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Mini Review Open Access

Fructose Metabolism and Health Risks

Gülçin Sağdıçoğlu Celep[1], Reza Rastmanesh[2*] and Faruk Bozoğlu[3]

[1]*Industrial Arts Education Faculty, Family and Consumer Sciences, Food and Nutrition Technology, Gazi University, Ankara, Turkey*

[2]*Department of Human Nutrition and Dietetics, Shahid Beheshti University of Medical Sciences, Tehran, Iran*

[3]*Food Engineering Department, Middle East Technical University, Ankara, Turkey*

[*]**Corresponding author:** Reza Rastmanesh, Department of Human Nutrition and Dietetics, Shahid Beheshti University of Medical Sciences, Tehran, Iran, Tel: 9821-22357484; E-mail: r.rastmanesh@gmail.com

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Mini Review

Fructose is a monosaccharide mainly found in fruits, vegetables and honey [1]. It has been commonly consumed in human diet, however the daily intake has increased in the past 40 years due to its industrial production [2]. High fructose corn syrup (HFCS), also called glucose or fructose syrup, is used as a sweetener in many products such as sweets, cakes and drinks. Consumption of fructose as a single nutrient is rare and its absorption decreases due to high fiber content of its natural sources. Chemical structures of glucose and fructose are presented in Figure 1.

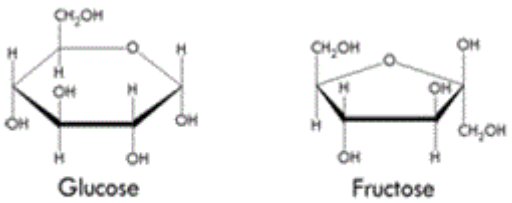

Figure 1: Chemical structures of glucose and fructose.

The main source of fructose in human diet is sucrose or HFCS that is composed of fructose and glucose in different ratios such as HFCS 55 indicating 55% fructose [1,2]. These sweeteners are preferred in food industry because they are much cheaper and have better functional characteristics.

In recent years, there has been a parallel increase in dietary exposure to fructose as well as in the incidences of metabolic diseases. This leads to the idea that consumption of high fructose may have a negative impact on human health. In a number of scientific reports, dietary fructose has been implicated in several diseases. In a study carried out with young men and women, high fructose corn syrup was reported to increase postprandial triglycerides, LDL cholesterol, and Apolipoprotein-B which are indicators of cardiovascular disease risk factors [3]. In a cross-sectional analysis of the data collected from the National Health and Nutrition Examination Survey NHANES from 2003 to 2006, high fructose intake was determined to be significantly associated with elevated blood pressure levels [4]. Recent literature survey based on article search in scientific databases including PubMed after the year 2000, high fructose intake was assessed to be associated to nonalcoholic fatty liver disease and fructose malabsorption [5]. However, there are also contradictory results extracted from human studies reporting no association between high fructose intake and liver diseases [6] and insufficient association was reported due the data obtained from meta analysis of studies on children and adults [7].

Fructose absorption and metabolism

Fructose either from the natural sources or HFCS is transported across the intestinal epithelium by the facilitative glucose transporter GLUT5 of the enterocytes [8]. Fructose in the cell is transported through blood by GLUT2 located on the basolateral surface of the enterocytes. GLUT2 is Na^+ dependent whereas GLUT5 is Na^+ independent and Km of GLUT5 for fructose is approximately 10 times lower than GLUT2 [9,10]. GLUT2 is not constitutively located on that membrane but it is reported to be transiently upregulated by glucose [8]. GLUT2 recruitment to the brush border membrane of human is thought to be an important adaptation when exposed to high doses of fructose [11]. GLUT5 is detected in the small intestine, kidney, heart, skeletal muscles and the brain, and in plasma membranes of adipocytes [12].

Fructose in the blood is transported to the liver where it is mainly metabolized. In the muscles and kidneys, fructose can be phosphorylated by hexokinase as a major pathway, however in the liver, fructose is metabolized by fructokinase into fructose-1-phosphate which is converted to glyceraldehyde and **dihydroxyacetone phosphate** (DHAP) by **fructose-1-phosphate aldolase (aldolase B)**. DHAP is converted into glyceraldehyde-3-phosphate (GA3P) by triose phosphate isomerase. Glyceraldehyde is phosphorylated by ATP and triose kinase to GA3P. Therefore, both products of fructose hydrolysis enter the glycolytic pathway as GA3P [10] (Figure 2).

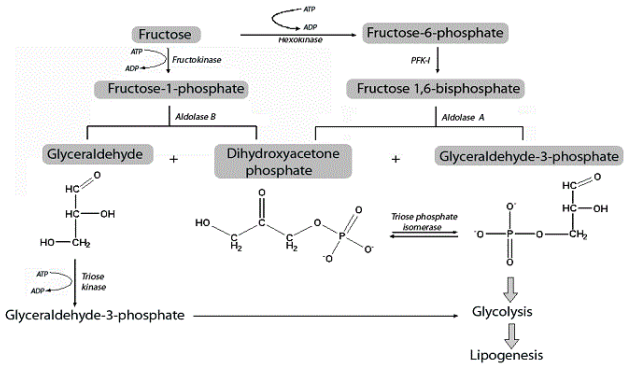

Figure 2: Fructose metabolism in liver.

Glucose and fructose carbons are utilized through the glycolysis, gluconeogenesis, glycogenolysis, tricarboxylic acid cycle, Cori cycle, pentose phosphate pathway and lipid synthesis pathways [1]. After entering into the cells, glucose is phosphorylated to glucose-6-phosphate by hexokinase/glucokinase, which is further converted to fructose-6-phosphate by isomerase enzyme. The critical enzyme phosphofructokinase 1 (PFK-1) phosphorylates fructose-6-phosphate to fructose1,6-bisphosphate which is the rate limiting step in glycolysis. Aldolase A acts on fructose 1,6-bisphosphate to produce GA3P and DHAP, which are further metabolized into pyruvate. Fructose metabolism bypasses the PFK-1 enzyme which exerts a very significant control over the whole metabolism. Fructose is metabolized much faster than glucose. With the consumption of high amounts of fructose, GA3P and DHAP synthesis, consequently Acetyl-CoA will be increased, favoring lipid biosynthesis in the liver.

Glucose is the primary fuel used for energy production in human body and almost all cells can utilize glucose however fructose metabolism differs from glucose metabolism in several ways. Glucose enters the cells by insulin dependent (GLUT 4) mechanisms in adipose tissues and skeletal muscles, whereas fructose transport is non-insulin dependent (GLUT5). Insulin increases the number of glucose transporters on the cell membranes which affects the glucose transport into the cells. Fructose does not cause insulin release from pancreatic beta cells, as they lack fructokinase.

Fructose consumption and metabolic diseases

It is denoted that the consumption of HFCS currently accounts for 40% of all added caloric sweeteners [13]. The Dietary Guidelines Advisory Committee suggested that a maximal intake level of 25% or less of total energy should be consumed from added sugars, on their report of their report released in June, 2010 on the Dietary Guidelines for Americans 2010 [14]. In 2008, Vos et al. [15] investigated the dietary fructose consumption patterns by 24-hour dietary records among US children and adults with a total sample number of 21,483. That study was the third national health and nutrition examination survey and they reported that fructose consumption was estimated to be in the range of 38-73 g/day with a mean value of 55 g/day equivalent to 10 % of total caloric intake and fructose consumption was highest among adolescents at 73 g/day accounting for 12 % of total calories [15].

A systematic review and meta-analysis of prospective cohort studies providing a total 2,502,357 person-years of follow-up was undertaken by Jayalath et al. [16], to quantify the association between fructose-containing sugar intake and incident hypertension. Median fructose intake was 5.7-6.0% total energy in the lowest quintile and 13.9-14.3% total energy in the highest quintile and the results showed no association between fructose-containing sugar intake and hypertension, where fructose constituted up to 14% of the total energy intake [16]. Just two 355-mL soft drinks are proposed to supply up to 50 g/fructose (200 kcal) which makes up more than 10% of the energy requirements for an average-weight woman, verifying the significance of the fructose consumption and related energy intake of an American diet [17].

Fructose was initially thought to be favorable for patients with diabetes due to its low glycemic index however depending on the observations that chronically high consumption of fructose in rodents leads to insulin resistance, obesity, type 2 diabetes mellitus, and high blood pressure, it was removed from the hospital protocols [18]. Stanhope et al. [19] reported that consumption of fructose-sweetened beverages increased visceral adipose deposition and de novo lipogenesis, produced dyslipidemia, and decreased glucose tolerance/insulin sensitivity in older, overweight/obese men and women, however consumption of glucose-sweetened beverages at the same ratios did not cause such effects [19]. There are existing data on the metabolic and endocrine effects of dietary fructose that suggest that increased consumption of fructose may be detrimental in terms of body weight as well [17].

Fructose metabolism by-passing the feedback regulatory steps in the glucose metabolic pathway, is thought to lead to increases of fatty acid synthesis and contribute to causes of obesity [1]. The PFK-1 catalyzed reaction is critical in the overall regulation of ATP production and consumption. Since hypothalamic fructose metabolism also bypasses this important regulatory step its metabolism depletes ATP in the hypothalamus very rapidly and this depletion of ATP causes an increase in AMP which also has important effects on the whole metabolism as well as in the hormonal control of food intake. Fructose does not increase insulin and leptin or suppress ghrelin, which suggests an endocrine mechanism by which it induces a positive energy balance [20]. Because leptin production is regulated by insulin, fructose consumption also reduces circulating leptin concentrations and lowered circulating leptin and insulin after high dietary fructose consumption could increase the likelihood of weight gain [17].

The fructose is immediately converted to fructose-1-phosphate by the enzyme fructokinase, intracellular phosphate of the hepatocyte is depleted, leading to activation of the enzyme adenosine monophosphate (AMP) deaminase-1, which converts the adenosine phosphate breakdown products into the cellular waste product uric acid [21,22]. Fructose is unique among sugars in that it rapidly causes depletion of ATP and increases both the generation and the release of uric acid. Experimental data support a link between fructose intake, hyperuricemia, and increases in blood pressure. Uric acid is expressed to inhibit endothelial nitric oxide synthase (eNOS), causing a reduction in nitric oxide (NO) and contributing to hypertension [23]. High sugar-sweetened beverage consumption is referred to be associated with higher serum uric acid levels and accordingly with higher systolic blood pressure [24,25].

In a number of animal studies, high fructose consumption is correlated with several pathologies. Fructose feeding has been shown to alter gene expression patterns in rats [26], alter satiety factors in the brain of rats [27], increase inflammation in rats [28] increase reactive oxygen species in rats [29] and portal endotoxin concentrations in mice [30].

Also recent human studies indicate that, high dietary fructose leads to Non alcoholic fatty liver disease and augmented de-novo triglyceride synthesis, based on an analysis of hormone regulated lipid pathways in the liver [31]. High fructose consumption is also denoted to alter gene expression patterns in healthy man [32] High dietary levels of fructose is reported to increase serum triglycerides and cause certain metabolic diseases, obesity and weight gain [33]. A significant relationship between fructose malabsorption and fructose dose was reported by Jones et al. [8]. Younger children are denoted to have a reduced capacity to absorb fructose, particularly even small quantities of high-fructose fruit juices [8]. Fructose that is not absorbed in the small intestine reaches the large intestine, where it is metabolized by intestinal flora, resulting in hydrogen production. Certain epidemiological and experimental data supporting a relationship between increased dietary fructose and cancer risk have also been presented [34,35].

When the data drawn from animal and human studies are considered, following possible risks of high fructose consumption still exists:

Fructose-1-phosphate accumulation and toxicity to hepatocytes, inhibition of metabolic enzymes

Reduction in phosphate pools, depletion of ATP, leading to activation of the AMP enzyme and production of uric acid, leading to hyperuricemia and increase in blood pressure causing hypertension.

By-passed insulin control over the metabolism leading to reduced hormonal regulation of metabolism and satiety since fructose does not increase insulin and leptin or suppress ghrelin.

Fast metabolism of fructose-1-phosphate to DHAP and GA3P, leading to increase in pyruvate and acetyl-CoA production, further leading to lipid biosynthesis.

Conclusion

High fructose consumption is reported to induce insulin resistance, impaired glucose tolerance, and hypertension in animal models. Although the data in humans are not sufficient, the present findings should be considered about limiting the consumption of high amounts of fructose. Further research is to be done to better explain the metabolic effects of high fructose consumption and related health consequences.

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