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Chapter

Fructose Intake: Metabolism and Role in Diseases

Luke He, Ghufran S. Babar, Jacob M. Redel, Sabetha L. Young, Callie E. Chagas, Wayne V. Moore and Yun Yan

Abstract

Fructose consumption has dramatically increased worldwide over the past decades. There are numerous clinical, experimental, and epidemiological studies evidenced that increased consumption of fructose negatively impacts carbohydrate metabolism and lactate formed from fructose can also affect whole-body energy balance. Excessive fructose intake stimulates endogenous glucose production and lipid synthesis in the liver. Currently fructose is believed to be a major contributing factor to chronic metabolic diseases, including obesity, insulin resistance, hypertriglyceridemia, and non-alcoholic fatty liver disease, hyperglycemia, type 2 diabetes, and cancer. These new findings bring challenges to researchers today because of what is still to be discovered, and how to apply what has been discovered to modern health. Further investigation should seek to analyze and understand specific mechanistic effects of fructose in metabolic pathways, and how to apply this knowledge to our daily lives. Conducting this monosaccharide research is important to improve the diet of the general population and to attenuate the epidemics of metabolic disease and associated diseases. Here, we focus on the mechanism and role of fructose in diseases as well as its potential as a dietary interventional target.

Keywords: fructose, glucose, sucrose, obesity, insulin resistance, uric acid, hypertriglyceridemia, hyperglycemia, type 2 diabetes, hypertension, retinopathy, free oxygen radicals, cancer

1. Introduction

Fructose is a common form of sugar found naturally in fruits, honey, and table sugar. It is often used as an additive to modern foods and drinks. Its sweetening effects and low costs of production have made fructose increasingly popular [1, 2]. Fructose consumption has increased since the 1970s. Mean fructose intake per person increased approximately 32% from the 1970s to early 2000s. Of note, total carbohydrate intake over that period increased by 41%, indicating an increase in glucose consumption as well [3]. In a 2008 study analyzing fructose consumption of 21,483 people, the mean fructose intake per capita was about 54.7 g/day (10.2% of total caloric intake/day) [1]. Dietary Guidelines for Americans 2015–2020 recommended that average intake of added sugars should be less than 10% of total calories per day [4]. Worldwide the consumption of sugar varies by age, setting and county. Among different European countries, for example, intake ranges widely, from 7 to 25% of total energy intake [5].

Fructose intake in the diet has been linked to certain human diseases [6–10]. However, the precise role of fructose in disease is poorly understood and some findings are still controversial. There are numerous studies associating fructose with negative impacts on multiple components of metabolism in animals and humans [11–14]. The past few decades of research have expanded our understanding of fructose, yet there is still much to learn. It is important to establish an accurate scientific understanding of fructose and its implications on human health because of its increasing popularity worldwide. This chapter focuses on up to date findings related to the metabolism and the role of fructose in human disease, including hypertension, hyperglycemia, metabolic syndrome, free oxygen radicals, retinopathy, diabetes, and cancer.

2. Structure, uses, and metabolism

Fructose is one of three major monosaccharides consumed by humans, in addition to glucose and galactose. Its catabolism produces the same energy content as glucose, 4 kilocalories per gram. Fructose is found as a monosaccharide in honey and fruits. It is found as part of the disaccharide sucrose in cane sugar, used to make table sugar. Sucrose is comprised of glucose bound to fructose in a 1:1 ratio (**Figure 1**). Fructose, a potent sweetener, is also artificially added to foods and sugar-sweetened beverages (SSB), often in the form of high fructose corn syrup (HFCS). HFCS refers to the fructose content relative to corn syrup, which is entirely glucose, rather than the fructose content relative to other sweeteners. Indeed, as in sucrose and in honey, most HFCS compounds used as food additives contain nearly the same 1:1 ratio of glucose to fructose. Therefore, it is important to understand that concerns pertaining to fructose consumption might also be inferred to a wide range of sweeteners, not only HFCS.

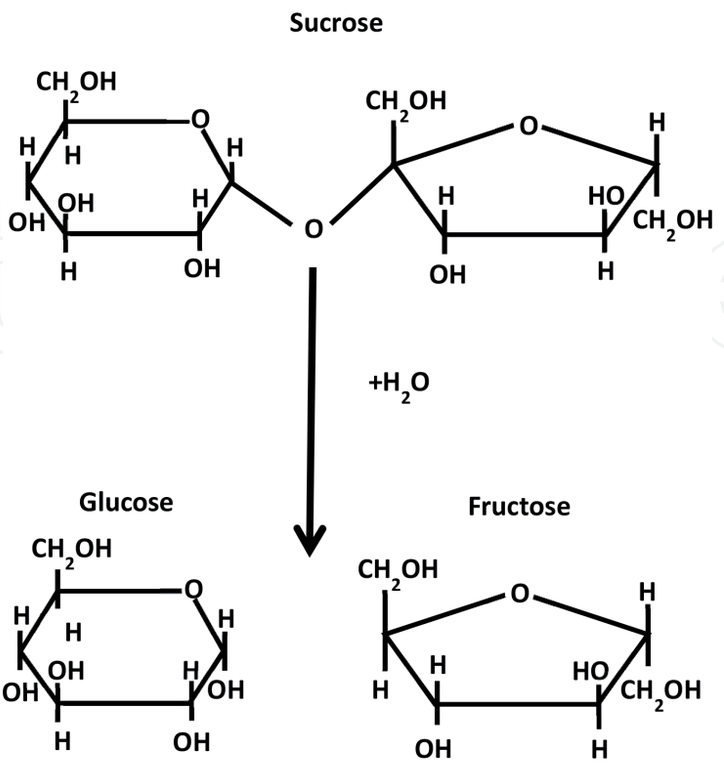

Figure 1.
Structural formula of the sucrose, glucose and fructose. Sucrose is a disaccharide consisting of one glucose and one fructose molecule. Hydrolysis breaks the glycoside bond converting sucrose into glucose and fructose.

Digestive and intestinal brush border enzymes break down polysaccharides and disaccharides into monosaccharides—fructose, glucose, or galactose. Free fructose is absorbed directly from the intestinal lumen and is transported into circulation primarily by glucose transporter 5 (GLUT5) and glucose transporter 2 (GLUT2). Once in the portal circulation, almost all absorbed fructose enters the liver [15]. Fructose is transported into hepatocytes primarily via hepatic GLUT2. In addition, other family members of glucose transporters are involved in fructose absorption and metabolism [16]. After ingestion into liver, fructose is metabolized to either glucose [17], glyceraldehyde or acetyl CoA [18]. The liver distributes energy to other cells in the form of glucose, lactate, and triglycerides or converts this energy into hepatic glycogen or fat (**Figure 2**) [19, 20].

Extrahepatic fructose metabolism is generally considered minimal. Extrahepatic cells do not express fructokinase, so fructose metabolism must be catalyzed by hexokinase in these cells. Hexokinase has a much higher affinity for glucose than fructose. Thus, conversion from fructose to fructose 6-phosphate proceeds slowly in extrahepatic cells, preventing them from playing a large role in fructose metabolism [21].

Under diabetic conditions, excess glucose may enter the polyol pathway and can be converted to exogenous fructose (**Figure 3**). In this pathway, aldose reductase reduces glucose to sorbitol and NADPH is oxidized to $NADP^+$. Sorbitol dehydrogenase then oxidizes sorbitol to fructose, which produces NADH from NAD^+ [6, 22, 23]. The polyol pathway can result in NADH/NAD^+ redox imbalances in diabetes [22]. Excessive activation of this pathway increases reactive oxygen species (ROS), and decreases nitric oxide (NO) and glutathione, promoting microvascular damage to the retina, kidney and nerves [24–27].

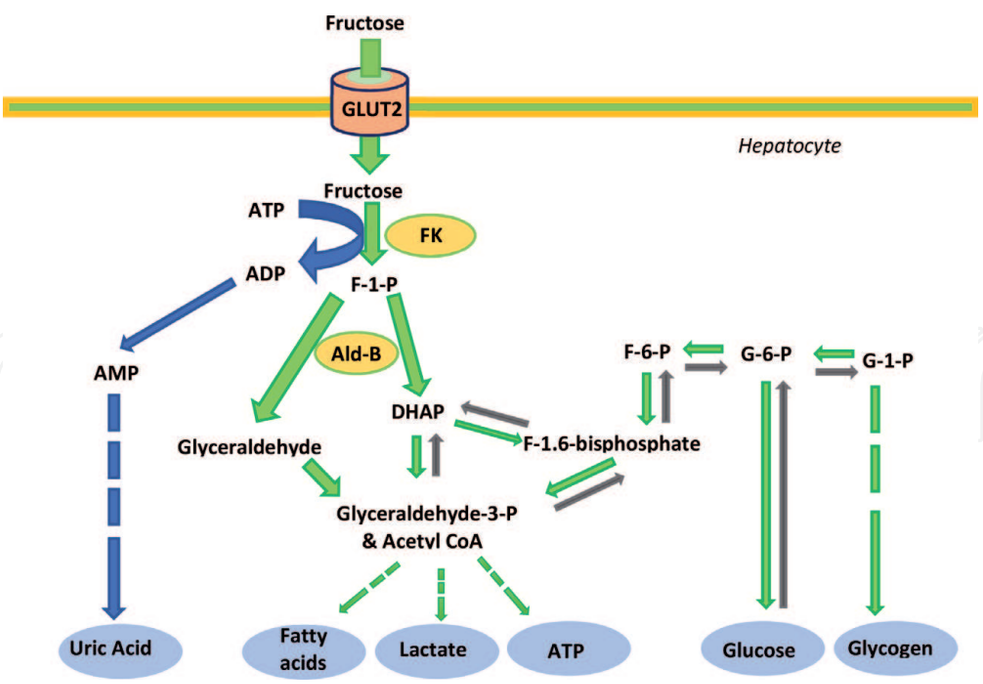

Figure 2.
Fructose metabolism in hepatocyte: After absorption from intestine, fructose is taken by hepatocyte via the glucose transporter 2 (GLUT2) and rapidly converted to fructose-1-phosphate (F-1-P) by fructokinase. F-1-P is then metabolized to glyceraldehyde or dihydroxyacetone phosphate (DHAP) via aldolase B (Ald-B). Glyceraldehyde will be further converted to glyceraldehyde-3-phosphate and acetyle CoA, finally will convert to fat acids, lactate or ATP. In liver, F-1-P also can convert into glucose and glycogen via DHAP and glyceraldehyde-3-p to improve glycogenesis. In addition, intracellular phosphate levels decrease stimulates formation of uric acid and increases the level of uric acid at blood. F-6-P; fructose-6 phosphate, G-6-P; glucose-6-phosphate; G-1-P, glucose-1-phosphate.

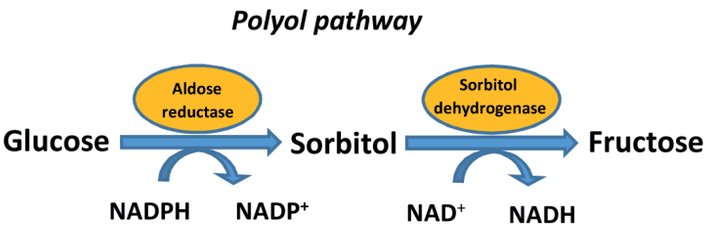

Figure 3.
Polyol pathway: Under normal physiological conditions, glucose is used for energy (ATP) production via glycolysis. In diabetes, excess glucose enters the polyol pathway. Aldose reductase reduces glucose to sorbital and oxidizes NADPH to NADP+, then sorbitol dehydrogenase oxidizes sorbitol to fructose, which produces NADH from NAD+.

3. Free oxygen radicals and endothelial dysfunction

By comparing the aorta of rats exposed to fructose with controls exposed to mannitol and testing them with the superoxide anion scavenger superoxide dismutase (SOD), fructose has the effect of inducing NADPH-derived superoxide anion production. SOD incubation increased the response to acetylcholine in the fructose-exposed group. The group exposed to fructose showed a leftward shift in the concentration-response curve to acetylcholine when apocynin was added, but the group exposed to mannitol did not. Additionally, the concentration response curves for both groups to phenylephrine were shifted to the right after SOD incubation, but this effect was greater in the fructose-exposed group [28]. In addition, it was found that high-fructose diet (HFrD) increased ROS 2.8 times in the aorta of rat [29]. Another study found that fructose increased blood pressure, superoxide anion, and expression of NADPH oxidase subunits $p47^{phox}$ and $p22^{phox}$ in rat endothelium [30].

Fructose can induce expression of the pro-inflammatory molecule intracellular adhesion molecule-1 (ICAM-1) on human and rat endothelial cells. This is due to a fructose-induced reduction of endothelial NO synthase (eNOS) expression [31]. Moreover, eNOS gene therapy helped repress the damaging the effect induced by a HFrD, indicating that eNOS has a protective effect [32]. HFrD can impair cardiac AKT/eNOS signaling. In contrast, estradiol can activate the Akt/eNOS signaling that is impaired by HFrD in rat heart [33].

The effect of topical fructose and dextrose on the adherence of leukocyte adherence in rat mesenteric venules was observed with intravital microscopy. The result showed that fructose induced significant inflammation, but dextrose did not. It was determined that fructose was mediating endothelial damage via ROS generation because the damage was blocked by NO donors spermine NONO-ate and antioxidant lipoic acid [34]. A recent study in human endothelial cells found that exposure to high fructose concentrations significantly affected gene expression, decreased the cellular angiogenic capability, and impaired endothelial vascular function [35].

4. Hypertension

Several articles have reviewed the effects of fructose on blood pressure (BP) [36, 37]. Various mechanisms have been proposed, including increased sympathetic activation [38], inflammation [31], endothelial dysfunction [39], increased uric acid stimulation [40], inhibition of eNOS system [32], increased salt and water retention [41, 42], increased homocysteine levels [43] and in utero programmed hypertension of offspring [44].

Few epidemiological studies have examined the association between fructose intake, uric acid, and BP levels. Some studies have conflicting conclusions about

the relationship between fructose and blood pressure [45]. A cross-sectional epidemiological study using the data collected from the National Health and Nutrition Examination Survey indicated that a high intake of fructose of ≥74 g/day is associated with elevated BP in the adults without a medical history of hypertension [39]. Studies have shown that HFrD of 60% fructose chow in rats leads to hypertension [46]. Recent epidemiological studies [39, 45] and meta-analysis [47] have indicated that there is an association between fructose and BP. In addition, when fructose is provided in a beverage, there is an acute BP raising effect [37, 48]. Moreover, lowering sugar-sweetened beverages intake was significantly associated with reduced BP in adults with hypertension [49]. There may also be epigenetic impact, because the HFrD of pregnant women was associated with BP programming in the offspring [44, 50].

In a mouse model, high salt intake caused leptin resistance and obesity by stimulating endogenous fructose production and metabolism. It also raised BP and induced metabolic syndrome which was abrogated when fructose metabolism was blocked [51]. It was found that after 30 minutes of 40 mM fructose exposure on the rat aorta, with and without the endothelium lining, the contractile responses induced by phenylephrine (a selective α_1–adrenergic receptor agonist) were increased in the rat aorta with endothelium present. This demonstrated that the effects of fructose on contractile response resulted from fructose acting on the endothelium and not the smooth muscle [28]. NO, an important vasodilator, was shown to have reduced availability when NO synthase was blocked with L-NAME. The result showed that a smaller shift occurred in NO production in the aorta segments exposed to fructose ranging from 0 to 40 mM concentrations. It was also shown that fructose increased activation of NADPH oxidase of the aorta, leading to production of superoxide anions and less NO bioavailability. The NO bioavailability may also be affected by hydrogen peroxide, which is known as an endogenous regulator of NO synthase [52]. Catalase, a hydrogen peroxide scavenger, was used to study the rat aorta segments. The results showed that catalase reduced the vasodilatory response to acetylcholine only in the rings incubated with mannitol, and not with fructose. This suggests that the vasodilator effects of hydrogen peroxide were impaired after fructose exposure. Additionally, catalase reduced the response to phenylephrine in the aorta incubated with fructose, suggesting that fructose increased hydrogen peroxide, leading to increased contractility [28]. Fructose may also reduce NO bioavailability by generating uric acid, which reduces NO levels by blocking L-arginine uptake, stimulating arginase, inhibiting eNOS, and by direct scavenging [53, 54]. Fructose can enhance expression of apical chloride/base exchanger Slc26a6 (PAT1, CFEX), which increased salt and water absorption, Slc26a6 and Glut5 play an essential role in fructose-inducing hypertension [41].

The National Health and Nutrition Examination Survey (NHANEX 2003 to 2006) examined the relationship between increased fructose intake and blood pressure in healthy adults. Their study consisted of 2253 diverse participants and showed that a high fructose intake (defined as >74 g/day) was associated with elevated blood pressure levels, both with and without adjusting for numerous risk factors. The results showed 26%, 30%, and 77% higher risk for the blood pressure cut offs: ≥135/85, ≥140/90, and ≥ 160/100 mmHg, respectively [39].

5. Dyslipidemia and obesity

The conversion of fructose to fat in the liver (de novo lipogenesis) may be a modifiable pathogenic pathway [55]. Fructose uptake increases triglycerides by conversion to trioses-phosphate. Tests in rats [43, 46] and humans [18, 56] have

shown that HFrD increase triglycerides. HFrD also increases fasting plasma triglycerides level and the diet significantly inhibited several pathways of lipid metabolism [57]. It increased plasma triglycerides in both males and females, but with a higher degree in males [58]. In obese individuals it increased triglycerides more than glucose [18].

In a rat animal model, HFrD for 5 weeks significantly increased plasma triglycerides (3.8-fold) and decreased high-density lipoprotein cholesterol by 14% [59]. Consuming fructose-sweetened beverages for 10 weeks has shown a significant increase in visceral adipose tissue, dyslipidemia, and an impaired glucose tolerance compared to the corresponding glucose cohorts, although weight gain was not different in either cohorts [60, 61].

The prevalence of overweight status and obesity in children has increased dramatically in recent decades. SSB is already a known risk factor for weight gain in children and adults [62, 63]. Numerous prospective cohort studies have illustrated that increasing intake of SSB contributes to obesity [62, 64–66], while reducing the intake of soft drinks can reduce weight [67]. HFrD promoted metabolic syndrome by inducing lipogenesis and causing triglyceride accumulation and insulin resistance [68]. Oxidative stress and inflammation due to HFrD also induced metabolic changes [6, 68]. Hyperhomocysteinemia is also associated with the changes seen in the individuals with metabolic syndrome [69]. Rats fed with high fructose for 5 weeks had 72% higher homocysteine levels compared to chow fed controls. Rats fed with HFrD developed metabolic syndrome, which includes hypertriglyceridemia and obesity [43].

6. Non-alcoholic fatty liver disease

The liver is essential for metabolism of proteins, fats, and carbohydrates. Liver disease may affect various components of metabolism and may contribute to metabolic syndrome. Non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH) can result from excessive fat accumulation in the liver leading to liver damage and inflammation. NAFLD is a manifestation of metabolic syndrome. NAFLD affects about 30–40% of the adult population [70] and about 10% children [71]. Persistent liver damage can cause cirrhosis and hepatocellular carcinoma [72].

An imbalance in fatty acid synthesis, β-oxidation, and triglyceride exportation processes leads to the accumulation of fat in hepatocytes. Fructose is a substrate and inducer of hepatic de novo lipogenesis [6]. Fructose has a role in inducing fatty liver disease by stimulating carbohydrates conversion into fatty acids and blocking β-fatty acid oxidation [73]. As mentioned previously, fructose is converted into glyceraldehyde-3-phosphate by avoiding the rate-controlling step of glucose metabolism in hepatocytes. Thus, the consumption of high fructose increases the hepatic de novo lipogenesis [74]. Excessive lipogenesis causes hepatic inflammation, a key pathophysiologic feature of NASH [75]. These processes also increase mitochondrial coupling, leading to oxidative stress [74]. Numerous studies have shown that fructose uptake causes ATP depletion because it floods the hepatocytes with fructose-1-phosphate via fructokinase [76–78].

The effects of fructose consumption on NAFLD and metabolic syndrome have been studied [79, 80]. Increased fructose consumption has been suggested to contribute to NAFLD [81, 82]. A study on zebra fish showed that when treated with 4% fructose or glucose, only the fructose-treated larvae developed NASH [83].

Fructose intake also affects insulin sensitivity and has been shown to increase fibrosis severity in patients who have NASH [84]. Short term (9 days) high fructose

intake of 25% of energy content was associated with increased hepatic fatty acid synthesis and liver fat in healthy men fed weight-maintaining diets [85]. There have been retrospective studies done on patients with NAFLD, showing that they correlate with a higher fructose intake, despite similar overall energy intake compared to healthy individuals. Another meta-analysis concluded that consumption of SSB plays a role in fatty liver disease [67]. However, results are not conclusive. A recent meta-analysis of six observational and 21 intervention studies concluded that the apparent association between indices of human health like liver fat and lipogenesis from fructose or sucrose intake appear to be confounded by excessive energy intake overall [86].

Increasing evidences show that Sirtuin 1 (Sirt1) plays a vital role in the development and rescue of NAFLD [87]. Sirt1 is a NAD^+-dependent histone deacetylase and is considered to be a core regulator in fatty acid oxidation and lipogenesis [88, 89]. Sirt1 reduces liver steatosis, improves mitochondrial function, and restores insulin sensitivity, thereby improving blood sugar and lipid regulation [90]. In addition, Sirt1 has anti-inflammatory activity, anti-aging activity and reduces oxidative stress of the vascular endothelium. Enhancing Sirt1 activation can reduce lipogenic enzymes expression [91] and lipid accumulation in liver [92]. Ablating the Skirt1 activation can exacerbate liver fat accumulation and hepatic steatosis [93, 94]. Diet has been shown to be involved in the regulation of Sirt1. An unhealthy diet can increase the risk of NAFLD and obesity [93, 94]. Nutritional and lifestyle interventions can increase the activation of Sirt1 and improve NAFLD [94, 95]. Fructose decreases the expression and activity of Sirt1 in liver, and inhibits lipid metabolism [96], whereas increased Sirt1 activity can attenuate fructose-induced hepatic lipid deposition and prevent NAFLD [90]. In high-fat diet mice, activation of the AMPK/Sirt1 pathway significantly improved obesity, lipid accumulation and hepatic steatosis [97]. In addition, metformin has been proposed to alleviate NAFLD, since metformin can increase autophagy by increasing the expression and activation of the Sirt1 [92].

In recent years, Sirt1 activators and inhibitors have been extensively studied, including some human trails [98, 99]. Ongoing research data suggests that NAFLD may benefit from targeting Sirt1 therapy [98].

7. Insulin resistance

Fructose consumption can result in insulin resistance, an effect that is similar to glucose [13]. In rats, high fructose consumption resulted in increased visceral adipose tissue, insulin resistance and hypertension [100, 101]. A higher C-peptide is often associated with insulin resistance [102]. A study was conducted to evaluate the link between fructose intake and C-peptide level in women, and it found that the serum C-peptide concentration of the subjects with the highest intake of fructose was 13.9% higher than those with the lowest intake [103]. In rats fed with HFrD resulted in a complete metabolic syndrome including hyperinsulinemia [43].

Fructose also sensitized pancreatic beta cells to TNF-alpha induced necroptosis [104]. Fructose showed increased insulin resistance in both obese men and women, more notable in males [58]. Fructose increased visceral adipose tissue, plasma insulin, blood triglyceride level, and HOMA index. There was a decreased stimulation of protein kinase B signaling in fructose fed rats. Insulin induced GLUT4 presence on plasma membranes of cardiac cells was decreased by fructose diet [105].

The body's use of insulin may be impaired by increased resistance in peripheral tissues, it is important to assess the effects of fructose on the insulin and the pancreatic beta cells. It is well known that hyperglycemia is detrimental to beta-cell

viability, which is a large part of the pathophysiology of development for diabetes mellitus. One factor in the beta cell death is a mitochondrial channel called the permeability transition pore (PTP, or MTP). PTP is associated with mitochondrial dysfunction and directly involved in insulin resistance [106]. There is evidence that PTP inhibitors prevent the pancreatic β cell death induced by hyperglycemia [107]. Comparing the effects of fructose and glucose on PTP, the results show that even low concentration of fructose (2.5 mM) can induce PTP open, similar to 30 mM glucose [108]. This indicated that the possible role of fructose on PTP and in the development of beta cell damage.

8. Diabetes

In healthy people, acute increases in plasma glucose concentration inhibit endogenous glucose production. This regulation is disrupted in type 2 diabetes patients, causing inappropriate endogenous glucose production and hyperglycemia [109]. Hyperglycemia inhibits glucose production when an intracellular influx of glucose is catalyzed to glucose-6-phosphate via glucokinase [110]. In healthy individuals, there is an autoregulatory mechanism in which glucose phosphorylation suppresses glucose production, primarily by inhibiting glycogenolysis [111].

Studies show that fructose may have an impact on glucose level. In one study, dogs were fasted for 42 hours, then they were administered different amounts of IV fructose. Fructose exposure caused an increase in net hepatic glucose uptake, glycogen synthesis and hepatic lactate output, the experiments show that about 70% of H3- labeled glucose captured by the liver is incorporated into glycogen and deposited in liver [112]. This is significant because glucokinase is known to activate the glycogen synthase enzyme [113]. Fructose has a role in determining glucokinase activity, glucokinase has a major role in determining hepatic glucose uptake [112].

Other animal studies have shown that after two weeks of high fructose intake, blood glucose levels were significantly increased in healthy rats [114]. A study in humans has shown small amounts of fructose stimulated hepatic glucose uptake and hepatic glycogen synthesis. Under euglycemic hyperinsulinemia, low-dose fructose infusion increased net hepatic glycogen synthesis by 3 times via stimulating glycogen synthase flux [115]. Glucose-fructose co-ingestion will significantly increase hepatic glycogen repletion rates compared with glucose ingestion alone [116].

It is important to understand that although insulin resistance and pancreatic cell damage may develop in rats fed with HFrD as reported by some studies, the presentations might not always mimic type 2 diabetes found in humans or rats. For example, HFrD combined with high fat diet to induce T2D in rodents. These animals only developed early stage of diabetes but did not develop β-cell failure as seen in the late stages of T2D in humans [117, 118]. The animal could develop a nutritional tolerance after eating a fructose diet for 3 months, but these animals could be not used as suitable fructose-fed animal model for diabetes study due to no signs of insulin resistance and β-cell dysfunction [119]. A new and alternative rat model was created by using a 10% fructose-fed diet followed by 40 mg/kg of streptozotocin to induce beta cell toxicity. In this animal model, rats developed both insulin resistance and pancreatic β-cell dysfunction [120].

In humans, the epidemic of T2D and diabetes-related metabolic complications have been linked to fructose consumption [121–125]. Indeed, fructose as a highly lipogeneic monosaccharide, fructose intake increases the risk of impairing

gluocse metabolism [63, 126]. However, results are conflicting. An excessive rate of endogenous glucose production is a major contributor to fasting hyperglycemia in diabetes. A study on human showed that infusion of small amounts of fructose during hyperglycemia partially corrected the regulation of glucose production and partially restored the ability of glucose to suppress glucose production in subjects with type 2 diabetes [127].

In diabetes mellitus, hyperglycemic condition increases the activity of polyol pathway; approximately 30% glucose can be converted to fructose via the polyol pathway. Persistent hyperglycemia increases fructose level and decreases NADPD/$NADP^+$ ratio, leading to NO production decrease, ROS production increase, oxidative stress, and protein glycation increase. These events damage the microvascular system and are implicated in diabetic complications, especially in retinopathy, nephropathy, and neuropathy [22].

9. Hyperuricemia

Hyperuricemia (HP) can cause metabolic, cardiovascular, and renal diseases [68]. Elevated level of uric acid can inhibit NO bioavailability; it also can promote smooth muscle cell proliferation and can activate the inflammation cascade, which can lead to damage of the endothelium of vessels [128, 129]. During fructose metabolism intracellular phosphate (PO4) is decreased, there is an activation of adenosine monophosphate deaminase which increases inosine monophosphate. Inosine monophosphate is further degraded to xanthine and hypoxanthine by xanthine oxidase (XO). The end product of these processes is uric acid [130, 131] (**Figure 4**). Furthermore, the increased insulin levels due to fructose intake lead to renal reuptake of urate, resulting in reducing the excretion of uric acid through the kidneys and further increases the serum uric acid level [53, 132].

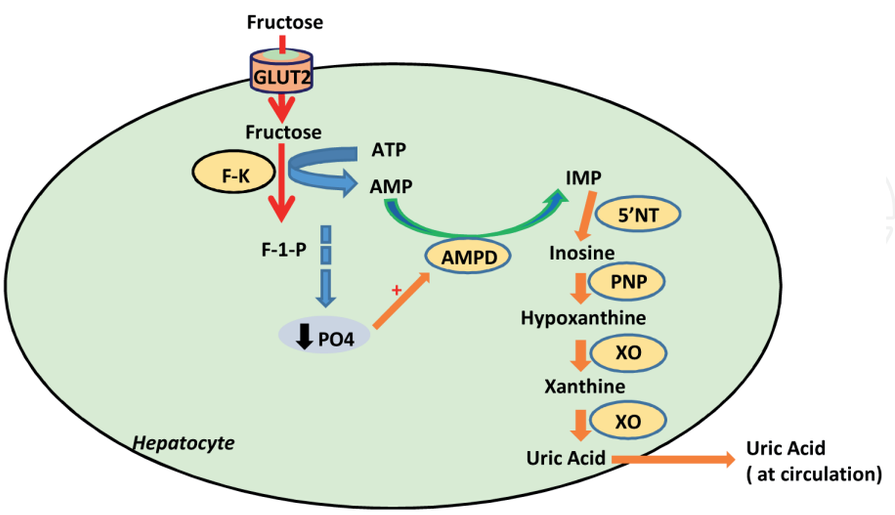

Figure 4.
Fructose stimulates hepatic uric acid synthesis. Fructose is transported into liver via hepatic GLUT2 and is phosphorylated by fructokinase (F-K) to fructose-1-phosphate (F-1-P), which uses ATP as a phosphate donor and results in intracellular phosphate (PO4) depletion. Intracellular phosphate levels decrease stimulates the activity of hepatic AMP deaminase (AMPD). AMPD catalyzes AMP to inosine monophosphate (IMP). IMP is converted to inosine by 5′ nucleotidase (5′NT) and then inosine is further degraded to hypoxanthine by purine nucleotide phosphorylase (PNP). Hypoxanthine is degraded into xanthine by xanthine oxidase (XO), and finally produced uric acid is released into circulation.

A meta-analysis of animal research showed that there is a significant relationship between fructose feeding and HP [133]. Research has also shown that when rats fed with HFrD, elevated uric acid blocked acetylcholine-mediated arterial dilation [53]. Human can also develop HP after high fructose consumption [11, 40, 129]. SSB consumption was significantly associated with increased uric acid concentration in adult population [134]. However, a meta-analysis showed that uric acid concentration was reduced by using glucose instead of fructose [135].

10. Retinopathy

Chronic uncontrolled hyperglycemia can cause microvascular damage which can manifest as diabetic retinopathy (DR). Pathological retinal findings include microaneurysms, capillary abnormalities, hyperpermeability, hypoperfusion, and neo-angiogenesis, which eventually can lead to loss of vision [136, 137].

Animal studies have showed that animals can develop metabolic syndrome while on fructose diet and can also develop choroidal neovascularization which can lead to exudative age-related macular degeneration [137–139]. The retinal neovascularization occurs as part of oxidative stress resulting in an activation and infiltration of phagocytic cells in the retina. High fructose diet can also modulate gene expression in the retina [138]. The genes are involved in the development of diabetic retinopathy [140]. Melatonin plays an important role in the maintenance of disc shedding, function of rod photoreceptors [141], and elongation of cone photoreceptors in the retina [142]. Melatonin also blocks apoptosis of retinal cells after experimentally induced ischemia [143]. Excessive fructose consumption leads to down regulation of melatonin, and decrease the effects of melatonin on anti-inflammation and anti-oxidative stress in the retina [144, 145].

The premature death of retinal pericytes is a pathophysiological hallmark of DR. One study showed that advanced glycosylated end-products (AGEs) can cause retinal pericytes dysfunction and death by reducing survival signals mediated by platelet-derived growth factor [146]. DR is also caused oxidative stress because of increased ROS production and antioxidant depletion [147]. Protein kinase C (PKC) also has an important role in diabetic retinopathy, PKC activation leads to upregulation of pro-inflammatory genes, loss of capillary pericytes and generation of ROS [148, 149].

11. Cancer

Research studies have provided clinical and experimental evidence that fructose intake is associated with development of cancer, especially if consumed in large amounts [150]. Adenomatous polyposis coli (APC) genes can develop biallelic mutations and in combination with fructose intake can trigger or promote the colorectal cancer [151, 152]. The fructose transporter GLUT5 receptors are expressed on the cancer cells like colorectal and breast cancers indicated that fructose can be used as fuel by several types of cancers [153, 154]. Excessive intake of fructose can lead to increased formation of RDS production via formation of glycolaldehyde [155]. Glyoxal is an autoxidation product during fructose metabolism and also a contaminant in the food processing promoted intestinal tumor growth in mouse model.

Fructose was shown to be carcinogenic even if it was only 3% of total daily caloric intake which are mediated through activation of GLUT5 and phosphofructokinase. If fructokinase (ketohexokinase) which is the first enzyme involved in fructose is knocked out in mice the cancer growth can be suppressed [156, 157].

Fructose can also promote cancer growth via pentose phosphate and increases protein synthesis and also cause hepatic inflammation, nonalcoholic fatty liver disease and hepatocellular carcinoma [158, 159].

Fructose promotes cancer growth by formation of lactate, which is an end-product of fructose metabolism. Lactate is likely needed at several steps during the cancer growth including escape from the immune system, cell migration, metastasis and self-sustenance [160]. Lactate levels were found to be 40-fold high in glycolytic tumors and it correlates with cancer cell metastasis and poor survival [161]. Lactate also promotes angiogenesis in the tumors by inducing vascular endothelial growth factor (VEGF) in endothelial cells. If the lactate production is blocked by a chemical inhibitor or gene deletion, the angiogenesis and cancer cell proliferation is stopped [162, 163].

Fructose and uric acid have been shown to stimulate mitochondrial ROS production which is needed for tumor cell growth [164, 165]. During the rapid cell division cancer cells can suffer from hypoxic conditions and have to tolerate them to maintain viability and growth [166]. Fructose metabolism is useful in rapidly dividing cancer cells since during the glycolytic pathway it can use one molecule of ATP to generate 4 molecules of ATP from fructose-1,6-bisphosphate through pyruvate [167].

Fructose consumption may promote breast cancer cell line MDA-MB-468 to an aggressive type [168]. Fructose intake is associated with more aggressive cancer behavior and may promote metastasis [168–170]. Fructose also has a role in pancreatic cancer growth via the induction of transketolase flux [171]. Prostate cancer cell may also use fructose as the preferred energy source to support the cell proliferation and metabolism [172].

Human cells have the ability to produce fructose endogenously, which is also possible in the cancer cells [173]. Endogenous fructose production takes place through the polyol pathway by utilizing aldolase reductase. This enzyme is found in an activated state in various types of human cancers, including liver, breast, ovarian, cervical, and rectal cancers and helps in synthesizing fructose from glucose [174].

Fructose can promote cancer cell growth by providing fuel to make nucleotides, lipids, and energy, especially for cancers that express GLUT5 receptors. Low fructose diet and fructokinase inhibitors can be novel techniques to treat cancers. Furthermore, blocking uric acid and lactate production could also be targets of cancer prevention and treatment [175].

12. Summary

The past decade of research on fructose has expanded our understanding of role of fructose in disease. The imbalance between high fructose intake and low physical energy consumption is a possible reason of the deleterious health effect of fructose. The consumption of excess fructose may promote the development of metabolic disorders directly or indirectly. Dietary fructose intake has been linked with some human diseases, including hypertension, obesity, dyslipidemia, diabetes, non-alcoholic fatty liver syndrome, and certain type of cancers. Further investigation to gain a better understanding about fructose metabolism will be important to define a potential dietary intervention to reduce disease.

Conflict of interest

The authors declare that there is no conflict of interest.

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