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 in advance 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.

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

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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 hepatocellular carcinoma[1-4]. 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[8,9]. 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[17] (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.

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...
diabetes mellitus \cite{18}. Recently, Brown et al \cite{19} showed that artificial sweeteners may trigger the secretion of glucagon-like peptide (GLP)-1 by the digestive tract, and thereby curb appetite and caloric 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 \cite{20,21}. 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 \cite{22}. Such diets have also caused increases in hepatic lipid peroxidation and activation of inflammatory pathways in the liver of rats \cite{23}. 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 \cite{24}.

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 \cite{25}.

**METABOLISM OF FRUCTOSE**

Fructose is a simple sugar with a chemical formula (C\textsubscript{6}H\textsubscript{12}O\textsubscript{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 glycerolaldheydes, 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 glycogen 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 \cite{24,25}. 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 \cite{24,25}. 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) \cite{26}. 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 \cite{26}.

**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** |
| Sunriset | 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 | Bang’s root beer | 10.7 | 17.8 | 57.1 |
| Coke classic | 140 | 250 | 800 | Pepsi | 9.8 | 16.3 | 52.3 |
| 7-Up | 140 | 250 | 800 | Squirt | 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 |
The “two hits” hypothesis proposed by Day et al.\textsuperscript{[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.\textsuperscript{[27]}

The progression of steatosis to steatohepatitis (NASH) is associated with other factors (“second hit”), such as lipotoxicity, inflammation, oxidative stress and insulin resistance.\textsuperscript{[25]} 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).

**PATHOPHYSIOLOGY OF NAFLD**

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

Fructose 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; thirdly, fructose can activate sterol receptor element binding protein-1c (SREBP-1c) independently of insulin, which then activates fat genes involved in DNL.\textsuperscript{[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.\textsuperscript{[33,34] (Figure 4)}

One study of lean women found that 4 d of overfeeding with a sucrose-sweetened (glucose + fructose) drink increased DNL by 200%-300\%\textsuperscript{[35]}.

**FRUCTOSE AND INSULIN RESISTANCE**

**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 glycero-3-phosphate and acetyl-CoA for hepatic lipogenesis.
resulted in decreased postprandial glucose concentration and insulin response and prolonged alimentary lipemia in women[36]. 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[38]. 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[39].

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[40], and high-fructose diets (72% by weight) resulted in the development of diabetes mellitus and diffuse glomerulosclerosis[41,46].

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[41] 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[41]. 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%)[42].

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 SD consumption is linked with fatty liver independently by metabolic syndrome diagnosis.

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

Fructose is lipogenic and stimulates TG synthesis. Splanchnic perfusion studies demonstrate that fructose produces higher rates of TG secretion from the liver than equimolar amounts of glucose. 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. 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. Indeed, total fructose intake averages approximately 12% of the total energy intake and may increase to 15% in some subgroups in the US population.

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

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. Indeed, fructose has been shown to cause ATP depletion in humans, and recovery from fructose-induced ATP depletion was found to be delayed in subjects with NAFLD in studies that used phosphorus-1 magnetic resonance spectroscopy to assess hepatic metabolism. In rats, fructose administration increases hepatic lipid peroxidation and activation of inflammatory pathways. Cirillo et al. found that incubation of endothelial cells or renal tubular cells with postprandial concentrations of fructose reduces intracellular ATP and activates pro-inflammatory 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.

Ouyang et al. 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. The increase in KHK levels is consistent with the known effect of fructose to upregulate KHK in the liver of rats.

Patients on a high fructose or sucrose diet show a greater uric acid response to a bolus of fructose consistent with the upregulation of KHK activity. Finally, uric acid levels can predict the development of NAFLD. There is also increasing evidence that the rise in uric acid may also have a potential role in causing features of the metabolic syndrome, in part by the ability of uric acid to deplete endothelial nitric oxide levels and by activating adipoocytes. 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 cardiovascular 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. 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. 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.

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.

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...
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\(^7\).

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\(^7\).

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\(^7\). 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\(^8\). 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.

REFERENCES

1 Browning JD, Szczepaniak LS, Dobbsin R, Nuremberg P, Horton JD, Cohen JC, Grundy SM, Hobbs HH. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. Hepatology 2004; 40: 1387-1395

2 Bugianesi E, Leone N, Vanni E, Marchesini G, Brunello F, Carucci P, Musso A, De Paolis P, Capussotti L, Salizzoni M, Rizzetto M. Expanding the natural history of nonalcoholic steatohepatitis: from cryptogenic cirrhosis to hepatocellular carcinoma. Gastroenterology 2002; 123: 134-140

3 Willner IR, Waters B, Patil SB, Ruben A, Morelli J, Riely CA. Ninety patients with nonalcoholic steatohepatitis: insulin resistance, familial tendency, and severity of disease. Am J Gastroenterol 2001; 96: 2957-2961

4 Angulo P. Nonalcoholic fatty liver disease. N Engl J Med 2002; 346: 1221-1231

5 Pi-Sunyer FX. The obesity epidemic: pathophysiology and consequences of obesity. Obes Res 2002; 10 Suppl 2: 975S-1045S

6 Haynes P, Liangpunsakul S, Chalasani N. Nonalcoholic fatty liver disease in individuals with severe obesity. Clin Liver Dis 2004; 8: 535-547, viii

7 Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, Frucht JC, James WP, Loria CM, Smith SC Jr. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention, National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009; 120: 1640-1645

8 Nielsens SJ, Popkin BM. Changes in beverage intake between 1977 and 2001. Am J Prev Med 2004; 27: 205-210

9 Gaby AR. Adverse effects of dietary fructose. Altern Med Rev 2005; 10: 294-306

10 Vlassara H, Cai W, Crandall J, Goldberg T, Oberstein R, Dar-daine V, Peppa M, Rayfield EJ. Inflammatory mediators are induced by dietary glycoctinos, a major factor for diabetic angiopathy. Proc Natl Acad Sci USA 2002; 99: 15596-15601

11 Hofmann SM, Dong HJ, Li Z, Cai W, Altomonte J, Tung SN, Zeng F, Fisher EA, Vlassara H. Improved insulin sensitivity is associated with restricted intake of dietary glycoctin products in the dlb/dlb mouse. Diabetes 2002; 51: 2082-2089

12 Mezez E. Dietary fat and alcoholic liver disease. Hepatology 1998; 28: 901-905

13 Fernández MI, Torres MI, Gil A, Rios A. Steatosis and collagen content in experimental liver cirrhosis are affected by dietary monounsaturated and polyunsaturated fatty acids. Scand J Gastroenterol 1997; 32: 350-356

14 Assay N, Nasser G, Kamayse I, Nseir W, Benashvili Z, Djibre A, Grososov M. Soft drink consumption linked with fatty liver in the absence of traditional risk factors. Can J Gastroenterol 2008; 22: 811-816

15 Abid A, Tahal O, Nseir W, Farah R, Grososov M, Assay N. Soft drink consumption is associated with fatty liver disease independent of metabolic syndrome. J Hepatol 2009; 51: 918-924

16 Dhingra S, Sullivan L, Jacques PF, Wang TJ, Fox CS, Meigs JB, D’Agostino RB, G A ziano JM, Vasan RS. Soft drink consumption and risk of developing cardiometabolic risk factors and the metabolic syndrome in middle-aged adults in the community. Circulation 2007; 116: 480-488

17 Popkin BM, Nielsen SJ. The sweetening of the world’s diet. Obes Res 2003; 11: 1325-1332

18 Ferland A, Brassard P, Poirier P. Is aspartame really safer in reducing the risk of hypoglycemia during exercise in patients with type 2 diabetes? Diabetes Care 2007; 30: e59

19 Brown RJ, Walter M, Rother KL. Ingestion of diet soda before a glucose load augments glucagon-like peptide-1 secretion. Diabetes Care 2009; 32: 2184-2186

20 Davali S, Rideau N, Bernadet MD, André JM, Guy G, Hoop-Maris R. Effects of dietary fructose on liver steatosis in over-fed mule ducks. Horm Metab Res 2005; 37: 32-35

21 Kelley GL, Allan G, Azafr S. High dietary fructose induces a hepatic stress response resulting in cholesterol and lipid dysregulation. Endocrinology 2004; 145: 548-555

22 Havel PJ. Dietary fructose: implications for dysregulation of energy homeostasis and lipid/carbohydrate metabolism. Nutr Rev 2005; 63: 153-157

23 Cook GC. Absorption products of D(-)fructose in man. Clin Sci 1969; 37: 675-687

24 Dencker H, Meeuwisse G, Norryd C, Olin T, Tranberg KG. Intestinal transport of carbohydrates as measured by portal catheterization in man. Digestion 1973; 9: 514-524

25 Rutledge AC, Adeli K. Fructose and the metabolic syndrome: pathophysiology and molecular mechanisms. Nutr Rev 2007; 65: S13-S23

26 Day CP, James OF. Steatohepatitis: a tale of two “hits”? Gastroenterology 1998; 114: 842-845

27 Leclercq IA, Horsmans Y. Nonalcoholic fatty liver disease: the potential role of nutritional management. Curr Opin Clin Nutr Metab Care 2008; 11: 766-773

28 Sanyal AJ, Campbell-Sargent C, Mirshahi F, Rizzo WB, Contos MJ, Sterling RK, Luketic V, Shiffman ML, Clare JN. Nonalcoholic steatohepatitis: association of insulin resistance and mitochondrial abnormalities. Gastroenterology 2001; 120: 1183-1192

29 Teff KL, Elliott SS, Tschop M, Kieffer TJ, Rader D, Heiman M, Townsend RR, Keim NL, D’Alessio D, Havel PJ. Dietary fructose reduces circulating insulin and leptin, attenuates postprandial suppression of ghrelin, and increases triglycerides in women. J Clin Endocrinol Metab 2004; 89: 2963-2972

30 Teff KL, Grudziak J, Townsend RR, Dunn TN, Grant RW, Adams SH, Keim NL, Cummings BP, Stanhope KL, Havel PJ. 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 2009; 94: 1562-1569

31 Mayes PA. Intermediary metabolism of fructose. Am J Clin Nutr 1993; 58: 7545-7635

32 Matsuzaka T, Shimano H, Yahagi N, Amemiya-Kudo M, Okazaki T, Yamura T, Izuoka Y, Ohashi K, Tomita S, Sekiya M, Hasty A, Nakagawa Y, Sone H, Toyoshima H, Ishibashi S, Osuga J, Yamada N. Insulin-independent induction of sterol regulatory element-binding protein-1c expression in the liver of streptozotocin-treated mice. Diabetes 2004; 53: 560-569

33 Nagai Y, Nishio Y, Nakamura T, Maegawa H, Kikkawa R, Kashiwagi A. Amelioration of high fructose-induced metabolic derangements by activation of PPARalpha. Am J Physiol Endocrinol Metab 2002; 282: E1180-E1190

34 Stanhope KL, Schwarz JM, Keim NL, Griffen SC, Bremer AA, Graham JL, Hatcher B, Cox CL, Dyachenko A, Zhang W, McGahan JP, Seibert A, Krauss RM, Chiu S, Schaefer EJ, Al M, Otsoskazawa S, Nakajima K, Nakano T, Beyes C, Hellerstein MK, Berglund L, Havel PJ. Consuming fructose-sweetened, not glucose-sweetened, beverages increases visceral adiposity and lipids and decreases insulin sensitivity in overweight/obese humans. J Clin Invest 2009; 119: 1322-1334

35 McDevitt RM, Bott SJ, Harding M, Coward WA, Black LJ, Prentice AM. De novo lipogenesis during controlled overfeeding with sucrose or glucose in lean and obese women.
Nseir W et al. Soft drinks consumption and fatty liver

J Clin Invest 1975; 56: 970-977

Ackerman Z, Oron-Herman M, Grozovski M, Rosenthal T, Pappo O, Link G, Sela BA. Fructose-induced fatty liver disease: hepatic effects of blood pressure and plasma triglyceride reduction. Hypertension 2005; 45: 1012-1018

Porikos KP, Van Itallie TB. Diet-induced changes in serum transaminase and triglyceride levels in healthy adult men. Role of sucrose and excess calories. Am J Med 1983; 75: 624-630

Howard BV, Wylie-Rosett J. Sugar and cardiovascular disease: A statement for healthcare professionals from the Committee on Nutrition of the Council on Nutrition, Physical Activity, and Metabolism of the American Heart Association. Circulation 2002; 106: 523-527

Taghibiglou C, Carpentier A, Van Linderstone SC, Chen B, Rudy D, Alton A, Lewis GF, Adeli K. Mechanisms of hepatic very low density lipoprotein overproduction in insulin resistance. Evidence for enhanced lipoprotein assembly, reduced intracellular ApoB degradation, and increased microsomal triglyceride transfer protein in a fructose-fed hamster model. J Biol Chem 2000; 275: 8416-8425

Taghibiglou C, Rashid-Kolvare F, Van Linderstone SC, Le-Tien H, Fantus IG, Lewis GF, Adeli K. Hepatic very low density lipoprotein-ApoB overproduction is associated with attenuated hepatic insulin signaling and overexpression of protein-tyrosine phosphatase 1B in a fructose-fed hamster model of insulin resistance. J Biol Chem 2002; 277: 793-805

Bode JC, Zelder O, Rumpelt HJ, Wittkamp U. Depletion of liver adenosine phosphates and metabolic effects of intravenous infusion of fructose or sorbitol in man and in the rat. Eur J Clin Invest 1973; 3: 436-441

Oberhaensli RD, Galloway GJ, Taylor DJ, Bore PJ, Radda GK. Assessment of human liver metabolism by phosphorus-31 magnetic resonance spectroscopy. Br J Radiol 1986; 59: 659-669

Cortez-Pinto H, Chatham J, Chacko VP, Arnold C, Rashid A, Diehl AM. Alterations in liver ATP homeostasis in human nonalcoholic steatohepatitis: a pilot study. JAMA 1999; 282: 1659-1664

Adachi F, Yu DT, Phillips MJ. An ultrastructural study of fructose-induced hepatic cell injury. Comparison of human and experimental lesions. Virchows Arch B Cell Pathol 1972; 10: 200-209

Cirillo P, Sautin YY, Kanelis J, Kang DH, Gesualdo L, Nakagawa T, Johnson Rj. Systemic inflammation, metabolic syndrome and progressive renal disease. Nephrol Dial Transplant 2009; 24: 1384-1387

Ouyang X, Cirillo P, Sautin Y, McColl S, Bruchette JL, Diehl AM, Johnson Rj, Abdelmalek MF. Fructose consumption as a risk factor for non-alcoholic fatty liver disease. J Hepatol 2008; 48: 993-999

Burant CF, Saxena M. Rapid reversible substrate regulation of fructose transporter expression in rat small intestine and kidney. Am J Physiol 1994; 267: G71-G79

Korieh A, Crouzoulon G. Dietary regulation of fructose metabolism in the intestine and in the liver of the rat. Duration of the effects of a high fructose diet after the return to the standard diet. Arch Int Physiol Biochim Biophys 1991; 99: 455-460

Stirpe F, Della Corte E, Bonetti E, Abbondanza A, Abbati A, De Stefano F. Fructose-induced hyperuricaemia. Lancet 1970; 2: 1310-1311

Israel KD, Michaelis OE 4th, Reiser S, Keeney M. Serum uric acid, inorganic phosphorus, and glutamic-oxyacetic transaminase and blood pressure in carbohydrate-sensitive adults consuming three different levels of sucrose. Am J Nutr Metab 1983; 27: 425-435

Sartorio A, Del Col A, Agosti F, Mazzilli G, Bellentani S,
Nseir W et al. Soft drinks consumption and fatty liver

Tiribelli C, Bedogni G. Predictors of non-alcoholic fatty liver disease in obese children. *Eur J Clin Nutr* 2007; 61: 877-883

Nakagawa T, Hu H, Zharikov S, Tuttle KR, Short RA, Glushakova O, Ouyang X, Feig DI, Block ER, Herrera-Acosta J, Patel JM, Johnson RJ. A causal role for uric acid in fructose-induced metabolic syndrome. *Am J Physiol Renal Physiol* 2006; 290: F625-F631

Khosla UM, Zharikov S, Finch JL, Nakagawa T, Roncal C, Mu W, Krotova K, Block ER, Prabhakar S, Johnson RJ. Hyperuricemia induces endothelial dysfunction. *Kidney Int* 2005; 67: 1739-1742

Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes* 1988; 37: 1595-1607

Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002; 106: 3143-3421

Targher G, Chonchol M, Miele L, Zoppini G, Pichiri I, Muggeo M. Nonalcoholic fatty liver disease as a contributor to hypercoagulation and thrombophilia in the metabolic syndrome. *Semin Thromb Hemost* 2009; 35: 277-287

Hansen E, Hajri T, Abumrad NN. Is all fat the same? The role of fat in the pathogenesis of the metabolic syndrome and type 2 diabetes mellitus. *Surgery* 2006; 139: 711-716

Reynisdottir S, Dauzats M, Thörne A, Langin D. Comparison of hormone-sensitive lipase activity in visceral and subcutaneous human adipose tissue. *J Clin Endocrinol Metab* 1997; 82: 4162-4166

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