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ABOUT COVER June 6, 2011
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 Happiness

AIM AND SCOPE *World Journal of Diabetes* (*World J Diabetes*, *WJD*, online ISSN 1948-9358, DOI: 10.4239), is a monthly, open-access, peer-reviewed journal supported by an editorial board of 323 experts in diabetes mellitus research from 38 countries.
 The major task of *WJD* is to report rapidly the most recent results in basic and clinical research on diabetes including: metabolic syndrome, functions of α , β , δ and PP cells of the pancreatic islets, effect of insulin and insulin resistance, pancreatic islet transplantation, adipose cells and obesity, clinical trials, clinical diagnosis and treatment, rehabilitation, nursing and prevention. This covers epidemiology, etiology, immunology, pathology, genetics, genomics, proteomics, pharmacology, pharmacokinetics, pharmacogenetics, diagnosis and therapeutics. Reports on new techniques for treating diabetes are also welcome.

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High dietary fructose intake: Sweet or bitter life?

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Abstract

Epidemiological data show that the consumption of added sugars as ingredients in processed or prepared foods and caloric beverages has dramatically increased. Fructose and fructose-based sweeteners are the most commonly added sugars and high-fructose corn syrup (HFCS-55: 55% fructose, 42% glucose and 3% higher saccharides) accounts for over 40% of all added caloric sweeteners. Concerns regarding the health risk of added sugar follow the demonstration that the consumption of foods and beverages high in sugars is associated with an increased prevalence of obesity, insulin resistance, dyslipidemia and, more recently, ischemic heart and kidney diseases. The molecular mechanism(s) underlying the detrimental effects of sugar are not completely understood and their elucidation is critical to provide new insights on the health risk of fructose-based sweeteners. A better understanding of the key role of fructose over-consumption in the development of metabolic disorders may contribute to planning new strategies for preventing deleterious dietary behaviors from becoming established and, thus, curbing the rise in the number of insulin-resistant, obese and diabetic populations worldwide.

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Key words: Fructose; High-fructose corn syrup; Insulin resistance; Metabolic syndrome

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INTRODUCTION

The consumption of large amounts of added sugars, a prominent source of low nutrient calories used as ingredients in processed or prepared foods and caloric beverages (i.e., soft-drinks, colas) is a relatively new phenomenon. It was not until the mid-19th century that these sweeteners became widely available and consumption began to increase dramatically^[1]. Today, one of the most commonly consumed added sugars is high-fructose corn syrup (HFCS-55). Normal sugar, known as saccharose, contains equimolar quantities of fructose and glucose whereas HFCS-55 syrup, synthesized by refining corn starch, contains 55% fructose and 41% glucose. HFCS-55 appeared in 1977, opening a new frontier for the sweetener and soft drink industries. In the USA where more accurate data are available, HFCS-55 accounts for the 42% of total consumption versus 16% in 1977-1978 and soft drinks account for over 70% of this intake^[2]. Bray *et al*^[3] noted that the average intake of HFCS-55 (the sole sweetener in US soft drinks) rose 1000% between 1970 and 1990. In other parts of the world, the problem has been less investigated than in the USA. According to a recent survey on over 3300 subjects^[4], in Italy the mean daily consumption of soft drinks is 132 g/d in female teenagers, 203 g/d in male teenagers (10 to 17.9 years), 114 g/d in adult women and 147 g/d in adult men (18 to 64.9 years). It has been recently confirmed that the consumption of foods and beverage with a high content in added sugars, mainly fructose, is associated with insulin resistance, dyslipidemia and an increased rate in obesity^[5-7]. In addition to effects on weight, soft drinks have been demonstrated to displace essential nutrients and contribute to overall poorer diets. Several cross-sectional studies have shown that increased soft drink intake is

related to lower consumption of milk and calcium, although the average effect sizes were small^[8-10]. Soft drink consumption was also related to higher intake of carbohydrates, lower intakes of fruit and dietary fiber and lower intakes of a variety of macronutrients in cross-sectional, longitudinal and longer-term experimental studies^[11-13]. The main diet issues involve a general lack of education and/or understanding of the implications with recent consumption patterns. Despite education programs to prevent obesity and diabetes worldwide, there has been little focus on the reduction of fructose and HFCS-55 in beverages.

FRUCTOSE METABOLISM

Fructose is readily absorbed and rapidly metabolized by human liver. Fructose enters the cells predominantly through the transporters GLUT5 and/or GLUT2^[14]. GLUT2 has high affinity for glucose and a moderate affinity for fructose, whereas GLUT5 predominantly transports fructose with very low affinity for glucose. GLUT5 is essential for the absorption of fructose in the intestine and its expression is increased in rats or mice fed a fructose-enriched diet^[15]. Both transporters are expressed in the liver, the primary site for fructose metabolism. In the liver, fructose undergoes a specific metabolism which differs markedly from that of glucose. Fructose is phosphorylated by fructokinase (ketohexokinase) to yield fructose-1-phosphate which is then cleaved by aldolase B to glyceraldehyde and dihydroxyacetone phosphate which directly forms methylglyoxal^[16]. Fructose can also be phosphorylated by hexokinase but the Km for fructose is much higher than for glucose which minimizes fructose phosphorylation through this pathway. Unlike hexokinase, the fructokinase pathway of fructose metabolism bypasses tightly regulated glycolytic checkpoints, especially phosphofructokinase. Thus, while glucose metabolism is *negatively* regulated by phosphofructokinase, fructose can *continuously* enter the glycolytic pathway. Therefore, fructose can uncontrollably produce glucose, glycogen, lactate and pyruvate, providing both the glycerol and acyl portions of acyl-glycerol molecules. These particular substrates and the resultant excess energy flux due to unregulated fructose metabolism will promote the over-production of triglycerides.

Another unique characteristic of fructose metabolism is the ability to raise uric acid levels. As fructokinase has no negative feedback, all fructose entering the cell is rapidly phosphorylated which can result in ATP depletion which has been well documented *in vitro* and *in vivo* in animal models and humans. ATP depletion activates enzymes of purine metabolism which degrade adenine nucleotides to uric acid via xanthine oxidoreductase with the development of hyperuricemia^[17].

CLINICAL CONSEQUENCES OF HIGH DIETARY FRUCTOSE CONSUMPTION

Excessive intake of fructose, primarily in the form of added dietary sugars, has been linked epidemiologically with the development of metabolic syndrome, a cluster of

clinical and biochemical features that includes abdominal obesity, insulin resistance, hypertension and dyslipidemia. It is well documented that the administration of fructose to humans induces all of the features of metabolic syndrome. A ten week trial of 32 overweight or obese individuals from 42 to 70 years demonstrated that plasma lipid and lipoprotein concentrations increased markedly during fructose consumption and were unchanged in subjects consuming glucose^[18]. In addition, subjects consuming fructose developed visceral obesity (measured by computed tomography scan) and insulin resistance. Interestingly, fasting plasma glucose and insulin levels increased and insulin sensitivity decreased in subjects consuming fructose-sweetened beverages but not in those consuming glucose. Recently Le *et al*^[19] reported that just one week of a high-fructose diet increased ectopic fat deposition in the liver and skeletal muscle in healthy young men without a family history of diabetes. Interestingly, healthy normal-weight offspring of patients with type 2 diabetes who are prone to develop metabolic disorders have a higher accumulation of intrahepatocellular lipids and VLDL-triacylglycerols, thus suggesting that they may be more susceptible to the development of dyslipidemia and related metabolic disorders when consuming significant amounts of fructose. A recent analysis of liver biopsies combined with survey answers from more than 400 people found a link between daily fructose consumption and increased hepatic inflammation and fibrosis^[20]. A statistically significant correlation between caloric sweeteners, mainly HFCS-55, and blood lipid levels has been also assessed in a cross-sectional study among over 6000 US adults from the National Health and Nutrition Examination Survey^[5]. Fructose ingestion has also been associated with higher blood pressure levels in both adolescents and adults with no previous history of hypertension^[21-23].

A clinical study performed in young, healthy male volunteers found that ingestion of 3 g of fructose per kilogram of body weight per day (as a 20% fructose solution for 6 d) led to a substantial increase in plasma triglycerides and an impaired insulin-induced suppression of adipose tissue lipolysis^[24]. Furthermore, a positive correlation was observed between plasma triglyceride concentration and hepatic de novo lipogenesis. These observations support the hypothesis that fructose-induced stimulation of hepatic de novo lipogenesis is indeed instrumental in increasing plasma triglycerides^[24]. In a crossover study, Hallfrisch *et al*^[25] fed 12 hyperinsulinemic men and 12 male controls with diets containing 0%, 7.5% and 15% of energy from fructose for 5 wk each. Total plasma cholesterol and low-density lipoprotein cholesterol concentrations were higher when the men consumed 7.5% or 15% of energy as fructose compared with starch. Plasma triacylglycerol concentrations in the hyperinsulinemic men increased as the amount of fructose increased.

TOWARDS MECHANISTIC INSIGHTS

Although detrimental effects of fructose have been established, the mechanisms whereby this happens are only now

being discovered. There is some experimental evidence that fructose enhances the production of tumor necrosis factor (TNF)- α ^[26,27], a potent pro-inflammatory cytokine that has been demonstrated to induce insulin resistance and lipoprotein production. Fructose may also evoke alteration of post-receptor insulin signaling. In skeletal muscle of rodents, a high-fructose diet decreased insulin receptor activation and the phosphorylation of insulin receptor substrate-1^[28]. Fructose is also known to induce oxidative stress and mitochondrial dysfunction, resulting in a stimulation of peroxisome proliferator-activated receptor gamma coactivator 1- α and β (PGC1- α and PGC1- β) that drive both insulin resistance and lipogenesis^[29]. Fructose effects on lipogenesis seem to be related to its ability to alter the activity of key lipogenic enzymes and transcription factors in the liver, such as pyruvate dehydrogenase kinase and sterol-regulatory-element-binding protein-1c (SREBP-1c), the principal inducer of hepatic lipogenesis^[30,31]. Fructose feeding has been reported to dramatically induce SREBP1c expression, compared with feeding with regular chow. This effect was largely diminished by treating fructose fed rats with PGC1 β antisense oligonucleotides^[29]. The decrease in SREBP1c expression led to decreased induction of lipogenic enzymes such as fatty acid synthase, which in turn accounted for the decreased accumulation of di- and triacylglycerol within the livers of fructose fed rats. This decrease in tissue lipid content was associated with improvements in insulin action. Another protein involved in the regulation of fructose-mediated lipogenesis is the X-box binding protein (XBP)1 which regulates the expression of many proteins that are involved in endoplasmic reticulum membrane expansion, including the lipogenic enzymes^[32]. XBP1 protein expression in mice is elevated after fructose feeding and is associated with the induction of critical genes involved in fatty acid synthesis^[33]. In contrast, deletion of XBP1 lowers expression of SREBP1 and key lipogenic enzymes, decreases rates of hepatic de novo lipogenesis and cholesterol synthesis and, *in vivo*, decreases plasma triglyceride concentration and secretion.

Another important molecular mechanism involved in the deleterious effects of high fructose intake is the biochemical process of non-enzymatic advanced glycation. The formation of advanced glycation end products (AGEs), also named Maillard reaction, starts from Schiff bases and the Amadori product, a 1-amino-1-deoxyketose, obtained by the reaction of the carbonyl group of a sugar, like glucose, with proteins or lipids amino groups. Glycation of proteins and lipids causes molecular rearrangements that lead to AGEs. The general mechanisms of AGEs effects are: (1) the formation of cross-links between key molecules in the basement membrane of the extracellular matrix; (2) the alteration of intracellular proteins; and (3) the interaction of AGEs with specific receptors on the cell surfaces, thus altering intracellular signaling and disrupting cell function. Although an elevated level of glucose exerts a primary role in the Maillard reaction, glucose has a low chemical reactivity in comparison with others sugars such as fructose. Recent findings show that fructose pro-

duces 10 times more AGEs than glucose because the anomerization equilibrium for fructose is shifted more to the reactive, open chain form of the sugar^[34]. The *in vivo* formation of fructose-derived AGEs has long been suspected but experimental evidence for their formation and chemical characterization are lacking. Several structures of glucose-induced protein glycation products have been recently identified by mass spectrometry techniques^[35]. In contrast, the types of AGEs produced in the presence of high fructose consumption have not yet been structurally clarified. The mechanism of fructose-induced hypertension has been also extensively investigated, demonstrating the involvement of endothelial dysfunction and sympathetic activation in hypertension etiology^[36,37]. Besides, fructose-induced hyperuricemia seems to contribute to the development of both hypertension and renal injury. Elevated uric acid levels have been found to be an independent risk factor for hypertension in multiple studies^[38]. In an animal experimental model of fructose-induced metabolic syndrome, the reduction in uric acid levels with a xanthine oxidase inhibitor resulted in prevention of systemic and glomerular hypertension as well as renal vasoconstriction induced by a high fructose diet^[39]. Hyperuricemia following high fructose intake was demonstrated to be associated with increased oxidative stress, activation of the renin angiotensin system and endothelial dysfunction, thus resulting in hypertension^[40-42]. Fructose ingestion has also been associated with induction of the potent vasoconstrictor endothelin-1 and treatment with the endothelin receptor antagonist has been demonstrated to prevent the development of fructose-induced hypertension and decreased plasma Ang II levels^[43].

CONCLUSION

The controversy that has existed for the last decade regarding the potential harmfulness of excess fructose is legitimate in view of the dramatic increases in both sweetened beverage consumption and the burdens of obesity and metabolic syndrome. Most recent findings suggest that high fructose intake induces a whole range of metabolic and cardiovascular alterations in both animal and human models. Nevertheless, at present there are no objective grounds to support that moderate intake of fructose or of fructose consumed with fruits or honey is unsafe. More extensive clinical and experimental studies are needed to provide new evidence on the health risk of fructose-based sweeteners. Although AGEs have been suggested to exert a key role in the organ damage evoked by fructose-fortified diets, the chemical characterization of the epitope structures of fructose-derived AGEs still needs to be elucidated by mass spectrometry techniques. Thus, future studies on qualitative-quantitative comparison among main AGEs deriving from fructose consumption are crucial for a better elucidation of the pathophysiological role of fructose overconsumption. Another unanswered question is whether or not fructose can cause hormonal disturbances in humans. Currently, results from human studies concern-

ing fructose effects on plasma leptin, insulin and adiponectin are ambiguous and further clinical data are required to clarify the potential contribution of dietary fructose to hormone dysregulation, of primary importance in the progression of metabolic syndrome. Similarly, we do not know whether there are subgroups of individuals (obese insulin-resistant patients, offspring of patients with type 2 diabetes) in whom the adverse metabolic effects of fructose may possibly be enhanced. Overall, these investigations are crucial for supporting health authorities to define new regulations and for planning new strategies to prevent deleterious dietary behaviors from becoming established. If widely implemented, these measures may help to correct unhealthy dietary habits and to develop new therapeutic approaches to metabolic disorders and the associated cardiovascular complications.

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