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ADVERSE METABOLIC EFFECTS OF DIETARY FRUCTOSE

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ABSTRACT

Metabolic syndrome is a cluster of disorders of metabolism associated high blood pressure, high blood glucose, excess body weight, abnormal cholesterol levels. Each of these disorders is by itself a risk factor for other diseases including type 2 diabetes (T2D), cardiovascular disease, and hypertension. Excessive sugar intake through the consumption of sugar-sweetened beverages has a direct association with the risk for metabolic syndrome including obesity and type 2 diabetes. High fructose corn syrup (HFCS) which contain fructose as primary component is an alternative sweetener that can serve as a replacement for sucrose may induce adverse metabolic effects. Although fructose is safe at typical intake levels, it can produce adverse metabolic effects when it is abused. Evidence consistent with this possibility is accumulating. Epidemiological, animal experimental and clinical trials have been proposed, although they may require further expansion and evaluation. Here, we aim to document several studies that indicate that dietary fructose in the form of HFCS induce adverse metabolic effects via several mechanisms. In one such mechanism, HFCS may enhance hepatic *de novo* lipogenesis, thus linking HFCS with the other metabolic conditions related to lipid regulation.

Keywords: fructose, metabolic syndrome, type 2 diabetes, cardiovascular disease

Introduction

Metabolic syndrome is a cluster of disorders of metabolism associated high blood pressure, high blood glucose, excess body weight, abnormal cholesterol levels. There are several definition emphasized the risk factors namely high waist circumferences, high triglycerides, blood pressure, and fasting blood glucose, and low high density lipoprotein cholesterol.[1] The 2003-2006 National Health and Nutrition Examination survey in US have reported that the prevalence of metabolic syndrome (MetS) among US adults is approximately 34%.[2] Moreover, some studies have been shown that MetS among US adults is associated with morbidity and all-cause mortality.[3-5] According to the 25 surveys in Asian populations (China, Hong Kong, Taiwan, Japan, Philippines, and Singapore), the prevalence of MetS has been increasing rapidly and appears to be similar to that of incidence among Western populations and this consistent increase of MetS prevalence is associated with the abdominal adiposity as the main factor lead to high risk of morbidity and mortality.[6]

Unhealthy diets characterized by 'Western'-style food with high energy density which accompanied with the present of metabolic risk factors have affected global trends associated with the increased prevalence of obesity and type 2 diabetes (T2D).[7] High levels of refined carbohydrates and, in particular, sugar have become the best-known feature of the Western diet.[8] Excessive sugar intake through the consumption of sugar-sweetened beverages has a direct association with the risk for obesity[9,10] and T2D.[11,12]

In the past 25 years, there has been a marked increase in the total per capita fructose intake, primarily in the form of sucrose (a disaccharide consisting of 50% fructose) and high fructose corn syrup with 55% of fructose content).[7] Indeed, fructose intake is linked to the epidemic of obesity and diabetes.[11,13] Soft drinks high in HFCS have also been associated with an increased risk for obesity in adolescents[13] and T2D in young and middle-aged women.[11] Furthermore, excess fruit juice (also rich in fructose) is associated with the development of obesity in children,[14] and fructose-fed rats were shown to develop features of metabolic syndrome.[15]

Metabolism of fructose

Fructose is also known as fruit sugar or laevulose, a six-carbon monosaccharide sugar (hexose) with a keto group on carbon-2 that serves as the free sugar in fruits and honey and a constituent of the disaccharide sucrose. Fructose is 1.7 times sweeter than sucrose and is absorbed by facilitated diffusion, producing a smaller rise in blood glucose.[16]

HFCS, also known as iso-syrup and high-fructose syrup (HFS), is produced through the hydrolysis of starch, during which almost half of the glucose is converted into fructose, and is similar to syrup produced from sucrose but cheaper.[16]

Absorbed fructose, either from direct ingestion of fructose or digestion of sucrose, is transported to the liver or phosphorylated to fructose-1-phosphate, an intermediate of the glycolytic pathway, which is further cleaved to glyceraldehyde and dihydroxyacetone phosphate (DHAP). DHAP is an intermediary metabolite in both glycolytic and gluconeogenic pathways. The glyceraldehyde can then be converted to glycolytic intermediary metabolites,which serve as precursors for glycogen synthesis, or it can be used for triacylglycerol synthesis if provided with sufficient amounts of malonyl-coenzyme A, a precursor of fatty acid synthesis.[17] Figure 1 shows the metabolism of fructose and glucose.[18]

Fructose is endogenously produced when the sucrose present in beverages is hydrolyzed by sucrase, which consists of one molecule of glucose and one molecule of fructose. Fructose is predominantly metabolized in the liver, which contains an abundance of the Glut-5 transporter protein that facilitates its entry.[19,20] Phosphorylation

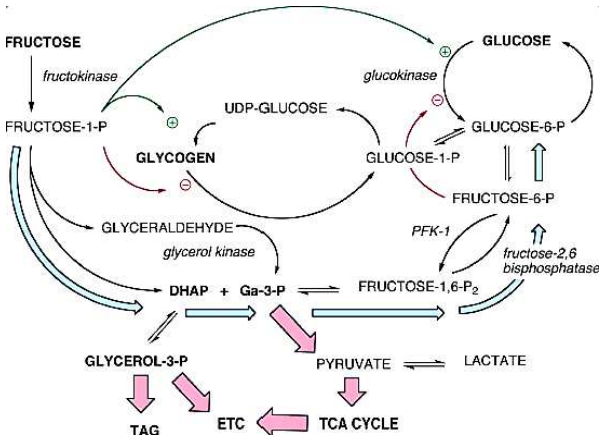

Figure 1 Fructose and glucose metabolism Adapted from Feinman RD 2013[18]

is the first step in its metabolism before its progression into uric acid.[20] The phosphorylated form of fructose is a ready substrate for aldolase, which produces triose as the backbone of triglycerides (TGs).[21]

Adverse metabolic effects of fructose

The American Heart Association Nutrition Committee recommend to reduce added sugar to less than 100 – 150 kcal per day for most American men and women, respectively.[22] In addition, a year later in 2010, a maximum intake level of 25% or less of total energy from added sugars has been suggested by the Report of the Dietary Guidelines Advisory Committee (DGAC) on the Dietary Guidelines for Americans 2010 (DGAC).[23]

Epidemiological studies have also provided evidence that sugar consumption is associated with metabolic disease. A meta-analysis of 10 prospective cohort studies in 2010, including 6 focusing on T2D, 3 on metabolic syndrome, and 1 on coronary heart disease, revealed that the risk of cardio-metabolic disease shows a clear and consistent positive association between sugar-sweetened soft-drink intake (including HFCS) and weight gain, as well as the risk of diabetes, cardiovascular disease, and metabolic syndrome. Among the 294,617 participants, the highest level of intake showed a 24% greater risk of cardio-metabolic disease than those in the lowest group (RR=1.24; 95% CI: 1.12–1.34).[24]

Three recent clinical studies investigated the association between the consumption of either sucrose or HFCS and increased risk factors for cardiovascular disease and metabolic syndrome. One of the studies, a randomized crossover trial, illustrated the effects of HFCS and sucrose on the pharmacokinetics of fructose and acute metabolic and hemodynamic responses in healthy subjects.[25] In this study, forty men and women consumed 24 oz. of HFCS- or sucrose-sweetened beverages. Blood and urine samples were collected over 6 hours, and the metabolic biomarkers measured included blood pressure, heart rate, and fructose level. Compared to sucrose, HFCS led to greater systemic exposure to fructose and unique acute metabolic effects.[26]

Healthy individuals consuming 25% of their energy requirements from HFCS-sweetened beverages for 2 weeks exhibited significant increases in fasting low-density lipoprotein (LDL) cholesterol, non-high density lipoprotein (non-HDL) cholesterol, and apo-lipoprotein B (ApoB). Moreover, the levels of postprandial TG, remnant cholesterol, remnant TG, and small dense LDL (sd-LDL) cholesterol in these subjects were comparable to those of individuals consuming fructose and greater than those consuming glucose, and these levels were up to 2-fold greater in subjects with 3-metabolic syndrome risk factors (MSRF) than in subjects with 0- to 2-MSRF. In addition, the fasting oxidized-LDL concentration was increased in subjects consuming fructose.[27,28]

Study have also suggested the possibility that prolonged consumption of fructose may contribute to the development of metabolic syndrome via the induction of specific pro-inflammatory and pro-thrombotic mediators.[29] However, the adverse metabolic effects following the consumption of fructose compared to glucose could not be

explained by the glycemic index/glycemic load of the diets, and these effects were also independent of postprandial glucose or insulin exposure.[30]

Fructose and T2D

Currently, the evidence for the risk of diabetes due to increased consumption of added sugars remains controversial. Several studies in cohorts and randomized controlled trials have revealed that no relationship between sugar consumption and risk factors for diabetes, where as other studies have reported such a relationship. Diabetes and obesity show a strong correlation, and any potential increase in weight through added sugar consumption may indirectly increase certain risk factors for diabetes.

Excess adiposity, particularly around the central depots, is one of the best-established risk factors for the development of T2D. A growing body of evidence clearly indicates that the consumption of sugar-sweetened beverages is associated with an increased risk of diabetes through effects on adiposity and independent of other metabolic effects.[31] A meta-analysis of prospective cohort studies on diabetes mellitus reported a positive relationship between sugar-sweetened soft drink intake and the risk of T2D.[24]

An increased risk for T2D may be independently associated with the intake of sugar-sweetened beverages via mechanisms related to either weight gain or glycemic effects after the consumption of large amounts of rapidly absorbable sugar due to the metabolic effects of fructose.[32] Indeed, it has been reported that consuming fructose or glucose (150 g/d) for a 4-week period resulted in a lowered insulin sensitivity and increased Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) in subjects of a similar age and body mass index (BMI) (31±9 years; 25.9±2.2 kg/m^2).[33] Eighteen other trials (n=209) also reported a reduction in glycated blood proteins followed by an isocaloric exchange of fructose for carbohydrates (Standardized Mean Differences 20.25 [95% CI: 20.46 to 20.04]; *P*=0.02), with significant inter-trial heterogeneity (I2=63%; *P*=0.001), and this result was equivalent to a ~0.53% reduction in HbA_{1c}. In contrast, fructose consumption was not shown to significantly affect fasting glucose or insulin; within a subgroup of analyses, no evidence in support of effect modification was reported for any end point.[34]

In comparison with glucose, dyslipidemia and insulin resistance can be affected by dietary fructose consumption in animals. Moreover, human studies have investigated overweight and obese subjects following the consumption of glucose - and fructose-sweetened beverages providing 25% of the energy requirement for 10 weeks. In fact, both groups consuming glucose and fructose beverages showed a similar weight gain, whereas the results for hepatic de novo lipogenesis (DNL) and the 23-hour postprandial TG Area Under the Curve (AUC) were increased following fructose consumption. On the other hand, approximately 10% of the fasting plasma TG concentration increased during the 10 weeks of glucose consumption. In subjects consuming glucose, fasting sd-LDL concentrations were initially decreased at 2 weeks but were similar to the baseline value after 10 weeks. In contrast, there was a progressive increase in the fasting sd-LDL concentrations in the fructose group and increased postprandial concentrations of both remnant-like particle lipoproteins; Remnant-like particle lipoprotein–TG (RLP-TG) and RLP-cholesterol (RLP-C).[27]

The first investigation of fructose metabolism in subjects with diabetes mellitus was conducted in 1953 by Smith et al.[35], who reported that the half-life of fructose was prolonged and that urinary glucose excretion after fructose infusion was greater in diabetics compared to normal subjects. This study suggested that the conversion of fructose to glucose is increased in diabetes. Moreover, higher rates of gluconeogenes is were associated with

lactate and pyruvate, which are generated from fructose in diabetic subjects.[35]

Fructose plays a role as a major product of the polyol/sorbitol pathway, and tissue fructose accumulation leads to the induction of further metabolic disease and worsening T2D; in addition, this condition has been implicated in diabetic neuropathy and other complications of diabetes.[36] In 1989, Osei and Bossetti[37] fed 60 g/d of fructose (10%–15% of energy) as part of an isocaloric weight-maintaining diet to 13 patients with poorly controlled T2D for 6 months in a crossover study and compared this condition to a control diet providing mainly complex carbohydrates. These authors found that fasting glucose levels decreased from 227 to 176 mg/dL, and glycosylated hemoglobin levels decreased from 11.3% to 9.9%.[37]

However, the potential impact of consuming large amounts of fructose occurs through its effect on lipid metabolism in subjects with T2D, who tend to be at an increased risk of cardiovascular disease. In diabetic subjects fed a 20% fructose diet for 2 weeks, increased levels of TGs were associated with higher baseline fasting TG levels (>150 mg/dL).[38] In another study with the same dietary intervention and target subjects but a longer duration (4 weeks), total and LDL cholesterol levels were increased by 7% and 11%, respectively.[39] Thus, the existing data regarding the effects of moderate amounts of dietary fructose on lipids in subjects with T2D are equivocal. Several short-term studies have also implicated fructose in promoting unfavorable lipid profiles, and both short-term and long-term fructose consumption was shown to increase postprandial TG levels. In a preliminary study, the hyper triglyceridemia effects of fructose were more pronounced after 10 weeks than after 2 weeks, and fructose consumption also increased the postprandial levels of atherogenic Apo B.[19] Increased TG levels are also an independent risk factor for coronary heart disease, and mode rate increases in Very Low Density Lipoprotein (VLDL) are associated with other lipoprotein changes, including reduced HDL[40] and small dense-LDL,[41] which are components of the metabolic syndrome and are recognized as risk factors for atherosclerotic disease.

The impact of dietary fructose consumed in combination with high-fat meals, in a setting of positive energy balance rather than in the setting of neutral energy balance (eucaloric feeding) has been evaluated in most clinical nutrition studies. However, these complications could reflect the worsening progression of diabetes, which may result in increased protein fructosylation. Indeed, increased glycation (fructosamine and glycated hemoglobin) and markers of lipid peroxidation and aging have been observed in rats fed a high-fructose diet compared to animals fed a high-glucose diet. Fructose feeding also impairs antioxidant defense systems, and oxidative stress has been implicated as a contributing factor in insulin resistance and impaired beta-cell function. Some, but not all, studies have suggested the potential for undesirable effects due to fructose consumption on lipid metabolism in patients with T2D. Moreover, patients with existing hyperlipidemia may be at an increased risk for fructose-induced dyslipidemia.[19]

Fructose and cardiovascular disease

Excessive fructose consumption from added sugars may play a role in the epidemics of heart disease, insulin resistance, T2D, hypertension, dyslipidemia, and obesity. A metabolic study of overweight and obese adults suggested that the consumption of fructose-sweetened beverages led to dyslipidemia, increased fasting blood glucose, decreased insulin sensitivity, and increased visceral adiposity.[27] In addition, increased inflammatory markers secondary to fructose consumption may also contribute to an increased risk of metabolic syndrome. Moreover, increased levels of TGs are often associated with increased carbohydrate consumption, may increase the risk for metabolic syndrome.

An elevated level of TGs can be caused by an imbalance between the rates production and clearance of VLDL-TG.[27,42] Hepatic TG secretion is mainly controlled by the availability of fatty acid, and there are two process in which hepatic DNL can increase fatty acid availability: 1) the direct effect of *de novo* fatty acid synthesis and 2) the indirect effect of increased levels of hepatic malonyl-CoA, which potently inhibits fatty acid oxidation by blocking fatty acid transport into the mitochondria via carnitine palmitoyl transferase-1 (CPT-1).[43] Both mechanisms lead to increased esterification/re-esterification of fatty acids and increased hepatic TG synthesis, which in turn leads to increased circulating VLDL-TG levels. Acetyl CoA is the principal component of fatty acids produced through DNL, and, as previously been discussed, high levels of dietary fructose serve as an unregulated source of hepatic acetyl-CoA production. Thus, fructose consumption promotes the development of metabolic syndrome through increased adiposity and adipose insulin resistance, leading to increased circulating and portal levels of free fatty acids.[27]

Fractional hepatic DNL is dramatically increased during fructose ingestion compared with glucose ingestion, and it has been reported that nearly 30% of the circulating palmitates in TGs after fructose ingestion are from fructose-derived DNL.[24] In contrast, study by Hellerstein[44] showed that there is little DNL from glucose under eucaloric conditions in humans. There is also evidence that the effect of fructose on increased postprandial TG levels is exacerbated in subjects with existing hypertriglyceridemia or insulin resistance. Therefore, chronic hyperinsulinemia and increased circulating fatty acids, which are commonly associated with central obesity and insulin resistance, may increase hepatic DNL during fructose consumption in subjects with metabolic syndrome.[27]

Another body of evidence has revealed the relationship between elevated postprandial TG concentrations and proatherogenic conditions. Clinical evidence supports the association between elevated concentrations of postprandial TG and an increased risk of cardiovascular disease. In a prospective cohort study of 7,587 women and 6,394 men followed for 26 years, elevated non-fasting TG levels were associated with an increased risk of myocardial infarction, ischemic heart disease, and death.[45] In the Women's Health Study, 26,509 women were followed for 11 years, and incident cardiovascular events were associated independently of traditional cardiac risk factors, levels of other lipids, and markers of insulin resistance through measures of non-fasting TG levels. Based on two of these studies, a significant linear relationship was observed between increased non-fasting TG and increased hazard ratios for all outcomes.[45]

It is important to note from the study by Stanhope et al.[28] that sugar consumption at the rate of 25% of the energetic need increased the risk factors for cardiovascular disease, supporting data from epidemiological studies on the association between sugar consumption and dyslipidemia and cardiovascular disease. However, these results contradicted those of a previous review indicating that sugar intakes as high as 25–50% of the daily energy have no adverse long-term effects on components of the metabolic syndrome and that up to 140 g/d of fructose ingestion has no biological relationship with increased levels of fasting or postprandial TGs in healthy, normal-weight[46] and overweight or obese humans.[47]

Conclusion

HFCS is composed of fructose and glucose but has a percentage of fructose that is slightly higher than that of glucose. Generally, the food and beverage industry uses HFCS-55 as a sweetener in soft drinks. To evaluate whether HFCS may have potential adverse metabolic effects on humans, epidemiological studies should be supported with

further evidence in experimental, clinical, and mechanistic studies to reveal the possible mechanisms of action of HFCS-induced adverse metabolic effects.

Fructose is the primary component of HFCS. Although it is safe at typical intake levels, fructose can produce adverse metabolic effects when abused-as is true of most nutrients. The consumption of fructose (25% of energy requirement) may affect plasma TG levels, both fasting and non-fasting, in both normal weight and overweight individuals. Although evidence has shown that this effect does not occur in healthy subjects, these factors significantly contribute to the lipogenic effects of fructose in subjects with hyperlipidemia, insulin resistance, or T2D.

Fructose in the form of HFCS or sucrose may trigger the accumulation of visceral adipose tissue and may induce additional adverse effects on lipids due to enhanced hepatic DNL and the production of uric acid, leading to an increased risk of hypertension. Fructose is also the only sugar known to raise the levels of serum uric acid by stimulating the degradation of Adenosine triphosphate (ATP) to Adenosine monophosphate (AMP), a uric acid precursor.

Moreover, the risk of cardiovascular disease due to HFCS may be worsened in relation to the mechanism of fructose's induction of TG synthesis. This condition has shown an imbalance in both the production and clearance rates of VLDL-TG. Furthermore, these conditions can yield a proatherogenic state in blood vessels. Based on reviews of several studies, this mechanism might be responsible for DNL, diet, or fatty acids derived from adipose lipolysis.

A progressive association between HFCS consumption, obesity, and other injurious processes has been suggested by experimental and clinical evidence. However, experimental HFCS consumption seems to produce some of the changes associated with metabolic syndrome even without increasing the body weight. Presumably, the metabolic damage associated with HFCS is not limited to the obesity-pathway mechanism.

In the absence of fructose intolerance, a previous review by Wiernsperger et al.[48] concluded that fructose levels below 50-100 g/d are harmless in healthy individuals. On the other hand, caution was advised for individuals at risk of metabolic syndrome, T2D, or cardiovascular disease, as the evidence showed that these individuals are more prone to the effects of sugar than the general population. Future investigative studies should be expanded to observe the real effects of fructose consumption, particularly that of HFCS, and generate acceptable daily consumption levels for humans.

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