

Soft drink consumption is associated with fatty liver disease independent of metabolic syndrome[☆]

Ali Abid^{1,2}, Ola Taha², William Nseir², Raymond Farah³, Maria Grosovski⁴,
Nimer Assy^{1,5,*}

¹Liver Unit, Ziv Medical Center, P.O. Box 1008, 13100 Safed, Israel

²Department of Internal Medicine, Holy Family Hospital, Nazareth, Israel

³Department of Internal Medicine, Ziv Medical Center, Safed, Israel

⁴Department of Biotechnology, Ort-Braude College, Karmiel, Israel

⁵Technion Institute, Faculty of Medicine, Haifa, Israel

Background/Aims: The independent role of soft drink consumption in non-alcoholic fatty liver disease (NAFLD) patients remains unclear. We aimed to assess the association between consumption of soft drinks and fatty liver in patients with or without metabolic syndrome.

Methods: We recruited 31 patients (age: 43 ± 12 years) with NAFLD and risk factors for metabolic syndrome, 29 patients with NAFLD and without risk factors for metabolic syndrome, and 30 gender- and age-matched individuals without NAFLD. The degree of fatty infiltration was measured by ultrasound. Data on physical activity and intake of food and soft drinks were collected during two 7-day periods over 6 months using a food questionnaire. Insulin resistance, inflammation, and oxidant–antioxidant markers were measured.

Results: We found that 80% of patients with NAFLD had excessive intake of soft drink beverages (>500 cm³/day) compared to 17% of healthy controls ($p < 0.001$). The NAFLD group consumed five times more carbohydrates from soft drinks compared to healthy controls (40% vs. 8%, $p < 0.001$). Seven percent of patients consumed one soft drink per day, 55% consumed two or three soft drinks per day, and 38% consumed more than four soft drinks per day for most days and for the 6-month period. The most common soft drinks were Coca-Cola (regular: 32%; diet: 21%) followed by fruit juices (47%). Patients with NAFLD with metabolic syndrome had similar malonyldialdehyde, paraoxonase, and C-reactive protein (CRP) levels but higher homeostasis model assessment (HOMA) and higher ferritin than NAFLD patients without metabolic syndrome (HOMA: 8.3 ± 8 vs. 3.7 ± 3.7 mg/dL, $p < 0.001$; ferritin: 186 ± 192 vs. 87 ± 84 mg/dL, $p < 0.01$). Logistic regression analysis showed that soft drink consumption is a strong predictor of fatty liver (odds ratio: 2.0; $p < 0.04$) independent of metabolic syndrome and CRP level.

Conclusions: NAFLD patients display higher soft drink consumption independent of metabolic syndrome diagnosis. These findings might optimize NAFLD risk stratification.

© 2009 European Association for the Study of the Liver. Published by Elsevier B.V. All rights reserved.

Keywords: Soft drinks; Fatty liver; Risk factors; Fructose; Independent predictor; Metabolic syndrome; Dietary intake

Received 1 March 2009; received in revised form 17 May 2009; accepted 30 May 2009; available online 21 August 2009

Associate Editor: C.P. Day

[☆] The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

* Corresponding author. Tel.: +972 46828441; fax: +972 46828442.

E-mail addresses: assy.n@ziv.health.gov.il, assy.nimer@gmail.com (N. Assy).

Abbreviations: NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.

1. Introduction

The pathogenesis of non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH) is related to continuous delivery of free fatty acids to the liver from splanchnic lipolysis of visceral fat or from increased ingestion of fatty food, together with lipotoxicity, inflammation, oxidative stress, or lipid peroxidation and insulin resistance [1]. Clinical implications of NAFLD/NASH derive mostly from common occurrence in the general population (10–24%) and potential to progress to fibrosis (30–40%), cirrhosis (20–30%), or hepatocellular carcinoma [2]. NASH is the most common cause of cryptogenic cirrhosis and is an increasingly common indication for liver transplantation. Frequently associated with obesity, type 2 diabetes mellitus (DM), and hyperlipidemia, NAFLD is considered an important emerging health issue and is included among components of metabolic syndrome, as defined by the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel 111-ATP 111) [2,3]. Identification of new risk factors that permit early diagnosis and treatment is warranted.

Soft drinks are the leading source of artificially added sugar in the world and have been linked to obesity in children and adolescents [4]. Recent evidence suggests an association between the intake of sugar-sweetened soft drinks and the risk of obesity and diabetes because the drinks contain large amounts of high-fructose corn syrup (HFCS), which raises triglycerides and blood glucose similarly to sucrose [4,5]. Additionally, soft drinks contain caramel coloring, which is rich in advanced glycation end products that can increase insulin resistance and inflammation [4].

Intake of nutrients (including those found in sweetened beverages) may affect insulin resistance, carbohydrate levels, lipid metabolism, and hepatic steatosis, yet other factors also play a role [4]. Recently, it has been reported that intake of more simple carbohydrates and less saturated fat was higher in patients with fatty liver compared with the general population, suggesting that imbalanced diets play an important role in development and progression of NAFLD [6]. High-fructose diets have induced fatty liver in rats and ducks [7]. Such diets have also caused increases in hepatic lipid per oxidation and activation of inflammatory pathways in rat livers [8]. That fructose consumption can cause progressive liver disease in humans is demonstrated by hereditary fructose intolerance, a rare disease that results from a deficiency of aldolase B enzyme [9]. More recently, it has been shown that soft drink consumption is linked to obesity and results in an increased risk of metabolic syndrome [5]. Individuals consuming more than one soft drink daily showed a higher prevalence of metabolic syndrome than those consuming less than one soft drink per day [5]. We have shown previously that soft drink consumption is linked

with NAFLD [10], but the independent role of soft drink intake in NAFLD patients remains unclear. The present study was designed to assess the association between soft drink consumption and fatty liver in patients with or without metabolic syndrome.

2. Patients and methods

2.1. Study design

Two groups of 60 consecutive NAFLD patients from the liver unit at Ziv Medical Center in Safed, Israel, were included in the study. Group 1 was composed of 31 men and women (age: 53 ± 7 years) with NAFLD and risk factors for metabolic syndrome (DM, obesity, triglycerides). Group 2 included 29 subjects with NAFLD and without risk factors for metabolic syndrome (identified by lipid profile, fasting glucose, blood pressure, and body mass index [BMI]). All subjects had sought medical advice for abdominal discomfort, hepatomegaly, and/or abnormal liver enzymes. A similar age- and gender-matched healthy control group ($n = 30$) with normal ultrasound (same operator) and normal liver enzymes and without diabetes, obesity, and hyperlipidemia was randomly selected from the general population (teachers at the Catholic secondary school in Fassouta, western Galilee, Israel, were identified randomly and matched by the principal investigator). The healthy control group denied alcohol intake. Those reporting use of alcohol (>140 g/week or >20 g/day in females and 30 g/day in male), drugs (tamoxifen, steroids, amiodarone), and other risk factors that might induce hepatic steatosis (e.g., *Hepatitis C virus* or *Hepatitis B virus* infection, autoantibodies indicative of autoimmune hepatitis or celiac disease) were excluded by clinical and biochemical tests. Excessive soft drink consumption was defined as >50 g/day (>500 cm³/day or >12 teaspoons per day of added sugar) [5]. All study end points were obtained prospectively. The laboratory tests were done within 2 weeks of dietary consultation and study participation. Patients' medications including statins and insulin sensitization were taken into account when defining dyslipidemia and/or type 2 DM.

2.2. Interview

Interviews were conducted by an experienced dietician who collected data concerning dietary habits, physical activity, and other relevant information using the validated, self-administered Block food frequency questionnaire (1998 version). This tool is frequently used in mixed-gender and multiethnic populations for metabolic and dietary intervention studies. Daily average food and beverage intake was recorded during two 7-day periods, at the beginning and at the end of the study, over 6 months. Reported intake included (1) breads, pizza, and savory snacks; (2) pasta, rice, and corn; (3) potatoes, peas, and beans; (4) milk and dairy products; (5) juices and soft drinks; (6) nuts and fresh and dried fruits; (7) sugar, sweets, cakes, and chocolate; and (8) fresh vegetables. Physical activity was assessed by the Paffenbarger questionnaire, which is well validated [11]. The time frame included activity during the preceding week and every 6 weeks for 6 months.

2.3. Physical activity

Physical activity was measured. Light activity was defined as 5 kcal/min and included walking, gardening, dancing, and ice skating. Moderate activity (10 kcal/min) included swimming, running, jogging, basketball, and football. Combination activity (7.6 kcal/min) included weight lifting.

2.4. Alcohol intake

The abuse of alcohol was determined by interviewing patients and their relatives. Patients who were described as alcohol abusers were excluded from the study. Alcohol consumption was assessed with a

validated questionnaire [12]. Patients were asked how many times per week they usually drank as well as the usual amount consumed. They were asked to estimate the amount in terms of popular Israeli cups (60 cm³) or bottles of beer. The information obtained also included the style of drinking, the type of alcoholic beverage, the average and maximum amounts consumed each time, and the life events that affected drinking patterns. Based on this information, the amount of alcohol consumed per week was calculated.

2.5. Biochemistry and anthropometric measurements

Lipid, liver enzyme, glucose, and insulin levels were measured by standard biochemical methods. Insulin resistance was estimated using the oral glucose tolerance test – derived homeostasis model assessment (HOMA) based on the following equation: insulin resistance = (fasting plasma glucose level [mg%] × 0.055 mmol/L) × (fasting plasma insulin level [mU/L])/22.5). BMI was calculated as weight in kilograms divided by the square of height in meters. Obesity was considered to be present if the calculated BMI exceeded 28 kg/m², and diabetes was considered to be present if fasting plasma glucose levels were >126 mg/dL (two times the upper limit of normal). Metabolic syndrome was defined as the presence of three or more of the following factors: abdominal obesity (waist circumference ≥80 cm for women or ≥90 cm for men) or BMI >28 kg/m²; fasting blood glucose ≥100 mg/dL; serum triglycerides ≥150 mg/dL; blood pressure ≥135/85 mm Hg; and high-density lipoprotein (HDL) cholesterol <40 mg/dL for men or <50 mg/dL for women [5]. Biomarkers of insulin resistance (glucose, insulin, HOMA) and systemic inflammation (C-reactive protein [CRP], fibrinogen) and markers of oxidant-antioxidant status (malonyldialdehyde [MDA], paraoxonase, α -tocopherol) were measured in the plasma by commercial kits. The laboratory results were ready within 2 weeks of dietary consultation and study participation.

2.6. Radiology

Ultrasound examinations were obtained within 2 weeks of presentation. Each examination was performed using a real-time, high-resolution Acuson gray-scale/color ultrasound scanner (A. Cuson Diagnostic, San Francisco, CA, USA) by a single experienced sonographer who was blinded to the clinical status of the patients. Combination of brightness, liver–kidney contrast with two other well-known ultrasound findings of fatty liver, vascular blurring, and deep attenuation enabled us to diagnose and grade fatty change semiquantitatively [13,14].

Metabolic measures and physical activity and dietary information were retrieved by the validated food questionnaire. NAFLD risk factors were identified within 2 weeks of participation. The study was approved by the hospital institutional review board, and all patients signed informed consent for participation.

2.7. Statistics

Data are expressed as means ± standard deviation. Differences between two variables were assessed by the Wilcoxon rank sum test, univariate χ^2 test, and *t* test as appropriate. Correlations were assessed using a Spearman rank correlation and univariate regression analysis. We used multiple stepwise regression analysis after adjustment for all confounding factors to assess the association between soft drinks, markers of insulin resistance, inflammation by CRP, oxidant and antioxidant status, metabolic syndrome, and the presence of fatty liver. Results were expressed as an odds ratio (OR). Statistical significance was defined as *p* < 0.05. All statistical analyses were performed using the WinSTAT statistical software (R. Fitch Software).

3. Results

Table 1 shows the demographic, clinical, and metabolic characteristics of all subjects. Patients with

NAFLD with metabolic syndrome had similar MDA, paraoxonase, fibrinogen, and CRP serum levels but higher HOMA and higher serum ferritin than NAFLD patients without metabolic syndrome (8.3 ± 8 vs. 3.7 ± 3.7 mg/dL, *p* < 0.001; 186 ± 192 vs. 87 ± 84 mg/dL, *p* < 0.01) and higher HOMA and higher serum ferritin than healthy controls (8.3 ± 8 vs. 1.7 ± 0.5 mg/dL, *p* < 0.001; 186 ± 192 vs. 130 ± 80 mg/dL, *p* < 0.01). Moreover, NAFLD patients with metabolic syndrome had higher serum γ -glutamyl transferase and triglycerides but lower serum HDL than patients with NAFLD but without metabolic syndrome (Table 1). A significant correlation was found between the amount of soft drink consumption and the presence of fatty infiltration (*r* = 0.63; *p* < 0.001), whereas no relationship was observed with other food constituents.

Table 2 shows the dietary constituents of patients with NAFLD with or without metabolic syndrome and controls and the source of added sugar during two 7-day periods at the beginning and at the end of the study. Of patients with NAFLD, 80% had excessive soft drink intake (>500 cm³/day or >12 teaspoons per day of added sugar) compared to 17% of healthy controls (*p* < 0.001). Seven percent of patients had one soft drink daily, 55% had two or three soft drinks daily, and 38% had more than 4 soft drinks daily for most days and for 6 months. The most common soft drinks were Coca-Cola (53%, regular or diet) followed by flavored fruit juices (47%). The source of added sugar was significantly higher in NAFLD patients with metabolic syndrome compared to patients with NAFLD without metabolic syndrome and to healthy controls (80 ± 12 vs. 70 ± 8 vs. 20 ± 11 g/day, *p* < 0.001). For NAFLD patients with metabolic syndrome, 40% of added sugar was from soft drink consumption compared to 8% for healthy controls (*p* < 0.001). The source of added sugar was from regular soft drinks (regular cola [32%] and flavored juice [47%]) and not from diet soft drinks (diet cola [21%]).

Table 3 shows the results of a multivariate model for prediction of fatty liver in patients with or without metabolic syndrome after adjustment for all confounding factors revealed at univariate analysis. When controlled for dietary composition and physical activity, multiple logistic regression analysis demonstrated that the amount of soft drink consumption was the strongest predictor of fatty liver (OR: 2.0; *p* < 0.04) but not the biomarkers of inflammation (CRP), insulin resistance, oxidative stress, or diagnosis of metabolic syndrome. The association of soft drink consumption with fatty liver also remains significant after adjustment for both metabolic syndrome and CRP level (Table 3).

The association between the number of soft drinks consumed per day by NAFLD patients with or without metabolic syndrome and by controls is shown in Fig. 1.

Table 1**Clinical and metabolic biomarkers of non-alcoholic fatty liver disease (NAFLD) patients with and without metabolic syndrome (MS) and healthy controls.[†]**

	NAFLD with MS, <i>n</i> = 31	NAFLD without MS, <i>n</i> = 29	Controls, <i>n</i> = 30	<i>p</i> Value, ANOVA
Age (y)	43 ± 12	41 ± 11	40 ± 10	0.3
Gender (male)	50%	47%	49%	0.1
BMI	30 ± 3	29 ± 4.5	28 ± 5.0	0.08
ALT (U/L)	50 ± 32	48 ± 31	23 ± 11	0.03
GGT (U/L)*	80 ± 82	44 ± 24	25 ± 10	0.001
Glucose (mg/dL)	111 ± 27	96 ± 17	85 ± 13	0.02
Fasting insulin (μU/mL)	31 ± 33	20 ± 23	10	0.01
HOMA*	8.3 ± 8	3.7 ± 3.7	1.7 ± 0.5	0.001
TG (mg/dL)*	208 ± 69	142 ± 64	108 ± 34	0.001
HDL (mg/dL)***	39 ± 11	47 ± 10	40 ± 10	0.05
Ferritin (μg/L)**	186 ± 192	87 ± 84	130 ± 80	0.01
MDA (μmol/mL)	0.13 ± 0.04	0.14 ± 0.03	0.200 ± 0.1	0.1
Paraoxonase (mM/min)	0.28 ± 0.09	0.21 ± 0.07	0.27 ± 0.8	0.5
A-tocepherol (mg/mL)	0.03 ± 0.006	0.03 ± 0.07	0.03 ± 0.004	0.8
CRP (mg/dL)	11 ± 7	10 ± 6	2 ± 0.2	0.001
Fibrinogen (μg/L)	322 ± 99	364 ± 168	280 ± 100	0.04

Abbreviations: ALT, alanine aminotransferase; ANOVA, analysis of variance; BMI, body mass index; CRP, C-reactive protein; GGT, γ -glutamyl transferase; HDL, high-density lipoprotein; HOMA, homeostasis model assessment; MDA, malondialdehyde; TG, triglycerides.

[†] Data are presented as means ± standard deviation.

* $p < 0.001$.

** $p < 0.01$.

*** $p < 0.5$.

The NAFLD group consumed almost five times the amount of carbohydrate from soft drinks compared to healthy controls (source of added sugar in grams per day: 43%, 37%, and 8%; $p < 0.001$; Table 2).

The association between amount of soft drink consumption and severity of fatty liver disease in NAFLD patients and in controls is shown in Fig. 2. There was

a significant difference in the amount of soft drinks consumed per day between those with severe fatty liver versus those with mild fatty liver and between fatty liver subgroups and controls ($p < 0.001$). There was also a correlation between the number of soft drinks per day and the insulin resistance index (HOMA; $r = 0.4$; $p < 0.01$).

Table 2**Dietary constituents in non-alcoholic fatty liver disease (NAFLD) patients with or without metabolic syndrome (MS) and controls and the sources of added sugar during two 7-day periods at the beginning and at the end of the study.**

Dietary constituents [†]	NAFLD with MS, <i>n</i> = 29	NAFLD without MS, <i>n</i> = 31	Healthy controls, <i>n</i> = 30	<i>p</i> Value
Prevalence of excessive soft drinks (>50 g/d of added sugar)*	81%	79%	17%	0.001
Number of soft drinks per day**	5.4 ± 4.6	4.7 ± 4.7	0.3 ± 0.5	0.01
Source of added sugar (g/d)*	80 ± 12	70 ± 8	30 ± 11	0.001
Soft drinks plus juices*	43%	37%	8%	0.001
Sweetened grains (baked goods) plus sweets and candy (chocolate)	8%	14%	12%	0.5
Milk and dairy products	5%	4.5%	10%	0.03
Other [@]	44%	44.5%	70%	0.01
Total energy intake (kcal)	2207 ± 618	2164 ± 629	2100 ± 600	0.3
Fat (percent of energy)	20 ± 11	20 ± 8	22 ± 5	0.5
Carbohydrate (percent of energy)	71 ± 13	69 ± 13	70 ± 6	0.4
Protein (percent of energy)	9 ± 4	11 ± 6	8 ± 2	0.1
Carbohydrate intake (g/d)	279 ± 131	258 ± 133	255 ± 95	0.6
Physical activity (h/d)	Light 0.3 ± 0.36	Light 0.2 ± 0.3	Light 0.3 ± 0.46	0.1
Alcohol (g/d)	15 ± 7	10 ± 5	6 ± 2	0.8

[†] Percent contribution to dietary carbohydrate from different source of added sugar from regular soft drink (the recommended upper limit for a 2200-kcal diet is 50 g/day).

[@] Cereals, other beverage (tea, coffee), fresh vegetables, fresh and dried fruits (1 teaspoon of sugar = 4.2 g; 1 ounce = 1/16 pound, 28.349 g).

* $p < 0.001$.

** $p < 0.01$ between all NAFLD and controls.

Table 3
Multivariate model for prediction of fatty liver in patients with or without metabolic syndrome.

	OR*	95% CI	<i>p</i>
Soft drink consumption	2.0	1–5	0.03
Triglyceride (mg/dL)	0.5	0.8–1.1	0.7
HOMA	0.7	1–1.1	0.8
CRP (mg/dL)	0.5	0.8–0.9	0.4
MDA (μmol/L)	0.1	1–3	0.9
Ferritin (μg/L)	0.7	0.9–1	0.8
Paraoxonase (mM/min)	0.4	0.7–0.9	0.2
Metabolic syndrome	1.5	0.9–4	0.05

Abbreviations: CI, confidence interval; CRP, C-reactive protein; HOMA, homeostasis model assessment; MDA, malondialdehyde; OR, odds ratio.
* Adjusted ORs are shown and adjusted for age, sex, smoking habits, physical activity, dietary composition, body mass index, metabolic syndrome, triglyceride, HOMA, and metabolic biomarkers.

4. Discussion

The results of this study clearly indicate that NAFLD patients with or without metabolic syndrome consume more soft drinks compared to healthy controls. Moreover, this study indicates that soft drink consumption is a strong predictor of fatty liver (OR: 2.0; $p < 0.04$) independent of metabolic syndrome and CRP levels. The underlying mechanism remains unknown.

Soft drinks constitute the leading cause of added sugar in the diet [15]. Individuals who drank more soft drinks tended to be sedentary, to eat less fiber and dairy, to have greater intake of saturated fat and transfat, and to eat a higher-calorie diet (additional 150–300 kcal/day) that included more fructose and caramel [16]. These complexes of sugars and colorings may promote insulin resistance, lipid per oxidation, glycation end products, and hepatic inflammation [17–19]. One study of lean women found that 4 days of overfeeding with sucrose (glucose plus fructose) drink increased de novo lipogenesis by 200–300% [20]. Another feeding study showed that 2 days of high-fructose intake (30% of kilo-

calories per day, consumed as a sweetened beverage at every meal) resulted in decreased postprandial glucose concentration and insulin response and prolonged alimentary lipemia in women [21]. A very recent clinical study indicates that NAFLD patients have a higher intake of soft drinks and meat and a tendency toward lower intake of fish rich in omega-3 [22].

Additional evidence that fructose can cause steatohepatitis is that hepatic messenger RNA expression of fructokinase was increased [23]. Fructokinase is an important enzyme for fructose metabolism and fatty acid synthase, which is an important enzyme for lipogenesis. Fructose can also increase triglyceride levels, de novo synthesis of fatty acids, hyperuricemia, hyperferritinemia, and insulin resistance [22,24,25].

Fructose, especially HFCS, is now used extensively in carbonated beverages and other sweetened drinks, baked goods, candies, canned fruits, soda, jams, jellies, and dairy products [26]. Absorption of fructose in the small bowel is transported via the portal vein to the liver, where it is metabolized by fructokinase to fructose-1-phosphate. This molecule is cleaved by aldolase to form glycero phosphate and glyceraldehydes 3-phosphate, both of which can be further metabolized

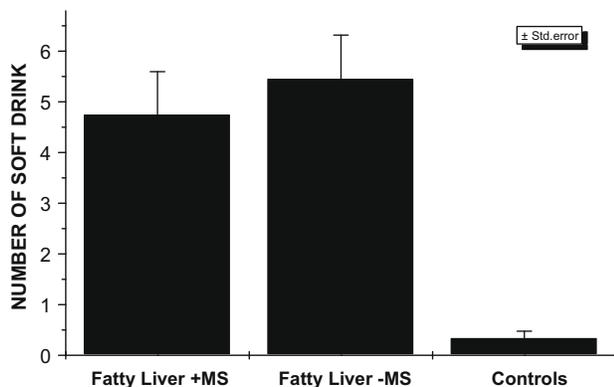


Fig. 1. Number of daily soft drinks in non-alcoholic fatty liver disease (NAFLD) patients with or without metabolic syndrome (MS) and in controls. * $p < 0.07$; NAFLD without metabolic syndrome versus NAFLD with metabolic syndrome. ** $p < 0.001$ between NAFLD subgroups and controls.

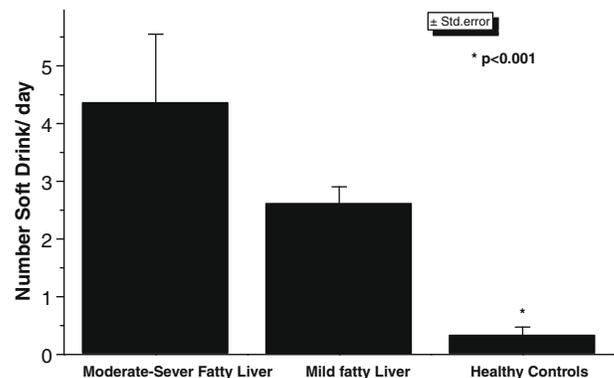


Fig. 2. Association of soft drink consumption and severity of fatty liver disease. * $p < 0.001$ between those with severe fatty liver versus those with mild fatty liver and between NAFLD subgroups and controls.

in the glycolytic pathway [27]. A soft drink containing 32.6 g of fructose could be expected to increase the fasting serum fructose 4-fold; 340 g of cola sweetened with fructose-55 contains about 40 g of the sweetener (ie, 22 g of fructose and 17 g of glucose), representing a fructose excess of 5 g per can [18,28]. Fructose affects each of the three major factors that are believed to contribute to the pathogenesis of diabetic end organ damage: glycosylation of tissue proteins, intracellular accumulation of sorbitol, and oxidative stress [4].

The association between consumption of beverages sweetened with sugars such as HFCS and risk of diabetes has been established by Schulze et al. [18]. From our study, it seems that not only fructose is important: 47% of our cohort was drinking fruit juices containing caramel and 40% of those drinking cola (21% of all NAFLD patients) had diet cola containing aspartame. The effect of caramel and aspartame has been involved in elevated liver enzymes and in metabolic syndrome and may be a potential source of advanced glycation end product [28], which may promote insulin resistance and can be proinflammatory [5,18,19,29]. This effect is a new element to consider in patients with NAFLD, but we cannot draw any conclusions about diet soft drinks and the role of aspartame or caramel in the pathogenesis of NAFLD.

When controlled for other factors including dietary composition and physical activity, soft drink intake was the only independent variable that predicted the presence of fatty liver. This factor remains significant after adjustment for CRP levels and metabolic syndrome. Vartanian et al. showed clear associations of soft drink intake with diabetes and metabolic syndrome [30]. Although we still do not know the most common soft drink coingestants that induce fatty liver, fructose and caramel constituents may have a role. These coingestants might also increase risk of fatty liver because of their high amounts of rapid absorbable carbohydrate [18]. They contain large amounts of HFCS, which has a similar effect on blood glucose as sucrose [31]; therefore, consumption of sugar-sweetened soft drinks induces a fast and dramatic increase in glucose, triglyceride, and insulin concentration [32]. Additionally, cola-type soft drink caramel coloring, which is rich in advanced glycation end products, may increase insulin resistance and inflammation [29,33]. The US Food and Drug Administration have established 200 mg of caramel per kilogram of body weight as an acceptable daily intake.

Oxidative stress may influence the risk of NAFLD, but there was no significant difference in pro-oxidant and antioxidant markers between patients with NAFLD and controls. Systemic inflammation may account for increased steatohepatitis. Recently, it has been shown that patients with elevated CRP who receive rosovastatin had a 48% reduction in stroke, a 46% reduction in the need for intervention to reopen blocked blood vessels, and a 20% drop in all cause mortality. The increase

in CRP or in tumor necrosis factor-alpha is key to the control of metabolism and inflammation [34]. Our study showed no significant difference in CRP levels between fatty liver with or without metabolic syndrome compared to controls.

The strength of the study includes the good selection of healthy controls from the community and the adjustment for potential confounders. Some limitations, however, merit comment. It cannot be excluded that other covariants present in food or some dietary habits (e.g., having a carbonated beverage facilitates the intake of fatty food like pizza) play a role in the observed relation between soft drink beverage intake and hepatic steatosis. The second limitation is that dietary and physical activity information was obtained through a self-reported questionnaire, which may be subject to underreporting and interviewer bias [35]. The rationale behind this choice is compliance, ethnic background, and the socio-cultural homogeneity of the population studied. Traditional habits in cooking practices are quite similar throughout the region and tend to persist in descendants [36]. Finally, increased soft drink consumption would increase total energy intake by increased appetite and increased fat intake; however, in our study population, the increase in soft drink did not increase energy intake. The reason for that is unknown. One explanation is that patients with NAFLD, with low education levels, or who are overweight underreport energy intake in dietary self-reports (especially men; women are typically more conscious of serving sizes than men) [37]. This may bias dietary interpretation. It also has been shown that when the nutrient values are energy adjusted or are expressed as percentages of energy intake, the effect of underreporting is minimized [38].

In conclusion, NAFLD patients have a higher prevalence of soft drink consumption independent of metabolic syndrome diagnosis. This study may add important insight into the role of sugar-sweetened beverages as a cause of metabolic syndrome in those both with or without risk factors.

References

- [1] Leclercq IA, Horsmans Y. Nonalcoholic fatty liver disease: the potential role of nutritional management. *Curr Opin Clin Nutr Metab Care* 2008;11:766–773.
- [2] Assy N, Kaita K, Mymin D, Levy C, Rosser B, Minuk G. Fatty infiltration of liver in hyperlipidemic patients. *Dig Dis Sci* 2000;45:1929–1934.
- [3] Vuppalanchi R, Chalasani N. Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: selected practical issues in their evaluation and management. *Hepatology* 2009;49:306–317.
- [4] Gaby AR. Adverse effects of dietary fructose. *Alt Med Rev* 2005;10:294–306.
- [5] Dhingra R, Sullivan L, Jacques PF, Wang TJ, Fox CS, Meigs JB, et al. Soft drink consumption and risk of developing cardiovascular metabolic risk factors and the metabolic syndrome in middle-aged adults in the community. *Circulation* 2007;116:480–488.

- [6] Toshimitsu K, Matsuura B, Ohkubo I, Niiya T, Furukawa S, Hiasa Y, et al. Dietary habits and nutrient intake in non-alcoholic steatohepatitis. *Nutrition* 2007;23:46–52.
- [7] Davail S, Rideau N, Bernadet MD, André JM, Guy G, Hoo-Paris R. Effects of dietary fructose on liver steatosis in overfed mule ducks. *Horm Metab Res* 2005;37:32–35.
- [8] Kelly GL, Allan G, Azhar S. Higher dietary fructose induces a hepatic stress response resulting in cholesterol and lipid dysregulation. *Endocrinology* 2004;145:548–555.
- [9] Santer R, Rischewski J, von Weihe M, Niederhaus M, Schneppenheim S, Baerlocher K, et al. The spectrum of aldolase B mutations and the prevalence of hereditary fructose intolerance in central Europe. *Hum Mutat* 2005;25:594.
- [10] Assy N, Nasser G, Kamayse I, Nseir W, Beniashvili Z, Djibre A, et al. Soft drink consumption linked with fatty liver in the absence of traditional risk factors. *Can J Gastroenterol* 2008;22:811–816.
- [11] Paffenbarger RS, Wing AL, Hyde RT. Physical activity as an index of heart attack risk in college alumni. *Am J Epidemiol* 1978;108:161–175.
- [12] Giovannucci E, Colditz G, Stampfer MJ, Rimm EB, Litin L, Sampson L, et al. The assessment of alcohol consumption by a simple self-administered questionnaire. *Am J Epidemiol* 1991;133:810–817.
- [13] Scatarige JC, Scott WW, Donovan PJ, Siegelman SS, Sanders RC. Fatty infiltration of the liver. Ultrasonographic and computed tomographic correlation. *J Ultrasound Med* 1984;3:9–14.
- [14] Saverymuttu SH, Joseph AE, Maxwell JD. Ultrasound scanning in the detection of hepatic fibrosis and steatosis. *Br Med J (Clin Res Ed)* 1986;292:13–15.
- [15] Ludwig DS, Peterson KE, Gortmaker SL. Relation between consumption of sugar-sweetened drinks and childhood obesity: a prospective, observational analysis. *Lancet* 2001;357:505–508.
- [16] Popkin BM, Armstrong LE, Bray GM, Caballero B, Frei B, Willett WC. A new proposed guidance system for beverage consumption in the United States. *Am J Clin Nutr* 2006;83:529–542.
- [17] Nandhini AT, Balakrishnan SD, Anuradha CV. Response of liver antioxidant system to taurine in rats fed high fructose diet. *Indian J Exp Biol* 2002;40:1016–1019.
- [18] Schulze MB, Manson JE, Ludwig DS, Colditz GA, Stampfer MJ, Willett WC, et al. Sugar-sweetened beverages, weight gain, and incidence of type 2 diabetes in young and middle-aged women. *JAMA* 2004;292:927–934.
- [19] Vlassara H, Vlassara H, Cai W, Crandall J, Goldberg T, Oberstein R, et al. Inflammatory mediators are induced by dietary glycotoxins, a major risk factor for diabetic angiopathy. *Proc Natl Acad Sci USA* 2002;99:15596–15601.
- [20] McDevitt RM, Bott SJ, Harding M, Coward WA, Bluck LJ, Prentice AM. De novo lipogenesis during controlled overfeeding with sucrose or glucose in lean and obese women. *Am J Clin Nutr* 2001;74:737–746.
- [21] Teff KL, Elliott SS, Tschöp M, Kieffer TJ, Rader D, Heiman M, et al. 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.
- [22] Zelber-Sagi S, Nitzan-Kaluski D, Goldsmith R, Webb M, Blendis L, Halpern Z, et al. Long term nutritional intake and the risk for non-alcoholic fatty liver disease (NAFLD): a population based study. *J Hepatol* 2007;47:711–717.
- [23] Ouyang X, Cirillo P, Sautin Y, McCall S, Bruchette JL, Diehl AM, et al. Fructose consumption as a risk factor for non-alcoholic fatty liver disease. *J Hepatol* 2008;48:993–999.
- [24] Simko V. Increase in serum lipids on feeding sucrose: the role of fructose and glucose. *Am J Clin Nutr* 1980;33:2217.
- [25] Hallfrisch J, Reiser S, Prather ES. Blood lipid distribution of hyperinsulinemic men consuming three levels of fructose. *Am J Clin Nutr* 1983;37:740–748.
- [26] Vuilleumier S. Worldwide production of high-fructose syrup and crystalline fructose. *Am J Clin Nutr* 1993;58 (Suppl.):733S–736S.
- [27] Michel G, editor. *Biochemical pathways: an atlas of biochemistry and molecular biology*. New York, NY: John Wiley & Sons; 1999. p. 27.
- [28] Marchesini G, Ridolfi V, Nepoti V. Hepatotoxicity of fast food? *Gut* 2008;57:568–570.
- [29] Hofmann SM, Dong HJ, Li Z, Cai W, Altomonte J, Thung SN, et al. Improved insulin sensitivity is associated with restricted intake of dietary glycoxidation products in the db/db mouse. *Diabetes* 2002;51:2082–2089.
- [30] Vartanian LR, Schwartz MB, Brownell KD. Effects of soft drink consumption on nutrition and health: a systematic review and meta-analysis. *Am J Public Health* 2007;97:667–675.
- [31] Akgun S, Ertel NH. The effect of sucrose, fructose, and high-fructose corn syrup meals on plasma glucose and insulin in non-insulin depend diabetes subjects. *Diabetes Care* 1985;8:279–283.
- [32] Janssens JP, Shapira N, Debeuf P, Michiels L, Putman R, Bruckers L, et al. Effects of soft drink and table beer consumption on insulin response in normal teenagers and carbohydrate drink in youngsters. *Eur J Cancer Prev* 1999;8:289–295.
- [33] Yoshida M, McKeown NM, Rogers G, Meigs JB, Saltzman E, D'Agostino R, et al. Surrogate markers of insulin resistance are associated with consumption of sugar-sweetened drinks and fruit juice in middle and older-aged adults. *J Nutr* 2007;137:2121–2127.
- [34] Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto Jr AM, Kastelein JJ, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008;359:2195–2207.
- [35] Pisani P, Faggiano F, Krogh V, Palli D, Vineis P, Berrino F. Relative validity and reproducibility of a food frequency dietary questionnaire for use in the Italian EPIC centre. *Int J Epidemiol* 1997;26 (Suppl. 1):S152–S160.
- [36] Nasreddine L, Hwalla N, Sibai A, Hamzé M, Parent-Massin D. Food consumption patterns in an adult urban population in Beirut, Lebanon. *Public Health Nutr* 2006;9:194–203.
- [37] Bedard D, Shatenstein B, Nadon S. Underreporting of energy intake from a self-administered food-frequency questionnaire completed by adults in Montreal. *Public Health Nutr* 2004;7:675–681.
- [38] Gnardellis C, Boulou C, Trichopoulou A. Magnitude, determinants and impact of under-reporting of energy intake in a cohort study in Greece. *Public Health Nutr* 1998;1:131–137.