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EDITORIAL

# Soft drinks consumption and nonalcoholic fatty liver disease

William Nseir, Fares Nassar, Nimer Assy

William Nseir, Department of Internal Medicine, Holy Family Hospital, Nazareth, 16126, Israel
Fares Nassar, Department of Internal Medicine, Western Galilee Hospital, Nahariya, 22356, Israel
Nimer Assy, Liver Unit, Ziv Medical Center, Safed, 13100, Israel; Technion Institute, Haifa, 32000, Israel
Author contributions: Nseir W wrote the manuscript and participated in the design; Nassar F revised the manuscript and participated in the design; Assy N wrote the manuscript, and participated in the design, figures, tables, editing and polishing.
Correspondence to: Nimer Assy, MD, Liver Unit, Ziv Medical Center, PO Box 1008, Safed, 13100, Israel. assy.n@ziv.health.gov.il
Telephone: +972-4-6828441 Fax: +972-4-6828442
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## Abstract

Nonalcoholic fatty liver disease (NAFLD) is a common clinical condition which is associated with metabolic syndrome in 70% of cases. Inappropriate dietary fat intake, excessive intake of soft drinks, insulin resistance and increased oxidative stress combine to increase free fatty acid delivery to the liver, and increased hepatic triglyceride accumulation contributes to fatty liver. Regular soft drinks have high fructose corn syrup which contains basic sugar building blocks, fructose 55% and glucose 45%. Soft drinks are the leading source of added sugar worldwide, and have been linked to obesity, diabetes, and metabolic syndrome. The consumption of soft drinks can increase the prevalence of NAFLD independently of metabolic syndrome. During regular soft drinks consumption, fat accumulates in the liver by the primary effect of fructose which increases lipogenesis, and in the case of diet soft drinks, by the additional contribution of aspartame sweetener and caramel colorant which are rich in advanced glycation end products that potentially increase insulin resistance and inflammation. This review emphasizes some hard facts about soft drinks, reviews fructose metabolism, and explains how fructose contributes to the development of obesity, diabetes, metabolic syndrome, and NAFLD.



**Key words:** Aspartame; Caramel; Carbonated beverage; Cola; Diabetes; Fatty liver; Fructose; Metabolic syndrome; Obesity; Soda; Soft drink; Sweetened beverage

**Peer reviewers:** Dr. Vance Matthews, PhD, BS, Cellular and Molecular Metabolism Laboratory, Baker University of Texas Medical Branch, IDI, PO Box 6492, St Kilda Road Central, VIC 8008, Melbourne, Australia; Dr. Sang Geon Kim, PhD, MS, BS, Professor, Chairman, College of Pharmacy, Seoul National University, Sillim-dong, Kwanak-gu, Seoul 151-742, South Korea; Dr. Juan Carlos Laguna Egea, Catedràtic de Farmacologia/Pharmacology Professor, Unitat de Farmacologia/Pharmacology Laboratory, Facultat de Farmàcia/School of Pharmacy, Universitat de Barcelona/University of Barcelona, Avda Diagonal 643, Barcelona 08028, Spain; Fabrizio Montecucco, MD, Assistant, Division of Cardiology, Department of Internal Medicine, University of Geneva, Avenue de la Roseraie 64, 1211 Geneva, Switzerland

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## INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a significant health problem affecting 20%-30% of the adult population[1]. NAFLD can progress to nonalcoholic steatohepatitis (NASH), a fatty liver with hepatitis. This form of liver injury carries a 20%-50% risk for progressive fibrosis, 30% risk for cirrhosis, and 5% risk for hepato- cellular carcinoma[2-4]. Although the mechanisms underlying dis-

ease progression remain unclear, insulin resistance and obesity-related inflammation are thought to play a key role, along with possible genetic, dietary and lifestyle factors. The rising incidence of obesity in today's generation is associated with many health complications in addition to NAFLD[5,6]. These include cardiovascular diseases, diabetes, hyperlipidemia, and hypertension. This constellation is recognized as metabolic syndrome. 70% of patients with fatty liver have metabolic syndrome and 30% of patients with metabolic syndrome have fatty liver[7] (Figure 1).

A global change in dietary habits has occurred over the last few decades resulting from the introduction of sweeteners such as fructose and sucrose by the food industries. For example, regular soft drinks (SD) and fruit drinks, major sources of high fructose corn syrup (HFCS) or sugar, have increased from 3.9% of the total energy intake in 1977 to 9.2% of the total energy intake in 2001[8].

Worldwide, SD are the leading cause of added sugar. Recent evidence suggests an association between the intake of sugar sweetened SD and the risk of obesity and diabetes resulting from large amounts of HFCS used in their manufacture, which raises blood glucose similar to sucrose[9]. In addition, diet SD contain aspartame sweetener and caramel coloring, which are rich in advanced glycation end products that potentially increase insulin resistance and inflammation[10,11].

Human studies and animal models suggest that dietary factors can affect fatty infiltration and lipid peroxidation in various types of liver disease including NAFLD[12,13]. More recently, increased ingestion of SD was found to be linked to NAFLD[14] independent of metabolic syndrome, with NAFLD patients consuming 5 times the amount of carbohydrates from SD as compared to healthy persons[15] (Figure 2 and Table 1). Individuals consuming > 1 soft drink daily showed a higher prevalence of metabolic syndrome than those consuming < 1 soft drink per day[16].

This review emphasizes some hard facts about SD, reviews fructose metabolism, and explains how fructose contributes to the development of obesity, diabetes, metabolic syndrome, and NAFLD.

## SOFT DRINKS

The term SD more commonly known as soda, soda pop, pop, Coke™, Pepsi™ or tonic, refers to a nonalcoholic beverage that is usually carbonated. Two types of SD are used; regular SD which are sweetened with sugar (fructose) and diet SD which are sweetened with non-caloric sweeteners (aspartame). Up to the 1980s, SD contained most of their food energy in the form of refined cane sugar or corn syrup. Today, HFCS is used almost exclusively as a sweetener in the United States and in other countries because of its lower cost. The calories and sugar content in various soft drinks are shown in Table 2.

Added sweeteners in regular SD are an important component of our diet, representing 318 kcal of dietary intake, or 16% of all calorie intake[17]. HFCS made by enzymatic isomerization of glucose to fructose was introduced as HFCS-42 (42% fructose) and HFCS-55 (55% fructose) in 1967 and 1977, respectively, and opened a new frontier for the sweetener and SD industries.

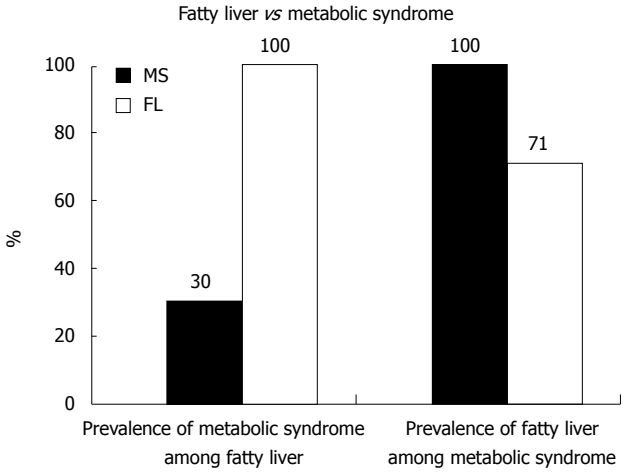


**Figure 1 Prevalence of fatty liver among metabolic syndrome and prevalence of metabolic syndrome among fatty liver.** MS: Metabolic syndrome; FL: Fatty liver. Alberti, Circulation (2009). $P < 0.001$.

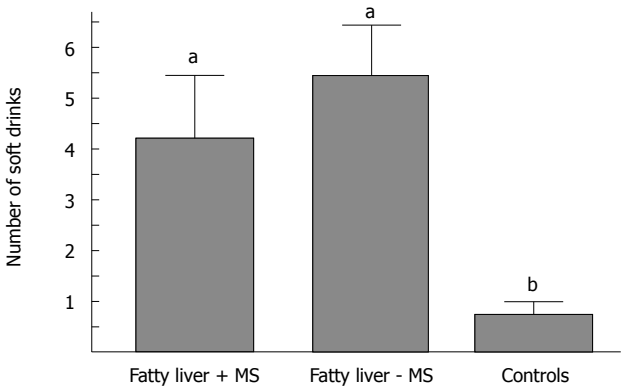


**Figure 2 Daily amount of soft drinks consumption in nonalcoholic fatty liver disease (NAFLD) patients with ($n$ = 31) or without metabolic syndrome ($n$ = 29) and in controls ($n$ = 30).** [a]$P < 0.07$; fatty liver without metabolic syndrome *vs* fatty liver with metabolic syndrome, [b]$P < 0.001$ between fatty liver subgroups and controls[14,15].

**Table 1 Soft drink consumption linked with NAFLD**

| Dietary constituents | Controls ($n$ = 30) | NAFLD ($n$ = 31) | $P$ value |
|---|---|---|---|
| Total energy intake (kcal) | 2200 ± 600 | 2300 ± 500 | 0.300 |
| Added sugar (g/d) | 33.6 ± 12.6 | 75.6 ± 8.4 | 0.001 |
| Percent of added sugar from soft drinks | 8% | 43% | 0.001 |

NAFLD: Nonalcoholic fatty liver disease.

Aspartame and caramel (colorant) are also used as sweeteners in the beverage industry mainly in diet SD[18]. Aspartame is an amino-acid compound that is about 160 times sweeter than sugar. Aspartame is absorbed from the intestine and metabolized by the liver to form phenylalanine, aspartic acid and methanol. Aspartame can contribute to weight gain, obesity, insulin resistance, and type 2

**Table 2 Calories and sugar content in different soft drinks**

| Soft drinks: calorie content (number of calories) | | | | Soft drinks: sugar content (numbers of teaspoons of sugar) | | | |
|---|---|---|---|---|---|---|---|
| | 12- oz. Can | 20 oz. Bottle | 64 oz. Big cup | | 12- oz. Can | 20 oz. Bottle | 64 oz. Big cup |
| Sunkist | 190 | 325 | 1040 | Orange slice | 11.9 | 19.8 | 63.5 |
| Mountain dew | 165 | 275 | 880 | Mint maid orange soda | 11.2 | 18.7 | 59.7 |
| Dr. Pepper | 160 | 250 | 800 | Mountain dew | 11.0 | 18.3 | 58.7 |
| Pepsi | 150 | 250 | 800 | Barq's root beer | 10.7 | 17.8 | 57.1 |
| Coke classic | 140 | 250 | 800 | Pepsi | 9.8 | 16.3 | 52.3 |
| Sprite | 140 | 250 | 800 | Squirt | 9.5 | 15.8 | 50.7 |
| 7-Up | 140 | 250 | 800 | Dr. Pepper | 9.5 | 15.8 | 50.7 |
| | | | | 7-Up | 9.3 | 15.5 | 49.6 |
| | | | | Coke classic | 9.3 | 15.5 | 49.6 |
| | | | | Sprite | 9.0 | 15.0 | 48.0 |

diabetes mellitus[18]. Recently, Brown *et al*[19] showed that artificial sweeteners may trigger the secretion of glucagon-like peptide (GLP)-1 by the digestive tract, and thereby curb appetite and calorie intake.

Caramel is made by the carefully controlled heat treatment of carbohydrates, generally in the presence of acids and alkalis, in a process called caramelization. Soft drinks contain caramel coloring, which is rich in advanced glycation end products which increase insulin resistance and inflammation[9,10]. The FDA has established 200 mg of caramel per kg body weight as an acceptable daily intake.

High fructose diets have induced fatty liver in rats and ducks[20]. Such diets have also caused increases in hepatic lipid peroxidation and activation of inflammatory pathways in the liver of rats[21]. The inborn error of metabolism known as hereditary fructose intolerance, a rare disease which results from a deficiency in the fructose metabolizing enzyme, aldolase B, has demonstrated that fructose consumption can cause progressive liver disease in humans[22].

The extent to which excessive fructose might contribute to the high prevalence of NAFLD in Western societies has not been systematically investigated. It has been shown that consumption of SD is linked to obesity and results in an increased risk of metabolic syndrome. Individuals consuming > 1 soft drink per day had a higher prevalence of metabolic syndrome than those consuming < 1 drink per day[16].

## METABOLISM OF FRUCTOSE

Fructose is a simple sugar with a chemical formula ($C_6H_{12}O_6$) similar to that of glucose. Fructose differs from glucose by the presence of a keto group attached to carbon 2 of the molecule, while glucose has an aldehyde group at carbon 1. In the diet, fructose is consumed in various amounts with fruits, honey, beverages sweetened with HFCS/sucrose and as a constituent of sucrose, the most common sugar (a disaccharide composed of fructose through a 1-4 glycoside bond) (Table 2).

Absorption of fructose from the intestine into the portal blood is aided by glucose transporter-5 at the brush border and basolateral membranes of the jejunum. This route of absorption results in massive fructose uptake by the liver. Fructose is phosphorylated by fructokinase, forming fructose-1-phosphate, which can then be converted to several three-carbon molecules, including glyceraldehydes, dihydroxyacetone phosphate and glyceraldehyde-3-phosphate (Figure 3). Some of these 3 carbon molecules can be converted to glucose through gluconeogenesis, or they can be used to generate other products such as triglyceride (TG).

The second metabolism of fructose, i.e. the extrahepatic metabolism that bypasses fructokinase, allows the carbons from fructose to enter glycolysis downstream of this enzyme. The 3 carbon molecules can eventually be used for the synthesis of glycerol and fatty acids, which through esterification can form TGs.

The concentration of fructose in fasting blood of healthy humans is typically 1 mg/dL or less. After oral administration of fructose load in doses ranging from approximately 18 g (0.25 g/kg of body weight) to 100 g, the mean plasma or serum fructose concentration increased in a dose-dependant manner, to values ranging from 4.5-13.0 mg/dL and peak fructose concentrations were seen 30-60 min after fructose ingestion. A 20-ounce soft drink containing 32.6 g of fructose would therefore be expected to increase the fasting serum fructose concentration by approximately four-fold[23,24]. Fructose is 7 times more likely than glucose to form advanced glycation end products (AGEs). Fructose does not suppress ghrelin and does not stimulate insulin or leptin[23,24]. Some key molecular features involved in the metabolism of fructose include the roles of cellular signaling molecules including nuclear factor-κB (NF-κB), tumor necrosis factor-α (TNF-α), c-Jun amino terminal kinase 1 (JNK-1), protein tyrosine phosphatase-1B (PTP-1B), phosphatase and tensin homolog deleted on chromosome ten (PTEN), liver X receptor (LXR), farnesoid X receptor (FXR), and sterol regulatory element-binding protein-1c (SREBP-1c)[25]. Fructose activates JNK-1, which causes hepatic inflammation and increased insulin receptor substrate-1 (IRS-1). Fructose induces lipogenesis *via* upregulation of SREBP-1c and CHREBP, thereby increasing the hepatic pool of free fatty acids[25].

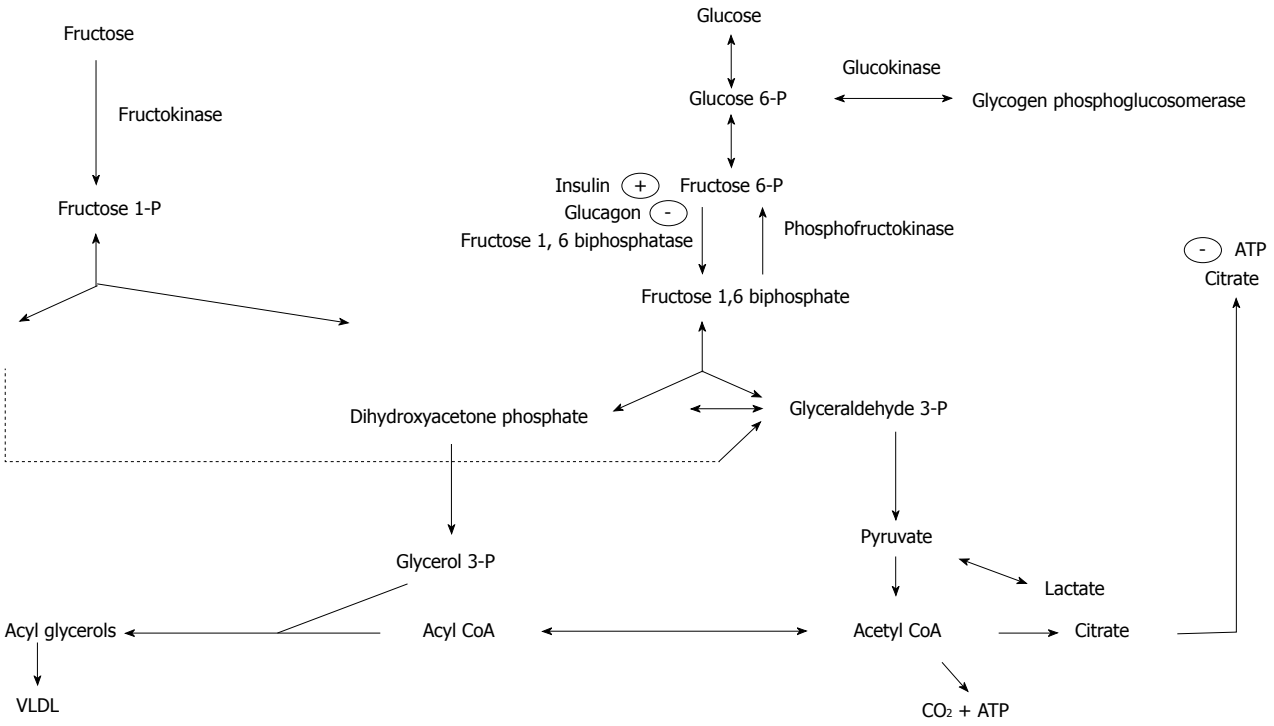


**Figure 3 Fructose metabolism in the liver.** Hepatic fructose metabolism begins with phosphorylation of fructokinase. Fructose carbon enters the glycolytic pathway at the triose phosphate level. Thus, fructose bypasses the major control point by which glucose carbon enters glycolysis. This allows fructose to serve as an unregulated source of glycerol-3-phosphate and acetyl-CoA for hepatic lipogenesis.

## PATHOPHYSIOLOGY OF NAFLD

The "two hits" hypothesis proposed by Day *et al*[26] remains the prevailing pathophysiological theory. According to the authors, the first "hit" describes a net retention of lipids within hepatocytes, mostly in the form of TGs, and is a prerequisite for the development of NAFLD. A continuous delivery of free fatty acids to the liver from splanchnic lipolysis of visceral fat (60%) or from increased ingestion of fatty food (10%), combined with peripheral insulin resistance, and *de novo* lipogenesis (30%) results in excessive fat accumulation and an increased liver concentration of TG and cholesterol esters. High blood TG concentration in the form of very low density lipoprotein (VLDL) tends to accompany this condition and induces cholesterol ester transfer protein activity, resulting in an increased transfer of TG from VLDL to high density lipoprotein (HDL) and a subsequent increase in HDL clearance and decreased HDL concentration which leads in the end to liver steatosis[27].

The progression of steatosis to steatohepatitis (NASH) is associated with other factors ("second hit"), such as lipotoxicity, inflammation, oxidative stress and insulin resistance[26]. Consumption of SD may act as a first or as a second hit in the pathogenesis of NAFLD. Recently, it has been suggested that cholesterol metabolism may have a role in the accumulation of liver fat and that inflammation may be the first hit followed by TG accumulation as a second hit (www.easl.eu/bologna 2009).

## FRUCTOSE AND INSULIN RESISTANCE

Fructose consumption increases postprandial TG concentrations within 24 h[28,29], which suggests that postprandial hypertriglyceridemia is the earliest metabolic perturbation associated with fructose consumption. The most likely mechanism for postprandial hypertriglyceridemia is increased hepatic de-novo lipogenesis (DNL), which in turn upregulates VLDL production and secretion[30].

Fructose consumption can promote hepatic lipogenesis primarily because the liver is the main site of fructose metabolism; secondly, entry of fructose into glycolysis *via* fructose-1-phosphate bypasses the main rate controlling step of glycolysis catalyzed by phosphofructokinase, thus providing unregulated amounts of the lipogenic substrates acetyl-CoA and glycerol-3-phosphate[30]; thirdly, fructose can activate sterol receptor element binding protein-1c (SREBP-1c) independently of insulin, which then activates fat genes involved in DNL[31,32].

Recently, Stanphone demonstrated that consuming fructose-sweetened beverages, not glucose-sweetened beverages increases DNL, promotes dyslipidemia, decreases insulin sensitivity and increases visceral adiposity in overweight and obese adults[33,34] (Figure 4).

One study of lean women found that 4 d of over feeding with a sucrose-sweetened (glucose + fructose) drink increased DNL by 200%-300%[35]. Another feeding study showed that 2 d of high fructose intake (30% of kcal/d, consumed as sweetened beverage at every meal)

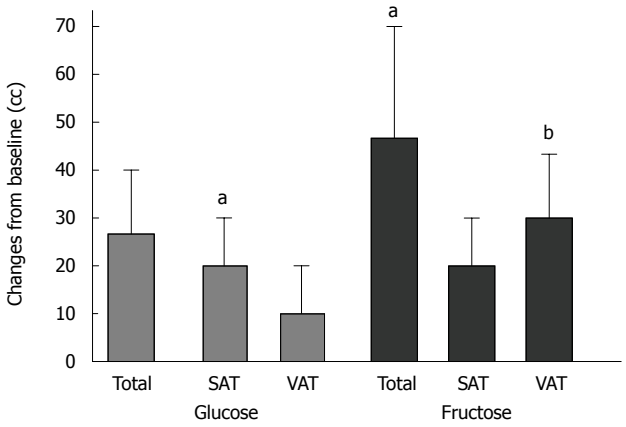


**Figure 4 Changes in total abdominal adipose tissue, superficial adipose tissues (SAT), and visceral adipose tissue (VAT) volume after consuming glucose- or fructose-sweetened beverages for 10 wk.** $^{a}P < 0.05$, $^{b}P < 0.01$, 10 wk *vs* 0 wk; paired Student's *t* test. Glucose, $n = 14$; Fructose, $n = 17$. Data represent mean ± SE (Stanhope, *J Clin Invest*, 2009).

resulted in decreased postprandial glucose concentration and insulin response and prolonged alimentary lipemia in women[29]. A recent clinical study indicates that NAFLD patients have a higher intake of SD and meat and a tendency towards a lower intake of fish rich in omega-3[36].

## FRUCTOSE AND DIABETES MELLITUS

Lipotoxicity can promote insulin resistance in type 3 diabetes mellitus by accelerating pancreatic β-cell failure. Elevated plasma free fatty acids are associated with the progression from pre diabetes (impaired fasting glucose IFG, impaired glucose tolerance IGT) to type 2 diabetes mellitus[37]. The presence of diabetes mellitus in patients with NASH have significant clinical implications, as NASH appears to follow a more aggressive course in the presence of hyperglycemia, placing a growing number of diabetic patients at risk of progressive liver disease[37]. In short-term studies in humans, fructose ingestion had no deleterious effect on glucose metabolism. In studies lasting 3-8 d, substitution of sucrose or starch with fructose improved glycemic control in patients with type 1 or type 2 diabetes mellitus. Similarly, no adverse effects of fructose feeding on glycemic control were seen in studies lasting 1-3 mo. In a series of patients with diet controlled type 2 diabetes, substitution of sucrose by fructose (13% of calories) for three months had no significant effect on fasting plasma glucose levels or postprandial plasma glucose and insulin responses[37].

Long-term fructose consumption may promote the development of diabetes, even though fructose usually has no adverse effects on glucose tolerance in the short- and intermediate term. In rats, long-term feeding of moderate amounts of fructose (15% of the diet by weight) resulted in impaired glucose tolerance[38], and high-fructose diets (72% by weight) resulted in the development of diabetes mellitus and diffuse glomerulosclerosis[39,40].

The association between consumption of sugar-sweetened beverages and risk of type 2 diabetes was assessed in an eight-year prospective study of 51 603 women participating in the Nurses' Health Study Ⅱ[41]. After adjustment for potential confounders, women consuming one or more sugar-sweetened soft drink daily had a relative risk (RR) of type 2 diabetes of 1.83 ($P < 0.001$) compared with those who consumed > 1 of these beverages per month. The results were attenuated after further adjustment for body mass index and caloric intake, but remained statistically significant (RR = 1.32, $P < 0.04$). Consumption of fruit punch was associated with a similar increase in diabetes risk.

## FRUCTOSE AND OBESITY

The association between HFCS consumption and obesity is due in part to metabolic changes induced by fructose or HFCS, rather than merely to an increase in total energy intake[41]. In baboon studies, consumption of sucrose compared with glucose promoted the development of abdominal obesity, suggesting that the fructose moiety of sucrose was responsible for the increase in abdominal fat[42,43]. In addition, some strains of mice showed an increase in visceral fat accumulation when fed a high-fructose diet[44]. Although it has long been suspected that SD contribute at least in part to the obesity epidemic, only in recent years have large epidemiologic studies begun to investigate the relation between SD consumption and long-term weight gain. Obesity among children has increased dramatically during the past two decades and is approaching epidemic proportions[45,46]. Various environmental, genetic and social factors relating to diet have been associated with obesity in children[47-50].

The results of the study by Dubois *et al*[51] indicated that regular sugar-sweetened beverage consumption, especially between meals, may put children at greater risk for obesity in childhood. Because there is a positive association between the consumption of sugar-sweetened beverages and body weight among preschool-aged children, they advise that parents should limit the quantity of such sweetened beverages consumed during preschool years[51]. In the FIELD trial, 644 British schoolchildren (ages 7-11 years) were randomly assigned to a control group or to an education program designed to reduce their consumption of carbonated drinks (both sweetened and unsweetened). The mean consumption of carbonated drinks decreased by 50 mL/d in the intervention group and increased by 16.7 mL/d in the control group (mean difference 0.7, 95% confidence interval 0.1 to 1.3). After 12 mo, the approximate percentage of overweight and obese children had increased in the control group from 20% to 27.5%, compared with a decrease in the intervention group from 20% to 19.8% (mean difference 7.7%, 2.2% to 13.1%)[52].

## FRUCTOSE AND NAFLD

Risk factors for NAFLD include obesity, type 2 diabetes, insulin resistance and hypertriglyceridemia. Of note,

each of these risk factors can occur as a result of excessive fructose consumption. Recently we have shown that[14,15] SD consumption is linked with fatty liver independently by metabolic syndrome diagnosis.

High-fructose diets have induced fatty liver in rats[53] and ducks[54], such diets have also caused increases in hepatic lipid peroxidation[55] and activation of inflammatory pathways in the liver of rats[21].

Fructose is lipogenic and stimulates TG synthesis[31]. Splanchnic perfusion studies demonstrate that fructose produces higher rates of TG secretion from the liver than equimolar amounts of glucose[56]. The long-term administration of fructose to rats results in hepatic macro- and micro vesicular steatosis with a 198% increase in hepatic TGs and an 89% increase in hepatic cholesterol concentration[57]. Furthermore, the administration of a diet with 25% of the total energy as sucrose (which contains 50% fructose) resulted in a rise in hepatic aminotransferases (ALT and AST) levels within 18 d[58,59]. Indeed, total fructose intake averages approximately 12% of the total energy intake and may increase to 15% in some subgroups in the US population[22].

Animals maintained on a chronic high fructose diet develop elevated non-esterified fatty acids (NEFAs) and hyperinsulinemia at the expense of glycemic control[39]. This is not surprising, as fructose-induced metabolic dyslipidemia is usually accompanied by whole body insulin resistance[60] and reduced hepatic insulin sensitivity[61].

A potential mechanism by which fructose may cause liver injury is shown in Figure 5. The metabolism of fructose is distinct from glucose. Before converging with the glycolytic pathway, initial fructose metabolism involves phosphorylation of fructose to fructose-1-phosphate by fructokinase (ketohexokinase, KHK) using the substrate ATP. Unlike glucokinase, the phosphorylation of fructose by fructokinase is specific for fructose and not rate limited. The high activity of fructokinase in phosphorylating fructose to fructose-1-phosphate in the liver, can result in hepatic ATP depletion[22]. Indeed, fructose has been shown to cause ATP depletion in humans[62,63], and recovery from fructose-induced ATP depletion was found to be delayed in subjects with NALFD in studies that used phosphorus-1 magnetic resonance spectroscopy to assess hepatic metabolism[63,64]. In some respects, fructose-induced ATP depletion resembles hepatic ischemia[65]. In rats, fructose administration increases hepatic lipid peroxidation and activation of inflammatory pathways[21,55]. Cirillo *et al*[66] found that incubation of endothelial cells or renal tubular cells with postprandial concentrations of fructose reduces intracellular ATP and activates proinflammatory and prooxidative responses. Therefore, high fructose consumption may contribute to NAFLD pathogenesis because fructose-induced ATP depletion promotes hepatic necroinflammation. Moreover, fructose promotes insulin resistance, lipid peroxidation, dyslipidemia, increased arterial blood pressure, increased AGEs, and increased hepatic inflammation[66].

Ouyang *et al*[67] found that subjects with NAFLD have a significantly greater intake of sweetened beverages by history, representing a 2-fold greater intake than the mean intake in both controls and in population-based studies. Their second finding was that the key initiating enzyme in fructose metabolism, KHK (ketohexokinase), was also increased 2-fold in the liver biopsies of these patients compared to controls[67]. The increase in KHK levels is consistent with the known effect of fructose to upregulate KHK in the liver of rats[68,69].

Patients on a high fructose or sucrose diet show a greater uric acid response to a bolus of fructose[70,71] consistent with the upregulation of KHK activity. Finally, uric acid levels can predict the development of NAFLD[72]. There is also increasing evidence that the rise in uric acid may also have a potential role in causing features of the metabolic syndrome[73], in part by the ability of uric acid to deplete endothelial nitric oxide levels[74] and by activating adipocytes[68]. What does fructose become in our liver? Fructose becomes free fatty acids (the building blocks of all lipids), becomes VLDL lipoproteins and TGs (the nasty lipids most associated with cardio- vascular disease), and becomes uric acid (oxidative stress, vascular inflammation, Figure 5).

## FRUCTOSE AND METABOLIC SYNDROME

Reaven noted that several risk factors (e.g. dyslipidemia, hypertension and hyperglycemia) are commonly clustered together[75]. This clustering he called Syndrome X, and he recognized it as a multiplex risk factor for cardiovascular disease (CVD). Other researchers use the term metabolic syndrome for this clustering of metabolic risk factors. ATP Ⅲ used this alternative term[76]. Beyond CVD and type 2 diabetes, individuals with metabolic syndrome are susceptible to other conditions, notably polycystic ovary syndrome, fatty liver, cholesterol gallstones, asthma, sleep disturbances, some forms of cancer, and is associated with a proinflammatory/prothrombotic state that include elevated levels of C-reactive protein, endothelial dysfunction, hyperfibrinogenemia, increased platelet aggregation, increased levels of plasminogen activator, elevated uric acid levels, microalbuminuria, and a shift toward small, dense particles of low-density lipoprotein[77].

The major characteristics of metabolic syndrome include insulin resistance, abdominal obesity, elevated blood pressure, and lipid abnormalities (i.e. elevated levels of TGs and low levels of HDL cholesterol).

The role of fructose in insulin resistance, hyperglycemia, and obesity that constitute important elements of the metabolic syndrome were discussed above[77].

Visceral adipose tissue and dyslipidemia induced by fructose/sucrose consumption play a major role in the development and progression of metabolic syndrome. The main role of adipose tissue is to take up excess fatty acids provided by the diet and to store them in the form

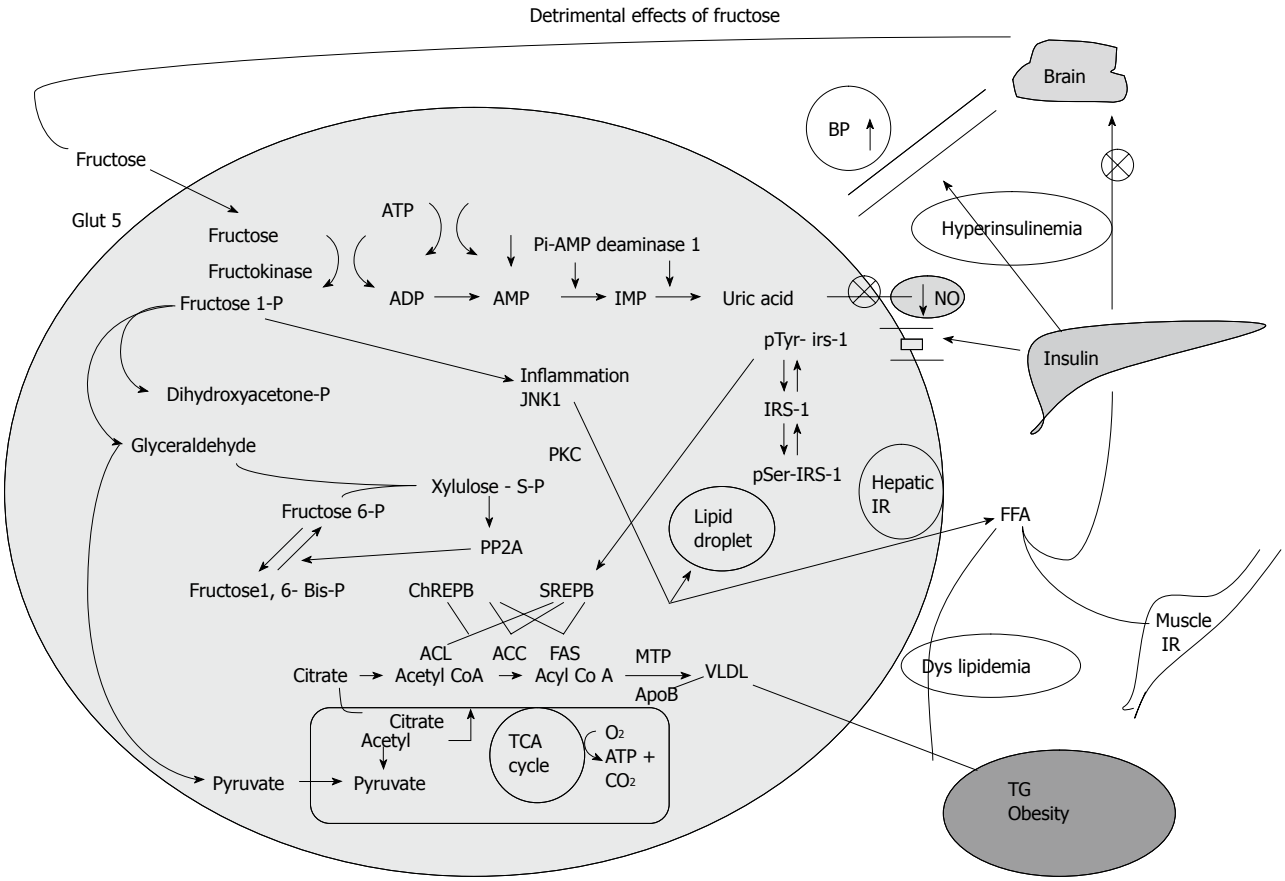


**Figure 5 Mechanisms of detrimental effects of fructose.**

of TGs to be used as an energy supply for the body in times of starvation, however, adipose tissue has a limited capacity to store fat. This maximum capacity may be reached in states of obesity, resulting in an impaired ability of adipose tissue to acquire dietary fatty acids and, therefore, increased levels of fatty acids are found in the circulation[77].

Signaling abnormalities in adipocytes can also trigger lipolysis of TG stores and the efflux of fatty acids into the bloodstream, augmenting the problem. The presence of high levels of NEFAs in the bloodstream is proposed to function as a key mechanistic link between obesity and insulin resistance, type 2 diabetes, and metabolic dyslipidemia. Eventually, these NEFAs may be taken up ectopically by non-adipose tissues such as the liver and skeletal muscle, where they may be stored as TG or diacylglycerol and interfere with metabolic pathways such as the response to insulin, contributing to insulin resistance and the metabolic syndrome[78].

Differences exist in the metabolic properties of the various sites of adipose tissue. Visceral or abdominal fat stores are believed to pose a greater risk for the development of insulin resistance and the metabolic syndrome than subcutaneous fat stores. Reasons for this include reduced responsiveness of visceral fat to the anti-lipolytic effects of insulin (due to lower expression and activity of hormone sensitive lipase, reduced tyrosine phosphorylation of the insulin receptor, decreased IRS-1 expression, and increased PTP-1B activity); greater responsiveness of visceral fat to the lipolysis-inducing effects of catecholamines; and decreased uptake and acylation of fatty acids compared with subcutaneous fat, all of which result in amplification of NEFA levels in the blood[79]. Visceral fat is also located conveniently for these NEFAs to enter the portal circulation for direct delivery to the liver, where they pose a risk to hepatic insulin responsiveness.

Fructose consumption can induce perturbations in cell signaling and inflammatory cascades in insulin-sensitive tissues[25]. The contribution of fructose/sucrose in dyslipidemia was discussed above. Consuming such large amounts of fructose/sucrose can lead to the development of a complete metabolic syndrome by increasing plasma TGs and altering hepatic glucose homeostasis, gaining weight, and decreasing insulin sensitivity.

## CONCLUSION

The use of sweeteners has increased considerably worldwide and soft drink beverages seem to be a major contributor for obesity, diabetes mellitus, hyperlipidemia, insulin resistance, hypertension, metabolic syndrome, and cardiovascular disease. In this review we sought to focus attention on the impact of soft drinks on the accumulation of fat in the liver. This has significant clinical implications, as

the presence of NAFLD correlates strongly with diabetes, cardiovascular disease and diffuse atherosclerosis.

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