

Brief communication (Original)

Adipokines, insulin resistance, hepatic steatosis, and necroinflammation in patients with chronic viral hepatitis

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Background: Hypoadiponectinemia and hyperleptinemia, and reductions in the ratio of adiponectin to leptin (A/L ratio) are associated with the development of hepatic necroinflammation in nonalcoholic fatty liver, but the association of the adipokines with hepatic steatosis in chronic viral hepatitis is unclear.

Objective: To investigate the relationship between serum A/L ratio, insulin resistance, degree of hepatic steatosis, and necroinflammation in patients with chronic viral hepatitis.

Methods: We measured serum adiponectin, leptin, and resistin levels, insulin resistance, and analyzed the association between liver histopathology and the level of the adipokines in 44 patients with chronic viral hepatitis before they started treatment.

Results: We found that insulin resistance, leptin, and resistin levels tended to increase in the group with a greater degree of hepatic steatosis and necroinflammation, but that the increase was not significant. The adiponectin/leptin ratio (A/L ratio) in a group with a low degree of hepatic steatosis was significantly higher than it was in the group with a high degree of hepatic steatosis (3.1 ± 3.1 vs 1.2 ± 0.8 ; $P = 0.008$). The A/L ratio in a group with low histological activity index (HAI) scores was significantly higher than in the group with high HAI scores (3.7 ± 3.4 vs 1.1 ± 1.1 ; $P = 0.006$). Abdominal obesity was the only variable that showed a significant association with the HAI score ($P = 0.03$).

Conclusion: The serum A/L ratio in patients with chronic viral hepatitis showed a significant inverse association with their degree of hepatic steatosis and necroinflammation.

Keywords: Adiponectin/leptin ratio, chronic viral hepatitis, insulin resistance

Adipokines, such as adiponectin, leptin, and resistin, are released abundantly by adipocytes and stimulate the release of cytokines, such as tumor necrosis factor- α , interleukin -6, and interleukin-1 from inflammatory cells infiltrating fat. The consequences of these processes are local and generalized inflammation, mediated as a cause of obesity-related vascular disorders that are found in MetS including hypertension, diabetes, atherosclerosis, and insulin resistance. There are many reports related to adipokine hormones, which play an important role in insulin resistance, and are a major cause of pathophysiology in patients with nonalcoholic fatty liver disease (NAFLD). Low adiponectin

concentration is independently associated with the probability of hepatic steatosis in patients with MetS [1-5]. The link between low adiponectin concentration and hepatic steatosis, degree of hepatic necroinflammation and fibrosis, was studied and confirmed in patients with NAFLD. Hypoadiponectinemia and hyperleptinemia or the reduction of adiponectin/leptin ratio (A/L ratio) are associated with alanine aminotransferase elevation and the development of hepatic necroinflammation [6]. In chronic viral hepatitis, which also includes some degree of hepatic steatosis, adipokines may contribute to the mechanisms of progression in necroinflammatory and fibrosis such as found in chronic viral hepatitis C (CHC). Hepatic steatosis has been described in 31%–72% of CHC liver biopsies. Hepatic steatosis has been shown to influence disease progression and is known as an independent predictor of a poor treatment response in CHC treatment [4, 7]. A study

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to explore the association between leptin, metabolic factors, and liver histology was conducted in CHC patients, but the results showed that leptin was poorly predictive of severe steatosis [8]. Therefore, the aims of this study were to investigate the relationship between serum A/L ratio, insulin sensitivity, hepatic steatosis, and degree of hepatic necroinflammation in patients with chronic viral hepatitis B (CHB) and CHC.

Patients and methods

Patients

This prospective analytical study was conducted of consecutive patients with CHB or CHC who were naïve to treatment and underwent liver biopsy at King Chulalongkorn Memorial Hospital between January 2006 and January 2007. All participants had hepatitis B virus surface antigen (HBsAg) or antibody against hepatitis C virus (anti-HCV), serum alanine aminotransferase level ≥ 40 U/L, with liver histopathology being compatible with CHB or CHC. Hepatitis B virus DNA (HBV-DNA) being more than 100,000 copies/mL for patients with positive hepatitis B virus e antigen (HBeAg positive) and more than 10,000 copies/mL for those negative for hepatitis B virus e antigen (HBeAg negative) or were positive for hepatitis C virus RNA (HCV-RNA) were included into these study. None of these patients had any previous treatment of CHB or CHC.

medications that are commonly known to induce hepatic steatosis such as corticosteroid, valproic acid, amiodarone, and tamoxifen; human immunodeficiency virus infection, and other chronic liver diseases. The study was approved by the institutional ethics committee of Chulalongkorn University and each patient gave written informed consent to participate.

Clinical and laboratory assessment

The following data were collected at the time of liver biopsy: age, sex, body weight, height, waist circumference, hip circumference (waist circumference was measured at a level midway between the lower rib margin and the iliac crest, while hip circumference was measured at the widest level over the greater trochanters), and blood pressure. After an overnight fast of 12 hours, a blood sample was taken to assay the level of adipokines, including adiponectin, leptin, and resistin. The adipokine concentrations were determined on serum, using a specific commercial kit (Human Adiponectin ELISA/Leptin RIA Kit; Linco Research, St. Charles, MO, USA). Intra- and interassay coefficients of variation for adiponectin were 5.2% and 9.8%, respectively. Insulin resistance was determined using the homeostasis model assessment (HOMA) method with the following equation:

$$\text{Insulin resistance (HOMA-IR)} = \frac{\text{Fasting insulin (mIU/mL)} \times \text{Fasting glucose (mmol/L)}}{22.5}$$

According to the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) criteria for Asians, the definition of metabolic syndrome (MetS) recommended by the Asia Pacific Working Party on NAFLD in 2006, includes any 3 or more of the following 5 criteria: central obesity, waist circumference >90 cm (men), >80 cm (women) and/or body mass index (BMI) >25 kg/m² in either sex; fasting blood triglycerides ≥ 150 mg/dL; low high-density lipoprotein cholesterol (men <40 mg/dL (1.04 mmol/L), women <50 mg/dL (1.30 mmol/L)); elevated blood pressure $\geq 130/85$ mmHg; and elevated fasting glucose ≥ 100 mg/dL (5.6 mmol/L) or previously diagnosed type 2 diabetes. The following conditions were excluded: diabetes mellitus, body mass index (BMI) ≥ 30 kg/m²; active alcohol drinking (≥ 20 g or 2 units/day of alcohol in past 6 months); the use of

Liver histopathology

All of the enrolled patients were admitted for liver biopsy and blood tests. Standard liver biopsy was performed under ultrasound guidance. Liver tissue was evaluated by an experienced gastrointestinal pathologist who was blinded to the adipokine data. The degree of necroinflammatory activity and fibrosis were scored using the histological activity index (HAI), also known as the Knodell score. A low level of necroinflammation was defined by an HAI score <8 . The degree of steatosis was assessed as the percentage of hepatocytes containing macrovesicular fat droplets according to Brunt's classification [9] and was graded as 0 (no steatosis), 1 ($<33\%$ of hepatocytes affected), 2 (33% – 66% of hepatocytes affected), or 3 ($>66\%$ of hepatocytes affected). Significant hepatic steatosis was defined as grade 2 and 3. Then we

categorized the patients into 2 groups: “low degree of steatosis group” for grade 0–1 steatosis and “high degree of steatosis group” for grade 2 or 3 steatosis.

Data analysis

Baseline descriptive data are expressed as means and standard deviations for continuous variables, and as percentages and frequencies for categorical variables. Differences between groups were assessed using a Student *t* test for parametric data, and a Mann–Whitney *U* test for nonparametric data. Proportional data were assessed using a chi-square test.

Results

Forty-four patients with chronic viral hepatitis were enrolled in this study between January 2006 and January 2007. There were 19 patients who had CHB and 25 patients who had CHC. Among the 19 patients with CHB, there were 9 in the in HBeAg-positive group, 9 in the HBeAg-negative group, and 1 patient with unknown HBeAg status. HBV-DNA was reported to be over 20 million copies/mL in 8 of the 19 patients (42%). Among the 25 patients with CHC, there were 6 patients with genotype 1, 12 patients with genotype 3, and the genotypes of the remaining 7 patients were unknown.

The degree of hepatic steatosis was classified into 2 groups being a low and a high degree of steatosis. The proportion of patients with a high degree of hepatic steatosis (grade 2 or 3) with CHB was 16% and 16% for patients with CHC. Their demographic data and biochemical parameters are shown in **Table 1**. There was no significant difference between the groups of patients with low and high degree of hepatic steatosis.

There was no patient in this study who met the 3 criteria for a diagnosis of MetS. As shown in **Table 2** about 84% patients had ≤ 1 criterion of MetS and only 7 patients had 2 of the 3 criteria required for a diagnosis of MetS. Most frequent criteria for MetS found were high blood pressure and abdominal obesity using waist circumference. There was no association between abdominal obesity and the type of chronic viral hepatitis ($P = 0.21$). Moreover, there was no difference in the proportion of criteria for MetS between the groups of patients with high or low degrees of hepatic steatosis ($P = 0.98$).

The degree of liver necroinflammation, which was represented by HAI score, showed no association with the causes of chronic hepatitis ($P = 0.15$). However, there was a significant association between HAI score and abdominal obesity ($P = 0.03$), as shown in **Table 3**.

Table 1. Patient demographic data, biochemical, and metabolic features of 44 CHB and CHC patients

Variables	Overall (n = 44)	Low degree of hepatic steatosis grade 0–1 (n = 37)	High degree of hepatic steatosis grade 2 or 3 (n = 7)	<i>P</i>
Number of female/total (%)	7/44 (16 %)	6/37 (16 %)	1/7 (14 %)	
Age (years old)	40.9 ± 10.0	41.6 ± 10.2	37.7 ± 9.0	0.35
Body mass index (kg/m ²)	22.8 ± 2.9	22.8 ± 2.8	22.8 ± 3.8	0.98
Waist circumference (cm)	83.4 ± 7.6	83.3 ± 7.3	84.1 ± 9.6	0.78
Hip circumference (cm)	94.5 ± 5.9	94.1 ± 5.9	96.4 ± 6.3	0.36
Waist/hip ratio	0.88 ± 0.05	0.88 ± 0.04	0.87 ± 0.08	0.73
Glucose (mg/dL)	87.6 ± 11.4	87.7 ± 12.1	86.8 ± 7.2	0.85
Alanine aminotransferase (U/L)	112.3 ± 82.0	116.5 ± 87.6	90.5 ± 38.2	0.45
Total cholesterol (mg/dL)	181.7 ± 41.3	180.5 ± 37.6	188.6 ± 60.3	0.64
Triglycerides (mg/dL)	88.4 ± 38.4	93.2 ± 39.3	63.4 ± 21.2	0.06
High-density lipoprotein cholesterol (mg/dL)	54.5 ± 13.4	54.3 ± 13.0	56.0 ± 16.5	0.76
Insulin level (mIU/mL)	6.0 ± 5.9	6.4 ± 6.4	3.9 ± 1.9	0.32
Mean HAI score (range)	5.9 (1–10)	6.0 ± 2.4	5.4 ± 1.3	0.59

Table 2. Number of chronic viral hepatitis patients who met metabolic syndrome (MetS) criteria

Criteria of MetS (NCEP-ATP III)		Frequency	Percent (%)
Number of criteria	0	13	30
	1	24	54
	2	7	16

Table 3. Association between histological activity index (HAI) score and abdominal obesity

	Abdominal obesity		Total (%)
	Obese	Non obese	
HAI score			
<8	4	22	26 (59%)
≥8	8	10	18 (41%)
Total	12	32	44

The HOMA-IR, leptin, and resistin level tended to be increased in the group of patients with a high degree of hepatic steatosis and necroinflammation, but this tendency was not significant. The A/L ratio in patients from the group with a low degree of steatosis was significantly higher than in patients from the group

with a high degree of hepatic steatosis (3.1 ± 3.1 vs 1.2 ± 0.8 ; $P = 0.008$) as shown in **Table 4**. Moreover, the A/L ratio in patients from the group with low HAI scores was significantly higher than in the group with high HAI scores (3.7 ± 3.4 vs 1.1 ± 1.1 ; $P = 0.006$) as shown in **Table 5**.

Table 4. Baseline homeostasis model assessment insulin resistance and adipokine levels in 44 patients with chronic viral hepatitis divided according to their degree of hepatic steatosis

Variables	Low degree of hepatic steatosis grade 0–1 (n = 37)	High degree of hepatic steatosis grade 2 or 3 (n = 7)	P
Homeostasis model assessment insulin resistance	1.5 ± 1.6	7.5 ± 2.2	0.73
Leptin (ng/mL)	6.5 ± 6.4	37.7 ± 9.0	0.35
Adiponectin (μg/mL)	8.9 ± 4.1	9.3 ± 7.0	0.83
Resistin (ng/mL)	26.7 ± 16.3	32.3 ± 9.9	0.46
A/L ratio*	3.1 ± 3.1	1.2 ± 0.8	0.008*

* $P < 0.05$

Table 5. Baseline homeostasis model assessment insulin resistance and adipokine level of 44 patients with chronic viral hepatitis divided according to their histological activity index (HAI) score

Variables	HAI <8 (n = 26)	HAI ≥8 (n = 18)	P
Homeostasis model assessment insulin resistance	1.1 ± 1.5	2.1 ± 1.3	0.11
Leptin (ng/mL)	5.5 ± 4.8	10.6 ± 9.7	0.07
Adiponectin (μg/mL)	9.5 ± 4.4	6.9 ± 3.5	0.17
Resistin (ng/mL)	29.1 ± 15.8	27.8 ± 14.6	0.85
A/L ratio*	3.7 ± 3.4	1.1 ± 1.1	0.006*

* $P < 0.05$

Discussion

We measured the serum levels of adipokine hormones in a consecutive cohort of 44 patients with CHB and CHC, none of whom met the criteria for a diagnosis of MetS. Patients with diabetes mellitus, a BMI ≥ 30 kg/m², and active alcohol drinking were excluded to eliminate confounding factors in the evaluation of serum adipokine levels. The degree of hepatic steatosis and necroinflammation was reviewed intensively by liver pathologists. The present study demonstrates that the severity of hepatic steatosis and necroinflammation is not associated with insulin resistance or the level of any single adipokine. However, the A/L ratio appears a strong indicator with which to assess the severity of hepatic steatosis and level of necroinflammation. The A/L ratio had a negative association with the degree of both steatosis and necroinflammation. These findings were independent of age, sex, viral type, BMI, and adipokine level. Thus, the A/L ratio may be used as a sensitive test to detect a higher severity of liver necroinflammation in nonobese patients with CHB or CHC. We also showed that abdominal obesity using waist circumference is a good clinical criterion for assessing the association between HAI score and abdominal obesity, and waist circumference showed a significant positive association with HAI score.

In addition, we confirmed the presence of significant hepatic steatosis in both CHB and CHC, which was found in only about 16%, being quite low compared with that reported in other studies, which ranged between 31% and 72% [10-12]. Most of those studies showed a high frequency of hepatic steatosis was found predominantly in CHC patients with genotype non-3. Those CHC patients frequently had a MetS, such as high BMI. Therefore, the population selection in previous studies is quite different from that in the present study in which none of the patients met the required criteria for a diagnosis of MetS (nonobese patients). However, a limitation of our study was the low number of patients, especially in the group with a higher degree of hepatic steatosis and necroinflammation.

The association of inflammatory process in liver histopathology with steatosis and adipokines was clearly suggested in patients with nonalcoholic fatty liver disease (NAFLD), but it was inconclusive in chronic viral hepatitis [13-17]. Obesity itself may contribute to disease progression in CHC through inflammation and steatosis, and affect the response

to treatment. Sanyal et al. showed the importance of the presence of fatty liver and disease progression in patients with HCV. They showed that fatty liver was strongly associated with features of MetS and may be a risk factor for advanced fibrosis. However, the BMI of their patients was >30 kg/m², so obesity may be involved in their disease progression [18-20]. The degree of advanced liver fibrosis in such patients is related to body weight, the presence of diabetes, and the presence and degree of cytological ballooning. The endocrine function of adipose tissue, which produces adipokines, could partially explain these complex associations. The source of adipokines from the obese patients (high BMI) and from visceral fat are being studied to determine their relationship with the severity of liver fibrosis [21-26].

The present study, which consisted mainly of nonobese patients (BMI <25 kg/m²) also confirms that there was no patient showing a high grade of severe liver necroinflammation and fibrosis. However, other mechanisms and associated factors may affect the severity of liver disease including the quantitative viral infection load, viral hepatitis C genotype, and host-mediated insulin resistance [27, 28]. All of these factors may enhance the process of fibrosis, alter immune responses, and decrease the response rate to interferon-based therapy. A larger number of chronic viral hepatitis patients is needed to further elucidate these associations [29-33].

In conclusion, the serum A/L ratio showed a significant negative association with the degree of hepatic steatosis and degree of hepatic necroinflammation (HAI score) in patients with chronic viral hepatitis. Abdominal obesity was the only single clinical criterion that showed a significant association with the HAI score, and may be used in clinical practice to screen for a high risk of liver disease progression.

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