumption on hepatic DNL in obese subjects after 10 weeks of consumption of glucose- or fructose-sweetened beverages providing 25% of energy requirements. Postprandial DNL was increased after fructose consumption (MIDA of palmitate labeled with 13C-acetate) (Stanhope *et al.* 2009).

The effects of different hexoses on hepatic DNL were investigated by Parks *et al.* (2008). Healthy subjects ($n=6$) were challenged with sweetened beverages (85 g sugar) containing pure glucose (100:0) or mixtures of fructose and glucose (50:50 or 75:25) on three separate occasions in a random and blinded order. The beverages containing fructose stimulated DNL more potently compared with the beverages containing pure glucose (MIDA of palmitate labeled with 13C-acetate) (Parks *et al.* 2008).

Aside from the postprandial effect of fructose consumption on DNL which has been studied extensively, the effect of regular fructose consumption on basal hepatic lipogenic activity is of interest. Formation of new FAs requires both the expression of lipogenic enzymes and the availability of substrate (acetyl-CoA). FA synthesis, as measured by a constant infusion of glucose (as a substrate for FA synthesis) and 13C-acetate, reflects hepatic lipogenic activity, which is determined by lipogenic enzyme expression. Thus, in such a setting, differences regarding absorption rates of different sugar types do not influence the measurement. The effect of daily SSB consumption on liver lipogenic activity was studied in 94 healthy men by

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Table 1 Overview of studies measuring the effects of dietary interventions on hepatic DNL by tracer methodology.

Intervention	Duration	Subjects	*N*	DNL measurement	Result	Reference
Eucaloric liquid formula diets –Low-fat diet (10% of calories as fat and 75% as glucose polymers) –High-fat diet (40% of calories as fat and 45% as glucose polymers)	25 days	Healthy men and women Younger adults Normal weight	10	Postprandial DNL labeling of palmitate with 13C-acetate, MIDA; linoleate dilution method	Dietary substitution of carbohydrate (CHO) for fat stimulates the hepatic fatty acid synthesis	Hudgins *et al.* (1996)
Isocaloric diets with the same macronutrient composition –High-fructose diet (25% caloric intake; beverage) –Complex CHO (solid) diet (replaced fructose)	9 days	Healthy men All age groups Normal weight	8	Postprandial DNL Labeling of palmitate with 13C-acetate, MIDA	High-fructose diet is associated with higher hepatic DNL	Schwarz et al. (2015)
Daily SSB consumption (25% of required caloric intake provided as SSB; 8-week outpatient intervention with *ad libitum* diet, 2-week energy-balanced inpatient intervention) –Glucose-SSB –Fructose-SSB	10 weeks	Men and women Middle-aged Overweight/obese	32	Postprandial DNL Labeling of palmitate with 13C-acetate, MIDA	High fructose increases hepatic DNL	Stanhope *et al.* (2009)
Beverage consumption containing glucose (GLC) and/or fructose (FRC) –100:0 GLC:FRC –50:50 GLC:FRC –25:75 GLC:FRC	Single exposure	Healthy men and women Younger adults Normal weight	6	Postprandial DNL Labeling of palmitate with 13C-acetate, MIDA	Acute intake of fructose stimulates hepatic lipogenesis	Parks *et al.* (2008)
Daily SSB (3×0.2 L SSB/day equivalent to 80g sugar intake/day) consumption or SSB abstinence –Glucose–SSB –Fructose–SSB –Sucrose–SSB	6 weeks	Healthy men Younger adults Normal weight	94	Basal DNL Labeling of palmitate with 13C-acetate, MIDA	Fructose and sucrose increase basal hepatic lipogenic activity	Geidl-Flueck *et al.* (2021)
Dietary sugar restriction –Low free sugar diet –'Usual' diet	8 weeks	Obese boys with NAFLD	29	Labeling of palmitate with $2H_2O$, MIDA	Dietary sugar restriction reduces hepatic DNL	Cohen *et al.* (2021)
Isocaloric fructose restriction –Starch substituted for sugar (reduced caloric intake from fructose from 12% to 4% of total energy intake)	9 days	Children (male and female) with obesity and metabolic syndrome and habitual high sugar consumption (fructose intake >50 g/day)	41	Postprandial DNL Labeling of palmitate with 13C-acetate, MIDA	Isocaloric fructose restriction decreases hepatic DNL	Schwarz *et al.* (2017)

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providing daily glucose, fructose, or sucrose-containing drinks (3×0.2 L SSB/day resulting in a sugar intake of 80g/day) in a randomized way during 6 weeks. The study with SSB consumption in a close to real-life setting showed that fructose and sucrose, but not glucose, increased the basal lipogenic activity of the liver (MIDA of palmitate labeled with 13C-acetate) ($n=94$, randomized controlled trial (RCT)) as compared to a control group. This is most likely due to fructose-containing beverages causing an increase in the expression of lipogenic genes in the liver (Geidl-Flueck *et al.* 2021).

Further studies assessed and clarified the role of DNL in fructose-induced hypertriglyceridemia and whether physical activity prevents hypertriglyceridemia. Egli *et al.* examined healthy subjects ($n=8$) after 4 days of either a weight-maintaining low-fructose diet (control), a high-fructose diet with low physical activity, or a high-fructose diet with high physical activity. Fasting and postprandial TAG and 13C-palmitate in triglyceride-rich lipoproteins were increased after a high-fructose diet compared to control after an oral challenge with 13C-fructose. Those parameters remained unchanged after the high-fructose/high physical activity intervention, indicating that sport protects against fructose-induced triglyceridemia. The underlying mechanism induced by physical activity (i.e. reduced DNL from fructose or improved TAG clearance) was not resolved by this study. The same authors also tested the hypothesis that exercise prevents a fructose-induced rise in VLDL triglycerides (VLDL-TGs) by decreasing fructose conversion into glucose and VLDL-TGs and fructose carbon storage into hepatic glycogen and lipids (Egli *et al.* 2016). Eight healthy men were placed on a weight-maintenance high-fructose diet (SSB) for 4 days before the metabolic fate of 13C-labeled fructose with or without physical activity was investigated. Exercise increased fructose oxidation. However, it did not abolish fructose conversion into glucose or did not prevent DNL (AUC of VLDL-13C palmitate). These findings imply that fructose-induced DNL occurs regardless of the degree of saturation of other fructose metabolism pathways.

So far, studies that assessed the effect of increased CHO/sugar/fructose consumption on DNL were discussed. Overall, findings from various clinical studies indicate that carbohydrates, particularly when consumed as simple sugars and in liquid form, promote hepatic lipogenesis even when maintenance dietary interventions are used. Furthermore, studies using fructose and glucose interventions revealed that fructose is a more potent inducer of hepatic lipogenesis than glucose.

In addition to these findings, some studies deal with the question of how a reduction/restriction of sugar/fructose consumption impacts DNL.

There is evidence that a general dietary sugar restriction (which also leads to a reduction in fructose intake) results in lower DNL. A link between free sugar consumption and DNL was confirmed by Cohen *et al.* (2021) who conducted a trial with adolescent boys suffering from NAFLD. A low-sugar diet for 8 weeks reduced DNL (and hepatic fat content) compared to their usual diet, as measured by a lower percentage of newly synthesized palmitate in plasma TAG (labeled with deuterated $2H_2O$) (Cohen *et al.* 2021) ($n=29$, RCT). Similarly, Schwarz *et al.* (2017) demonstrated in a study with obese children that restricting sugar/fructose intake for 9 days reduced hepatic DNL (fractional DNL after a test meal containing 13C-acetate) ($n=41$). In this study, dietary sugars were substituted by complex carbohydrates.

Both intervention studies that increased sugar/fructose intake and those that reduced fructose intake provide evidence that sugar/fructose intake influences hepatic DNL. Importantly, the few studies that specifically assessed the effects of different hexoses (i.e. glucose and fructose) support the hypothesis that fructose is a more potent inducer of lipogenesis than glucose (Parks *et al.* 2008, Geidl-Flueck *et al.* 2021).

Fructose vs glucose metabolism – mechanistic insights from animal studies

Insights into mechanisms underlying the differences in glucose and fructose metabolism were gained from animal studies (Maruhama & Macdonald 1973, Geidl-Flueck & Gerber 2017). Several important transcription factors control carbohydrate metabolism. We focus on the role of ChREBP (Yamashita *et al.* 2001) and SREBP-1 (Wang *et al.* 1994) in the regulation of CHO flux. They regulate glycolytic and fructolytic gene expression, as well as the expression of lipogenic genes. Glucose and fructose, to varying degrees, stimulate their expression and activity. Importantly, the expression of both transcription factors is increased in the livers of NAFLD patients (Kohjima *et al.* 2007, Benhamed *et al.* 2012).

ChREBP is most strongly expressed in the liver, white and brown adipose tissue, and also the small intestine and muscle (Iizuka *et al.* 2004). Lipogenic enzyme expression is reduced in mice with a genetic deletion of the ChREBP transcription factor (Iizuka *et al.* 2004). They display an impaired glucose tolerance as a consequence

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of reduced glucose disposal. ChREBP deletion shifts the flux from excess CHO to glycogen storage. It increases glycogen content in the liver and reduces the hepatic fat content. ChREBP-knockout animals are fructose intolerant due to decreased expression of fructolytic and lipogenic enzymes, resulting in death when fed high-sugar diets. Liver-specific knockout of ChREBP in mice (L-ChREBP$^{-/-}$) results in reduced SREBP1c at RNA and protein levels, suggesting that both transcription factors coordinately regulate lipogenic gene expression (Linden *et al.* 2018).

Feeding studies revealed that fructose induces hepatic ChREBP and its targets more potently than glucose (Koo *et al.* 2009, Kim *et al.* 2016, Softic *et al.* 2016, Softic *et al.* 2017). Further, it is also activated by glycerol that is generated during fructolysis. As a result, ChREBP activation is thought to be related to hexose- and triose-phosphate levels (Kim *et al.* 2016).

SREBP is expressed in different isoforms. SREBP-1c induces lipogenic gene expression in response to carbohydrate feeding. SREBP1c mRNA expression is regulated by the TOR signaling pathway and the insulin signaling pathway. For full induction of SREBP-1c expression as well as for its translocation to the nucleus, hepatic insulin signaling is required (Haas *et al.* 2012). In mice, a high-fructose diet induces SREBP-1c expression more potently than a standard chow diet.

Furthermore, mechanistic studies provided evidence that fructose reduces hepatic FA oxidation by different mechanisms. One early *in vitro* study found that fructose, as a competing substrate for oxidation, inhibits long-chain FA oxidation (Prager & Ontko 1976). A further study showed that fructose feeding reduces the expression of peroxisome proliferator-activated receptor and FA oxidation enzymes (Nagai *et al.* 2002). Furthermore, fructose feeding raises malonyl-CoA levels (which inhibits transport of FA by CPT1a into the mitochondria), causes mitochondrial dysfunction (reduced mitochondrial size and protein mass, specifically FA oxidation pathway proteins and CPT1a levels), and increases acetylation of mitochondrial proteins in mice (Softic *et al.* 2019).

The levels of expression of fructolytic pathway enzymes determine the relative contribution of tissues to fructose metabolism. KHK-C is considered to be a key enzyme in fructose metabolism phosphorylating fructose at a high rate as described above. KHK-C is highly expressed in hepatocytes (Diggle *et al.* 2009), but it is also found in the intestine, adipose tissue, kidney, and pancreas (Ishimoto *et al.* 2012). KHK-C knockout mice fail to metabolize fructose, leading to high-fructose concentrations in the blood and urine (Patel *et al.* 2015*b*). Both KHK-C deletion and KHK-C blockade protect against fructose-induced metabolic perturbations (Patel *et al.* 2015*b*, Lanaspa *et al.* 2018, Softic *et al.* 2019). Deletion of the KHK-A isoform exacerbates fructose-induced metabolic syndrome probably due to an increased fructose supply to the liver (Ishimoto *et al.* 2012).

Clinical studies show that patients with NAFLD have increased expression of KHK-C in the liver (Ouyang *et al.* 2008) and that inhibiting KHK-C reduces liver fat in NAFLD (Kazierad *et al.* 2021).

Possible mechanisms by which sugar/fructose consumption impacts fat distribution/deposition

Ectopic fat deposition is linked to metabolic syndrome and NAFLD and is thought to be exacerbated by a high sugar intake (Ma *et al.* 2016). It is suggested that lipid deposition is promoted by CHO-induced DNL that reduces FA oxidation and by alterations of FA flux. A meta-analysis of randomized controlled trials demonstrated that high-sugar (fructose or sucrose) hypercaloric diets increased liver and muscle fat in comparison to eucaloric control diets (Ma *et al.* 2016). Of course, data from studies that used 'close to real-life interventions' with high but not excessive sugar intake would provide the most relevant information about the effects of sugar consumption on fat distribution in individuals. A study by Maerks *et al.* compared the effects of SSB containing sucrose to those of isocaloric milk and a non-caloric soft drink (one liter of drink/day for 6 months) on ectopic fat deposition. Consumption of sucrose-containing SSB for 6 months increases not only hepatic fat content but also muscle and visceral fat in obese subjects, whereas no such effects were observed in the other groups (Maersk *et al.* 2012). However, studies that specifically compare the impact of different types of sugars on fat distribution are scarce (Lecoultre *et al.* 2013). Stanhope *et al.* compared the effects of fructose and glucose-sweetened beverages on body fat distribution in subjects with obesity by quantification of subcutaneous, visceral, and abdominal fat. Consumption of fructose- but not glucose-sweetened beverages (providing 25% of energy requirements) for 10 weeks significantly increased visceral abdominal fat (Stanhope *et al.* 2009). In contrast, glucose consumption increased subcutaneous fat. Data about a fat deposition in

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the liver and muscle were not collected. In a later study, Schwarz *et al.* used magnetic resonance spectroscopy to investigate the effects of a high-fructose weight-maintenance diet on liver fat. They discovered that 9 days of a high-fructose diet (25% energy content) increased both liver fat and DNL (Schwarz *et al.* 2015). Different mechanisms underlying fat deposition have been suggested that implicate fructose. It is hypothesized that fructose consumption reduces FA oxidation more than glucose consumption and that fructose consumption raises cortisol levels, promoting visceral adiposity and/or lipid deposition in the liver. Cox *et al.* investigated the effects of SSB consumption on substrate utilization and energy expenditure in subjects with obesity. They found that the intake of fructose, but not glucose, reduced resting energy expenditure and postprandial fat oxidation while increasing postprandial carbohydrate oxidation. This finding suggests that lipid deposition may result from sparing FA from oxidation. DiNicolantonio *et al.* proposed that fructose plays a specific role in visceral fat deposition via glucocorticoid-mediated mechanisms (DiNicolantonio *et al.* 2018). Visceral fat is known to accumulate under pathological conditions where cortisol levels are increased, such as Cushing's syndrome. Fructose consumption is thought to raise cortisol levels by promoting inflammatory processes in adipose tissue and stimulating the hypothalamus, resulting in the release of corticotropin-releasing factor. Cortisol increases the flux of FA from subcutaneous adipose tissue to visceral fat depots, impairing organ function (DiNicolantonio *et al.* 2018) and leading to an unfavorable fat distribution in lean individuals, i.e. a body shape described as thin outside, fat inside, which is associated with an increased risk for the metabolic syndrome (DiNicolantonio *et al.* 2018). Taken together, studies provide evidence that fructose and sucrose consumption promote ectopic fat deposition associated with an increased risk for metabolic disease and cardiovascular events (Gruzdeva *et al.* 2018). This is most likely due to a simultaneous increase in DNL and decrease in FA oxidation, but it could also be due to increased FA flux from subcutaneous adipose tissue to other tissues (visceral fat and the liver).

Conclusions

A high intake of free sugar as SSB increases the risk of obesity, cardiometabolic diseases, and NAFLD. A central role must be attributed to fructose in the development of these diseases. It is not only a strong inducer of DNL, but it is also a known cause of ectopic fat deposition by reducing fat oxidation and increasing FA flux to visceral fat and the liver. Most importantly, fructose-specific effects occur independently from overfeeding in healthy subjects. There are several mechanisms by which high-fructose consumers increase fructose absorption and catabolism in the liver, exacerbating the metabolic effects. Sugar/fructose consumption should be reduced to avoid these unfavorable metabolic adaptations.

Declaration of interest
The authors declare no conflict of interests regarding this work.

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