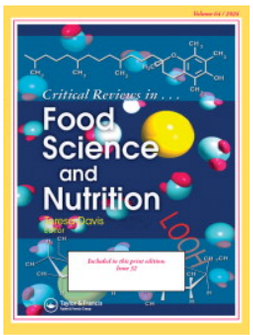

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REVIEW ARTICLE

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Dietary fructose: from uric acid to a metabolic switch in pediatric metabolic dysfunction-associated steatotic liver disease

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ABSTRACT

Fructose consumption in pediatric subjects is rising, as the prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH). Despite increasing evidence supporting the detrimental effects of fructose in the development of Metabolic Syndrome (MetS) and its related comorbidities, the association between fructose intake and liver disease remains unclear, mainly in youths. The current narrative review aims to illustrate the correlation between fructose metabolism and liver functions besides its impact on obesity and MASLD in pediatrics. Fructose metabolism is involved in the liver through the classical lipogenic pathway *via* de novo lipogenesis (DNL) or in the alternative pathway *via* uric acid accumulation. Hyperuricemia is one of the main features of MALSD patients, underlining how uric acid is growing interest as a new marker of disease. Observational and interventional studies conducted in children and adolescents, who consumed large amounts of fructose and glucose in their diet, were included. Most of these studies emphasized the association between high fructose intake and weight gain, dyslipidemia, insulin resistance, and MASLD/MASH, even in normal-weight children. Conversely, reducing fructose intake ameliorates liver fat accumulation, lipid profile, and weight. In conclusion, fructose seems a potent inducer of both insulin resistance and hepatic fat accumulation.

KEYWORDS

Metabolic syndrome; fructose; MASLD; pediatric; uric acid

Introduction

According to the World Health Organization, nearly 60% of adults and approximately 30% of children are affected by overweight and obesity (WHO European Regional Obesity Report 2022). The prevalence of these conditions is on the rise among 5 to 9-year-olds, with 11.6% and 29.5% of children experiencing obesity and overweight, respectively. Conversely, in the 10 to 19-year age group, a slight decrease has been recorded, with 7.1% of children facing obesity and 24.9% grappling with overweight. This chronic condition is more prevalent in Mediterranean countries for both age groups. Moreover, over 1.2 million deaths occur annually in Europe, accounting for more than 13% of the total deaths, and are attributed to comorbidities related to obesity. Additionally, overweight and obesity amplify the risk of disability, contributing to 7% of the total years lived with disability in Europe (WHO European Regional Obesity Report 2022).

Obesity in children is strongly influenced by environmental factors such as a sedentary lifestyle or high-calorie diets. While environmental factors only account for a partial explanation of the risk of obesity, they are crucial targets for treatment due to their potential modifiability. Recently, there is increasing evidence concerning the association between the intake of sugar-sweetened beverages (SSBs) and the risk of obesity, along with its related complications at any age (Cordova et al. 2023; Lim et al. 2010; Geidl-Flueck and Gerber 2023). A recent meta-analysis on 169 trials designed by energy intake as ad libitum, substitution, addition, and subtraction of energy from sugars in 10,357 adults older than 20 years demonstrated that food sources/matrix influence the effect of fructose-containing sugars on body adipose tissue excess over a median follow-up of 6–18 wk. In detail, fruits decreased whereas added nutritive sweeteners and mixed sources (with SSBs, particularly if > 20% of daily energy or 100 g/day) increased adiposity (Chiavaroli et al. 2023; Geidl-Flueck and Gerber 2023).

SSBs refer to any liquid sweetened with various forms of added sugars, such as brown sugar, corn sweetener, corn sirup, dextrose, fructose, glucose, high-fructose corn sirup (HFCS), honey, lactose, malt sirup, maltose, molasses, raw sugar, and sucrose. HFCS is a mixture of fructose and

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glucose (typically 55% of fructose and 45% of glucose) like cane sugar, and it is one of the most widely used food ingredients in nearly all soft drinks, canned jams, breakfast cereals, and baked goods. It is cheap, provides a long shelf life, and maintains long-lasting hydration in industrial bakeries. A high-fructose diet and the widespread commercial use of HFCS are reported to be linked to the rising prevalence of metabolic syndrome (MetS) globally, leading to functional impairment in various tissues and organs resulting in cardiovascular diseases (CVDs), type 2 diabetes (T2D), of metabolic dysfunction-associated steatotic liver disease (MASLD) hyperuricemia, gout, and chronic kidney disease (CKD) (Zhang, Jiao, and Kong 2017; Faienza et al. 2022). MASLD, the newly coined term to overcome the limitations of the previous term NAFLD (non-alcoholic fatty liver disease), denotes a pathological condition characterized by the presence of intrahepatic fat accumulation (steatosis) along with one of the following criteria also in the pediatric age: excess adiposity, presence of prediabetes or T2D, or signs of metabolic dysregulation (Eslam et al. 2021; Hampl et al. 2023; WHO guideline: Use of non-sugar sweeteners 2023).

The mechanisms implicated in lipid influx or clearance leading to MASLD are complex and mainly included: 1. increased ingestion of dietary fat; 2. increased influx of free fatty acids; 3. increased de novo lipogenesis (DNL); 4. impaired hepatic β-oxidation of fatty acids; 5. impaired triglyceride export. Recent evidence highlights a correlation between fructose and MASLD, and this association seems to be independent of the degree of obesity. Fructose acts specifically on several mechanisms to determine MASLD development, among which de novo lipogenesis (DNL), insulin resistance, and hyperuricemia secondary to nutrient overload (Teff et al. 2004; Geidl-Flueck and Gerber 2023).

Since fructose intake and MASLD in pediatric obesity are two emerging phenomenons, aim of this review is to depict the role of fructose, one of the most consumed nutrients in children, in the pediatric MASLD. Since in several studies is difficult to define the precise amount of fructose consumption derived from HFCS and SSBs, we will discuss of fructose including them among the food sources.

Fructose intake in children's diet and impact on health

Fructose intake

The dramatic effect of excess sugars on health is now widely known (Johnson et al. 2017. Obesity, T2D, and metabolic diseases are just some consequences of excessive sugar consumption (Geidl-Flueck and Gerber 2023). Since the use of sugars, mainly free fructose is becoming popular due to a wrong misperception (Taskinen, Packard, and Borén 2019), and their effects on health, the major international societies (WHO, American Heart Association, UK Scientific Advisory Committee on Nutrition and European Society of Pediatric Gastroenterology, Hepatology and Nutrition), have suggested limitations. Table 1 shows the main indications of free sugar consumption. Although these recommendations, the consumption of sugar is higher in the overall population (13–14% of total energy intake for adults and 15–18% of total energy intake for children). Thus, the latest WHO guidelines provide suggestions about the intake of carbohydrates and non-sugar-sweeteners carbohydrates. WHO suggests the use of whole fruits as a source of sweetness in a healthy diet, to be preferred to food containing free sugars including free fructose at any age starting from weaning (WHO guideline: Carbohydrate intake for adults and children 2023).

Sugar is mainly introduced into the diet as sucrose and HFCS. HFCS is one of the most widely used food ingredients in nearly all soft drinks, canned jams, breakfast cereals, and baked goods. In the US, sweeteners containing free fructose and free glucose have progressively replaced sucrose due to their cost. HFCS is commonly found in two forms: HFCS-42 or HFCS-55, based on the percentage of fructose, along with glucose and water. Generally, 42% of fructose (HFCS-42) is used in processed foods including cereals, desserts, dairy products, fast food and candies, while 55% of fructose (HFCS-55) is used in sweetened carbonated soft drinks. Since the 1960s, fructose intake increased over time

Table 1. Sugar intake suggested by international societies.

	Population	Sugar daily recommendation	Original definition
WHO guidelines, (WHO guideline: Carbohydrate intake for adults and children 2023)	Adult and Children	Free sugar < 10% of RDCI Free sugar < 5% of RDCI (conditional)	*Free sugar*: monosaccharides and disaccharides added to foods and beverages by the manufacturer, cook or consumer, and sugars naturally present in honey, sirups, fruit juices and fruit juice concentrates.
AHA (Johnson, Perez-Pozo, et al. 2009)	Adult and Children	Added sugar < 9 teaspoons, 36 grams, 150 calories for men Added sugar < 6 teaspoons, 25 grams, 100 calories for women Avoid consuming any added sugar for children < 2 years < 25 grams for children and adolescents	*Added sugars:* sugars and sirups put in foods during preparation or processing, or at the table.
UK SACN (Pyne and Macdonald 2016)	Adult and children	Free sugar < 5% of RDCI from 2 years	*Free sugar*: monosaccharides and disaccharides added to foods and beverages by the manufacturer, cook or consumer, and sugars naturally present in honey, sirups, fruit juices and fruit juice concentrates.
ESPGHAN (Fidler Mis et al. 2017)	Children and adolescents	Free sugar < 5 % of energy intake for children and adolescents (2–18 years). Free sugar intake should be even lower in infants and toddlers below the age of 2 years.	*Free sugar*: monosaccharides and disaccharides added to foods and beverages by the manufacturer, cook or consumer, and sugars naturally present in honey, sirups, fruit juices and fruit juice concentrates.

Abbreviation: RDCI, relative daily carbohydrates intake.

in adolescents and young adults, and now soft drinks with HFCS contribute to 8% of the total energy intake in children and adults (Malik and Hu 2015).

In children and adolescents, the highest consumption of fructose comes from SSBs, participating in the phenomenon of nutrition transition, also associated with the socioeconomic status of the family and eating habits. In the nutrition transition phenomenon, the intake of fructose derived from fruits, vegetables, and honey is relatively low (Gortmaker et al. 1999; Baker et al. 2020; Preedy and Watson 2020). Studies have also shown that SSBs intake is associated with the socioeconomic status of the family and eating habits (Gortmaker et al. 1999). The US Nutrition Examination Survey showed that 64% of children and adolescents (2–19 years) consume SSBs daily (Kit et al. 2013). The consumption of SSBs in the US is increased along with the prevalence of pediatric obesity. About 11% of RDCI among young children is covered by added sugars, increasing to 15% during adolescence. In childhood, SSBs account for about 15%–25% of sources of added sugars, up to 32% during adolescence. Significant data are provided by the NHANES, an American analysis from 1978 and 2004, which included subjects from 1 year and showed the increase of fructose consumption since 1978 from 37 g/day to 49 g/day (with only 8 g provided by fruits) (Marriott, Cole, and Lee 2009). In the Dutch National Food Consumption Survey 2007–2010, children aged 7–13 years had a median fructose intake of 58 g/day (Sluik, Engelen, and Feskens 2015). On the other hand, there is a lack of studies in younger children. Focusing on adolescents, several cohort studies demonstrated as boys aged 15–18 years old results to have the highest intakes of fructose from all the food sources (63–75 g/day); girls generally have lower fructose consumption (51 g/day), but the age group with the highest consumption is 19–22 years (61 g/die) (Marriott, Cole, and Lee 2009; Béghin et al. 2021; Sluik, Engelen, and Feskens 2015). Furthermore, the HELENA study described also fructose intake in adolescents from non-natural food sources that reached about 24.4 g/day in girls and 35.8 g/day in boys (Béghin et al. 2021).

In Europe, added sugars contribute about 14% of daily energy intake in 2 to 9 years old children (Svensson et al. 2014). Adolescents consumed almost 500 ml of sugar-containing beverages/day. In general, across Europe and the USA, the prevalence of daily soft-drink consumption is increasing between 11 and 15 years (Fidler Mis et al. 2017).

Fructose intake and metabolic health

SSBs intake, with its high added fructose content, may contribute to obesity, inflammation, insulin resistance, and T2D also in pediatrics (Malik et al. 2010; Geidl-Flueck and Gerber 2023). The latest trials are focused on the association between high fructose consumption and the increase in cardio-metabolic risk. Excess fructose intake has effects on multiple cardiovascular risk factors (Taskinen, Packard, and Borén 2019). In particular, SSBs provide excess energy that leads to a significant increase in body weight both in children and adults, as reported in several meta-analyses (Malik et al. 2013; Kaiser et al. 2013; Chiavaroli et al. 2023).

In adults the consumption of SSBs is positively related to triglycerides, LDL cholesterol, and inflammatory cytokines as seen in cross-sectional analysis in the Health Professionals Follow-up Study (HPFS) and Nurses' Health Study (NHS) (Yu et al. 2018; De Koning et al. 2012). This growing body of evidence leads to thinking about a correlation between SSBs and increased risk of T2D in adults. Despite the evidence from RCTs being scarce, prospective cohort studies have related the habitual consumption of SSBs to the 26% greater risk of T2D compared to the lowest consumption (Malik and Hu 2015). A similar association was demonstrated also in the European Prospective Investigation into Cancer and Nutrition (EPIC), with a 22% increased risk (InterAct Consortium et al. 2013). Moreover, the association between habitual consumption of SSBs and a greater incidence of type 2 diabetes seems to be independent of adiposity (Imamura et al. 2015).

Fructose can also be consumed from natural sources, which seems to be related to better metabolic features. Several studies associate fruit consumption with weight control and a lower risk of Mets at all ages (Tian et al. 2018; Fulgoni, Painter, and Carughi 2017), also 100% fruit juice and dried fruits led to a moderate reduction in body weight and BMI in adults (Chiavaroli et al. 2023). A higher fruit intake could also be associated with gut microbiota benefit alteration that would lead to a lower risk of T2D in adults (Jiang et al. 2020). In addition to fructose, natural sources also contain fiber, and evidences of the beneficial effects of consuming adequate levels of whole fruits have been growing, decreasing the risk of diseases, such as obesity, T2D, and CVD at all ages (Dreher 2018). In the pediatric age, data from the Healthy Lifestyle in Europe by Nutrition in Adolescence (HELENA) study showed an association between high quantities of non-natural foods containing high doses of fructose with elevated diastolic blood pressure (DBP) in girls. Conversely, the consumption of natural fructose coming from whole fruits seems to have a positive impact on blood pressure (Béghin et al. 2021).

However, recent evidence highlights a correlation between fructose and hepatic steatosis, and this association seems to be independent of the degree of obesity (Teff et al. 2004; Geidl-Flueck and Gerber 2023). As a consequence, most of the studies in the pediatric subjects with and without obesity focused on the role of fructose intake on the presence of MASLD. The following sections will describe the role of fructose in MASLD and the intervention to reduce its consumption in children with obesity and MASLD.

Metabolism of fructose: a hallmark of MASLD

Hepatic steatosis is an obesity-associated liver condition characterized by lipids deposition in the liver (> 5% of total liver weight or accumulation of fat in > 5% of hepatocytes) (Temple et al. 2016). Liver steatosis is graded based on the percentage of fat within the hepatocytes: grade 0 (healthy, <5%), grade 1 (mild, 5%–33%), grade 2 (moderate, 34%–66%), and grade 3 (severe, >66%) (Nassir et al.

2015). MASLD is considered to be the hepatic manifestation of metabolic dysfunction. Despite this, "pediatric" MASLD remains under-recognized and potentially underestimated. The degree of intrahepatic lipids predicts metabolic dysfunctions even better than the degree of visceral adipose tissue, and hepatic steatosis may precede the onset of MetS and its complications (Temple et al. 2016). Histologically, MASLD is similar to alcoholic fatty liver disease (AFLD). It is probably the result of two distinct but related "hits" to the hepatocytes. These two steps of hepatic injury are similar to those caused by ethanol and are observed in AFLD. The first "hit" is the development of intrahepatic lipids and hepatic steatosis owing to an imbalance of normal hepatic lipid metabolism, which results in either excessive lipid influx, decreased lipid clearance, or both. At this point, steatosis is potentially reversible and does not necessarily lead to permanent hepatic injury. The second, less common, but more virulent "hit," which occurs in 5% of individuals with steatosis, is a concomitant inflammatory process that presumably results from oxidative stress, lipid peroxidation, and cytokine action (Bush, Golabi, and Younossi 2017). The resulting lobular inflammation leads to ballooning degeneration and perisinusoidal fibrosis, which promotes apoptosis and hepatocellular death, resulting in scarring and progression to metabolic dysfunction-associated steatohepatitis (MASH) (Bush, Golabi, and Younossi 2017).

As previously introduced, recent evidence highlights a correlation between fructose and hepatic steatosis (Teff et al. 2004; Geidl-Flueck and Gerber 2023). The hepatic metabolism of fructose is very different than glucose, as it is insulin-independent, bypasses the process of glycolysis, and increases DNL to a greater extent. Indeed, the hepatic metabolism of fructose is more similar to that of ethanol (Yu et al. 2021).

Fructose is specifically and passively transported by the facilitative glucose transporter 5 (GLUT5) across the intestinal apical membrane and then is transported from the cytosol to the blood by GLUT2 (Geidl-Flueck and Gerber 2023). High fructose consumption strongly induces GLUT5. GLUT5 binds to Thioredoxin-interacting protein (TXNIP), resulting in increased GLUT5 gene expression and protein synthesis. This process facilitates the migration of GLUT5 to the apical membrane, thereby enhancing fructose absorption. (Muriel, López-Sánchez, and Ramos-Tovar 2021). Obese children with MASLD may absorb and metabolize fructose better than lean subjects, which could contribute to the pathophysiology of MASLD. It has yet to be determined whether this is linked to the up-regulation of GLUT5 and fructokinase due to prior fructose exposure, or if it is attributable to genetic/ethnic differences (Sullivan et al. 2015).

In humans, fructose is almost entirely metabolized in the liver; only few other tissues, such as intestine, kidney, adipose tissue, and muscle, can metabolize it (Sun and Empie 2012). It is transported by GLUT2 in the cytosol of the hepatocyte where fructokinase (or ketohexokinase, KHK) phosphorylates it to fructose-1-phosphate (F1P) and initiates fructose catabolism (Figure 1). Aldolase B catalyzes the lysis of fructose-1-P to generate glyceraldehyde (GA) and dihydroxyacetone phosphate (DHAP).

DHAP is primarily converted into pyruvate; pyruvate can then be metabolized to lactate or acetyl-CoA, which is a substrate for fatty acid and sterol synthesis, or for incorporation into the Krebs cycle (Tricarboxylic Acid Cycle, TCA). GA has three fates: (1) it is converted to glycerol, *via* alcohol dehydrogenase, to serve as a backbone for triglyceride synthesis; (2) it produces glycerate, *via* aldehyde dehydrogenase, which can contribute to the production of pyruvate *via* glycerate kinase; or (3) it produces glyceraldehyde 3-phosphate (GA3P), *via* triose kinase (TK). Induction of TK is another

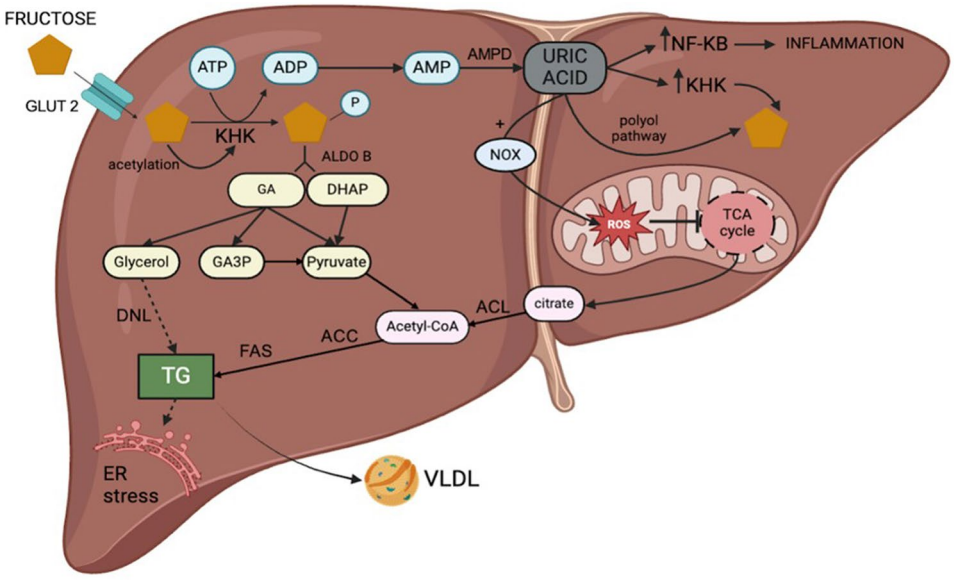

Figure 1. Fructose metabolism into the liver.
Legend: KHK, ketohexokinase; Aldo B, Aldolase B; DHAP, dihydroxyacetone phosphate; GA, glyceraldehyde; GA3P, glyceraldehyde 3-phosphate; DNL, de novo lipogenesis; TG, triglicerides; ER, Endoplasmic Reticulum; VLDL, Very Low Density Lipoprotein; AMPD, AMP deaminase; NOX, NADPH oxidase; ROS, Reactive Oxygen Species; TCA cycle, Tricarboxylic Acid Cycle; NF-kB, Nuclear Factor kappa B; ACL, ATP citrate lyase; ACC, Acetyl-CoA carboxylase; FAS, Fatty Acid Synthase.

specific step of fructose metabolism (Mao et al. 2023; Johnson et al. 2023).

By converging onto common intermediates, fructose can be converted to glucose and thus support glycogen synthesis.

Although glucose and fructose metabolism appear very similar, as they share common intermediate metabolites, the flux through the glycolytic and fructolytic pathways is very different. Glycolysis is highly regulated at the level of phosphofructokinase (PFK) by insulin, ATP, and citrate. Conversely, fructose catabolism is 10 times faster than that of glucose, and it is not regulated by its end products or by insulin. Furthermore, phosphorylation of fructose by KHK in the liver is 10 times faster than phosphorylation of glucose by glucokinase (Helsley et al. 2020). This leads to rapid intracellular ATP depletion that stimulates AMP deaminase (AMPD) to catalyze the degradation of AMP to inosine monophosphate (IMP) leading to uric acid accumulation and Reactive Oxygen Species (ROS) within hepatic cells. The increase in intracellular uric acid is followed by an acute rise in uric acid in the circulation likely due to its release from the liver (Johnson, Perez-Pozo, et al. 2009; Johnson et al. 2013).

Uric acid-induced oxidative stress appears to be mediated by the stimulation of NADPH oxidase (NOX), which translocates to mitochondria. The induction of oxidative stress in the mitochondria causes a reduction in aconitase-2 activity in the Krebs cycle, resulting in citrate accumulation that is transported into the cytoplasm where it activates ATP citrate lyase (ACL), acetyl CoA carboxylase (ACC), and fatty acid synthase (FAS), leading to fat synthesis (Johnson et al. 2013).

There are therefore two lipogenic pathways of fructose, a classical and an alternative mediated by uric acid (Figure 1).

Uric acid further stimulates KHK expression in a fast-forward loop accelerating fructose metabolism. Furthermore, uric acid can also play a part in increasing lipogenesis and decreasing beta-oxidation. Uric acid blocks enoyl-CoA hydratase and decreases AMP kinase (AMPK) activation, thus contributing to fructose-induced decrease in fatty acids oxidation (FAO). In addition to being produced by fructose metabolism, uric acid may stimulate endogenous fructose production by activating aldose reductase in the polyol pathway (Softic et al. 2020).

From fructose to uric acid in pediatric obesity-related complications

Direct effect of fructose on insulin resistance

Accumulating evidence indicates that fructose intake is strongly associated with the development of hepatic insulin resistance, which is the hallmark of MetS.

This effect is thought to be secondary to an increase in hepatic de novo lipogenesis (DNL), a decrease in fatty acids oxidation (FAO), augmentation of endoplasmic reticulum (ER) stress, and potentiation of inflammation (Figure 2) (Jegatheesan and De Bandt 2017).

In the previous paragraph, we described how the hepatic metabolism of fructose determines the accumulation of lipids within the hepatocytes (increasing DNL, reducing FAO). Chronic intake of fructose increases DNL also activating several key transcription factors such as Sterol Response Element Binding Protein 1c (SREBP1c) and Carbohydrate-Responsive Element-Binding Protein (ChREBP). As a consequence, their key target enzymes regulating lipid synthesis, such as Fatty Acid Synthase (FASN) and Acetyl-CoA

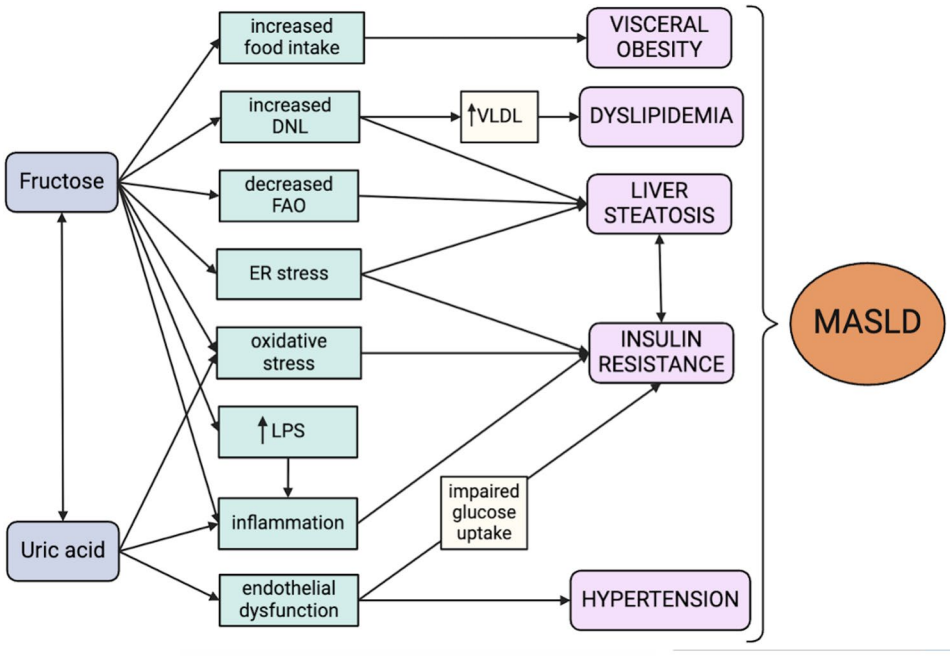

Figure 2. Uric acid: a key player leading to inflammation and metabolic syndromes.
Legend: DNL, de novo lipogenesis; VLDL, Very Low Density Lipoprotein; FAO, Fatty Acids Oxidation; ER, Endoplasmic Reticulum; LPS, lipopolysaccharide; MASLD, Metabolic dysfunction-Associated Steatotic Liver Disease.

Carboxylase (ACC), also increase (Jegatheesan and De Bandt 2017).

Acute fructose load induces protein fructosylation; this reaction is non-enzymatic and is seven times faster than glycation by glucose. In addition, fructose generates 100 times more ROS than glucose. Compared with glucose, prolonged fructose feeding in mice led to a higher hepatic accumulation of carboxymethylysine, a glycation product that, for example, can interact with SREBP-cleavage activating protein to induce sustained SREBP1c activation (Jegatheesan and De Bandt 2017).

Traditionally, decreased FAO has been thought to be secondary to increased DNL. Indeed, malonyl-CoA, an intermediate in lipogenesis, inhibits CPT1α (carnitine palmitoyltransferase 1α), the rate-limiting enzyme of FAO.

Furthermore, chronic fructose intake leads to hyperinsulinemia, which also decreases FAO.

The decrease in mitochondrial beta-oxidation is, at least in part, mediated by fructose-induced impairment of peroxisome proliferator-activated receptor alpha (PPARα) signaling, leading to decreased expression of its target genes, such as CPT1α, long-chain acyl-CoA dehydrogenase (ACADL) and very long chain acyl-CoA dehydrogenase (ACADVL). This may be mediated by fructose-induced hypermethylation of PPARα and CTP1α promoter regions, resulting in decreased mRNA levels of these genes.

These effects are also, in part, mediated *via* fructose-induced upregulation of ChREBP as previously discussed, since ChREBP is known to negatively regulate PPARα expression in the liver and other tissues. In a recent study, Helsley et al. (2023) showed that KHK-C-induced acetylation is a novel mechanism by which dietary fructose augments lipogenesis and decreases fatty acid oxidation to promote the development of metabolic complications (Helsley et al. 2023).

The development of hepatic steatosis and insulin resistance resulting from excessive DNL is closely associated with ER stress (Ren et al. 2012). ER stress can directly induce mitochondrial dysfunction, as these organelles are intimately connected, resulting in excessive calcium flux, leading to increased mitochondrial fragmentation and decreased membrane potential (Softic et al. 2020).

Mitochondrial dysfunction may also be induced by the lipotoxicity related to the fructose-induced perturbation of hepatic lipid metabolism. The disequilibrium between DNL and VLDL release may promote alterations of the respiratory chain and to the uncoupling of oxidative phosphorylation with excess ROS production. ROS overproduction by mitochondria contributes to ER stress (Jegatheesan and De Bandt 2017).

Fructose also causes gut-barrier deterioration through the disruption of tight-junction proteins. Endotoxins produced by Gram-negative bacteria alter intestinal permeability and cause bacterial translocation. Lipopolysaccharide (LPS) and other bacterial toxins cross the gut barrier and bind to Toll-Like Receptor 4 (TLR-4) on the macrophages or Kupffer cells' plasma membranes, which activates the proinflammatory signaling pathway (Figure 2), with a consequent increase in the expression of proinflammatory cytokines including tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6, and IL-1β (14). These proinflammatory cytokines are known to modulate T helper cell polarization and promote skewing of naive CD4+ T cells into Th17 subset. In fact, Th17 cells play a central role in the pathogenesis of diet-induced liver inflammation as mice lacking either IL-17A or IL-17RA, needed for Th17 signaling, are protected from either a high-fat or high-fat, high-sugar diet-driven progression of fatty liver disease. In addition, the link between ROS and Th17 cell polarization has been demonstrated in the context of liver inflammation. Further, peroxisomal beta-oxidation, which impacts ER stress and mitochondrial function, also regulates inflammation and Th17 cell polarization in NAFLD. (Softic et al. 2020).

Evidences suggest that fructose can also directly upregulate an inflammatory cascade *via* c-jun NH(2)-terminal kinase (JNK) activity in liver parenchyma, since fructose supplementation in isolated primary rat hepatocytes is sufficient to activate JNK activity and decrease insulin signaling (Wei, Wang, and Pagliassotti 2005).

Fructose can lead to insulin resistance also through a direct mechanism, in fact it can directly decrease early steps of insulin signal transduction upregulating the protein tyrosine phosphatase non-receptor type 1 (PTP1b) that negatively regulates insulin signal transduction by removing tyrosine phosphorylation on insulin receptor and insulin receptor substrates 1 and 2 (IRS1/IRS2). Indeed, it has been shown that fructose-fed rats have lower insulin receptor levels in the liver and muscle (Softic et al. 2020).

Oral fructose stimulates autonomic and endocrine responses, which downregulate the cephalic phase of the insulin pathway in taste cells, reducing pancreatic insulin production. Moreover, consuming fructose, as opposed to glucose, induces heightened hunger and a greater desire to eat. This is attributed to the fact that fructose reduces leptin and glucagon-like peptide 1 (GLP-1) levels while both fructose and glucose suppress ghrelin, but glucose does so much more (Prodam et al. 2006; Teff et al. 2004). Ghrelin activates the neuronal activity of neuropeptide Y, increasing food intake, and GLP-1 inhibition causes a decrease in insulin secretion. Increased dietary fructose intake significantly accelerated the half-emptying time in the stomach compared to a similar intake of glucose. Intriguingly, fructose, but not glucose, oral ingestion resulted in a higher GLP-1 and insulin answer in adolescents with obesity than in lean subjects. These results suggest that fructose intake may one of the players contributing to the hyperinsulinemic phenotype of youths with obesity through a GLP-1-mediated mechanism (Galderisi et al. 2019). Furthermore, nutrients, and mainly different carbohydrates could differentially modulate the anorexic effect of GLP-1, likely coupled with a different ghrelin response to them, an aspect not investigated in the previous study (Galderisi et al. 2019; Burmeister et al. 2013; Campbell and Drucker 2013). Fructose, in the mouth and gut, may impact eating behavior by sweet-tasting mechanisms. Sugary foods exert potent reinforcing effects, partly mediated by dopamine receptors. In vulnerable individuals, these foods may override the brain's homeostatic control mechanisms, potentially leading to behavioral alterations

reminiscent of addiction, such as anxiety or cravings (Jacques et al. 2019)

Uric acid-mediated effect of fructose on insulin resistance

Fructose phosphorylation in the liver consumes adenosine triphosphate (ATP): as phosphorylation by fructokinase is fast and the cleavage reaction by aldolase B relatively slow, an excess of fructose could cause hepatic phosphate deficiency, leading to AMP accumulation with resulting increased uric acid synthesis. Uric acid in turn stimulates the production of ROS *via* the activation of Transforming Growth Factor β and NADPH oxidase 4 (Jegatheesan and De Bandt 2017).

Increasing evidence suggests that uric acid may play a role in the development of the MetS (Figure 2). The strongest evidence derives from studies in animal models showing that decreasing uric acid levels can prevent or reverse features of the MetS (Feig, Kang, and Johnson 2008). Two mechanisms have been suggested to explain how hyperuricemia might induce the MetS.

The first one is related to endothelial dysfunction. Uric acid inhibits endothelial nitric oxide generation causing vasoconstriction and a reduction in glucose uptake by skeletal muscle. Vasoconstriction leads to increased blood pressure and predisposes to essential hypertension development. Impaired glucose uptake leads to insulin resistance. The observations that hyperuricemia could induce endothelial dysfunction in rats and that the treatment with allopurinol could improve endothelial function would support this hypothesis (Yanai et al. 2021; Kanbay et al. 2014).

The second one concerns the inflammatory and oxidative changes that uric acid induces in adipocytes, a crucial process in MetS pathogenesis in obese mice (Feig, Kang, and Johnson 2008). In addition, xanthine oxidoreductase, the enzyme that produces uric acid from xanthine, is expressed in adipocytes and is crucial for adipogenesis. In fact, xanthine oxidoreductase knockout mice have only half the adipocyte mass of their control littermates (Feig, Kang, and Johnson 2008).

Many studies demonstrated a significant association between elevated levels of serum uric acid and various components of MetS in animal models. However, a few studies have established this association in the pediatric population until now (Ford et al. 2007; Goli et al. 2020; Ricotti et al. 2018). In detail, Feig and Johnson (2003) and Ricotti et al. (2018) demonstrated a direct correlation between serum uric acid and blood pressure in untreated children with obesity. They found that a serum uric acid value exceeding 5.5 mg/dL strongly indicates primary hypertension, as opposed to white-coat or secondary hypertension (Feig, Kang, and Johnson 2008). Furthermore, hyperuricemia was also associated with a high prevalence of microalbuminuria in children and adolescents with obesity (Ricotti et al. 2018). These results are consistent with the hypothesis that uric acid plays a role in the early pathogenesis of primary hypertension.

Apart the role on insulin resistance and hypertension, a positive correlation between the degree of liver damage and uric acid concentration in non-obese patients with MASLD has been found (Oral et al. 2019). This effect could be linked to the fact that uric acid promotes fat synthesis within hepatocytes through the translocation of the NADPH oxidase subunit 4 to the mitochondria, increasing superoxide formation. In turn, this increase in ROS inhibits the enzyme aconitase, which catalyzes the conversion of citrate to isocitrate in the mitochondrial matrix in the Krebs cycle and promotes citrate accumulation; then, citrate migrates to the cytosol where is converted by ATP citrate lyase (ACLY) to acetyl-CoA for DNL by fatty acid synthase (FASN) (Figure 1).

Furthermore, its role in inflammation could worsen the picture, since it is a potent inducer of the inflammatory response by activating the nuclear factor kappa B (NF-κB) signaling pathway that upregulates the transcription of the NOD-like receptor pyrin domain containing 3 (NLRP3) inflammasome and pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α (Muriel, López-Sánchez, and Ramos-Tovar 2021).

In line with this evidence, uric acid has also been shown to induce oxidative stress in islet cells. Pancreatic islet cells from neonatal rats incubated with uric acid reduced insulin secretion by 65%. Removing uric acid from the medium rapidly restored insulin secretion, suggesting its cytostatic or cytotoxic effects on β-cells in the pancreas (Scott et al. 1981). This aligns with findings that demonstrated that hyperuricemia in pediatric individuals with obesity is associated with an elevated insulin resistance during fasting, high glucose levels, and reduced insulin sensitivity during an oral glucose tolerance test. (OGTT) (Ricotti et al. 2018). The impact of reducing uric acid on insulin resistance in human studies is limited. Nevertheless, a small, randomized trial reported an improvement in insulin resistance with benzbromarone, a uricosuric molecule (Ogino et al. 2010).

Obesity-associated oxidative stress in the adipose tissue has been recently recognized as a major causative factor for obesity-related inflammation and the MetS. Oxidative stress and inflammation in adipose tissue create an imbalance in the production of adipocyte-specific hormones and cytokines (adipokines). This imbalance significantly contributes to the development of insulin resistance and the cardiovascular risks associated with obesity. Sautin et al. (2007) demonstrated that adipocyte differentiation is associated with an increased uptake of uric acid and the accumulation of reactive oxygen species (ROS). Elevated uric acid further induces an increase in intracellular ROS production in differentiated adipocytes, mediated by the activation of NADPH oxidase (NOX). This is followed by redox-dependent stress signaling, a decrease in nitric oxide bioavailability, and oxidative modifications of proteins and lipids. The inflammatory state of adipose tissue determines the release of free fatty acids into the circulation, which can reach toxic levels within non-adipose tissues. The detrimental effects of lipid accumulation in non-adipose tissues are known as lipotoxicity. Accumulation of lipids in skeletal muscle leads to insulin resistance; while the accumulation of lipids in islet cells determines a reduction in insulin secretion. As previously described, fat accumulation in the liver associated with metabolic dysfunction defines MASLD. In a cohort of children and adolescents with hepatic steatosis, Mosca et al. (2017)

showed that uric acid concentrations and dietary fructose consumption are independently and positively associated with MASH. They also demonstrated that dietary fructose consumption is positively and independently associated with hyperuricemia (Figure 2).

All these evidences clearly associate high uric acid levels with insulin resistance, oxidative stress, and MASLD. However, the picture in literature is debated, mainly in adults, since systemic uric acid administration increases serum antioxidant capacity (Waring et al. 2003; Amaro et al. 2015). At a physiologic pH, uric acid exists primarily as urate, accounting for free-radical-scavenging properties and the antioxidant capacity of blood (Packer 2024). Furthermore, drugs as allopurinol and febuxostat that inhibit xanthine oxidase, one of the enzymes that leads to uric acid synthesis coupled with ROS, do not give a reduction in cardiovascular risk (Givertz et al. 2015; Packer 2024). These findings could appear contrasting with previous described evidence. However, we need to consider nutrients surplus and purine production through the pentose phosphate pathway as the needle of the scale. Hyperuricemia is firstly a marker of nutrient surplus and cellular stress, since upregulation of xanthine oxidase may represent an adaptive mechanism (Packer 2024). However, chronic high uric acid production leads to inflammation, insulin resistance, and organ damage discussed before (Burnier 2023; Packer 2024).

Clinical trial on fructose intake in the pediatric age and the risk of MASLD

As previously reported, fructose intake seems associated with obesity and metabolic diseases, mainly MASLD, in children and adolescents. Studies in the pediatric age are less numerous, in particular as RCTs, but are in line with those in adults (Geidl-Flueck and Gerber 2023).

In detail, many of the pediatric studies on MASLD were observational including a total of 1,485 children and adolescents mainly Caucasian (Mager et al. 2010; Vos et al. 2012; O'Sullivan et al. 2014; Hamza et al. 2016; Nier et al. 2018; Mosca et al. 2017, 2019; Jin, Willment, et al. 2014) (Table 2). Liver disease was diagnosed with ultrasound sonography (US) alone or with liver biopsy (Vos et al. 2012; Mosca et al. 2017, 2019; Jin, Willment, et al. 2014; Nier et al. 2018). Most of the studies were conducted on overweight or obese pediatric subjects, and few reports presented normal-weight individuals (O'Sullivan et al. 2014; Hamza et al. 2016; Nier et al. 2018). Dietary intakes were evaluated with different food frequency questionnaires often unable to detect total daily fructose intake. All the studies confirmed an association between high fructose intake in diet or as SSBs and high weight score, as well as an association with MASLD and MASH (Mager et al. 2010; O'Sullivan et al. 2014; Hamza et al. 2016; Nier et al. 2018; Mosca et al. 2017, 2019; Jin, Willment, et al. 2014) with only one exception (Vos et al. 2012). However, the latter study reported similar low sugar and fructose intake in children with and without MASLD or MASH, but high levels of uric acid, an indirect marker of fructose intake, in those with MASH respect to those with MASLD. These data suggested that other sources of fructose, as processed foods, could have a role in MASH development but the dietary methods used by the Authors were unable to measure the complete daily fructose intake. O'Sullivan et al. (2014) calculated that an increase in daily intake of fructose of 10% (4.7 g) respect their mean daily consumption in obese adolescents aged 14 years old resulted in an increased risk of 50% to have a diagnosis of MASLD at 17 years old. Also, normal-weight children with high fructose intake developed later on MASLD, suggesting a role of chronic exposition independently by adipose tissue accumulation (O'Sullivan et al. 2014). Furthermore, fructose intake was associated with a worse metabolic profile apart from MASLD or MASH presence (Mager et al. 2010; Vos et al. 2012; O'Sullivan et al. 2014; Hamza et al. 2016; Nier et al. 2018; Mosca et al. 2017, 2019; Jin, Willment, et al. 2014). Interestingly, if obesity is considered to be the most important determinant for the development of MASLD, with or without a high intake of fructose, subjects of this cohorts presented other risk factors, as low intake of vitamins, sedentary behaviors, high consumption of processed food, socioeconomic and environmental complex factors. The interplay of them with fructose intake could be additive.

The RCTs focused on the role of sugars in pediatric MASLD/MASH currently comprises only 321 subjects aged 5–18 years over a follow-up of days, weeks, or months (maximum 12 months) (Table 3). Studies included overweight or obese children with or without MASLD and other components of metabolic syndrome (Mager et al. 2015; O'Sullivan et al. 2014; Jin et al. 2012, Jin, Willment, et al. 2014; Nier et al. 2018; Schwarz et al. 2017; Goss et al. 2020; Schwimmer et al. 2019; Erkin-Cakmak et al. 2019; Cohen et al. 2021; Olson et al. 2022). Two studies included normal weight controls (O'Sullivan et al. 2014; Mager et al. 2015). Interestingly, most of the intervention studies were conducted in Hispanic, African, and Asian subjects, diversely from those observational. Intervention protocols varied from dietary counseling to reduce fructose and/or glucose intake in a short (Schwarz et al. 2017; Erkin-Cakmak et al. 2019; Cohen et al. 2021) or longtime period (Nier et al. 2018; Goss et al. 2020; Schwimmer et al. 2019; Mager et al. 2015) to standardized meals or beverages with fructose or glucose for several days (Jin et al. 2012, Jin, Willment, et al. 2014; O'Sullivan et al. 2014). In all the studies in which dietary advises to decrease fructose/glucose content were given, lipid profile, insulin resistance, and inflammation improved with decreased features (liver steatosis, liver volume) including DNL (Nier et al. 2018; Schwarz et al. 2017; Schwimmer et al. 2019; Mager et al. 2015; Erkin-Cakmak et al. 2019; Cohen et al. 2021; Olson et al. 2022). Weight decreased in studies longer at least 6 months (Nier et al. 2018, Mager et al. 2015), although a study reported a slight decrease in BMISD after 8 wk (Cohen et al. 2021). Weight and fat mass decreased in one of the 8-week trials (Goss et al. 2020), but not in the other probably due to the caloric amount suggested (Schwimmer et al. 2019). Data on weight decrease are consistent with the 18-month trial involving 641 primarily normal-weight children without MASLD aged 4–10 years old who were assigned to receive 250 ml per day of a sugar-free

Table 2. Observational studies on dietary fructose intake and MASLD.

Reference	Study population	Ethnicity	Study design/methods	Main observation	Association between fructose intake and MASLD
Mager et al. 2010	38 children with MASLD, overweight or obese 12F; 26 M 5–19 years	Mixed (48% Caucasian, 28% Hispanic, 21% Asian, 3% other).	Retrospective Dietary intake: self-reported using a diary. Diet Analysis Plus Software for analysis of nutrients Diagnosis MASLD: US	Abdominal obesity and metabolic features of MASLD (hyperinsulinemia, hypertriglyceridemia, insulin resistance) Diet: low vitamin E, fiber, PUFA, omega-3 intake; high sugar and fat intake. Sucrose and fructose: 24% of daily CHO Kcal (habits in consuming fruit juice and soft drinks) Sedentary lifestyle. High fructose intake was associated with ▲ WC, WHR TNF-α, γGT, ALT, HOMA-IR, ▼ adiponectin in MASLD children	↑
Vos et al. 2012	149 children with different grades of MASH, overweight/obese 110 M; 39 F 13 ± 2.6 years No MASH ($n = 39$) Borderline Z3 ($n = 27$) Borderline Z1 ($n = 36$) MASH ($n = 47$)	Mixed	Prospective, cross-sectional MASH grades: NAS score >5%. Dietary intake: Block Brief questionnaire Diagnosis MASH: liver biopsy.	Low intake of self-reported SSBs Calorie intake = among groups: (median, 50.4% CHO; 35% fat) Uric acid levels ▲ in MASH subjects	=
O'Sullivan et al. 2014	592 adolescents of any weight (Raine Study; longitudinal birth cohort study) 315 M; 277 F 14 and 17 years	Caucasian	Longitudinal, population base Dietary intake: At 14 ys food intake was self-recorded with a 3-days reporting eating habits. FoodWorks for analysis of nutrients. At 17 ys diagnosis of MASLD: US	Prevalence of MASLD at 17ys was 12.8% (mainly obese adolescents) Fructose intake in obese adolescents with MASLD was ▲ than in obese without MASLD. Sugar and fructose intake are + related to ALT, AST, y-GT Underweight children with ▲ fructose intake had MASLD at 17 ys.	↑
Hamza et al. 2016	85 children (55 obese; 30 normal weight) 36 F; 49 M 6–14 ys	African	Cross-sectional, case-control Dietary intake: FFQ adapted from Dwyer JL Diagnosis MASLD: US	90% of the obese group had MASLD grade 1 (75%) or 2 (25%) Dietary fructose intake from processed and natural sources ▲ in obese patients Fructose intake correlated + with lipid profile, insulin resistance, P3NP, blood pressure, and – with fasting glucose/ insulin ratio Fructose intake correlated + with US MASLD grade Fructose intake was not associated with uric acid	↑
Mosca et al. 2017	271 obese/overweight children with MASLD 116 F; 155 M mean age 12.5ys	Caucasian	Cross-sectional Diagnosis MASLD/MASH: liver biopsy Dietary intake: FFQ Food composition database for nutrient intake (INRAN)	102 of 271 patients have MASH Patients with MASH had ▲ BMI, lipid profile, uric acid, inflammatory markers Fructose intake was ▲ in MASH patients. Dietary intake was = between MASH or not MASH subjects (skipping breakfast, highly processed food, afternoon snacks, SSBs more than 3 times/week) Fructose intake was + correlated with WC, uric acid, HOMA-IR, ALT, lipid profile, inflammatory markers Fructose intake and uric acid were independently + associated with MASH	=

(*Continued*)

Table 2. Continued.

Reference	Study population	Ethnicity	Study design/methods	Main observation	Association between fructose intake and MASLD
Mosca et al. 2019	182 children with overweight/obesity and MASLD or liver fibrosis F80; M 102 Age 5–12 ys	Caucasian	Cross-sectional, Case-control Diagnosis MASLD/MASH: liver biopsy 3 groups (fibrosis = 0, fibrosis >1; fibrosis > 2). Dietary intake: FFQ Food composition database for nutrient intake (INRAN)	Children with liver fibrosis had parents with obesity more than children without fibrosis. Children with fibrosis and MASH consumed ▲ fructose and low vitamin D	↑
Jin, Willment, et al. 2014	43 obese adolescents Age 11–18 ys 26 F; M 17	Hispanic	Cross-sectional, case-control Diagnosis MASLD: MRI/MRS Dietary intake: self-reported weekly SSBs Subjects on hepatic fat: > 5% (n = 36; case); < 5% (n = 11, control)	Obese adolescents with MASLD consumed ▲ SSBs than obese without MASLD. Anthropometric and clinical parameters = among subjects AST, ALT, inflammatory markers, and endotoxin were ▲ in obese patients with MASLD	↑
Nier et al. 2018	125 children recruited (89 overweight of whom 16 with MASLD, 36 normal-weight) 56 F; 53 M (presented) Age 5–9 ys	Caucasian/Asian	Cross-sectional Diagnosis MASLD: MRI/MRS and liver biopsy Dietary intake: 24h recall Food composition with the EBISpro German food software	Anthropometric parameters and inflammatory markers were ▲ in overweight children with MASLD. SSBs and CHO (fructose and glucose) intake were ▲ in children with MASLD. Sedentary activities were = in all subjects	↑

All the studies reported in the table below exclude patients having other causative liver disease and diabetes from the analysis. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CHO, carbohydrates; F, female; FFQ, food frequency questionnaire; γ-GT, gamma-glutamyltranspeptidase; HOMA-IR, homeostatic model assessment – insulin resistance, fasting insulin; M, males; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; MASLD, metabolic dysfunction-associated steatotic liver disease; NAS, MASLD activity score; MASH, metabolic dysfunction-associated steatohepatitis; P3NP, procollagen type III N- terminal peptide; PUFA, polyunsaturated fat; SSBs, sugar-sweetened beverages; TNF-α, tumor necrosis factor alpha; US, ultrasound sonography; WC, waist circumference; WHR, waist-to-hip ratio; ys: years.

sweetened beverage (sugar-free group) or an SSB (104 kcal). The group receiving SSB increased the BMI z score more than the control (0.12 vs 0.06 SD units) (de Ruyter et al. 2012).

In the acute trials, high glucose and fructose intake increases insulin secretion and resistance, mainly in subjects with MASLD (Jin et al. 2012, Jin, Willment, et al. 2014; Erkin-Cakmak et al. 2019). Glucose and triglycerides increased more after fructose than glucose again in subjects with MASLD (Jin et al. 2012, Jin, Willment, et al. 2014; O'Sullivan et al. 2014). These results suggest that insulin resistance observed in MASLD is also exacerbated at hepatic levels when elevated serum fructose concentrations are chronic due to an unhealthy diet. Furthermore, subjects with MASLD had a decreased urinary fructose excretion that coupled with high glucose and insulin levels after its ingestion was consistent with a more efficient metabolism of fructose in MASLD pediatric subjects (O'Sullivan et al. 2014), and serum D-lactate, an end-product of the detoxification methylglyoxal (the most toxic glycating agent, one of the key precursors of the Maillard reaction) decreased in a very fast way (Erkin-Cakmak et al. 2019). Also ceramides, sphingolipids which contribute to lipotoxicity, and insulin resistance, decreased in parallel with DNL (Olson et al. 2022). Since the effect of fructose seems to be also acute, in both directions, any type of advice to decrease its intake could have prompt efficacy.

Conclusion and perspectives

In recent decades, the intake of fructose as SSBs, HFCS, and processed/palatable food has notably increased, strictly related to the rising of obesity and MASLD prevalence in both adult and pediatric populations. Globally the consumption of fructose could have beneficial effects if it comes from natural sources. Otherwise, given the poor quality of fructose-sweetened products, high levels of consumption may increase the risk of metabolic diseases. In this review, we have carefully described how a high intake of fructose *via* added sugars or SSBs in children and adolescents increases the risk of Mets and its sequelae paying the light on MASLD. Fructose exacerbates ectopic fat accumulation in the liver and oxidative stress. Fructose favors DNL through the classical pathways or in the alternative one *via* uric acid accumulation into the liver. Indeed, hyperuricemia is one of the main features of MALSD patients. The mentioned observational and interventional studies attribute to fructose a central role in the development of this disease and highlight that fructose appears to be independent of obesity in the onset of hepatic steatosis, thereby increasing glucose levels, insulin resistance, and dyslipidemia even in lean pediatric subjects. Fructose restriction ameliorates liver fat accumulation, lipid profile, and weight, and decreases DNL in a fast fashion. Despite the interesting results of these trials, further investigations *via* larger cohort studies are essential to

Table 3. Intervention studies on dietary fructose intake and MASLD.

References	Study subjects	Ethnicity	Study design/methods	Type of intervention	Main observation
Nier et al. 2018	12 overweight children with MASLD (6 control; 6 intervention) 5 F; 7 M Age 5–9 ys	Caucasian/Asian	Open trial randomized for the intervention Diagnosis MASLD: MRI/MRS and liver biopsy Dietary intake: 24h recall Food composition with the EBISpro German food software	1 year of dietary intervention in which children and their parents reduced about the 50% the intake of fructose (personal counseling)	Dietary counseling ▼ weight, BMI, inflammatory markers, adiponectin, diastolic blood pressure Leptin, AST, ALT, HOMA-IR=
Jin et al. 2012	*N* = 19 obese and normal-weight children and adolescents 2 F; 17 M age 11–18 ys	Hispanic	Crossover study, randomized for age, sex, and ethnicity (9 cases: children with MASLD; 10 controls: children without MASLD). Diagnosis MASLD/MASH: MRI/MRS and liver biopsy	24h of standardized meal 700 kcal (50% CHO, 30%fat, 20% protein) plus 78 g of sugar (fructose-SSB (FB) or glucose SSB(GB) consumed each meal). Meals were administered at 8, 12, and 16h. Only ad libitum water was consented outside the meal.	Subjects with MASLD had ▲ weight, BMI, and insulin resistance. Consumption of FB and GB ▲ insulin level and glucose in both groups. FB caused ▲ fasting plasma glucose than GB. In the control group post-prandial insulin response ▲ more after GB than FB. Lipid profile (excluded HLD-c) was ▲ in MASLD both after FB and GB FB ▲ TG in MASLD. Adverse metabolic response after FB also in non-MASLD
Jin, Willment, et al. 2014	24 overweight adolescents with hepatic fat >8% 13 F; 11 M age 11–18 ys	Hispanic/American	4-week randomized, controlled, double-blinded beverage intervention study. Randomization based on gender, age, and weight. Evaluations and blood sample collection at 2 and 4 wk Diagnosis MASLD/MASH: MRI/MRS	4 week of beverage intervention trial: 1 group glucose beverage (GB; *n* = 13) 1 group fructose beverage (FB; *n* = 11) 3 sugar beverages per day with 33 g of fructose or glucose.	Children consumed SSBs at least 3 times per day. After 4-w, GB ▼ insulin resistance, FFA, oxidative LDL, TG (▼ fructose intake). weight and hepatic fat = in GB and FB
Schwarz et al. 2017	41children and adolescents with obesity and metabolic syndrome and high fructose intake (< 50 g/day) F 26; M 15 Age 9–18 ys	African American (15) and Latino (26)	9-day intervention trial (no control) Diagnosis MASLD/MASH: MRI/MRS (repeated on day 10) Dietary intake; FFQ and dietician interview Evaluation of de novo lipogenesis and insulin kinetics	Controlled and personalized dietary intake Diets were restricted in sugar and fructose intake to 10% and 4% of the total energy intake. (sugar intake was substituted with starch for a total CHO intake around 50%).	Subjects consumed ▲ sugars at baseline (28 ± 8% sugar; 12 ± 4%% fructose). ▲ insulin resistance, VAT (body fat mean 48.6%), liver fat (>5%) at baseline After intervention: sugars intake▼ (10 ± 2% sugar; 4 ± 1%% fructose); VAT and liver fat ▼ (123 cm2 to 110cm2; 7% to 3%), ▼ insulin resistance; ▼ de novo lipogenesis; ▲ insulin sensitivity
O'Sullivan et al. 2014	24 obese and normal-weight children and adolescents (Tanner 2–4) Case: obese with (9) and without (6) MASLD 9 lean controls 12 F; 12 M Age 9–18 ys	Hispanic	Open intervention trial (case-control), randomized for age and gender. Diagnosis MASLD/MASH: US and liver biopsy Dietary intake: assessed by a dietician.	Oral fructose challenge (1 g/kg based on ideal body weight; maximum 75 g dissolved in 8 oz of water) with evaluation of blood samples, breath hydrogen testing, and urine	Obese children with MASLD/MASH had ▲ fructose intake, systolic blood pressure, fasting uric acid, glucose levels After fructose ingestion, MASLD group had ▲ glucose, insulin, TG, FFA, and uric acid than obese without MASLD and controls Stimulated serum fructose levels and fructose urinary excretion were ▼ in MASLD subjects compared to controls

(*Continued*)

Table 3. Continued.

References	Study subjects	Ethnicity	Study design/methods	Type of intervention	Main observation
Goss et al. 2020	32 children and adolescents with obesity and MASLD 16F;16M age 9–17 ys	Mixed (Hispanic, non-Hispanic, and Asian)	Randomized two-arm parallel dietary intervention for 8 wk. Diagnosis MASLD/MASH: MRI (repeated 3 times). DXA and indirect calorimetry Dietary intake: food diary for 3-d a week Nutrient intake analysis: NDSR software.	8-w of CHO-restricted diet (CRD) or fat-restricted diet (FRD) with a dietician counseling and meal planning CRD diet minimized the intake of refined CHO sources (added sugars, high glycaemic grains; fructose (≤25% energy CHO, 25% protein; ≥50% fat, not saturated) FRD comprised low sugar, high-quality food with low energy density (based on the USDA MyPlate Daily Food Plan for teenagers with 55:25:20% energy from CHO:protein: fat)	CRD ▼ body weight, BMI, total fat mass, and abdominal fat compared to FRD. CRD ▼ more than FRD liver fat, liver inflammation, and insulin resistance. = ▼ in CRD and FRD in fasting glucose, hsCRP, total cholesterol, LDL-C, HDL-C, triglycerides, γGT
Schwimmer et al. 2019	40 obese adolescents with MASLD 0 F; 40 M age 11–16 ys	Hispanic (95%) others (5%)	An open-label, 8-week 1:1 randomized clinical trial. Dietary counseling was conducted baseline, after 4 and 8 wk to assess dietary intake and create personalized diet, based on in physical activity level and family habits. Diagnosis MASLD: MRI-PDFF Dietary intake: 24h recall	Dietary intervention. Low sugar diet vs usual diet Dietary counseling at 0–4–8 wk intervention group: sugar intake < 3% of daily Kcal intake Energy intake in intervention group at 8 wk: 1665 kcal (43% CHO, 1% of free or added sugars; 36% fat; 22% protein). Usual diet 1603 Kcal at 8 wk (49% CHO, 10% free sugar; 13% added sugars; 33% fat; 19% protein).	Baseline free sugar intake was 10% and 11% total kCal in the intervention and usual diet. ▼ Hepatic steatosis, inflammatory liver markers, AST, ALT, γGT were ▲ in the intervention group than the usual diet. Body weight, TG, glucose, insulin resistance, LDL-c, HDL-c = between groups
Mager et al. 2015	12 obese children with MASLD and 14 normal weight controls 10 F; 16 M Age 7–18ys.	Mixed	3–6 months dietary intervention trial (case-control), not randomized for gender and age. Diagnosis MASLD/MASH: US and liver biopsy Dietary intake: prospective food records (2 weekdays and 1 weekend day) Nutrient intake analysis: food processor (SQL 10.8.0, ESHA Research 2011)	dietary counseling: promotion of low GI (45–55), GL (<80), and fructose (<7% of total energy intake) in both study groups. Children were provided example menus with 3 meals and 2 snacks (CHO 45%–50%; fat 25%–30%; protein 15%–20%; 1600–2300 kcal).	At baseline children with MASLD consumed ▲ CHO and fructose, had ▲ GI, GL, and total fat compared to controls. Children with MASLD had ▲ weight, BMI, WC, WC/height, hip, WC/hip, %BF, skin fold thickness. %BF and skin fold thickness ▼ at 3 and 6 months in MASLD children. = other anthropometric variables ▼ systolic blood pressure, % BF, ALT, APO-B100, HOMA-IR in MASLD (mainly in MASH)
Erkin-Cakmak et al. 2019	20 obese children with MetS(2019)	African-American (8) and Latino (12)	9-days intervention clinical trial	sugar and fructose intake was reduced to 10% and 4% respectively.	95% of patients ▼ serum D-lactate levels of 50%
Olson et al. 2022	43 obese children with at least one feature of MetS (2022) 15 F; 5 M Median age 14.5 ys (range, 12.6 to 15.8 ys) Habitual sugar consumers (>15% sugar, >5% fructose)		Diagnosis of liver fat, VAT, subcutaneous fat: MRI on a 3-Tesla scanner. Diagnosis of impaired fasting insulin: OGTT (75 g) Measure of post-prandial DNL: isotope feeding study.	An equal amount of starch was provided to maintain the isocaloric intake. Serum D-lactate, DNL, liver fat and insulin sensitivity were evaluated before and after dietary intervention.	DNL and insulin sensitivity ▲ ▼ liver fat fraction, triglycerides, and ceramides. ▲ TG/HDL ratio ▲ insulin sensibility Weigh ▼ 1.1 kg

(*Continued*)

Table 3. Continued.

References	Study subjects	Ethnicity	Study design/methods	Type of intervention	Main observation
Cohen et al. 2021	40 male adolescents with MASLD Age 11–16 ys Mean age of control group (13.3 ys); mean age of treatment group (12.6 ys)	Hispanic	8 wk randomized (1:1), open-label controlled clinical trial (case-control). Intervention group, 20 subjects underwent caloric restriction. Control group, 20 subjects maintained the usual diet. MASLD/MASH diagnosis: MRI-PDFF Nutritionist counseling each 2 wk; FFQs (24-recall); physical activity learning with multiple pass approach. DNL assessment with stable isotope tracers.	Intervention group: 8 wk of low sugar dietary intake. Control group: 8 wk of usual diet. Dietary counseling was assessed by nutritionists before starting the diet; all eating products had no sugar or low-free sugar substitutes. Foods and beverages were provided by the research staff. MRI-PDFF was performed before and after the intervention.	DNL ▼ from 34% (baseline) to 24% at 8 wk in intervention group ▼ hepatic fat content in the intervention group (from 23% to 17%) ▼ ALT levels Fasting glucose and TG levels = BMI-SDS ▼

All the studies reported in the table below exclude patients having other causative liver disease and diabetes from the analysis. Abbreviations: ALT, alanine aminotransferase; APO-B, apolipoprotein B; AST, aspartate aminotransferase; %BF, % body fat; BMI, body mass index; CHO, carbohydrates; CRD, carbohydrate-restricted diet; F, female; FB, fructose sugar-sweetened beverages; FFA, free fatty acids; FRD, fat restricted diet; FFQ, food frequency questionnaire; GB, glucose sugar-sweetened beverages; GI, glycemic index; GL, glycemic load diet; γ-GT, gamma-glutamyltranspeptidase; HDL, high-density lipoprotein; HDL-c, HDL cholesterol; HOMA-IR, homeostatic model assessment – insulin resistance, fasting insulin;; hsCRP, high sensitive C reactive protein; LDL, low-density lipoprotein; LDL-c, LDL cholesterol; M, males; MRI, magnetic resonance imaging; MRI-PDFF, MRI proton density fat fraction; MRS, magnetic resonance spectroscopy; MASLD, metabolic dysfunction-associated steatotic liver disease; NAS, MASLD activity score; MASH, metabolic dysfunction-associated steatohepatitis; P3NP, procollagen type III N- terminal peptide; PUFA, polyunsaturated fat; SSBs, sugar-sweetened beverages; TG, triglycerides; TNF-α, tumor necrosis factor alpha; US, ultrasound sonography; VAT, visceral adipose tissue; WC, waist circumference; WHR, waist-to-hip ratio; DNL, de novo lipogenesis; BMI-SDS; body mass index – standard deviation score.

provide definitive evidence about the metabolic effects of fructose and its role in MASLD development. Furthermore, studies focused on the role of high fructose intake on the other components of Mets in the pediatric age are warranted.

However, a reduction in sugar/fructose consumption is almost imperative in the pediatric population to avoid the risk of developing precociously metabolic disorders. Since the latest WHO guidelines suggest favoring whole fruits as a source of sweetness in a healthy diet, to be preferred to food containing free sugars by children from 6 months (WHO guideline: Carbohydrate intake for adults and children 2023), strong efforts are needed to educate the general population to decrease the intake of fructose. Therefore, new strategies are being sought and should be implemented to educate children and youths. In particular, school-based intervention programs have been shown to be effective in increasing healthy behaviors. The CATCH study (Coordinated Approach to Child Health) involves the participation of primary-school students, their families, food service personnel, and physical education teachers with the aim of changing the behavior of students. After a three-year follow-up, the students maintained a lower-fat diet and more vigorous physical activity compared to peers not included in the study (Luepker et al. 1996). The Planet Health study, a 21-month randomized controlled study in public middle schools demonstrated how stressing the importance of decreasing television viewing leads to a reduction in television watching and a significant decrease in the prevalence of obesity among girls, and an increase in fruit and vegetable consumption (Gortmaker et al. 1999; Wiecha et al. 2004). Since misperception of healthy and unhealthy food is frequent, as previously discussed, education strategies to reduce sucrose and fructose intake involving several players are warranted to protect children and adolescents from obesity and its complications, including MASLD.

Author contributions

Conceptualization, F.P., and M.F.F; Introduction, E.C, I.F, A.A, V.A, T.S, M.F.F, and FP; Conclusion, T.S., V.A., and F.P; Formal Analysis, V.A, S.T., and F.P; Writing Original Draft Preparation, M.F.F., E.C., I.F., and F.P; Writing Review and Editing, F.P., and M.F.F.; Supervision, F.P., and M.F.F.; Founding acquisition, F.P., and M.F.F. All the authors contributed to the final manuscript and affirm that the present work is original and has not been published previously. Each person listed as an author significantly contributed to the work. All authors have read and approved the final version of the manuscript for publication.

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