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REVIEW

Recent advances in the pathogenesis of hereditary fructose intolerance: implications for its treatment and the understanding of fructose-induced non-alcoholic fatty liver disease

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Abstract

Hereditary fructose intolerance (HFI) is a rare inborn disease characterized by a deficiency in aldolase B, which catalyzes the cleavage of fructose 1,6-bisphosphate and fructose 1-phosphate (Fru 1P) to triose molecules. In patients with HFI, ingestion of fructose results in accumulation of Fru 1P and depletion of ATP, which are believed to cause symptoms, such as nausea, vomiting, hypoglycemia, and liver and kidney failure. These sequelae can be prevented by a fructose-restricted diet. Recent studies in aldolase B-deficient mice and HFI patients have provided more insight into the pathogenesis of HFI, in particular the liver phenotype. Both aldolase B-deficient mice (fed a very low fructose diet) and HFI patients (treated with a fructose-restricted diet) displayed greater intrahepatic fat content when compared to controls. The liver phenotype in aldolase B-deficient mice was prevented by reduction in intrahepatic Fru 1P concentrations by crossing these mice with mice deficient for ketohexokinase, the enzyme that catalyzes the synthesis of Fru 1P. These new findings not only provide a potential novel treatment for HFI, but lend insight into the pathogenesis of fructose-induced non-alcoholic fatty liver disease (NAFLD), which has raised to epidemic proportions in Western society. This narrative review summarizes the most recent advances in the pathogenesis of HFI and discusses the implications for the understanding and treatment of fructose-induced NAFLD.

Keywords Hereditary fructose intolerance · Glucokinase regulatory protein · Ketohexokinase · Fructose · De novo lipogenesis · Non-alcoholic fatty liver disease

Introduction

Hereditary fructose intolerance (HFI; OMIM 22960), an inborn error of fructose metabolism, was first reported in 1956 by Chambers and Pratt [1]. A 24-year-old woman was admitted for evaluation of faintness, abdominal pain, and nausea upon fruit or sugar ingestion. The physicians subjected her to systematic, single-blinded exposure to a variety of oral sugars. Administration of solely fructose and sucrose, not glucose, galactose or lactose, provoked symptoms of nausea in a dose-dependent manner. Based on these findings, the patient was diagnosed with 'idiosyncrasy to fructose' [1]. Six years later, Hers and Joassin identified the enzymatic defect of HFI in two liver biopsy specimens as a 'functional deficiency of fructose-1-aldolase activity,' i.e., aldolase B [2].

Recent experimental and clinical studies have provided more insight into the pathogenesis of HFI, in particular its liver phenotype. In the present narrative review, we will give

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an overview of these studies and subsequently elaborate on the implications, not only for the treatment of HFI, but also for the current epidemic of fructose overconsumption.

Background

Clinical manifestations

The first symptoms of HFI appear when a neonate is exposed to fructose-containing infant formulas [3] or when fructose-containing foods, such as fruits and vegetables, are introduced to young infants [4, 5]. Signs of acute intoxication are vomiting, abdominal pain, lactic acidosis, hyperuricemia, hypoglycemia, and acute liver failure. Persistent fructose ingestion can lead to failure to thrive, liver disease (i.e., hepatic steatosis, fibrosis, and cirrhosis), signs of proximal renal tubular dysfunction (i.e., Fanconi syndrome), and eventually death. These sequelae can be prevented when treated with a fructose-restricted diet. Further, since fructose can also be synthesized endogenously from sorbitol (via the polyol pathway, Fig. 1), HFI patients additionally should avoid sorbitol-containing food products and high levels of high-glycemic foods [4, 5]. When adhering to these dietary restrictions, the prognosis of HFI appears excellent, although little is known about the long-term pathology of adults with HFI [6–9].

Genetics and epidemiology

The human gene for aldolase B *(ALDOB)* has been mapped to chromosome 9q22.3 [10, 11]. At present, over 40 causative mutations of the *ALDOB* gene have been documented, of which c.448G > C (p.A149P), c.524C > A (p.A174D), c.357delAAAC (Δ4E4), and c.1005C > G (p.N334 K) account for 59% and 86% of HFI mutations in North Americans and Europeans, respectively [12–17]. Based on the carrier frequency of the most common mutations in neonates, it has been estimated that the incidence of HFI is 1:18,000–20,000 in live births [18, 19].

Metabolic derangements

The metabolic derangements of aldolase B deficiency have been the scope of previous, high-quality review papers [9, 20, 21]. Briefly, fructose-1,6-bisphosphate aldolase (aldolase; EC 4.1.2.13) is responsible for the reversible conversion of fructose 1,6-bisphosphate (Fru 1,6-P_2) or fructose 1-phosphate (Fru 1P) to the triose phosphate dihydroxyacetone phosphate (DHAP) and either glyceraldehyde 3-phosphate (G3P) or glyceraldehyde, respectively, which are intermediates of the glycolytic/gluconeogenic pathway (Fig. 1) [22]. At least three aldolase isozymes (A, B, and C)

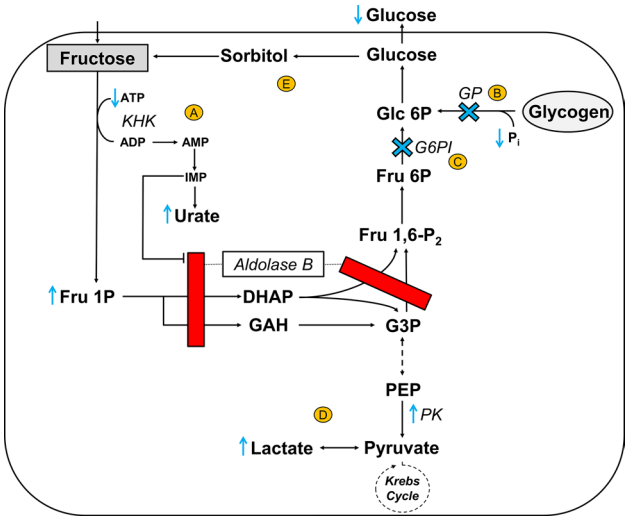

Fig. 1 Metabolic consequences of aldolase B deficiency in the liver after an oral fructose load. In physiological states, fructose is rapidly phosphorylated by KHK and subsequently converted by aldolase B to trioses (DHAP and GAH) that enter the glycolytic/gluconeogenic pathways. Aldolase B also catalyzes the conversion of Fru 1,6-P_2 to triose phosphates (DHAP and G3P). In aldolase B deficiency, the catabolism of Fru 1P is impaired, and the metabolism of Fru 1,6-P_2 is blocked (red bar). Accumulation of Fru 1P has several *acute* downstream effects denoted in yellow circled letters as follows: (1) depletion of intracellular inorganic phosphate (P_i) and ATP, and consequently formation of IMP and urate (A); (2) impairment of glycogenolysis (by inhibition of GP and loss of P_i) (B) and gluconeogenesis (by inhibition of G6PI) (C), resulting in hypoglycemia; and (3) stimulation of PK activity that—in combination with an impaired gluconeogenesis—promotes hyperlactatemia (D). Further, fructose, which can be produced endogenously from sorbitol (via the polyol pathway), may contribute to the accumulation of Fru 1P (E). Blue cross indicates blocked pathway as a consequence of Fru 1P accumulation. Dashed arrow indicates multiple intermediate enzymatic steps that have not been visualized for simplicity purposes. *ADP* adenosine diphosphate, *AMP* adenosine monophosphate, *ATP* adenosine triphosphate, *DHAP* dihydroxyacetone phosphate, *Fru 6P* fructose 6-phosphate, *Fru 1P* fructose 1-phosphate, *Fru 1,6-P_2* fructose 1,6-biphosphate, *G3P* glyceraldehyde 3-phosphate, *Glc 6P* glucose 6-phosphate, *G6PI* glucose-6-phosphate isomerase, *GAH* glyceraldehyde, *GP* glycogen phosphorylase, *IMP* inosine monophosphate, *KHK* ketohexokinase, *PEP* phosphoenolpyruvate, *P_i* inorganic phosphate, *PK* pyruvate kinase

have been described which differ in tissue expression and activity for the substrates Fru 1,6-P_2 and Fru 1P. Aldolase B is expressed in the liver, kidney, and small intestine and has activity for both Fru 1,6-P_2 and Fru 1P. This is in contrast to both aldolase A (predominantly expressed in skeletal muscle) and aldolase C (predominantly expressed in brain and smooth muscle) which have the highest efficiencies for Fru 1,6-P_2 as a substrate [23, 24], although aldolase C may perform fructose metabolism in the brain [25].

Liver biopsies of HFI patients show substantially reduced Fru 1P aldolase activity (0–15%), but preserved Fru 1,6-P_2 aldolase activity (5–30%) leading to a marked

increase in the ratio of Fru 1,6-P_2 to Fru 1P activities, which was used as a diagnostic before the introduction of genetic testing [26]. This remains the only definitive diagnostic test as so many HFI-causing mutations remain unknown or variants found by DNA testing have unknown consequences [15]. The relatively preserved Fru 1,6-P_2 aldolase activity could theoretically be explained by residual aldolase A activity in the liver that compensates for the defect in aldolase B activity for the substrate Fru 1,6-P_2, but not for Fru 1P [20], or, alternatively, aldolase A activity in erythrocytes, which are also present in liver lysates.

As a consequence of the catalytic deficiency of aldolase B, a fructose load in HFI patients results in the rapid accumulation of Fru 1P and, hence, intracellular inorganic phosphate (P_i) and adenosine triphosphate (ATP) depletion [27, 28]. Reduced P_i concentrations lead to an increased rate of degradation of adenosine 5'-monophosphate (AMP) [29]. As a result, adenosine deaminase and xanthine oxidase activities are increased and inosine monophosphate (IMP) and urate are rapidly formed (Fig. 1) [29]. The specific inhibition of aldolase B by the increased IMP further accentuates the increase in Fru 1P [28].

High levels of intrahepatic Fru 1P—in combination with the loss of P_i—inhibit glycogenolysis by impairment of glycogen phosphorylase (GP) [30–33]. This is also illustrated by the failure of exogenous glucagon to correct for the fructose-induced hypoglycemia in HFI patients [34, 35]. Further, high levels of Fru 1P impair gluconeogenesis by competitive inhibition of glucose-6-phosphate isomerase (G6PI) [36, 37]. The rate of gluconeogenesis may also depend on the intrahepatic concentration of ATP [38], which is low in case of HFI following fructose ingestion. The impaired gluconeogenesis is evidenced by the inability of dihydroxyacetone administration (which enters the gluconeogenic pathway) to prevent fructose-induced hypoglycemia in HFI patients [35]. In conclusion, fructose-induced, impaired glycogenolysis and gluconeogenesis both result in a decreased hepatic glucose production and, consequently, the rapid development of hypoglycemia. Of note, in the absence of fructose, gluconeogenesis is not impaired in HFI [39].

In addition, an impaired gluconeogenesis together with Fru-1P-induced activation of pyruvate kinase (PK) promotes accumulation of lactate and, consequently, hyperlactatemia [40, 41] (Fig. 1). Notably, these metabolic defects do not only occur after oral intake of fructose, but also upon sorbitol consumption [4, 42]. This is due to the oxidation of sorbitol to fructose via the polyol pathway (Fig. 1). This pathway of endogenous fructose production can be activated through dehydration and hyperosmolarity as well as high-glycemic foods [43–46].

Recent advances from animal studies

The phenotype of aldolase B knockout mice resembles the human HFI phenotype

Recent work has demonstrated that aldolase B knockout (ALDOB-KO) mice exhibit similar metabolic features as HFI patients [47, 48]. In these mice, chronic exposure to fructose resulted in growth retardation and death [47, 48]. An acute, oral fructose load caused a rise in serum liver enzymes and intestinal injury, characterized by the destruction of apical villi and the presence of apoptotic cells in the duodenum and jejunum [48]. In addition, ALDOB-KO mice exposed to an oral fructose load showed decreased hepatic ATP and phosphate levels, and elevated serum urate concentrations [48]. Finally, oral fructose provoked severe hypoglycemia in a dose-dependent fashion [48]. Exploration of the gluconeogenic pathway by a pyruvate tolerance test revealed a reduced, but not absent ability for gluconeogenesis [48]. This is remarkable given the absence of aldolase B, which not only affects fructolysis but also glycolysis/gluconeogenesis (Fig. 1). Furthermore, there was no residual aldolase A or C expression in the liver (Lanaspa, personal communication) and suggests that gluconeogenesis occurs in other tissues [49]. Some key enzymes of gluconeogenesis (i.e., phosphoenolpyruvate carboxykinase and glucose-6-phosphatase) were found to be upregulated in the livers of ALDOB-KO mice [48].

Although Fru-1P-mediated impairment of glycogenolysis was not specifically studied, the ALDOB-KO mice were characterized by an increased hepatic glycogen content after an oral fructose load [48]. Of interest, glycogen synthase activity—determined by the ratio of phosphorylated to total glycogen synthase—was increased [48], suggesting an enhanced glycogenesis. Of additional interest, the increased hepatic glycogen content and decreased serum glucose and insulin were also observed in ALDOB-KO mice that were not exposed to an acute oral fructose load [48]. This chronic feature could be due to the endogenous fructose production via the polyol pathway [4, 42] or, alternatively, an increased hepatic glucose uptake (see below).

Aldolase B knockout mice are characterized by an increased intrahepatic triglyceride content

In addition to the above-described metabolic features, ALDOB-KO mice chronically exposed to small amounts of fructose in the chow (~0.3%) displayed an increased amount of hepatic triglycerides, hepatic inflammation—characterized by the presence of apoptotic and necrotic

cells, and diffuse macrophage infiltration—and signs of periportal fibrosis [47, 48]. Hepatic expression of enzymes involved in de novo lipogenesis (DNL), i.e., ATP-citrate lyase (ACL), acetyl-CoA carboxylase (ACC), fatty acid synthase (FAS), was greater in ALDOB-KO mice, suggesting that this pathway accounts, at least in part, for the increased hepatic triglycerides levels [48]. In addition, cytosolic glucokinase (GCK) was more abundant in ALDOB-KO mice when compared to wild-type mice [48].

GCK converts glucose to glucose 6-phosphate (Glc 6P) in the liver, pancreas, and pituitary and is the first step in glycolysis. Thanks to its unique kinetic properties, GCK is a major regulator of hepatic glucose uptake and pancreatic insulin secretion [50]. In the post-absorptive state, hepatic GCK is bound to glucokinase regulatory protein (GKRP), a liver-specific protein. The GKRP-GCK complex resides in the nucleus and thus inactivates GCK [51, 52]. In the postprandial state, a rise in intracellular glucose facilitates the dissociation of GCK from GKRP and migration of GCK to the cytosolic space where it facilitates phosphorylation and, hence, storage of glucose. Of interest, Fru 1P is a very potent disruptor of the GKRP-GCK complex. Experimental studies have shown that only trace amounts of Fru 1P are required to dissociate GCK from GKRP [52–57]. Notably, intrahepatic Fru 1P concentrations in ALDOB-KO mice were also elevated after chronic exposure to only small amounts of fructose in the chow [48]. From these studies, it can be speculated that accumulation of Fru 1P in ALDOB-KO mice chronically fed small amounts of fructose induces dissociation of the GKRP-GCK complex, which would explain the greater cytosolic GCK activity in ALDOB-KO mice. Consequently, hepatic glucose uptake is stimulated, thereby contributing to the reduced serum glucose and insulin levels in these mice. The metabolic fate of the glucose taken up by the liver can be several fold, among others an enhanced storage of glycogen and fat. Although the latter requires glycolysis (which appears to be blocked in case of aldolase B deficiency) and subsequent DNL, the pentose phosphate pathway (PPP)—a metabolic pathway that parallels glycolysis—may serve as an alternative pathway to convert Glc 6P to G3P (Fig. 2). Of interest, a previous experimental study has shown that the PPP increases in parallel to DNL in rat fatty livers [58].

There are other biologically plausible mechanisms that could explain the upregulated DNL pathway leading to hepatic fat accumulation in ALDOB-KO mice. First, experimental studies have shown that activation of the AMP-deaminase pathway and formation of urate (Fig. 1) induces mitochondrial dysfunction, which results in downregulation of fatty acid oxidation and stimulation of DNL [59]. Second, carbohydrate-responsive element-binding protein (ChREBP) is activated upon intracellular phosphate depletion and stimulates expression of glucose-6-phosphatase and DNL genes [60, 61], all in accordance with the observations in ALDOB-KO mice [48].

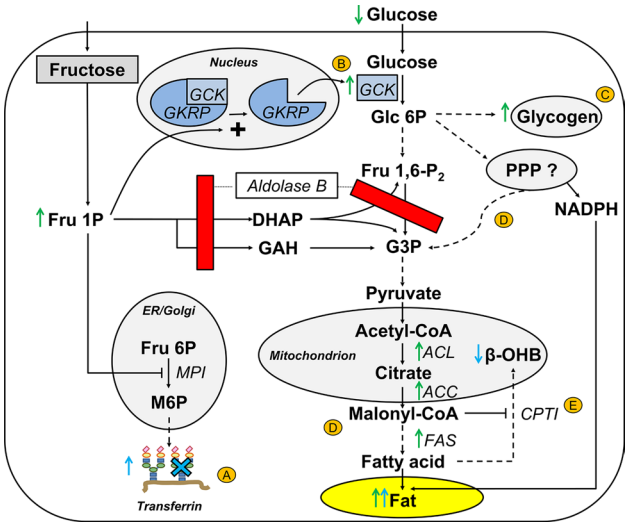

Fig. 2 Hypothesized pathogenesis of hepatic fat accumulation in aldolase B deficiency. Accumulation of Fru 1P has several *chronic* downstream effects leading to fat accumulation denoted in yellow circled letters. ALDOB-KO mice fed a low-fructose diet (~0.3%) display increased hepatic Fru 1P concentrations. This also seems to be the case in adult HFI patients treated with a fructose-restricted diet, as can be deduced from an abundancy of circulating hypoglycosylated transferrin. Hepatic Fru 1P inhibits glycosylation of transferrin by impairment of MPI (A). Catalytic amounts of Fru 1P dissociate GCK from GKRP in the nucleus, which allows migration of GCK toward the cytosolic space where it converts glucose to Glc 6P and, as a consequence, facilitates hepatic glucose uptake (B). The metabolic fates of an increased hepatic glucose uptake can be: (1) storage as glycogen (C) and (2) storage as fat via DNL with carbons and electrons derived from possibly the pentose phosphate pathway (PPP) (D). Malonyl-CoA, an intermediate of DNL, inhibits fatty acid beta-oxidation (and formation of β-OHB) through impairment of the mitochondrial fatty acid transporter CPTI (E). Of note, alternative mechanisms may contribute to the development of hepatic fat accumulation in aldolase B deficiency as well, such as Fru 1P-induced formation of urate and activation of ChREBP, which both stimulate DNL (see text). Green arrows indicate observations in ALDOB-KO mice. Blue arrows and blue cross indicate observations in HFI patients. Dashed arrow indicates multiple intermediate enzymatic steps that have not been visualized for simplicity purposes. *ACC* acetyl-CoA carboxylase, *ACL* ATP-citrate lyase, *ALDOB* aldolase B, *β-OHB* beta-hydroxybutyrate, *CPTI* carnitine palmitoyltransferase I, *DHAP* dihydroxyacetone phosphate, *ER* endoplasmic reticulum, *Fru 6P* fructose 6-phosphate, *FAS* fatty acid synthase, *Fru 1P* fructose 1-phosphate, *Fru 1,6-P$_2$* fructose 1,6-biphosphate, *G3P* glyceraldehyde 3-phosphate, *Glc 6P* glucose 6-phosphate, *GAH* glyceraldehyde, *GCK* glucokinase, *GKRP* glucokinase regulatory protein, *M6P* mannose 6-phosphate, *MPI* mannose-6-phosphate isomerase, *NADPH* nicotinamide adenine dinucleotide phosphate, *PPP* pentose phosphate pathway

Inhibition of ketohexokinase protects ALDOB-KO mice from metabolic derangements

The importance of Fru 1P in the pathogenesis of the metabolic derangements as observed in ALDOB-KO mice was unequivocally demonstrated by inhibition of ketohexokinase (KHK), the enzyme that catalyzes the first step in fructose metabolism: the phosphorylation of fructose to yield Fru 1P. In most mammals, including humans, KHK exists as two isoforms, A and C [62]. KHK-C has high affinity for fructose and is abundant in the liver, intestine, and kidney. In contrast, KHK-A has much lower affinity for fructose and is more ubiquitously expressed [63]. Nearly, all of the aforementioned metabolic abnormalities in ALDOB-KO mice ameliorated when they were crossed with KHK knockout (KHK-KO) mice, i.e., both KHK-A and KHK-C [48]. Further, similar results were observed after treatment with osthole, a natural KHK inhibitor [64]. Fructose-loaded ALDOB-KO mice treated with osthole were protected from intrahepatic ATP depletion, hyperuricemia, rise in liver enzymes, and severe hypoglycemia [48]. In addition, osthole treatment resulted in a decrease in the GCK cytosol/nucleus ratio, indicative of more GCK bound to GKRP in the nucleus [48].

Importantly, ALDOB-KO mice were not protected from the above-mentioned metabolic abnormalities when crossed with KHK-A specific knockout mice [48]. In fact, the mice possessing only KHK-C resulted in an exacerbated phenotype [48]. This observation is likely explained by the fact that inhibition of KHK-A results in reduced metabolism of fructose in peripheral tissues and, hence, a greater supply to the liver, which is detrimental in case of aldolase B deficiency. These findings suggest that inhibition KHK-C may serve as a therapeutic target that could make the fructose-restricted diet redundant in HFI patients.

Recent advances in humans

Patients with HFI are characterized by an increased intrahepatic triglyceride content

Until recently, only anecdotal reports suggested that hepatic fat accumulation persists in HFI patients, despite a fructose-restricted diet [6]. A recent cross-sectional observational study including 16 genetically diagnosed HFI patients reported a high prevalence of fatty liver, as assessed by ultrasound or hepatic magnetic resonance imaging [65]. This issue was recently more structurally addressed in 15 adult HFI patients who were on a lifelong fructose-restricted diet, ranging from 0.3 to 7.0 grams of fructose per day (the average fructose intake of American adults ranges from 32 to 75 grams per day [66]). Magnetic resonance imaging spectroscopy of the liver revealed that intrahepatic triglyceride (IHTG) content was higher in HFI patients in comparison with 15 healthy age-, sex-, and BMI-matched individuals [67]. Although liver stiffness, a non-invasive marker of liver fibrosis, was not significantly different between both groups, one HFI patient displayed a liver stiffness measurement compatible with liver fibrosis stage 3 or higher. Metabolic profiling revealed that HFI patients were more glucose intolerant, as reflected by higher plasma glucose excursions during a standard 75-gram oral glucose tolerance test [67].

Further investigations to delineate the underlying mechanism that leads to an increased IHTG content in HFI patients were limited due to the noninvasive nature of human studies. Nevertheless, the use of liver-specific plasma biomarkers allowed some insight. First, hypoglycosylated transferrin, a liver-specific protein, was more abundant in HFI patients, which is in line with previous studies [68, 69]. Experimental studies have shown that Fru 1P inhibits mannose-6-phosphate isomerase (MPI) activity, one of the first enzymes involved in the glycosylation process (Fig. 2) [70]. The higher levels of hypoglycosylated transferrin (yet within the normal range) therefore suggest that intrahepatic Fru 1P concentrations are higher in HFI patients than in controls, even on a fructose-restricted diet. This may be explained by the minute levels of ingested fructose (blocked by aldolase B) or, alternatively, by endogenous fructose production via the polyol pathway. Despite the suggestion of higher intrahepatic Fru 1P levels in HFI patients on a fructose-restricted diet, plasma uric acid concentrations were not different between both groups [67]. This finding is consistent with observations in ALDOB-KO mice, which only displayed increased plasma uric acid levels after an oral fructose load [48].

Second, plasma beta-hydroxybutyrate levels, a liver-specific biomarker of beta-oxidation, were significantly lower in HFI patients compared to healthy individuals [67]. Notably, DNL and beta-oxidation are reciprocally regulated. Malonyl-CoA, a precursor of de novo synthesized fatty acids, inhibits the activity of the long-chain fatty acid transporter carnitine palmitoyltransferase I (CPTI). Consequently, the transport of long-chain fatty acids over the mitochondrial membrane is hampered and beta-oxidation is impaired [71]. It can therefore be concluded that the biomarker patterns in HFI patients are similar to the in-depth phenotyping of the ALDOB-KO mice (as illustrated in Fig. 2).

Variants in the GKRP gene show phenotypic similarities with ALDOB-KO mice and HFI patients

Unfortunately, it is not possible to non-invasively measure the GKRP-GCK interaction as a potential explanation for the increased IHTG content in HFI patients, since this would require liver biopsies. Nevertheless, genetic epidemiology is a valuable tool in predicting the metabolic consequences

of increased GKRP-GCK disruption in humans [72]. Rs1260326 and rs789004 are common variants in the GKRP gene (*GCKR*), which are in strong linkage disequilibrium. The former is a functional variant that encodes a GKRP protein that dissociates from GCK more easily [73], comparable to the effect of Fru 1P on the GKRP-GCK complex. The previously reported associations of these common gene variants with cardiometabolic traits in the general population show some striking similarities with the metabolic abnormalities observed in ALDOB-KO mice and HFI patients (Table 1). First, variants in *GCKR* have been associated with reduced beta-hydroxybutyrate levels, pronounced DNL, and a greater IHTG content [74–77]. Further, these variants have been associated with lower fasting insulin concentrations [78, 79] and higher 2-h post-glucose load glucose levels [80], the former in agreement with ALDOB-KO mice [48] and the latter with HFI patients [67]. Of note, despite the consistently reported association between *GCKR* variants and increased plasma triglycerides [78, 79], HFI patients were characterized by normal plasma triglycerides levels [67]. This discrepancy may be explained by the fact that HFI patients were (relatively) metabolically healthy, i.e., non-(abdominally) obese [67]. We previously reported that *GCKR* interacts with metabolic health on plasma triglycerides, i.e., the unhealthier the greater the effect on plasma triglycerides levels [81]. Finally, a recent meta-analysis suggested that the common variants in *GCKR* protect against chronic kidney disease, but predisposes to cardiovascular disease (CVD) [82]. These relevant clinical endpoints have not been addressed in HFI patients chronically treated with a fructose-restricted diet and therefore deserve further study.

Implications for the current epidemic of fructose overconsumption

Since the industrial revolution, the intake of fructose in the USA has risen dramatically [66]. Fructose—which has a sweeter taste than glucose—is often added as a sweetener (e.g., as high fructose corn syrup) to processed foods. Given the parallel increase in fructose consumption and the current obesity epidemic and its sequelae (dyslipidemia, type 2 diabetes mellitus [T2DM], gout, and CVD) in Western society, fructose has been implicated as a major contributing factor [83–86].

Non-alcoholic fatty liver disease (NAFLD), a histological spectrum ranging from simple steatosis to steatohepatitis, fibrosis, and cirrhosis, is another frequently encountered phenomenon in obese individuals [87]. NAFLD may not only progress to end-stage liver failure and hepatocellular carcinoma, and it has also been associated with new-onset T2DM and CVD [88, 89]. The pathogenesis of NAFLD involves a complex interaction between genetic factors and unhealthy lifestyle habits [90].

Table 1 Cardiometabolic features in ALDOB-KO mice, HFI patients, and human carriers of common variants in the *GCKR* gene

	ALDOB-KO mice[a]	HFI patients[b]	*GCKR*[c]	References
Intrahepatic triglycerides	↑	↑	↑	[48, 65, 67, 105]
Serum AST/ALT[d]	↑	↑	↑	[48, 65, 106]
DNL[e]	↑	?	↑	[48, 76]
Serum beta-hydroxybutyrate	?	↓	↓	[67, 74]
Intrahepatic glycogen	↑	?	?	[48]
Serum glucose	↔	↔	↓	[48, 67, 78–80]
Serum glucose, 2 h post-glucose load	?	↑	↑	[48, 67, 80]
Serum insulin	↓	↔	↓	[48, 67, 79, 80]
Serum urate	↔	↔	↑	[48, 67, 107, 108]
Serum triglycerides	?	↔	↑	[65, 67, 78, 79, 81]
eGFR[f]	?	?	↑	[82]
Coronary artery disease	?	?	↑	[82]

Arrows indicate the direction of association, not the effect size

[a]Observations in ALDOB-KO mice fed a low-fructose diet (~0.3%)

[b]Observations in adult HFI patients chronically treated with a fructose-restricted diet

[c]Common variants in rs1260326 and rs780084, which encode a GKRP protein that binds glucokinase less effectively

[d]Aspartate transaminase (AST) and alanine transaminase (ALT)

[e]De novo lipogenesis (DNL) is assessed by hepatic expression of key enzymes (ALDOB-KO mice) and stable isotopes (*GCKR*)

[f]*eGFR:* estimated glomerular filtration

Experimental studies in rodents and humans have unequivocally demonstrated that fructose overfeeding leads to an increased hepatic fat content [91–95] and many symptoms of the metabolic syndrome [96]. The mechanism by which fructose causes hepatic fat accumulation can be directly by serving as a substrate for DNL. Further, fructose can also indirectly enhance DNL via the hitherto mentioned mechanisms: (1) Fru 1P-induced disruption of the GKRP-GCK complex, which facilitates hepatic glucose uptake and consequently DNL (Fig. 2); (2) Fru 1P-induced ATP depletion and urate formation, which stimulates DNL [27–29]; and (3) Fru 1P-induced intracellular phosphate depletion, which activates ChREBP, a transcription factor with multiple downstream effects, among other stimulation of DNL [60, 61]. Of note, these processes have been observed in humans with normal aldolase B function [97–99].

The recent studies in ALDOB-KO mice and HFI patients suggest that the direct lipogenic effects of fructose do not necessarily play a role in the pathogenesis of fructose-induced NAFLD [48, 67]. Moreover, they suggest that the accumulation of intermediates of fructolysis, i.e., Fru 1P, is a key element in the pathogenesis of fructose-induced NAFLD.

From these findings, it can also be deduced that inhibition of Fru 1P formation by blocking upstream KHK activity may be a novel therapeutic modality, not only for HFI, but also for fructose-induced NAFLD. Indeed, the fatty liver phenotype in fructose-fed mice improved after treatment with liver-specific small interfering RNA (siRNA) targeting KHK expression [100]. Further, previous experimental studies have demonstrated that fructose-fed KHK-KO mice were protected from hepatic fat accumulation and other metabolic abnormalities, such as obesity and hyperinsulinemia, when compared to wild-type mice [101–103]. Again, analogous to the observations in ALDOB-KO [48], specific knockout of KHK-A resulted in an exacerbation of the metabolic abnormalities, including increased hepatic fat accumulation [102, 103]. Of interest, in humans, a loss of KHK results in essential fructosuria (OMIM #229800) [39]. This benign condition is not known to provoke any clinical symptoms [39] and, hence, emphasizes the therapeutic potential of KHK inhibition.

Future perspectives

The recent studies in aldolase B-deficient mice and HFI patients have contributed to our understanding of the pathogenesis of HFI and fructose-induced NAFLD [48, 67]. There are, however, several issues that deserve further study.

First, experimental studies are warranted to establish the exact roles (and their relative contributions) of the GKRP-GCK complex, urate, and ChREBP as potential mediators in the pathogenesis of hepatic fat accumulation in aldolase B deficiency. Furthermore, although the recent studies have convincingly identified Fru 1P as the key driver behind hepatic fat accumulation in aldolase B deficiency, the exact contribution of endogenous fructose production (via the polyol pathway) to the accumulation of intrahepatic Fru 1P remains to be elucidated. Future studies are warranted to determine to what extent gluconeogenesis and glycolysis are functional in aldolase B-deficient livers, and which alternative pathways (e.g., PPP) are involved. Long-term follow-up of a large cohort of HFI patients is needed to study whether these patients are protected from chronic kidney disease and predisposed to CVD, similar to individuals carrying common variants in *GCKR* [82]. Finally, clinical studies are required to demonstrate whether KHK inhibition will: a) replace the fructose-restricted diet as a treatment for HFI and b) be efficacious in the treatment of fructose-induced NAFLD in the general population. Interestingly, Huard et al. [104] recently reported the discovery of a small molecule that selectively inhibits KHK activity in vitro and in vivo more effectively than osthole.

Concluding remarks

HFI is a rare inborn error of fructose metabolism. Recent studies in ALDOB-KO mice and HFI patients have proposed a prominent role for Fru 1P in the pathogenesis of hepatic fat accumulation, and suggest that an increased dissociation of GCK from GKRP is involved. These findings have therapeutic implications for not only HFI, but also for fructose-induced NAFLD in the general population. These studies clearly demonstrate that fructose-induced NAFLD can benefit from the insight gained from rare inborn errors of metabolism, and vice versa.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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