

The Role of Fructose in Type 2 Diabetes and Other Metabolic Diseases

Bernadine Ruiza G Ang^{1*} and Gracia Fe Yu²

¹University of the Philippines Diliman, Manila, Philippines

²Department of Biochemistry and Molecular Biology, University of the Philippines Diliman, Manila, Philippines

Abstract

Fructose is a hexose that when ingested in high amount increases the risk of type 2 diabetes and other metabolic diseases. Type 2 diabetes is estimated to be the 7th leading cause of mortality by 2030, according to the World Health Organization (WHO). The number of people with diabetes has risen from 108 million in 1980 to 422 million in 2014. Food security which is defined as the availability, stability, access and utilization of safe foods is a major determinant in the incidence of type 2 diabetes and other metabolic diseases. Cost-effective food products are highly available and usually utilized abundantly. For example, high fructose corn syrup (HFCS) found in numerous food products such as pastries, yogurt and ice cream are used excessively due to its low cost and versatility.

Fructose in its pure form or from HFCS supplemented in our diets can be one of the determining factors that cause type 2 diabetes and other metabolic diseases. Fructose, once ingested, can be oxidized, converted to glucose or converted to lactic acid or enter *de novo* lipogenesis. These metabolic pathways could lead to the development of type 2 diabetes and metabolic diseases such as obesity and metabolic syndrome. Avoiding excessive intake of fructose can reduce the propensity for type 2 diabetes and other metabolic diseases. In this research study, the methodology from human and animal studies were searched in PubMed and Google Scholar databases. The following key words were searched in each paper: fructose, high fructose corn syrup, sugar, sucrose, metabolic syndrome, type 2 diabetes, insulin resistance, blood glucose, blood sugar, triglycerides, lipoproteins, high density lipoprotein, cholesterol, and low-density lipoprotein. Overall, approximately 150 articles and books were gathered. In this review article, it has been concluded that high fructose ingestion increases risk of metabolic diseases such as type 2 diabetes and the metabolic syndrome. The aim of this research study is to elucidate the role of fructose metabolism in type 2 diabetes and other metabolic diseases.

Keywords: Type 2 diabetes; Metabolic diseases; Isomerization; Insulin resistance

Introduction

General context

This review investigates the role of fructose in metabolism of type 2 diabetes, and other metabolic diseases. Diabetes is associated with various factors such as dietary intake, genetics, physical activity and obesity (Figure 1). Type 2 diabetes is determined by measuring the amount of glucose in our blood. A reference range between 60-100 mg/dL shows a normal range while 101-125 mg/dL is considered prediabetes and 126 mg/dL or higher shows you have diabetes. There is very little scientific literature on how fructose may also affect type 2 diabetes. Very few human studies on fructose and type 2 diabetes are present and the exact mechanism on how fructose affects insulin secretion is still under speculation. Only evidence from animal studies have shown the relationship between fructose and type 2 diabetes. Human studies have shown fructose in conjunction with another nutrient or compound to increase likelihood of type 2 diabetes. One study blocked fructose metabolism pathway in a diabetic mouse model which in turn mitigated the development of tubulointerstitial injury in diabetes [1].

Historical perspective

Fructose was first discovered in 1847 by French chemist Augustin-Pierre Dubrunfaut. Sugar consumption had remained low until the 18th century, when the development of technology to extract refined sugars became available. It was initially mostly extracted and refined from sugar cane and imported to Europe and North America. In England, sugar consumption increased by 1,500% between the 18th and 19th centuries and by the turn of 20th century, sugars had become the main constituent of our diet [2].

Sucrose became an exclusive sweetener to be used, with small amounts of glucose and fructose from fruits until the 1960s, when technology developed allowing starch to be extracted from corn, hydrolyse it to glucose, and convert part of glucose to fructose through enzymatic isomerization. This resulted to the development of high fructose corn syrup which was more cost effective and has longer shelf life. This was preferred by the industry users instead of sucrose [3].

Definition of Fructose

Fructose is a 6-carbon sugar that is a monosaccharide found in fruits and honey. Fructose is joined with glucose to obtain sucrose which is the table sugar we consume. Fructose is also a hexose which has a similar chemical formula with glucose. This could be the reason why fructose also passes by the same pathway as glucose. Fructose and sucrose are widely used as a sweetener in the medical and food industry. The sweetening power of fructose is 1.5 to 1.7 times that of sucrose [4]. Fructose can be toxic to humans when ingested in large amounts. After ingestion of large amounts of fructose, increases of hepatic acetyl CoA lead to increased production of very low-density lipoprotein and triglycerides which is associated with type 2 diabetes [5].

***Corresponding author:** Bernadine Ruiza G Ang, MS Candidate, University of the Philippines Diliman, Manila, Philippines, Tel: +63 2 981 8500; E-mail: angbernadine@hotmail.com

Received January 04, 2018; **Accepted** January 15, 2018; **Published** January 25, 2018

Citation: Ang BRG, Yu GF (2018) The Role of Fructose in Type 2 Diabetes and Other Metabolic Diseases. J Nutr Food Sci 8: 659. doi: [10.4172/2155-9600.1000659](https://doi.org/10.4172/2155-9600.1000659)

Copyright: © 2018 Ang BRG, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Fructose Metabolism

Fructose absorption and metabolism in the gut

Fructose enters cells by facilitated diffusion on the GLUT5 transporter. Expression of GLUT5 in the intestine is upregulated by fructose and not sucrose. As it enters the enterocyte, fructose diffuses into the blood vessels through a transport mediated by GLUT2 at the basolateral pole of the enterocyte [6]. GLUT8 has also been shown to regulate enterocyte fructose transport. The study tested the hypothesis that GLUT8 regulates intestinal hexose uptake and metabolic homeostasis *in vivo*. DeBosch et al. demonstrated that GLUT8 deficiency enhanced fructose uptake in cultured Caco2 human intestinal epithelial cells and in jejunum isolated from mice lacking gene encoding GLUT8, *Slc2a8*. In addition, mice lacking GLUT8 rapidly developed significantly higher serum fructose concentration after oral glucose [7]. Therefore, GLUT8 is not involved in fructose uptake.

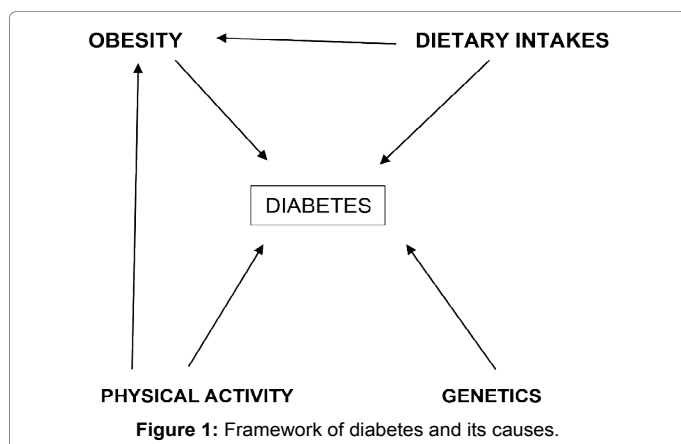
Hepatic metabolism

Fructose can be found in equimolar amounts with glucose from sucrose. Its metabolism takes place in the liver, where fructose is converted to pyruvate, or under fasting conditions to glucose. It is then metabolized to intermediates of glycolysis. For fructose to enter the pathways of intermediary metabolism, it must be phosphorylated. This can be done by hexokinase or fructokinase. It then becomes fructose 1-phosphate and is cleaved by aldolase B to form dihydroxyacetone phosphate (DHAP) and glyceraldehyde, which is phosphorylated by ATP to form glyceraldehyde 3-phosphate. Both of them are intermediates of glycolysis. Alternatively, the fructose can be converted to glucose by gluconeogenesis. Fructose metabolism parallels that of glycolysis. When it becomes pyruvate, it enters the tricarboxylic acid cycle and fatty acid synthesis (Figure 1) [8]. This is the reason why excess fructose can cause obesity, thereby affecting type 2 diabetes.

Fructose and exercise

Exercise has a positive effect on fructose content in the body. Studies show that exercise performed immediately after fructose ingestion increases fructose oxidation and decreases fructose storage [9]. Exercise has been known to increase blood volume due to the pumping of blood by the heart. As the heart pumps faster, more blood is released, thereby making the blood more solvent and decreasing the solutes which in this case would be fructose.

In measuring the effects of fructose and insulin secretion, regular exercise enhances insulin signaling, glucose transport and substrate



metabolism in the muscles [10]. Therefore, despite the fact that high fructose causes postprandial plasma lipids, increased exercise would offset this by altering intracellular substrate utilization. Many studies have evaluated the potential benefits of fructose ingestion and labeled fructose was indeed shown to be oxidized during exercise (Figure 2) [11].

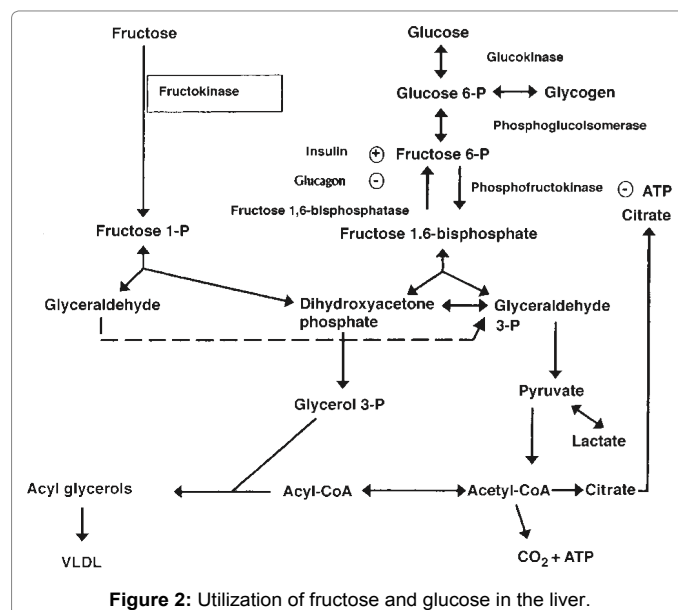
Fructose and food intake

Excessively high intake of fructose may cause a suppression of hypothalamic malonyl CoA signaling pathway, thereby exerting an orexigenic effect. Hypothalamic malonyl-CoA is known to suppress food intake. Unlike glucose, research proved that centrally administered fructose increases food intake. More rapid initial steps of central fructose metabolism deplete hypothalamic ATP level, whereas the slower regulated steps of glucose metabolism elevate hypothalamic ATP level. Fructose increases phosphorylation or activation of hypothalamic AMP kinase causing phosphorylation or inactivation of hypothalamic acetyl-CoA carboxylase, whereas glucose has the inverse effects. Fructose administration reduce hypothalamic malonyl-CoA level and thereby increase food intake [12].

Uses of Fructose

Fructose can be used in several forms. The most common usage of fructose is high fructose corn syrup (HFCS) which is used commercially as sweeteners in pastries, yogurt, ice cream, and other frozen desserts. HFCS is produced by the enzymatic isomerization of dextrose to fructose [13]. HFCS is produced from corn. The corn grain undergoes several processes starting with steeping to soften the hard kernel followed by wet milling and physical separation into corn starch (from the endosperm), corn hull (bran) and protein and oil (from the germ). The corn starch which composed of glucose molecules also consists of amylose and amylopectin and requires heat, caustic soda and hydrochloric acid plus activity of different enzymes to break it down to simple sugars glucose and fructose present in HFCS [14]. HFCS can also function as a sweetener in various types of medicines. It can be found in cough suppressants, decongestant drops, liquids for children and adults and nighttime medicines used for cough and colds.

Crystalline fructose is another type of fructose which does not contain glucose, like HFCS. It is the pure form of fructose and is



included in powdered beverages, low-calorie food options, flavored enhanced water, carbonated sodas and drinks, energy and sports drinks, chocolate flavored milk, cereals and oatmeal, yogurts and baked goods.

Fructose Causes Metabolic Syndrome

Fructose and metabolic syndrome metabolism

Metabolic syndrome is a cluster of conditions- increased blood pressure, high blood sugar, excess body fat around the waist, and abnormal cholesterol or triglyceride levels that occur together increasing risk of heart disease, stroke and diabetes. Fructose is a major factor in increasing tendency of metabolic syndrome. Clinical and epidemiological evidence suggest progressive association between fructose consumption and the development of metabolic syndrome [15]. According to Nakagawa et al., fructose- unlike other sugars, causes serum uric acid levels to rise rapidly. They recently reported that uric acid reduces levels of endothelial nitric oxide (NO), a key mediator of insulin action. NO increases blood flow to skeletal muscle and enhances glucose uptake. Animals deficient in endothelial NO develop insulin resistance and other features of the metabolic syndrome. As such, they proposed that epidemic of metabolic syndrome is due in part to fructose-induced hyperuricemia that reduces endothelial NO levels and induces insulin resistance [16].

Fructose Causes Type 2 Diabetes in Humans

Type 2 diabetes metabolism

Type 2 diabetes is a disease caused by insufficient insulin that captures glucose and transfers it to the organs in the body. Instead, high blood glucose accumulates in the blood due to the lack of insulin from the pancreas.

Human studies with fructose and type 2 diabetes

Intake of fructose elicits a low glycemic index and, does not require insulin to be transported among cells, unlike glucose, that does require insulin [2]. After absorption of fructose, it is transported to the liver where it is effectively absorbed by liver cells. In the liver, fructose can enter metabolic pathways: it can be oxidized, converted to glucose (and glycogen) or converted to lactic acid, or enter *de novo lipogenesis* (DNL). After an overnight fast, approximately 50% of fructose eaten as an oral dose of approximately 30-70g is converted to glucose via gluconeogenesis. The other metabolic fate of fructose to form lactic acid only happens at high fructose intakes. Lactic acid can cause muscle soreness and pain. Excessive intake of fructose also has been shown to increase DNL. Conversion of fructose to glucose thus increases risk of type 2 diabetes. Furthermore, fructose may also contribute negatively to blood glucose homeostasis by causing insulin resistance in the liver. In human studies, fructose has been shown to cause insulin resistance. The daily intake of fructose has been as high as 110 g, approximately 250 g, 80 g and 138 g. This indicates that fructose intake must be high to potentially cause insulin resistance [17].

Fructose and energy release

One paper cited that fructose has a direct correlation with energy while another paper cited there is no correlation or effect with energy. Recent studies show that fructose- sweetened beverages do not differentially affect energy intake compared with glucose- sweetened beverages [18]. Since fructose can be converted to glucose any way, it follows the pathway of glucose oxidation and therefore yields the same amount of ATP or energy released. For instance, when fructose

is oxidized as lactation extra hepatic cells, the overall number of ATP used (2ATP) and synthesized (29.5ATP) is the same as for glucose oxidation, and the overall energy efficiency is similar to glucose [19].

Fructose and obesity

Large evidence shows that fructose is a major contributor to excess liver fat deposition. People with overweight or obesity who consumed beverages sweetened with either glucose or fructose for 10 weeks, in amounts supplying 25% of their daily energy requirements have been examined in closely controlled conditions. Despite similar weight gain in the two groups, the fructose group had significant increases in visceral adipose tissue mass (14% *versus* 3%) and in hepatic *de novo* lipogenesis (75% *versus* 27%) [20].

Genetic factors also play a major part in obesity. However, environmental factors seem to have a more impact on obesity. HFCS which comes from the environment have led to the increases in caloric and fructose consumption that are important contributors to obesity. Bray et al. suggested that HFCS may have an environmental link with the epidemic of obesity [21].

Mechanisms for Fructose Induced Insulin Resistance

Insulin resistance is a condition in which cells fail to respond normally to insulin. Insulin resistance is shown to increase the production of pro-inflammatory cytokines which are predictors of cardiovascular events [22]. Numerous studies have shown the increase in insulin resistance upon ingestion of fructose [23]. Although fructose does not stimulate insulin in the short term, the insulin resistance and obesity induced by long term fructose feeding in experimental animals induces hyperinsulinemia [13]. Hyperinsulinemia may then lead to hypoglycemia or type 2 diabetes. Medical treatment may help to relieve the symptoms of hyperinsulinemia. Decrease in skeletal and hepatic insulin receptor number was discovered utilizing *in situ* autoradiography technique as well as decrease in gene expression found by 66% fructose feeding for two weeks in rats. Furthermore, decreased insulin-induced insulin receptor phosphorylation was demonstrated in liver of fructose fed rats [24]. This marks another mechanism for fructose induced insulin resistance.

Conclusion

Fructose metabolism and its relation to type 2 diabetes and other metabolic diseases has been examined. Based on studies conducted, fructose can cause obesity, type 2 diabetes, increase hypertension and induce insulin resistance. Foods such as juices and pastries which are known to be plentiful in HFCS should be avoided. Regulating the consumption of fructose and consuming it minimally (only 25-40 g daily) is the best solution to prevent these metabolic diseases.

References

1. Bjornstad P, Lanasp MA, Ishimoto T, Kosugi T, Kume S, et al. (2015) Fructose and uric acid in diabetic nephropathy. *Diabetologia* 58: 1993-2002.
2. Tappy L, Lê KA (2010) Metabolic effects of fructose and the worldwide increase in obesity. *Physiol Rev* 90: 23-46.
3. Campos VC, Tappy L (2016) Physiological handling of dietary fructose-containing sugars: implications for health. *Int J Obes* 40: S6-S11.
4. Steinman B, Gitzelmann R, Berghe van den G (2015) Essential fructosuria, hereditary fructose intolerance, and fructose- 1, 6-diphosphatase deficiency. The online metabolic and molecular bases of inherited disease pp: 118-140.
5. Teff KL, Grudziak J, Townsend RR, Dunn TN, Grant RW, et al. (2009) Endocrine and metabolic effects of consuming fructose and glucose- sweetened beverages with meals in obese men and women: influence of insulin resistance on plasma triglyceride responses. *J Clin Endocrinol Metab* 94: 1562-1569.

6. Tappy L, Lê KA, Tran C, Paquot N (2010) Fructose and metabolic diseases: new findings, new questions. *Nutrition* 26: 1044-1049.
7. DeBosch BJ, Chi M, Moley KH (2012) Glucose transporter 8 (glut8) regulates enterocyte fructose transport and global mammalian fructose utilization. *Endocrinology* 153: 4181-4191.
8. Lieberman M, Marks AD, Peet A (2013) *Basic medical biochemistry: a clinical approach*. Baltimore, Philadelphia: Lippincott Williams & Wilkins, Wolters Kluwer, p: 1014.
9. Egli L, Lecoultre V, Cros J, Rosset R, Marques AS, et al. (2016) Exercise performed immediately after fructose ingestion enhances fructose oxidation and suppresses fructose storage. *Am J Clin Nutr* 103: 348-355.
10. Bidwell AJ, Fairchild TJ, Redmond J, Wang L, Keslacy S, et al. (2014). Physical activity offsets the negative effects of a high fructose diet. *Med Sci Sports Exerc* 46: 2091-2098.
11. Tappy L, Rosset R (2017) Fructose metabolism from a functional perspective: implications for athletes. *Sports Med* 47: 23-32.
12. Chaa SH, Wolfgang M, Tokutakeb Y, Chohnanb S, Lane MD (2008) Differential effects of central fructose and glucose on hypothalamic malonyl- CoA and food intake. *Proc Natl Acad Sci U S A* 105: 16871-16875.
13. Elliott SS, Keim NL, Stern JS, Teff K, Havel PJ (2002) Fructose, weight gain, and the insulin resistance syndrome. *Am J Clin Nutr* 76: 911-922.
14. Parker K, Salas M, Nwosu VC (2010) High fructose corn syrup: production, uses, and public health concerns. *Biotechnol Mol Biol Rev* 5: 71-78.
15. Sánchez-Lozada LG, Tapia E, Jiménez A, Bautista P, Cristóbal M, et al. (2007) Fructose-induced metabolic syndrome is associated with glomerular hypertension and renal microvascular damage in rats. *Am J Physiol Renal Physiol* 292: 423-429.
16. Nakagawa T, Tuttle KR, Short RA, Johnson RJ (2006) Hypothesis: fructose-induced hyperuricemia as a causal mechanism for the epidemic of the metabolic syndrome. *Nat Clin Pract Nephrol* 1: 80-86.
17. Kolderup A, Svihus B (2015) Fructose metabolism and relation to atherosclerosis, type 2 diabetes, and obesity. *J Nutr Metab* 2015: 1-12.
18. Kuzma JN, Cromer G, Hagman DK, Breymeyer KL, Roth CL, et al. (2015) No difference in ad libitum energy intake in healthy men and women consuming beverages sweetened with fructose, glucose, or high fructose corn syrup: a randomized trial. *Am J Clin Nutr* 102: 1373-1380.
19. Tappy L, Egli L, Lecoultre V, Schneider P (2013) Effects of fructose-containing caloric sweeteners on resting energy expenditure and energy efficiency: a review of human trials. *Nutr Metab* 10: 54.
20. Goran MI, Dumke K, Bouret SG, Kayser B, Walker RW, et al. (2013) The obesogenic effect of high fructose exposure during early development. *Nat Rev Endocrinol* 9: 494-500.
21. Bray GA, Nielsen SJ, Popkin BM (2004) Consumption of high fructose corn syrup in beverages may play a role in the epidemic of obesity. *Am J Clin Nutr* 79: 537-543.
22. Li T, Lu X, Sun Y, Yang X (2016) Effects of spinach nitrate on insulin resistance, endothelial dysfunction markers and inflammation in mice with high fat and high fructose consumption. *Food Nutr Res* 60: 32010.
23. Hwang IS, Ho H, Hoffman BB, Reaven GM (1987) Fructose-induced insulin resistance and hypertension in rats. *Hypertension* 10: 512-516.
24. Rizkalla SW (2010) Health implications of fructose consumption: a review of recent data. *Nutr Metab* 7: 82.