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Original Article

Association of serum omentin and adiponectin levels with the occurrence of liver cirrhosis

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Abstract: Omentin is a visceral fat-derived adipokine associated with insulin sensitivity. Insulin resistance is a major hallmark of liver cirrhosis. This study aimed to assess the association of serum omentin and adiponectin levels with the occurrence of liver cirrhosis. Seventy-nine patients with liver cirrhosis and 27 healthy controls were enrolled at Cangzhou Central Hospital between March 2014 and June 2015. ELISA was performed to assess serum omentin and adiponectin levels. Prothrombin time (PT), alanine aminotransferase (ALT), aspartate transaminase (AST), total bilirubin (TBIL), serum albumin (ALB), triglyceride (TG), total cholesterol (TC), high-density lipoprotein (HDL), and fasting plasma glucose (FPG) were assessed using an automatic biochemistry analyzer. Fasting insulin (FIns) was determined by immunoassays. Correlations of omentin and adiponectin levels with the above biochemical indicators were evaluated (Spearman method). Sensitivity and specificity of omentin and adiponectin in predicting the occurrence of liver cirrhosis were determined using ROC curves. Results showed that omentin and adiponectin levels were significantly higher in patients with liver cirrhosis than controls ($P<0.05$). Areas under the ROC curves of omentin and adiponectin were 0.841 and 0.939, respectively, with cutoff values for liver cirrhosis prediction of 901 ng/L and 764 μg/L, respectively. However, omentin and adiponectin levels were not significantly correlated with HOMA-IR and insulin levels. Omentin and adiponectin levels were positively correlated. In conclusion, omentin and adiponectin levels are elevated in patients with liver cirrhosis and could be considered indicators for predicting liver cirrhosis, but they are not associated with insulin resistance in patients with liver cirrhosis.

Keywords: Omentin, adiponectin, liver cirrhosis, insulin resistance

Introduction

Liver cirrhosis is the final stage of most chronic liver diseases [1], and is mainly induced by hepatitis C virus (HCV) and hepatitis B virus (HBV) infection, chronic alcohol abuse, and nonalcoholic steatohepatitis [2]. Liver cirrhosis prevalence in the United States is approximately 0.27% (i.e. 633,323 adults) as reported in 2015 [3]. With fast economic growth, the etiological factors of liver cirrhosis in China have significantly changed over the recent decades, with steatohepatitis-related liver cirrhosis increasing in frequency [4, 5]. Enhanced insulin resistance is often found in patients with chronic liver disease [6]; indeed, almost all liver cirrhosis patients show hyperinsulinemia and glucose intolerance [7].

Adipokines are major players in glucose and lipid metabolism and are closely related to the occurrence and development of liver cirrhosis, and their anti-fibrotic properties are well known [8, 9]. In addition to their involvement in glucose and lipid metabolisms to maintain the body's metabolic balance, adipokines also enhance insulin sensitivity and have anti-inflammation and anti-atherosclerosis properties [10]. Adiponectin (APN) is an adipokine specifically synthesized and secreted by mature adipocytes in white adipose tissues [11, 12]. Multiple studies have assessed the association between APN and cirrhosis, but yielded inconsistent conclusions [13, 14]. Omentin, a relatively new adipokine expressed by the omental adipose tissues in humans, may regulate insulin action [15]. Omentin tends to increase insulin sensitivity and is negatively correlated with the homeostatic model assessment of insulin resistance (HOMA-IR) and fasting insulin (Fins) levels [16], suggesting that it is a beneficial adipokine in terms of glucose metabolism [15].

Omentin is decreased in patients with non-alcoholic fatty liver disease (NAFLD) and has been suggested to be associated with insulin resistance in such individuals. However, others showed that omentin levels are not significantly correlated with HOMA-IR, indicating that its expression mechanism needs further investigation [17]. Previous studies have pointed out that omentin and APN levels are elevated in hepatitis C patients with aggravated fibrosis, but not significantly correlated with HOMA-IR; however, HOMA-IR was shown to be significantly increased in patients with hepatitis C compared with controls [18]. In patients with cirrhosis, hepatic sinusoidal endothelial cell dysfunction is associated with reduced vascular relaxing factors such as nitric oxide (NO), hereby increasing intrahepatic blood-flow resistance and portal hypertension [19]. APN tends to promote endothelial NO synthase (eNOS) generation: it alleviates the inhibitory effect of endothelial cells' modified low-density lipoproteins on eNOS, leading to increased eNOS levels [20]. Meanwhile, omentin is closely correlated to eNOS. Current studies have revealed that both APN and omentin are adipokines that tend to increase insulin sensitivity; they correlate with each other and are negatively correlated to HOMA-IR [21]. Interestingly, omentin levels are significantly associated with insulin levels, with omentin prone to improve insulin sensitivity by increasing APN levels [22]. Though most studies mainly focused on omentin levels in the portal system, where elevated omentin levels were suggested to be due to a close relationship between omentin and APN [23], the relationship between omentin and liver cirrhosis has been rarely assessed.

Based on the above findings regarding omentin and APN, this study aimed to assess the association of serum omentin and APN levels with the occurrence of liver cirrhosis, as well as the relationship between the levels of these adipokines and insulin resistance in patients with liver cirrhosis.

Materials and methods

Patients

A total of 79 patients diagnosed with liver cirrhosis and hospitalized at the Cangzhou Central Hospital of Hebei Province between March 2014 and June 2015 were enrolled. Inclusion criteria were: typical manifestations of liver cirrhosis on CT and symptoms of portal hypertension such as ascites, varicosis, and hypersplenism. Patients were excluded if they had (1) renal impairment, (2) cardiopulmonary dysfunction, or (3) metabolic diseases. Twenty-seven healthy participants were selected as controls, excluding individuals with diabetes, kidney disease, heart disease, obesity, tumors, severe infection, or any other diseases affecting hormone metabolism. Patients' heights and body weights were measured by professionals. This study was approved by the ethics committee of Cangzhou Central Hospital of Hebei Province. Written informed consent was provided by the patients.

Measurement of serum indicators

Participants were fasted overnight (>8 h), and venous blood samples were drawn early in the morning. An automatic biochemical analyzer was used to determine prothrombin time (PT), alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin (TBIL), serum albumin (ALB), triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and fasting plasma glucose (FPG) levels. Meanwhile, 6 ml of venous blood from each individual were centrifuged and the supernatant (serum) was collected and cryopreserved at -70°C for omentin and APN levels assessment by enzyme-linked immunosorbent assay (ELISA). Serum FIns levels were determined by electrochemiluminescence immunoassay (ECLIA) (Roche Diagnostics, Basel, Switzerland). Meanwhile, body mass index (BMI) = body weight/height^2 was calculated. Insulin resistance was assessed using HOMA-IR = FBG × FIns/22.5.

Statistical analyses

Continuous variables were presented as mean ± standard deviation (SD). Continuous variables were submitted to a normality test, and normally distributed data were analyzed using the Student's *t*-test. Categorical data were presented as frequencies and analyzed using the Fisher's exact test. Prediction of liver cirrhosis with serum APN and omentin levels was performed using receiver operating characteristics (ROC) analyses. Correlations of omentin and APN with each other and with ALT, AST, TBIL, ALB, TG, TC, HDL-C, PT, FPG, and FIns were

Table 1. Clinical parameters in the cirrhosis and control groups (mean ± SD)

Parameter	Cirrhosis (n=79)	Control (n=27)	*P*
Gender (M/F)	45/34	15/12	0.899
Age (year)	53.17±9.69	51.81±9.06	0.523
BMI (kg/m^2)	23.75±2.94	24.06±2.91	0.642
ALT (U/L)	46.81±52.31	17.91±10.98	0.005
AST (U/L)	59.94±52.87	17.31±4.78	<0.001
TBIL (μmol/L)	43.02±63.57	9.36±5.23	0.007
ALB (g/L)	32. 37±5.52	42.00±3.68	<0.001
TG (mmol/L)	0.73±0.35	1.61±0.64	<0.001
TC (mmol/L)	3.49±1.15	4.71±0.95	<0.001
HDL-C (mmol/L)	0.79±0.35	0.91±0.19	0.094
PT (s)	15.24±3.79	10.88±0.57	<0.001
HBsAg-positive (n)	79		
Child Pugh Class A/B/C	27/28/24		
Fins (pmol/L)	59.97±16.002	34.11±6.94	<0.001
FBG (mmol/L)	5.17±0.51	5.07±0.35	0.349
HOMA-IR	13.79±4.00	7.64±1.38	<0.001

BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate transaminase; TBIL, total bilirubin; ALB, serum albumin; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; WBC, white blood cell; HGB, hemoglobin; PLT, platelet; PT, prothrombin time; FIns, fasting insulin; FPG, fasting plasma glucose; HOMA-IR, insulin resistance index.

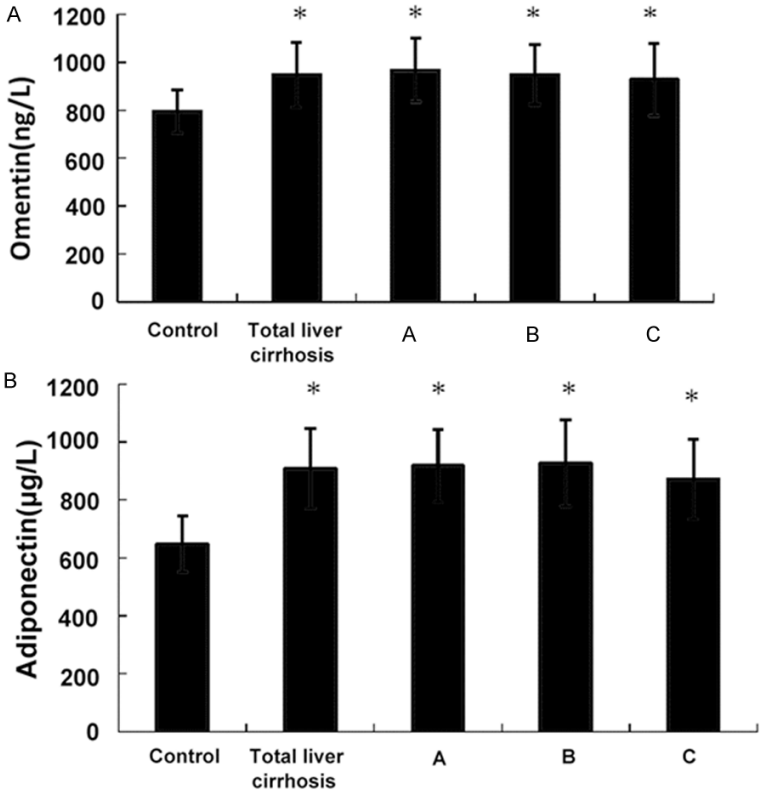

Figure 1. A. Omentin levels in patients with liver cirrhosis and healthy controls. B. Adiponectin levels in patients with liver cirrhosis and healthy controls. Data are presented as mean ± standard deviation. *P<0.05 vs. controls. A-C are Child-Pugh grades of liver function.

assessed by Spearman correlation analysis. Statistical analysis was performed using SPSS 13.0 (SPSS, Chicago, IL, USA). Two-sided *P*-values <0.05 were considered statistically significant.

Results

Baseline characteristics of the subjects

A total of 79 patients with liver cirrhosis were assessed, including 45 men and 34 women; they were 53.2±9.7 years old. The Child-Pugh classification revealed 27, 28, and 24 cases with Grades A, B, and C, respectively. The healthy control group consisted of 27 participants, including 15 men and 12 women; they were 51.8±9.1 years old. APN, omentin, ALT, AST, TBIL, PT, FINs, and HOMA-IR were markedly higher in the liver cirrhosis group compared with controls (all P<0.05). ALB, TG, and TC levels were significantly lower in patients with liver cirrhosis compared with controls (all P<0.05). Meanwhile, male-to-female ratio, age, BMI, and FBG values were similar between the two groups (all P>0.05) (**Table 1**).

Serum APN and omentin levels

In the liver cirrhosis group, the omentin levels in patients with Child Pugh Class A, B, and C were 968.3±131.7, 949.2±124.7, and 927.9± 151.9 ng/L, respectively, and were significantly elevated compared with controls (P< 0.05). However, the differences among the three cirrhosis subgroups were not statistically significant (all P>0.05) (**Figure 1A**).

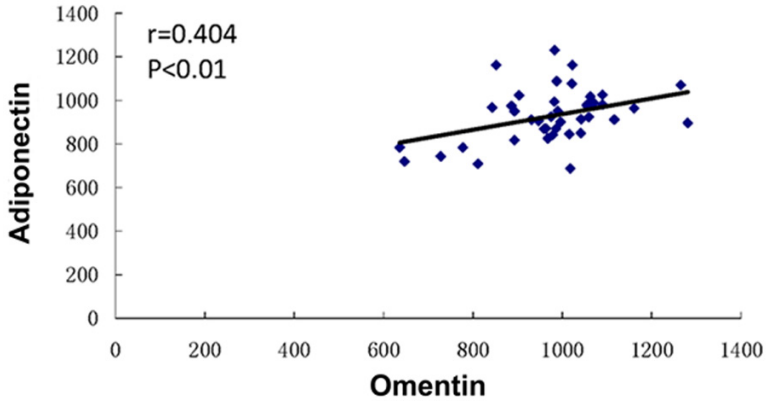

Figure 2. Correlation between serum adiponectin levels and omentin levels in patients with liver cirrhosis.

Table 2. Correlation of omentin and APN with cirrhosis indicators

	Omentin		APN	
	r	*P*	*r*	*P*
Age (year)	0.307	0.006	0.207	0.068
BMI (kg/m^2)	-0.49	0.680	-0.098	0.411
ALT (U/L)	0.009	0.936	-0.072	0.530
AST (U/L)	-0.063	0.581	0.011	0.923
TBIL (μmol/L)	-0.023	0.843	-0.023	0.841
ALB (g/L)	0.227	0.045	0.097	0.393
TG (mmol/L)	0.129	0.261	0.047	0.683
TC (mmol/L)	0.179	0.114	0.124	0.275
HDL (mmol/L)	0.256	0.024	0.234	0.040
PT (s)	-0.095	0.407	-0.201	0.078
FINs (pmol/L)	-0.205	0.070	0.008	0.943
FBG (mmol/L)	0.168	0.139	-0.175	0.123
HOMA-IR	-0.118	0.300	-0.051	0.654

BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate transaminase; TBIL, total bilirubin; ALB, serum albumin; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; WBC, white blood cell; HGB, hemoglobin; PLT, platelet; PT, prothrombin time; FIns, fasting insulin; FPG, fasting plasma glucose; HOMA-IR, insulin resistance index.

Similar findings were obtained for APN. In the liver cirrhosis group, patients with Child Pugh Class A, B, and C had APN levels of 918.5±124.3, 927.5±148.9, and 872.5±138.4 μg/L, respectively, which were higher than in controls (P<0.05). The differences among the three cirrhosis subgroups were not statistically significant (all P>0.05) (**Figure 1B**).

Correlation analyses indicated that serum APN levels were positively associated with omentin levels in patients with liver cirrhosis (r=0.404; P<0.01) (**Figure 2**).

Associations of omentin and APN with indicators of liver cirrhosis

To identify the factors affecting serum omentin and APN levels in patients with liver cirrhosis, we performed correlation analyses of omentin and APN with other indicators including age, BMI, ALT, AST, TBIL, ALB, TG, TC, HDL-C, PT, FIns, FBG, and HOMR-IR. As shown in **Table 2**, serum omentin levels were not significantly correlated to HOMA-IR and insulin amounts, but were positively associated with age, ALB, and HDL-C (r=0.307, r=0.227, and r=0.256, respectively; all P<0.05). APN was positively correlated to HDL-C only (r=0.234, P<0.05).

Sensitivity and specificity of omentin and APN in predicting the occurrence of liver cirrhosis

In order to further analyze the clinical significance of elevated omentin and APN levels in patients with liver cirrhosis, ROC curves were assessed. Areas under the ROC curves of 0.841 and 0.939 were found for serum omentin and APN levels, respectively. The cutoff value, sensitivity and specificity for liver cirrhosis prediction using serum omentin were 900.9 ng/L, 65.8% and 96.3%, respectively; 763.9 μg/L, 86.1% and 96.3% were obtained for APN, respectively (**Figure 3**).

Comparison of patients with cirrhosis according to insulin resistance

Table 3 shows the clinical parameters of patients with cirrhosis according to insulin resistance. Results show that BMI (P=0.02), ALT (P=0.03), TBIL (P=0.03), PT (P=0.002), Fins (P<0.001), and FBG (P=0.02) were higher in patients with insulin resistance, while ALB levels were lower (P<0.001). There were no differences in omentin and APN levels between the two groups (P=0.85 and P=0.15, respectively).

Discussion

This study revealed that serum omentin and APN levels were significantly elevated in patients with liver cirrhosis and that serum omentin and APN levels were positively correlated. Moreover, serum omentin and APN levels

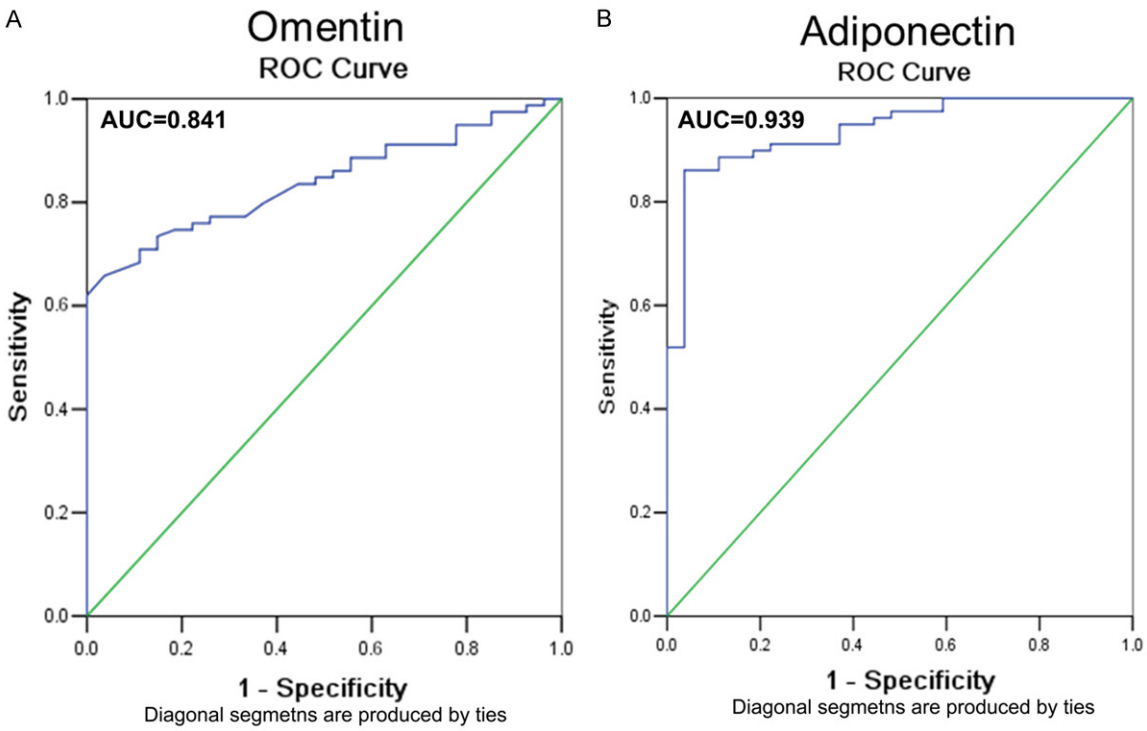

Figure 3. ROC curve analyses of the value of omentin and adiponectin for the prediction of liver cirrhosis.

Table 3. Clinical parameters of patients with cirrhosis according to insulin resistance

Parameter	HOMA-IR <2.33 (n=63)	HOMA-IR >2.33 (n=16)	*P*
Gender (M/F)	39/24	10/6	0.601
Age (year)	54.19±9.42	49.31±10.13	0.074
BMI (kg/m^2)	23.34±2.64	25.22±3.52	0.024
ALT (U/L)	37.71±42.32	82.10±71.37	0.029
AST (U/L)	54.64±52.48	80.84±50.71	0.077
TBIL (μmol/L)	27.78±15.81	103.04±123.15	0.028
ALB (g/L)	33.74±5.53	28.75±3.34	<0.001
TG (mmol/L)	0.75±0.38	0.66±0.19	0.352
TC (mmol/L)	3.46±1.05	3.61±1.53	<0.655
HDL-C (mmol/L)	0.79±0.35	0.91±0.19	0.094
PT (s)	14.18±2.26	19.41±5.47	0.002
Fins (pmol/L)	53.78±10.16	84.39±10.38	<0.001
FBG (mmol/L)	5.10±0.51	5.43±0.50	0.023
HOMA-IR	1.74±0.32	2.91±0.40	<0.001
Omentin (ng/L)	951±124	944±177	0.85
Adiponectin (μg/L)	922±127	853±169	0.15

BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate transaminase; TBIL, total bilirubin; ALB, serum albumin; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; WBC, white blood cell; HGB, hemoglobin; PLT, platelet; PT, prothrombin time; FIns, fasting insulin; FPG, fasting plasma glucose; HOMA-IR, insulin resistance index.

were associated with cirrhosis, but not with insulin resistance in patients with liver cirrhosis.

As shown above, serum omentin levels were elevated in patients with liver cirrhosis, but not with Child-Pugh classification. However, the molecular mechanisms underlying the association between cirrhosis and serum omentin remain unclear. Studies have demonstrated that insulin tends to decrease omentin levels, which might explain the decreased serum omentin levels observed in obese patients. In addition, it was found that omentin levels are higher in women than in men, which might be due to higher amounts of adipose tissues in women [24]. Interestingly, omentin-1 was shown to be downregulated by insulin and glucose, explaining to some extent the reduced omentin-1 levels found in overweight women with polycystic ovary syndrome (PCOS) [25]. A role for omentin has also been demonstrated in gestation and reproduction. Indeed, a strong correlation between antepartum and postpartum

maternal omentin levels combined with lack of association between maternal and newborn omentin amounts indicates that placental or fetal compartments do not contribute significantly to circulating maternal omentin [26]. It was also proposed that omentin might be an indicator of insulin resistance in pregnant women, although more studies are needed to confirm the clinical use of omentin for diagnosing gestational diabetes mellitus [27]. In patients with cirrhosis, aggravated Child-Pugh classification and malnutrition tend to decrease the lipid content, leading to weight loss. Therefore, decreased lipid content could be a major cause of elevated omentin. Whether peritoneum and omentum edemas in cirrhosis patients [28] affect the vessels in the omental adipose tissue matrix, thereby altering omentin expression requires further investigation. Cirrhosis is an inflammatory disease, in which omentin amounts may be altered in response to inflammation [29]. However, further studies are warranted to investigate the mechanisms underlying increased serum omentin levels of patients with liver cirrhosis.

In this study, serum APN levels were significantly higher in patients with liver cirrhosis compared with controls, but there were no differences among different grades of liver cirrhosis. Previous studies have shown that serum APN levels are elevated in patients with cirrhosis [13, 30], which was consistent with the present study. We propose that elevated APN levels in patients with liver cirrhosis could be associated with several factors: (1) reduced APN metabolic clearance by the liver [30]; (2) increased expression in impaired liver cells [31]; (3) although small amounts of APN are found in liver tissues from patients with cirrhosis, intrahepatic APN is not removed by biliary excretion, which results in increased serum APN generated by the adipose tissue [32]; and (4) cholestasis and reduced biliary output in such patients [32]. Chronic liver disease is an inflammatory ailment [33], where APN plays an anti-inflammatory role by preventing tumor necrosis factor (TNF)-α from activating endothelial cells and differentiating monocytes into macrophages, as well as suppressing the activities of nuclear factor-κB (NF-κB) and other pathways [34]. Elevated APN levels in cirrhosis suggest that APN is of auxiliary significance for cirrhosis diagnosis. Some studies reported that omentin might affect insulin sensitivity by impacting APN, and is involved in obesity, type 2 diabetes, inflammatory disorders, and other diseases [22, 35-38]. Although there were cases of hyperinsulinemia and insulin resistance in the cirrhosis group in the present study, serum APN levels were not significantly associated with HOMA-IR. Previous study indicated that total APN levels increase with progression of hepatic fibrosis regardless of insulin resistance [39]. Moreover, circulating APN is increased in liver cirrhosis independently of the etiology of liver disease and insulin sensitivity [13]. These results suggest that serum APN and omentin levels are independent of the regulation of insulin sensitivity, and are specifically correlated to liver fibrosis or cirrhosis, which need further study in the future.

The ROC curve analyses indicated that areas under the ROC curves were 0.768 and 0.908 for serum omentin and APN levels, respectively. The cutoff value, sensitivity and specificity for liver cirrhosis prediction using serum omentin were 900.9 ng/L, 65.8%, and 96.3%, respectively; 763.9 μg/L, 86.1% and 96.3% were obtained for APN, respectively. A previous study indicated that a serum APN level lower that 4.1 μg/mL is predictive of the presence of liver fibrosis in morbidly obese patients [40]. The 4.1 μg/mL is significantly higher than the 763.9 μg/L cutoff observed in present study, which could be due to the morbid obesity inducing higher levels of APN. This is the first report about serum omentin level as indicator of liver cirrhosis, which needs to be confirmed using larger sample size. Taken together, these results suggest that serum omentin and APN levels can be considered alternative indicators for liver cirrhosis. Furthermore, the mechanism of such association requires further in-depth studies.

This study is not without limitations. Though we increased the number of patients to 79 and the number of controls to 27, the sample size was still small, which might result in some bias; therefore further studies with larger sample sizes are required to confirm our findings. The differences in omentin and APN levels were not assessed in cirrhosis patients with various Child-Pugh scores, due to the limited sample size of the subgroups. Because of the small sample size, there was no multivariate analysis

in the present study. It is necessary to carry out a logistical multivariate analysis based on larger sample sizes to confirm the role of omentin and APN in liver cirrhosis. Despite these limitations, the changes of serum omentin and APN levels could be potential auxiliary indicators of liver cirrhosis, which have clinical significance.

In conclusion, omentin and APN levels were elevated in patients with liver cirrhosis, and positively correlated with occurrence of liver cirrhosis. The sensitivity and specificity of liver cirrhosis prediction were 65.8% and 96.3% for omentin, and 86.1% and 96.3% for APN, respectively. However, they were not associated with insulin resistance in patients with liver cirrhosis. Therefore, omentin and APN could be considered alternative indicators for liver cirrhosis.

Disclosure of conflict of interest

None.

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