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Association between Serum Sialic Acid Levels and Nonalcoholic Fatty Liver Disease: A Cross-Sectional Study

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Key Words

Sialic acid · Nonalcoholic fatty liver disease · Metabolic syndrome · Insulin resistance · Inflammation

Abstract

Background: To assess the association between serum sialic acid (SA) levels and nonalcoholic fatty liver disease (NAFLD) in a Chinese population. ***Methods:*** A cross-sectional study was performed among 3,898 Chinese who took their annual health examination. Serum SA levels and other clinical and laboratory parameters were measured. ***Results:*** A total of 18.11% fulfilled the diagnostic criteria of NAFLD. NAFLD subjects with/without metabolic syndrome (MS) had significantly higher serum SA levels than those without NAFLD. Serum SA levels were significantly and positively correlated with components of MS (body mass index, systolic blood pressure, diastolic blood pressure, triglyceride and fasting plasma glucose) in the NAFLD group. Stepwise logistic regression analysis showed that SA levels were significantly associated with the risk factor for NAFLD. Serum SA levels were negatively correlated with the FIB-4 score, and lower serum SA levels were independent factors predicting advanced fibrosis in subjects with NAFLD. ***Conclusions:*** Our results showed a significant association between serum SA levels and NAFLD.

Introduction

Nonalcoholic fatty liver disease (NAFLD) refers to a wide clinical and pathological spectrum from simple hepatic steatosis to steatohepatitis, advanced fibrosis and cirrhosis in the absence of significant ethanol consumption [1]. NAFLD is becoming a major health and economic concern paralleling the obesity pandemic in China, affecting 20–30% of the general population [2]. Metabolic syndrome (MS) is a cluster of metabolic disorders including obesity, diabetes mellitus, hyperlipidemia and hypertension [3]. Growing evidences suggest that NAFLD is strongly associated with MS and most patients with NAFLD have at least one of the associated features of MS [4, 5]. In this regard, NAFLD is considered to be the hepatic manifestation of MS.

Sialic acid (SA) is a 9-carbon monosaccharide attached to the terminal position of carbohydrate chains of glycoproteins and glycolipids in cell membrane [6]. A vast body of literature addressed that SA-mediated numerous biological functions including metabolic regulation of glycoproteins and lipids, cellular adhesion and molecular signaling pathway, involving various pathophysiologic activities [7–9]. Over the past few years, clinical data confirmed the association between circulating SA levels and MS [10, 11]. Serum SA levels are often elevated in subjects

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with MS and serum SA is also a potential risk factor for cardiovascular disease [12].

The liver secretes a large number of glycoproteins and further sialylation of lipids and proteins takes place in the liver [13, 14]. Therefore, SA has received a great attention as a marker of liver diseases during the past decades [15, 16]. Arif et al. [17] reported that serum SA level was increased in advancing and terminal stages of liver disease compared to controls, while in a very recent study, Gruszewska et al. [18] showed a decreased level of serum SA in patients with liver cirrhosis. These controversial data may be due to the small sample sizes, differences in the exclusion criteria, and differences in definition of illness course used in different studies. However, precise alterations of serum SA in patients with NAFLD are still vague.

Although simple hepatic steatosis and steatohepatitis are traditionally viewed as 2 subtypes of the spectrum of NAFLD, indeed, a high number of simple steatosis is rather stable without evolving towards steatohepatitis. In general, only one-third of patients with pure fatty liver develop steatohepatitis; nearly 10% patients with steatohepatitis are prone to the risk of fibrosis and cirrhosis [19, 20]. Currently, though liver biopsy is considered to be the gold standard for grading and staging of NAFLD, it is not broadly available and difficult to perform in large epidemiological studies due to its associated complications, raising the need for simple and reliable noninvasive tools in screening NAFLD [21]. It has been well demonstrated that FIB-4 index composed of readily available routine laboratory tests can accurately predict advanced fibrosis and cirrhosis in NAFLD [22, 23].

To verify the relationship between serum SA and NAFLD, we conducted a cross-sectional study in a large cohort of subjects with NAFLD in the Chinese population.

Methods

Subjects

Initially, 4,208 subjects who attended their annual health examination during the year of 2014 were enrolled at the First Affiliated Hospital, College of Medicine, Zhejiang University. Subjects who met the following criteria were excluded: (i) those with alcohol consumption >140 g/week for men and >70 g/week for women (n = 90); (ii) those with a history of viral hepatitis (n = 172), autoimmune hepatitis or other forms of chronic liver disease (n = 48). A total of the remaining 3,898 eligible subjects (1,792 males and 2,106 females, with mean age of 42.3 ± 8.1 years) were used in the current analysis. Verbal informed consent was obtained from all subjects and recorded by the physician who explained the study procedures. The study was approved by the ethics committee of the first affiliated hospital of the medical college at Zhejiang University in China.

Clinical and Anthropometric Parameters

The baseline examinations were conducted in the morning after an overnight fast using standard methods as previously reported [24]. In brief, Weight, height and blood pressure were measured, and body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Waist circumference was determined with the measuring tape positioned midway between the lowest rib and the superior border of the iliac crest as the subjects exhaled normally. FIB-4 index was calculated according to the following equation:

$$\text{Age}\,(\text{years}) \times \text{AST}\,(\text{U/l}) / \text{PLT}\,(10^9/\text{l}) \times \sqrt{\text{ALT}(\text{U/l})}\,.$$

Ultrasonic examination was carried out by an experienced ultrasonographist who was unaware of the patient details, using a Toshiba Nemio 20 sonography machine with a 3.5-MHz probe (Toshiba, Tokyo, Japan).

Biochemical Analyses

Fasting whole blood samples were obtained from an antecubital vein, and blood samples were used for the analysis of the haematological index and biochemical values. All samples were analysed by clinical laboratory medical personnel, who were specialists in their fields. All specimens for serum SA, alanine aminotransferase (ALT), aspertate aminotransferase (AST), glutamyltransferase (GGT), triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), fasting plasma glucose (FPG), uric acid (UA) and high-sensitivity C-reactive protein (hsCRP) were measured using a Hitachi 7600 clinical analyser (Hitachi, Tokyo, Japan), while white blood cell (WBC), hemoglobin (HGB), platelet (PLT) and mean platelet volume (MPV) were determined using the Sysmex XE-2100 automated hematology analyzer (Sysmex Corp., Kobe, Japan).

Diagnostic Criteria for NAFLD and MS

The diagnosis of NAFLD was based on the criteria established by the Fatty Liver Disease Study Group of the Chinese Liver Disease Association [25]. Specifically, hepatic steatosis was diagnosed according to characteristic echo patterns, such as diffuse hyperechogenicity of the liver relative to the kidneys, ultrasound beam attenuation, and poor visualisation of intrahepatic structures. The diagnosis of the MS was based on the criteria proposed by the new international diabetes federation definition. According to IDF guidelines, for a person to be defined as having MS, they must have 3 or more of the following conditions: central obesity (defined as a waist circumference >90 cm for Chinese men and >80 cm for Chinese women); BMI >25; raised circulating TG levels (defined as TGs ≥1.7 mmol/l) or specific treatment for this lipid abnormality; reduced HDL-C levels (defined as HDL-C <1.03 mmol/l in male patients and <1.29 mmol/l in female patients); raised systolic or diastolic blood pressure (defined as SBP ≥130 mm Hg or DBP ≥85 mm Hg) or treatment for previously diagnosed hypertension; and raised FPG (defined as FPG ≥5.6 mmol/l) or previously diagnosed type 2 diabetes.

Table 1. Demographic and biochemical characteristics of the study subjects

Variable	With NAFLD (n = 706)		Without NAFLD (n = 3,192)	p value
	with MS (n = 276)	without MS (n = 430)		
Age, years	49.9±9.4*	48.9±8.7*	40.8±7.5	0.007
Gender, male/female	176/100*	270/160*	1,346/1,846	<0.001
BMI, kg/m^2	26.9±2.1*, #	25.0±2.0*	22.3±2.5	<0.001
SBP, mm Hg	134.2±13.4*	133.1±13.7*	123.1±14.2	<0.001
DBP, mm Hg	84.0±12.2*	82.1±10.3*	75.1±10.4	0.002
WBC, 10^9/l	7.3 (4.2–13.2)*, #	6.6 (4.0–11.4)*	5.4 (4.4–9.1)	<0.001
HGB, g/l	153.9±11.8*	154.2±12.1*	138.0±11.2	0.008
PLT, 10^9/l	244.1±40.2*	242.3±42.4*	208.7±40.7	<0.001
MPV, fl	12.8±0.81*	12.4±0.89*	10.9±0.70	0.006
ALT, U/l	31 (11–217)*, #	26 (9–181)*	17 (4–38)	<0.001
AST, U/l	27 (10–123)*, #	24 (10–114)*	18 (9–42)	<0.001
GGT, U/l	36 (10–317)#, *	29 (9–241)*	18 (10–37)	<0.001
TG, mmol/l	2.15 (0.63–19.25)*, #	1.79 (0.51–13.20)*	1.06 (0.49–1.98)	<0.001
TC, mmol/l	5.48±0.92*, #	5.02±1.01*	4.32±0.47	<0.001
HDL-C, mmol/l	1.09±0.20*, #	1.27±0.22*	1.45±0.31	<0.001
LDL-C, mmol/l	2.97±0.45*	2.89±0.41*	2.51±0.36	<0.001
FPG, mmol/l	5.67 (4.89–16.51)*, #	5.09 (4.14–8.72)*	4.59 (4.01–6.01)	<0.001
UA, μmol/l	394.3±51.1*, #	350.1±41.5*	282.4±53.0	<0.001
hsCRP, mg/l	2.7 (0.8–20.8)*, #	1.8 (0.6–13.1)*	0.7 (0.4–7.9)	<0.001
SA, mg/dl	74.4±6.1*, #	62.4±5.3*	53.7±5.1	<0.001

Data are presented as mean ± SD or median (range).
p value: compared among 3 groups.
* $p < 0.05$, compared with and without NAFLD; # $p < 0.05$, NAFLD with MS compared with NAFLD without MS.

Data and Statistical Analysis

Statistical analyses were performed using SPSS, version 16 (SPSS, Chicago, Ill., USA). The Kolmogorov–Smirnov test was used to assess whether continuous data were normally distributed. Data are presented as the means ± SD when data were found to be normally distributed or as the median and range if the distribution was skewed. Differences between groups were analyzed using the Student's t test or the Mann–Whitney U test, while chi-square test was used for comparisons of categorical variables. Pearson correlation analysis was used to examine the correlation between serum SA levels and laboratory parameters. Stepwise logistic regression analysis was used to evaluate the risk factors for NAFLD. Multivariate logistic regression was used to examine the associations between SA and the advanced fibrosis in NAFLD subjects. All statistical tests were 2-tailed. A $p < 0.05$ was considered significantly different.

Ethics Statement

This study was approved by the Hospital Ethics Committee and was performed in accordance with the Helsinki Declaration.

Results

Characteristics of Study Subjects

Of the 3,898 enrolled subjects, 706 (18.11%) fulfilled the diagnostic criteria for NAFLD. Among them, 276 (39.09%) subjects met the diagnostic criteria for the MS. The general demographic and biochemical characteristics of the subjects are shown in table 1. NAFLD combined with/without MS groups were relatively older, predominantly male and had higher levels of BMI, SBP, DBP, WBC, HGB, PLT, MPV, serum liver enzymes (including ALT, AST and GGT), serum lipids (including TG, TC and LDL-C), FPG, UA and hsCRP but lower level of HDL-C, compared with those without NAFLD (all $p < 0.05$). BMI, WBC, serum liver enzymes (including ALT, AST and GGT), serum lipids (including TC, TG, HDL-C and LDL-C), FPG, UA and hsCRP levels were significantly different between NAFLD subjects with and without MS (all $p < 0.05$). As expected, the serum SA level was 74.4 ± 6.1 mg/dl in NAFLD participants with MS, significantly higher than that measured in NAFLD subjects without MS (62.4 ± 5.3 mg/dl) and subjects without NAFLD (53.7 ± 5.1 mg/dl), both $p < 0.05$.

Association of SA Levels with Components of MS

MS is tightly associated with NAFLD and widely accepted for a key risk factor of NAFLD sharing a common underlying mechanism. We then analyzed the associa-

tions between SA level and components of MS to explore the relationship between SA level and NAFLD. As shown in table 2, serum SA levels showed a positive correlation with BMI ($r = 0.201$, $p < 0.001$), TG ($r = 0.228$, $p < 0.001$), SBP ($r = 0.181$, $p = 0.003$), DBP ($r = 0.169$, $p = 0.021$) and FPG ($r = 0.265$, $p < 0.001$) in the NAFLD group.

Serum SA Levels and Risk Factor of NAFLD

Logistic regression analysis was performed to explore risk factors for NAFLD. Twenty variables consisting of age, gender, BMI, SBP, DBP, WBC, HGB, PLT, MPV, ALT, AST, GGT, TG, TC, HDL-C, LDL-C, FPG, UA, hsCRP and SA were entered into the original equation. The present results indicated that nine variables, namely age, BMI, ALT, GGT, TG, FPG, PLT and SA were positively associated with the risk for NAFLD, while HDL-C was inversely correlated with NAFLD. As shown in table 3, SA was found to be an independent risk factor for NAFLD (OR 1.122, 95% CI 1.053–1.196, $p < 0.001$).

Association of Serum SA Levels with FIB-4 Index

In this study, all subjects with NAFLD were classified into quartiles by their serum SA levels. The FIB-4 index in the subjects with different quartile levels of SA was analyzed. We found that the serum SA levels were negatively correlated with FIB-4 index. In contrast to the increasing serum SA, the FIB-4 value was 1.21 for the subjects with serum SA level in quartile 1, while it decreased to 0.91 for the subjects with serum SA level in quartile 4 (fig. 1).

Low Serum SA Predicted Increase Risk of Advanced Fibrosis in NAFLD Subjects

As shown in table 4, multivariate logistic regression analysis showed that the serum SA levels were negatively correlated with the advanced fibrosis in NAFLD. After age, BMI, ALT, FPG and PLT were adjusted, the low serum SA was a significant independent predictor of advanced fibrosis, the OR was 0.953 ($p = 0.020$).

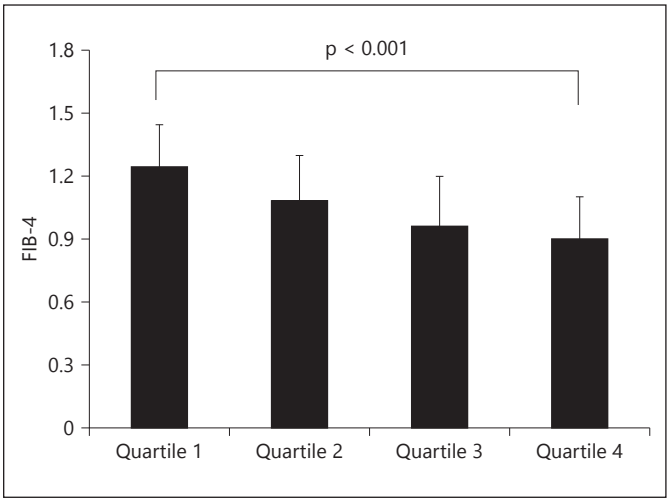

Fig. 1. The value of FIB-4 index according to serum SA quartile in subjects with NAFLD.

Table 2. Correlation analysis between serum SA levels and components of MS

Variables	Correlation coefficient	p value
BMI, kg/m^2	0.201	<0.001
TG, mmol/l	0.228	<0.001
HDL-C, mmol/l	–0.049	0.139
SBP, mm Hg	0.181	0.003
DBP, mm Hg	0.169	0.021
FPG, mmol/l	0.265	<0.001

Table 3. Risk factors associated with the presence of NAFLD

Variables	β	OR	95% CI	p value
Age	0.097	1.089	1.058–1.121	0.005
BMI	0.356	1.494	1.347–1.657	<0.001
ALT	0.047	1.048	1.009–1.089	0.015
GGT	0.019	1.017	1.001–1.034	0.038
TG	0.985	2.677	1.715–4.180	<0.001
FPG	0.150	1.218	1.005–1.438	<0.001
HDL-C	–0.910	0.045	0.020–0.117	<0.001
PLT	0.102	1.007	1.001–1.013	0.016
SA	0.140	1.122	1.053–1.196	<0.001

Discussion

In this study, we confirmed the significant association between serum SA levels and NAFLD from a large-sample-size Chinese population. To our knowledge, this is the first report on the clinical significance of SA in NAFLD. Subjects with NAFLD had higher serum SA levels and SA levels were significantly associated with the risk factor for NAFLD; serum SA levels showed a positive correlation with the majority of components of MS; logistic regression analysis showed that low serum SA level was an independent factor predicting advanced fibrosis after adjustment for confounding risk factors.

One of the possible explanations for the increased SA levels in NAFLD subjects is insulin resistance. Currently, it is well acknowledged that insulin resistance represents

Table 4. Independent predictors of advanced fibrosis in NAFLD subjects

Model	β	SE	Wald	p value	OR (95% CI)
Model 1	–0.028	0.016	3.812	0.041	0.975 (0.963–0.997)
Model 2	–0.035	0.013	6.762	0.009	0.966 (0.940–0.991)
Model 3	–0.029	0.018	3.647	0.049	0.970 (0.945–0.995)
Model 4	–0.041	0.019	4.878	0.027	0.960 (0.925–0.993)
Model 5	–0.048	0.021	5.373	0.020	0.953 (0.915–0.993)

Model 1: unadjusted; Model 2: adjusted for age and BMI; Model 3: adjusted for age, BMI and ALT; Model 4: adjusted for age, BMI, ALT and FPG; Model 5: adjusted for age, BMI, ALT, FPG and PLT.

the underlying mechanism in both NAFLD and MS [26]. The selection of serum SA as a candidate biomarker for NAFLD is supported by the significant link between serum SA and insulin resistance. Flynn et al. reported that insulin resistance increases serum SA levels [27]. Zulet et al. [28] observed that there was a significant positive correlation between serum SA and plasma insulin and lipids profiles in normal individuals. Recently, serum SA levels have been shown to be significantly elevated and positively correlated with indices of insulin resistance in obese subjects by Rajappa et al. [29]. As NAFLD is closely associated with the MS, the relation between SA and MS may indirectly support the link between SA and NAFLD. This result was consistent with the report from Sriharan et al. [30] and Yerlikaya et al. [31], who also observed that serum SA levels was strongly associated with the components of MS from studies of different designs. Notably, our results first demonstrated that serum SA levels were elevated and showed a positive correlation with BMI, SBP, DBP, serum TG and FPG concentrations in NAFLD subjects. In addition to the insulin resistance, emerging evidences have identified that low-grade inflammation is characteristic of the pathological progression in NAFLD [32]. Regarded as a reliable indicator of inflammation, an elevated SA may be due to an increase in serum concentration of sialic-acid-carrying acute-phase proteins secreted by the liver in response to proinflammatory cytokines [33, 34].

In light of the known limitations of liver biopsy, searching for noninvasive diagnostic tools is of paramount importance to evaluating fibrosis of NAFLD. Although slightly less accurate than liver biopsy, recent advances have repeatedly demonstrated that FIB-4 index was suitable for evaluating advanced fibrosis with significantly better area under the receiver operator characteristic curve than other noninvasive diagnostic tools in NAFLD patients [35–37]. Few studies suggested that serum SA levels were significantly lower in patients with compensated cirrhosis than those in the healthy group [15, 16]. On the other hand, it was reported that serum SA concentrations in alcoholics with liver cirrhosis did not differ in comparison to the controls [38]. Till now, little is known on the relationship between serum SA and the fibrosis score of NAFLD subjects. In this present study, we found that serum SA levels were negatively correlated with FIB-4 score and lower serum SA level was the risk factor of advanced fibrosis in subjects with NAFLD. The liver released a large number of glycoproteins and glycolipids into the circulation, most of which are sialylated on the termini of their glycans [39]. The decline in serum SA may be due to the downregulation of sialyltransferase participating in SA synthesis in the liver or the synthesis of proteins decreased in the liver cirrhosis.

Several limitations of this study should be mentioned. First, the nature of cross-sectional observation in this study precludes the identification of a causal association between serum SA and NAFLD. Second, our study enrolled NAFLD subjects who were selected from physical examination, including the possibility of including more mild and moderate NAFLD subjects than severe NAFLD patients. Third, we used the FIB-4 index for evaluating advanced fibrosis of NAFLD. However, it is not sensitive enough to identify subjects with a mild degree of fibrosis.

In conclusion, this cross-section study demonstrated a significant correlation between serum SA levels and NAFLD. Furthermore, the present study suggested that SA represented a novel and powerful biomarker in NAFLD.

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Author Contributions

X.J. designed the experiments. W.M. and J.Z. performed the experiments. J.H. and W.M. wrote the majority of the manuscript text. W.M. revised the paper. All authors reviewed the manuscript.

Disclosure Statement

The authors declare that there is no conflict of interest.

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