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# Dietary Fructose and Fructose-Induced Pathologies

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## Keywords

fructose, ketohexokinase, fatty liver, lipogenesis, intestine, gut microbiota

## Abstract

The consumption of fructose as sugar and high-fructose corn syrup has markedly increased during the past several decades. This trend coincides with the exponential rise of metabolic diseases, including obesity, nonalcoholic fatty liver disease, cardiovascular disease, and diabetes. While the biochemical pathways of fructose metabolism were elucidated in the early 1990s, organismal-level fructose metabolism and its whole-body pathophysiological impacts have been only recently investigated. In this review, we discuss the history of fructose consumption, biochemical and molecular pathways involved in fructose metabolism in different organs and gut microbiota, the role of fructose in the pathogenesis of metabolic diseases, and the remaining questions to treat such diseases.

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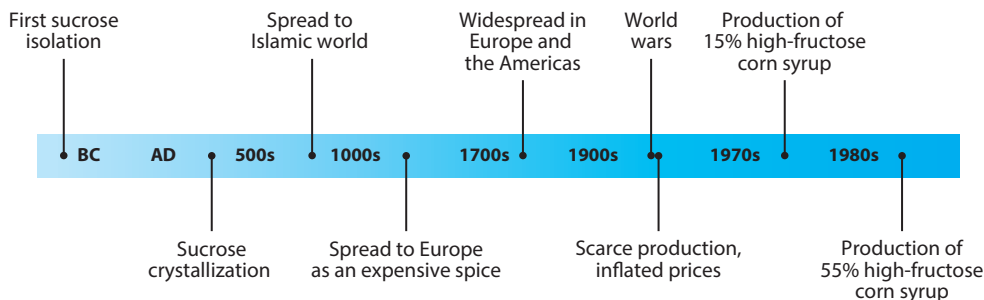
## 1. HISTORY OF FRUCTOSE CONSUMPTION

### 1.1. Fructose History

In all living creatures, glucose is a major carbohydrate in the animal kingdom, whereas sucrose, a disaccharide form of glucose and fructose, is a major carbohydrate in the plant kingdom. In some plants, a plentiful fructose monomer also exists. When animals consume plants, their digestion system quickly hydrolyzes sucrose into glucose and fructose monomers via the sucrase enzyme in the small intestine (56). Early *Homo sapiens* had consumed fructose in various plants and fruits, especially in the fall, to store energy for survival during the winter. The overall total energy intake from fructose was efficiently consumed without causing excessive energy accumulation. However, in modern society with readily available sugar-containing processed foods, fructose has become the major dietary carbohydrate (45) and contributes to diverse systemic diseases and health burdens.

Historically, it is believed that sucrose was first isolated from sugarcane and sugar beet in the form of juice around 800 BC in India (145) (**Figure 1**). In the early centuries AD, the Indians successfully produced granulated sucrose crystals from juice, promoting efficient trade to the Islamic world. Such sucrose was used for medicinal purposes as well as for an expensive spice called sweet salt. In the seventeenth century, widespread cultivation and advanced processing of cane sugar in Europe and the United States made sucrose more affordable. Since then, sucrose has become a semi-essential ingredient widely used in a vast variety of beverages and food.

In the mid-twentieth century, because of the destruction of the sugar industry and political instability during the two world wars, sucrose became scarce, and prices inflated. This caused



**Figure 1**

Fructose history: from the isolation of plant-based sucrose to the industrial production of 55% high-fructose corn syrup, a common sweetener in modern society.

producers to seek new ingredients for sweetness and led to the development of corn starch as an alternative. Corn starch, which was a plentiful and dependable agricultural raw material, was used to produce corn syrup. However, glucose, which is the main component of corn syrup, is not as sweet as sucrose. In the 1970s, a manufacturing breakthrough occurred in the sugar industry. High-fructose corn syrup (HFCS) containing 15% fructose was developed through an enzyme reaction in which glucose isomerase converts glucose into fructose (134). Then, manufacturers focused on increasing the fructose content in HFCS. In the 1980s, HFCS containing 55% fructose, which is a similar ratio of glucose and fructose to that in sucrose, was produced and has been widely used for beverages (56). It has replaced sucrose as a cheaper and sweeter substitute and has been used for almost all popular processed foods, including chocolate, jelly, ice cream, and sweetened drinks.

## 1.2. Increased Fructose Consumption in Modern Society

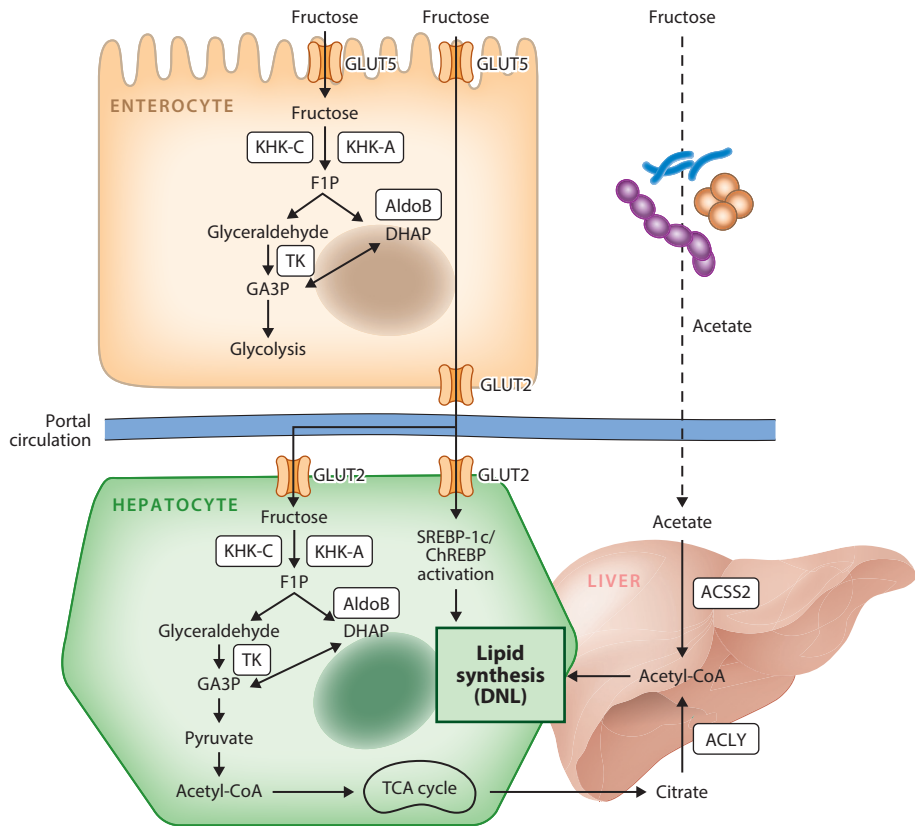
Since the 1980s, obesity and overweight have increased remarkably. Currently, approximately 35% of Americans are classified as obese or overweight (45). Such a fast rise is attributed to excess energy intake relative to energy expenditure because genetic backgrounds and other intrinsic biological processes cannot be changed in such a short time. In this respect, one of the most significant changes in food consumption in modern society was the increased intake of fructose.

In particular, fructose intake as HFCS has substantially increased in the United States over the past few decades (113). From the 1970s to 2000s, the average American's annual intake of HFCS increased tremendously from 0.23 kg to 28.4 kg, while intake of sucrose moderately decreased from 46.4 kg to 30.5 kg. Daily fructose consumption has also increased by 26%, from 64 g/day in the 1970s to 81 g/day in the 2000s (48, 100). Thus, fructose has become a significant proportion of energy intake in the typical American diet.

## 2. FRUCTOSE METABOLISM

### 2.1. Fructose Uptake in the Intestine, Liver, and Other Organs

Like other dietary nutrients, fructose is absorbed by the small intestine, regardless of pure fructose, sucrose, or HFCS ingestion. Fructose is transported through specific fructose transporters, glucose transporter 5 (GLUT5) and GLUT2 (53, 114) (**Figure 2**). GLUT5 is highly expressed in the small intestine, kidneys, adipose tissue, skeletal muscle, and brain, but barely expressed in the liver. GLUT5 is located on the apical side of the enterocyte luminal pole, facilitating fructose transport from the intestinal lumen into the epithelial cells with a high affinity for fructose ( $K_m = 6.0$  mM) (12, 114). Contrary to glucose, this process does not require adenosine



**Figure 2**

Fructose metabolism. Fructose is taken up by GLUT5 or GLUT2 in enterocytes or hepatocytes. Fructose is subsequently phosphorylated by KHK-C/A into F1P, which is cleaved by AldoB into DHAP and glyceraldehyde. Both then enter the glycolysis and TCA cycle. In liver, some citrate is converted to cytosolic acetyl-CoA via the ACLY enzyme. Alternatively, acetate, which is catabolized from fructose by gut microbiota, is converted into cytosolic acetyl-CoA by ACS2 and is used for hepatic lipid synthesis. Fructose catabolism also activates DNL signaling pathways via the transcription factors SREBP-1c and ChREBP. Abbreviations: acetyl-CoA, acetyl coenzyme A; ACLY, ATP citrate lyase; ACS2, acetyl-CoA synthetase 2; AldoB, aldolase B; ChREBP, carbohydrate-responsive element-binding protein; DHAP, dihydroxyacetone phosphate; DNL, de novo lipogenesis; F1P, fructose-1-phosphate; GA3P, glyceraldehyde-3-phosphate; GLUT2, glucose transporter 2; GLUT5, glucose transporter 5; KHK-A, ketohexokinase-A; KHK-C, ketohexokinase-C; SREBP-1c, sterol-responsive element-binding protein; TCA, tricarboxylic acid; TK, triose kinase.

triphosphate (ATP) hydrolysis and is independent of sodium absorption. GLUT2, which has a low fructose affinity ( $K_m = 66.0$  mM), diffuses fructose out of the enterocyte into the portal circulation (18, 53). GLUT5 immunoreactivity was also reported in the basolateral membrane of human enterocytes (9), but the release of fructose into the portal circulation through GLUT5 remains unclear. In the liver, fructose transport is primarily mediated by GLUT2 (37), which is also highly expressed in the kidneys. GLUT8 highly expressed in the liver and heart was reported to play a role in fructose transport in mice (27).

The importance of GLUT5 as a major intestinal fructose transporter has been demonstrated by genetically modified mice. GLUT5 whole-body knockout (KO) mice do not show any

defects under a typical chow diet but exhibit lethal phenotypes under fructose feeding (114). In contrast, *Glut2* whole-body KO mice develop only mildly decreased fructose absorption (53). In humans, hereditary fructose intolerance, potentially involving GLUT5 deficiency or other mutations in fructose catabolic enzymes, manifests a colonic dilation and increased intestinal permeability (5). GLUT5 expression can be stimulated by increased fructose consumption (23), largely through carbohydrate-responsive element-binding proteins (ChREBPs) (78), and the thioredoxin-interacting protein (35).

## 2.2. Fructolysis in the Intestine and Liver

Although glucose and fructose are chemically very similar (both are  $C_6H_{12}O_6$ ), fructose has a keto group, whereas glucose has an aldehyde group. This relatively small structural difference results in dramatically distinct cellular metabolisms of glucose and fructose. Ketohexokinase (KHK) initiates the fructose mechanism through phosphorylation of fructose to fructose-1-phosphate (F1P). This reaction can lead to ATP depletion when excessive fructose is catabolized (31, 59). KHK has two alternatively spliced isoforms: KHK-A and KHK-C. KHK-A is ubiquitously expressed in most tissues (31) but has a very low affinity ( $K_m = 1$  mM). KHK-C, with a high affinity for fructose ( $K_m = 20$   $\mu$ M), is expressed primarily in the liver, intestine, and kidney, making it of primary importance in fructolysis (31, 66). Although KHK-A has a low fructose affinity, KHK-C isoform-specific KO mice showed a high residual ( $\sim 30$ – $50\%$ ) intestinal fructose catabolic activity (69), suggesting that KHK-A significantly contributes to fructose metabolism, at least in the intestine where the luminal fructose level is high enough to activate KHK-A. Importantly, *Khk-A/C* whole-body double-KO mice showed resistance to metabolic syndromes induced by fructose consumption, with most fructose excreted by urine (66). This key finding led to the development of KHK inhibitors for the treatment of fructose-related pathology (see below).

Aldolase B (AldoB), the next enzyme that breaks down F1P, is also crucial for fructose catabolism. AldoB splits F1P into glyceraldehyde and dihydroxyacetone phosphate, the latter of which enters glycolysis (10, 51). Glyceraldehyde is converted to glyceraldehyde-3-phosphate via triose kinase, which is an important step that affects fructose-dependent fat synthesis and pathologies (93). *AldoB* whole-body KO mice showed high hepatic F1P accumulation with lethal fat accumulation and fibrosis in the liver, which in part mimics human patients with fructose intolerance (110). Importantly, these pathological phenotypes caused by AldoB depletion were largely rescued by KHK inhibition (86), demonstrating that F1P is the major cause of hepatic detrimental effects. AldoB deficiency in humans also impairs renal function upon fructose ingestion (83). KHK inhibitors are likely to suppress this fructose-induced kidney disorder, which requires more clinical investigations.

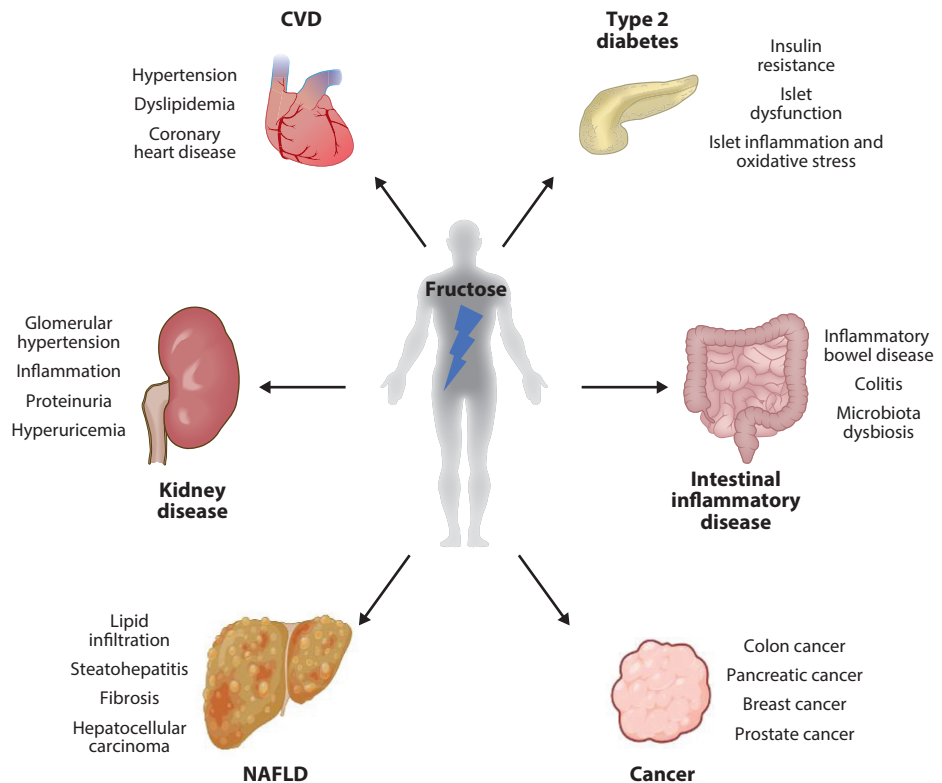
## 2.3. Fructose-Induced Lipogenesis

Compared with glucose, fructose is a more potent inducer of hepatic de novo lipogenesis (DNL), which converts excess carbons into lipids. Fructose-derived carbons first enter the tricarboxylic acid (TCA) cycle and generate citrate to provide cytosolic acetyl coenzyme A (acetyl-CoA) for DNL. ATP citrate lyase (ACLY) is the essential enzyme for generating such lipogenic cytosolic acetyl-CoA (74). Recently, an alternative pathway of DNL, especially under high-fructose feeding, was shown to be activated through acetyl-CoA synthetase 2 (ACSS2). When a high amount of fructose is consumed, unabsorbed fructose reaches the colon and is converted into short-chain fatty acids (SCFAs) (primarily acetate) by the gut microbiota (68). Acetate is then transported through the portal blood and feeds hepatic acetyl-CoA via ACSS2. To initiate DNL, cytosolic acetyl-CoA should be converted to malonyl-CoA by acetyl-CoA carboxylase, which is the rate-limiting step of

DNL. After palmitate is synthesized via fatty acid synthase, elongation and desaturation of palmitate subsequently occur (54, 131). Importantly, fructose not only provides carbons for DNL but also activates lipogenic transcription machinery. Such a signaling effect of fructose is mainly mediated by the transcription factors ChREBP (especially ChREBP- $\beta$ ) and sterol-responsive element-binding protein (SREBP-1c). Although the signaling molecule in the fructolysis pathway that activates ChREBPs and SREBP-1c remains controversial, the key role of ChREBP in fructose catabolism and consequent lipogenesis has been demonstrated (79).

### 3. FRUCTOSE-RELATED DISEASES AND UNDERLYING MECHANISMS

Epidemiological and experimental feeding studies have indicated the causal relationship between excessive fructose intake and metabolic diseases including obesity, nonalcoholic fatty liver disease (NAFLD), cardiovascular disease (CVD), and type 2 diabetes (Figure 3). For example, Olsen & Heitmann (109) found a positive correlation between the intake of sweetened beverages and obesity in a meta-analysis of 19 clinical studies. In the NAFLD study, 80% of patients had a soft drink more than once per day, while only 17% of healthy controls had a soft drink more than once per day for the 6-month observation period. Fructose consumption through soft drinks also had an association with higher CVD risk factors such as waist circumference, fasting blood glucose,



**Figure 3**

Fructose-related pathologies. Excessive fructose metabolism and consequent metabolic products contribute to diverse metabolic and inflammatory diseases, including nonalcoholic fatty liver disease (NAFLD), type 2 diabetes, dyslipidemia, colitis, cardiovascular disease (CVD), and renal disease. Fructose consumption is also linked to many different types of cancers.

blood pressure, serum triglycerides, and cholesterol. These factors had a 48% higher prevalence in individuals who consumed soft drinks more than once per day compared with individuals who consumed soft drinks less than once per day (30). In addition, individuals drinking more than one sweetened beverage per day showed an 83% higher risk of type 2 diabetes compared with individuals drinking less than one beverage per day in an 8-year prospective cohort study (128). In this section, we discuss the link between fructose and each disease and the potential molecular mechanisms.

### 3.1. Nonalcoholic Fatty Liver Disease

Among the many diseases related to fructose, NAFLD has emerged as the most prevalent disease associated with chronic fructose intake. NAFLD is diagnosed on the basis of the presence of hepatocytes with lipid infiltration but no evidence of infection, inborn metabolic disorder, or steatogenic drug or alcohol consumption (146). NAFLD can progress to nonalcoholic steatohepatitis, which is histologically characterized by the presence of steatosis and lobular inflammation in hepatocytes (16). NAFLD has the potential to evolve into cirrhosis, end-stage fibrotic liver disease, and occasionally hepatocellular carcinoma (16). Fructose intake has a dose-dependent correlation with NAFLD development and progression (1). Meanwhile, lifestyle changes along with restricting dietary fructose intake have reduced hepatic triglyceride accumulation (39). While some human studies did not find a clear association between fructose intake and NAFLD development due to many variable factors (genetic and environmental) (118), mounting evidence indicates that fructose consumption, especially in a liquid form, is linked to the development of NAFLD.

Fructose can induce NAFLD in many different ways. Due to its delightful taste, fructose increases food consumption, elevating total energy intake. Studies have also shown that fructose directly affects neuronal and hormonal signaling that controls appetite (96). In addition, the unique biochemistry and organ metabolism of fructose may mediate fructose-induced NAFLD. Unlike glucose, fructose is mainly catabolized by the small intestine followed by the liver (114). High-dose fructose, however, overwhelms the small intestinal fructose clearance, causing excess fructose to reach the liver (68).

Fructose catabolism by hepatocytes can deplete ATP and activate the adenosine monophosphate (AMP) deaminase pathway, inducing excessive uric acid production (70). Accumulation of uric acid in the hepatocytes inhibits CoA hydratase activity with consequent decrease of fatty acid  $\beta$ -oxidation, which leads to hepatic lipid accumulation (20). Interestingly, a recent paper shows an alternative relationship between fructose and metabolites in the AMP deaminase pathway in NAFLD development. The authors showed that inosine monophosphate can induce NAFLD via the induction of AMP deaminase 2 and purine degradation (3). While the epidemiological evidence between high circulating uric acid and NAFLD is ample, their causal relationship is less clear, as animal models with hyperuricemia do not develop NAFLD (97).

Another important effect of fructose intake on the liver is the induction of lipogenesis. In patients with NAFLD, DNL was shown to be threefold greater than in healthy individuals (84). It has long been believed that fructose itself delivers excessive carbons for lipogenesis to the hepatocytes. However, a recent study using liver-specific KO mice of *Acly*, an essential enzyme for lipogenesis, challenged this notion (148). While these mice were not able to use cytosolic citrate for lipogenesis, they still developed NAFLD under a high-fructose diet. Using isotope tracing, the group discovered that copious amounts of fructose feed hepatic lipogenesis via gut microbiota-derived acetate, which bypasses ACLY. Antibiotics treatment or liver-specific knock out of *Acs2*, the essential enzyme for acetate catabolism, sufficiently reduced fructose-dependent hepatic lipogenesis.



In addition to lipogenic acetate production, fructose that reaches the large intestine also has other detrimental effects that contribute to NAFLD, such as increased intestinal epithelial permeability (47). This causes the delivery of toxic microbial metabolites from the gut lumen to the liver, activating inflammatory signals in liver cells (hepatocytes and immune cells) to trigger NAFLD (105). Chronic fructose intake can also induce microbiota dysbiosis, which augments inflammatory signals (105). Mice lacking Toll-like receptor 4 (TLR4), the inflammatory signal receptor, showed reduced onset of NAFLD (44), while TLR4 agonists trigger lipogenesis and NAFLD (92). On the other hand, a recent systematic genetics approach using the progeny of fructose-sensitive and -resistant mouse strains found no connection between NAFLD and TLR4 (34). Therefore, the role of hepatic inflammation via TLR4 signaling in NAFLD development is likely context dependent.

Altogether, these findings highlight the complex interactions between the liver, intestine, and gut microbiota in NAFLD development. Several recent studies further support this organ cross talk by generating various mouse models, including liver- or intestine-specific *Kbk-A/C* KO mice, intestine-specific *Kbk-C* (the active isoform) KO mice, and intestine-specific *Kbk-C* overexpressing transgenic mice (69, 148). Two recent reviews nicely summarized the various phenotypes and implications of these mouse models (43, 61). Overall, these data showed that intestinal fructose catabolism shields the liver from excess fructose exposure while hepatic fructose metabolism is the major cause of NAFLD. Given that Pfizer's orally available KHK inhibitor is now in phase II clinical trials, understanding the drug's distribution and action in different organs will be crucial to maximizing its therapeutic effects.

### 3.2. Type 2 Diabetes

The incidence of type 2 diabetes has increased at an epidemic rate, and this increase is also linked to changes in diet and reduced physical activity. Type 2 diabetes prevalence is 20% higher in countries with higher availability of HFCS compared with countries that have low availability of HFCS, independently of obesity prevalence (52). Accumulative human studies suggest that fructose-induced liver fat accumulation contributes to hepatic lipotoxicity and the development of insulin resistance (139). Such hepatic insulin resistance leads to hyperlipidemia and consequent lipid accumulation and lipotoxicity in other organs including the skeletal muscle (137).

Type 2 diabetes is characterized by defective insulin responses and eventual failure of insulin secretion, which is related to pancreatic islet cell dysfunction or diminished  $\beta$ -cell mass. In pancreatic  $\beta$  cells, fructose treatment alone did not cause insulin secretion, yet constant exposure led to enhanced reactivity of pancreatic  $\beta$  cells to glucose (6). In a rat model of type 2 diabetes, fructose consumption accelerated islet dysfunction via induction of islet inflammation and oxidative stress (24). While these studies suggest that fructose may act directly on the pancreas, further investigations are needed to demonstrate whether circulating fructose after intestinal and hepatic clearance is sufficiently high to affect the pancreas in vivo.

Despite the strong epidemiological evidence, direct fructose feeding to human subjects has shown variable effects on insulin sensitivity and metabolic phenotypes. For example, fructose feeding in healthy subjects showed only a mild effect on insulin sensitivity (22), which contrasts with fructose-induced deleterious effects in obese and diabetic patients (98). Different kinetics and efficiency of intestinal and hepatic fructose absorption/catabolism between healthy and obese/diabetic individuals may be a potential explanation. Fructose effects are also potentiated by glucose, whose circulating levels are high in obese and diabetic patients (122). Therefore, future studies are required to identify genetic and environmental factors that confer interindividual variations in sensitivity to fructose-induced diabetes.



### 3.3. Kidney Disease

Fructose intake may also have a direct or indirect role in the development of chronic kidney disease (CKD), given the epidemiological relationship between fructose, hypertension, and diabetes. A cross-sectional analysis from the National Health and Nutrition Examination Survey (1999–2004) reported that the intake of two or more sugar-containing beverages per day was associated with an increased risk of albuminuria (129). In addition, epidemiological studies have linked dietary fructose with an increased risk for kidney stones (135). People who drink less than one 24-oz. can of soft drinks per week showed a 10% lower risk for kidney stones (130). Therefore, epidemiological findings provide a correlation between fructose intake and the risk for kidney diseases.

Experimental studies also support fructose intake being a mechanism for CKDs such as glomerular hypertension, renal inflammation, and tubulointerstitial injury. In fact, feeding fructose, but not glucose, accelerated the CKD progression by exacerbating proteinuria, renal dysfunction, and glomerulosclerosis in a rat remnant kidney model (49). Furthermore, the role of endogenous fructose in diabetic nephropathy has been suggested (87). Importantly, the lack of KHK activity protects against aging-associated renal disease in both mice and humans (121), indicating that fructose catabolism, not fructose itself, is crucial for pathogenesis. Fructose metabolism by renal KHK increases sodium hydrogen exchanger activity in renal proximal tubular cells by decreasing intracellular cyclic AMP. This results in increased renal sodium reabsorption and blood pressure, which were not observed in *Khk* KO mice (58). Finally, studies in rats documented that fructose intake results in glomerular hypertension and reduced renal blood flow, leading to the development of kidney vascular disease (40).

Interestingly, the renal injury associated with fructose intake mimics what is observed in subjects with an abnormally high level of blood uric acid. In a longitudinal study with 627 patients at the initial stage of CKD, serum levels of more than 7.5 mg/dL in uric acid were a risk factor for a renal malfunction (120). One potential source of such uric acid is fructose catabolism in kidneys. *Khk* KO mice showed protection from fructose-induced CKD phenotypes with decreased uric acid, oxidative stress, and inflammation (4). Taken together, these findings suggest that more clinical and mechanistic studies are needed to determine if limiting fructose intake to suppress uric acid production may benefit subjects with kidney disease.

### 3.4. Cardiovascular Disease

CVD comprises a group of disorders in the heart and blood vessels and is the number one cause of death worldwide. There is increasing evidence that higher fructose consumption increases CVD risk by contributing to the development of hypertension, dyslipidemia, inflammation, and coronary heart disease (103). The risk of CVD is increased by 26% by a high intake of fructose-sweetened beverages (99). Although increased CVD risk may be partially attributed to fructose-induced obese or insulin-resistant states, cardiac-specific fructose toxicity is also possible. Consistent with this notion, the relationship between fructose intake and increased risk for CVD is independent of body mass index (99).

One potential mechanism is related to direct fructose catabolism in the heart because both GLUT5 and KHK are expressed in cardiomyocytes (102). In normal, healthy individuals, intestinal and hepatic fructose catabolism efficiently clears fructose. Circulating fructose levels are thus unlikely high enough to trigger ATP depletion in the heart. Moreover, the heart normally expresses the KHK-A isoform, which further suggests that cardiac fructose metabolism is likely insignificant. However, a recent study showed that cardiac activation of hypoxia-inducible factor 1 $\alpha$  drives the ectopic expression of KHK-C through the induction of the splice factor SF3B1 (106). This KHK-C expression may trigger ATP depletion when an excessive amount of fructose reaches

the heart due to reduced intestinal and hepatic fructose clearance. Another suggested mechanism of fructose-induced CVD is the effect of fructose on the glycation of cardiac proteins. Fructose can directly impact the structure and function of cardiac proteins through posttranslational modifications such as glycation and *O*-GlcNAcylation (101), which are now regarded as novel targets for CVD interventions. Further studies are required to determine the causal relationships between these suggested mechanisms and CVD in humans.

### 3.5. Intestinal Inflammatory Disease

Given the fact that the intestine is the first organ that is exposed to high levels of dietary fructose and its catabolism, it is not surprising that excessive fructose intake is linked to intestinal diseases. Fructose is linked to intestinal inflammatory disease, including inflammatory bowel disease (IBD) and colitis, and its incidence has increased recently worldwide. In 2015, an estimated 1.3% of US adults had received a diagnosis of intestinal inflammatory disease, a number that had almost doubled since 1999 (25). Previous research in animal models has found that a high-fructose diet can cause intestinal inflammatory disease (75). However, human epidemiologic studies have not always shown a correlation between refined sugar intake and intestinal inflammatory disease (60). Intriguingly, a diet abundant in HFCS increases the risk of intestinal inflammatory disease only when dietary fiber intake is low (62). Similarly, the increased consumption of fructose along with ultraprocessed foods, which contain little dietary fiber (55), parallels the increasing incidence of intestinal inflammatory disease. It is crucial to investigate the mechanism behind fructose-induced intestinal inflammatory disease and whether restricting fructose in the diet can decrease this risk.

Fructose consumption was shown to worsen colonic inflammation with effects on the gut microbiome, including changes in their compositions, metabolism, and localization within the colon (107). Interestingly, the detrimental effects of high-fructose feeding on colitis severity are completely reversed by switching back to a nonfructose diet (108). Meanwhile, a recent study showed that fructose consumption increases the survival of intestinal epithelial cells in hypoxia conditions (136). This induces the elongation of the intestinal villi, enhancing the absorption of various nutrients such as fat and causing excessive calorie intake and obesity.

The intestinal immune system also can be a critical factor that mediates fructose-induced intestinal inflammatory disease. Recent findings showed altered activity of immune cells, such as dendritic cells and macrophages, after exposure to fructose. In dendritic cells, the critical antigen-presenting cells that initiate an immune response, acute exposure to high amounts of fructose, but not glucose, induced an increase in proinflammatory cytokines (67). Similarly, in human monocytes and mouse macrophages, the key cell types of the innate immune system, fructose increases inflammatory cytokine production (73). While these studies in cultured cells suggest a potential involvement of the gut immune system in fructose-induced intestinal pathologies, more *in vivo* studies are required.

### 3.6. Cancer

Fructose consumption is linked to many different types of cancers. The observation of GLUT5 expression in several types of tumors led to the idea that tumor cells may directly utilize fructose. For example, GLUT5 expression was observed in human epithelial colorectal adenocarcinoma (57). Expression of GLUT5 in pancreatic tumor cells (91) led to a cohort study involving 88,802 patients, which revealed that fructose consumption was the strongest risk factor for pancreatic tumors in subjects with obesity and little physical activity (104) and in women (126). Moreover, a 7.2-year follow-up study also showed that high sugar consumption results in a greater risk of pancreatic cancer (88). Importantly, in pancreatic cancer patients, the serum concentration of fructose

was higher than that in normal individuals (65). In addition to pancreatic tumors, GLUT5 is also overexpressed in brain cancer, liver cancer, and prostate cancer (17, 36). While these findings suggest direct fructose utilization by cancer cells, the question remains whether a sufficient amount of fructose is present in the circulation or in the tumor microenvironment.

Mounting experimental evidence indicates that increased fructose consumption can trigger tumor formation, progression, and metastasis. In lung adenocarcinoma, depletion of GLUT5 decreased tumor cell proliferation and invasion and increased cell death (144). On the other hand, overexpression of GLUT5 increased cell proliferation, migration, invasion, and tumorigenesis (144). In acute myeloid leukemia, fructose uptake increased cell proliferation, colony growth, migration, and invasion (19). In prostate cancer, dietary fructose increased the growth of patient-derived xenografts (15). In breast cancer, KHK-A overexpression induced metastasis under fructose-fed conditions (77). In intestinal cancer, daily gavage of high-dose fructose promoted tumor growth in the tumor-prone genetic mouse model (50).

The observation of ectopic expression of GLUT5 and increased fructose uptake by certain types of cancers raises the exciting potential of using positron emission tomography (PET)-fructose imaging as a specific tumor-detection tool, in conjunction with conventional glucose-PET imaging (133). Another important aspect to consider is whether blocking fructose usage by tumor cells can be a therapeutic strategy. While a fructose-restricted diet would be an approach, patients' compliance can be an issue given the fact that most processed foods contain high amounts of fructose. In addition, since fructose can be endogenously generated, KHK blockade may serve as a better approach.

## 4. THE NEXT FRONTIER: MICROBIAL FRUCTOSE METABOLISM

Recent studies found that high consumption of dietary fructose contributes to the development of diabetes, NAFLD, and IBD via gut microbial dysbiosis (85). The genetic contents of the human gut microbiome are over 100 times more diverse than those of human cells, indicating that the gut microbiome can produce an enormous diversity of exogenic molecules from fructose (90). Therefore, fructose-mediated gut microbial changes and their products can affect distinct host physiology (26) and pathology (41). In this section, we discuss how a high-fructose diet changes gut microbial activities and impacts host health.

### 4.1. Fructose-Induced Gut Microbiome Changes

Various human gut microbiota species encode fructose uptake and metabolizing genes (115). Among the 13 representative human gut bacterial species used in the study, 10 can grow on fructose as a sole carbohydrate source (29). However, because the human gut microbiota is a complex microbial community with competitive and mutualistic relationships for nutrient utilization (21), it may not be appropriate to focus on the fructose utilization of single bacterial species for an understanding of whole gut microbial changes during high fructose consumption.

It has been shown that high fructose consumption contributes to gut microbial dysbiosis and reduction of diversity in the mammalian intestine (132). To identify the causal microbiota species in host pathologies, recent studies intended to associate the host diseases induced by high fructose consumption with specific levels of gut microbiota. For example, high fructose intake causes a reduction of butyrate-producing bacteria (7). *Faecalibacterium* and *Ruminococcus*, which are known as the representative butyrate-producing bacteria, were decreased during a high-fructose diet feeding in healthy adult humans (7). In addition, the abundance of *Ruminococcaceae* and *Lachnospiraceae*, the major butyrate producers, was decreased in rats fed HFCS (132). Reduced levels of butyrate-producing bacteria in the gut correlated with diabetes and IBD (62).

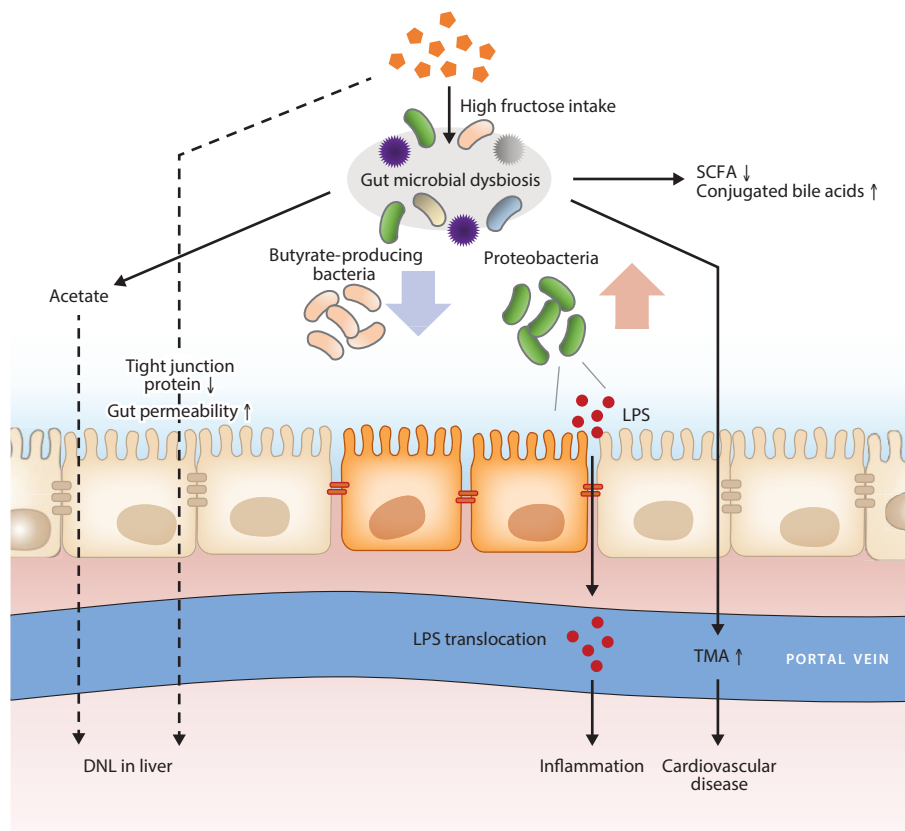
Even though various mechanisms were reported concerning butyrate-producing bacteria and host diseases, the most dominant theory is that butyrate-producing bacteria are required to enhance intestinal barrier function and mucosal immunity (46). Butyrate improves the intestinal barrier by facilitating tight junction assembly via activation of AMP-activated protein kinase (AMPK) in colonocytes (116). Moreover, butyrate reduces inflammation by inhibiting nuclear factor  $\kappa$ B activity (81). For these reasons, the reduction of butyrate-producing bacteria is linked with the host pathologies in high fructose consumption, but the exact causal relationships are still unclear. Therefore, further research is required to reveal the reason why high fructose intake reduces the levels of butyrate-producing bacteria and leads to the subsequent biological mechanisms in host pathologies.

During high fructose consumption, the other interesting feature in gut microbial changes is the increase in the composition of the phyla *Bacteroidetes* or *Proteobacteria* (7, 33). While high-fructose diet-fed mice showed overall decreased gut microbial diversity, the proportion of *Proteobacteria* markedly increased (33). These mice also showed increased gut permeability and inflammation. In another study, 10% fructose feeding led to significantly elevated *Bacteroidetes* and *Proteobacteria* in the murine fecal microbiome (132). Both *Bacteroidetes* and *Proteobacteria* are major phyla constituting the gram-negative bacteria of the human gut microbiome (123). Bacterial endotoxin or lipopolysaccharide (LPS), the cell wall components of gram-negative bacteria, are recognized by the innate immune system and induce inflammation (138). Therefore, high fructose intake increases gut permeability due to alterations to tight junction proteins caused by gut microbial dysbiosis, leading to LPS translocation to the portal vein (143). Evidence of LPS-induced liver injury has been reported in hepatitis and primary biliary cirrhosis patients (72). In this respect, the increases of *Bacteroidetes* and *Proteobacteria* in high fructose intake are presumed to be key causes for host pathologies.

Some studies showed gut microbial changes by high fructose consumption at the bacterial species level. Montrose et al. (107) found that elevated dietary fructose promotes the notable growth of *Citrobacter rodentium* in mice. *C. rodentium*, an enteric bacterial pathogen of the mouse intestinal tract, triggers severe inflammatory responses such as colitis (94). Furthermore, *Akkermansia* spp. was increased sevenfold after 8% fructose water feeding in C57/BL6 mice but not in FVB or DBA mouse strains (2). Interestingly, fecal transplantation of C57/BL6 mice or colonization of *Akkermansia muciniphila* suppressed fructose-induced weight gain and improved glycemic responses in the other strains. *A. muciniphila* is well known to strengthen intestinal barrier function and improve metabolism in obese and diabetic mice (14). In particular, Amuc\_1100, a specific protein isolated from the outer membrane of *A. muciniphila*, interacts with Toll-like receptor 2 and modulates host immune response with the gut barrier (111). Supplementation with *A. muciniphila* in overweight and obese humans improved insulin sensitivity and reduced insulinemia and plasma total cholesterol (28). Because of these characteristics, there are attempts to develop *A. muciniphila* as a next-generation probiotic bacterium (28).

## 4.2. Metabolic Changes in Gut Microbial Environments from High Fructose Intake

As outlined above, various gut bacteria species can readily grow with fructose and produce a variety of metabolic products that influence host physiology and pathology (**Figure 4**). Among the gut microbial metabolites, SCFAs are the most studied metabolites whose levels are changed during high fructose intake (64). Gut microbiota produce SCFAs (acetate, propionate, and butyrate) from fructose via their unique metabolic pathways (i.e., Wood-Ljungdahl pathway, butyryl-CoA:acetate CoA-transferase route) (95). Fructose-derived SCFAs can directly serve as energy



**Figure 4**

Role of gut microbiota in fructose-related pathologies. Chronic overconsumption of fructose induces gut dysbiosis, with decreased butyrate-producing bacteria and increased gram-negative Proteobacteria, which induces changes in microbial metabolites including SCFAs, TMA, LPS, and bile acids. Fructose also induces leaky gut, facilitating translocation of microbial toxic chemicals to the host organs. Abbreviations: DNL, de novo lipogenesis; LPS, lipopolysaccharide; SCFA, short-chain fatty acid; TMA, trimethylamine.

sources or activate G-protein-coupled receptors as signaling molecules. They can also affect epigenetics by providing carbon sources for histone acetylation (through acetate) or by inhibiting histone deacetylases (through butyrate) (82). Fructose-derived SCFAs thus affect various physiological processes and contribute to host health and diseases (140).

However, changes in SCFA levels during high fructose consumption remain controversial. Li et al. (89) showed that the fecal concentrations of all three SCFAs were significantly lower in fructose-fed mice. The cause of this reduction can be an altered and unhealthy status of the gut microbiota (89). Some studies have shown a connection between the reduction of SCFA levels and host pathologies such as obesity and colonic diseases (80). Supporting this notion, SCFA supplementation improved high-fructose-induced diseases through the increase of SCFA receptors in the kidney or amelioration of intestinal epithelial barrier impairment (64, 89). On the contrary, others reported that a high-fructose diet increased plasma levels of SCFAs (11, 63). The increase of SCFA levels in plasma is associated with the reduction of SCFA receptor expression in kidney and CVDs (8). This discrepancy may be due to the use of variable mouse strains, the amounts and methods of fructose feeding (liquid versus solid forms), and other unknown factors. Therefore,

to clarify the exact relationships between high fructose intake, gut dysbiosis, and SCFA levels, a more systematic analysis of various biological samples and control of variables will be needed.

Recently, other gut microbial metabolite changes have gained significant attention (107). For example, a high-fructose diet increases plasma levels of trimethylamine (TMA) (64). TMA is generated from choline, betaine, and carnitine by gut microbiota, and it can be metabolized into trimethylamine-*N*-oxide (TMAO) (64). Importantly, a high blood TMAO level is strongly associated with increased CVDs (127). This increased TMA production by fructose is at least in part because dietary fructose increases the abundance of *Escherichia*, which encodes genes required for the formation of TMA (11). On the other hand, a high-fructose diet reduced bile salt hydrolase-expressing microbes and increased luminal conjugated bile acids (107). Elevated levels of fecal conjugated bile acids disrupt the gut barrier, contributing to IBD and worsening chemically induced colitis in mice (38). In addition, supplementation of nonconjugated bile acids prevents fructose-induced hepatic steatosis in mice through mechanisms involving protection against the fructose-induced translocation of intestinal bacterial endotoxin (141). Together, these studies strongly suggest that several gut microbial metabolite levels are changed with high fructose consumption. It will be valuable to perform comprehensive mapping of microbiota metabolites altered by fructose with advanced metabolomics and isotope tracing techniques.

### 4.3. Probiotic and Prebiotic Strategies for Treating Fructose-Related Diseases

Due to the association between fructose-induced gut microbial dysbiosis and host pathologies, recent studies tested the effectiveness of probiotics and prebiotics as microbiota-management tools for improving health (125). Probiotics are defined as live microorganisms that, when administered in adequate amounts, confer a health benefit on the host. The main advantages of probiotics are the effect on the interference with potential pathogens, improvement of gut barrier function, immunomodulation, and production of beneficial metabolites (124). On the basis of these findings, studies showed that oral administration of probiotics mitigates the pathological features associated with high fructose consumption (112, 149). The administration of *Lactobacillus kefir* to mice fed a fructose-rich diet prevented weight gain, elevations of plasma triglycerides and leptin, and glucose intolerance (149). Moreover, the probiotic administration inhibited local inflammation in epididymal adipose tissue and increased the abundance of Bacteroidetes in the gut. In addition, the administration of *Lactobacillus curvatus* and *Lactobacillus plantarum* lowered plasma glucose, insulin, triglycerides, and oxidative stress levels in high-fructose diet-fed rats (112). It also reduced liver mass, cholesterol, and lipogenesis while increasing FA  $\beta$ -oxidation.

Probiotics also prevent steatosis and hepatic inflammation through the decrease of reactive oxygen species production and activation of hepatic AMPK (147). In addition, probiotic administration increases the expression of the intestinal tight junction proteins such as claudin-1, ZO-1, and occludin, which leads to reduced translocation of pathogenic bacteria and their products, endotoxin (mainly LPS), into the portal circulation (142). While the probiotic effects on high-fructose conditions are generally limited to liver and intestinal pathologies, they also have a beneficial effect on CVD risk factors and CKDs (32, 71).

On the other hand, prebiotics are predominantly types of fiber that promote the growth of beneficial bacteria in the gut. Studies evaluated the effect of prebiotics on improving health during high fructose consumption (42). Busserolles et al. (13) showed that insulin plasma concentrations were elevated in rats fed a high-fructose diet but not in those supplemented with fructooligosaccharide (FOS). Moreover, FOS lowered plasma leptin levels and triglyceride accumulation in the liver. FOS also increased the growth and functionality of specific bacteria with the enhancement of epithelial integrity, the elaboration of beneficial bacteria-derived antimicrobial agents, and



the reduction of pathogenic bacteria (42). Besides FOS, other oligosaccharides have recently gained attention as potential prebiotics (76). For instance, arabinoxylan oligosaccharides increase the SCFA pool size in the large intestine and decrease the risk of various diseases (117, 119). Therefore, identifying the best prebiotics to treat pathological features associated with fructose consumption will be an important future research direction.

## 5. CONCLUDING REMARKS

Due to the alarmingly increased incidence of metabolic diseases and associated fructose consumption, recent research has focused on the pathophysiological impacts of fructose on various organs and gut microbiota. Such efforts have greatly expanded our understanding of the complex interactions between dietary fructose, organ functions, and disease outcomes. While several molecular and biochemical mechanisms and their influence and pathophysiology have been elucidated using animal models, more clinical studies are required to pinpoint therapeutically targetable pathways for preventing and treating various human diseases associated with fructose consumption. The KHK inhibitors that target host organs hold promise, while more patient-specific personalized medicines that account for interindividual variations in gut microbiota can be another future direction.

## DISCLOSURE STATEMENT

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