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HEPATOLOGY

# Elevated plasma resistin concentrations in patients with liver cirrhosis

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**Key words**
adipocytokine, adiponectin, homeostatic model assessment insulin resistance (HOMA-IR), liver cirrhosis, quantitative insulin sensitivity check index (QUICKI), resistin.

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## Abstract

**Background:** Resistin, an adipose-derived polypeptide hormone, has been proposed to be a candidate in insulin resistance, although its role in humans remains controversial. Liver cirrhosis (LC) is characterized by an elevated number of circulating proinflammatory cytokines, hyperinsulinemia and insulin resistance. The aim of this study was to determine the plasma resistin levels in patients with LC.

**Methods:** Resistin levels were determined in 79 patients with LC and in 31 healthy controls. Patients included 34 with Child–Pugh grade A, 30 with Child's B and 15 with Child's C LC. Fasting plasma glucose, fasting plasma insulin, adiponectin, the homeostatic model assessment insulin resistance (HOMA-IR) index, quantitative insulin sensitivity check index (QUICKI) and biochemical parameters were also determined.

**Results:** Plasma resistin levels were $7.61 \pm 6.70$ ng/mL in the LC patients and $3.38 \pm 1.68$ ng/mL in the controls, respectively. The plasma resistin levels were significantly elevated in patients with LC in comparison to the controls ($P < 0.01$). The plasma resistin levels increased in a stepwise fashion in line with a higher grade according to Child–Pugh classification. Fasting plasma insulin, adiponectin and HOMA-IR index were also significantly elevated in patients with LC in comparison to controls. Inversely, QUICKI significantly decreased in patients with LC. According to Spearman's rank correlation, log resistin showed significantly positive correlation with fasting plasma insulin, log adiponectin, HOMA-IR index, and a negative correlation with QUICKI ($P < 0.01$). The plasma resistin levels did not correlate with sex, body mass index and fasting plasma glucose levels.

**Conclusion:** The plasma resistin levels increased in patients with LC, thus showing a positive correlation with fasting plasma insulin, adiponectin, HOMA-IR index, and a negative correlation with QUICKI. Although a decreased extraction of resistin due to reduced liver function cannot be ruled out, resistin may contribute to insulin resistance in patients with LC. The pathophysiological roles of resistin in LC still require further investigation.

## Introduction

Resistin is a novel adipocyte-secreted hormone which belongs to the family of cystein-rich resistin-like molecules.[1] As resistin serum levels have been found to be elevated in mouse models of obesity where they could antagonize insulin action, resistin was first described as a potential link between obesity and insulin resistance.[2] Furthermore, thiozolidinediones, a group of pharmaceuticals that improve insulin sensitivity, have been reported to downregulate resistin expression in rodents.[2–4] Resistin is thus suggested to play a potential role in the pathomechanism of insulin resistance. However, some studies investigating resistin mRNA and protein levels in different rodent models of obesity and diabetes could not clearly confirm resistin as a mediator of insulin resistance.[5–7] The situation in humans is even more controversial. Resistin serum levels were found to be related to body mass index (BMI) in human subjects,[8,9] while other studies did not reveal any correlation between BMI and resistin levels in blood.[10,11] Due to such conflicting data, the physiological role of resistin is still not well understood in humans.

In chronic liver disease, such as liver cirrhosis (LC), impaired insulin sensitivity and subsequent alterations in glucose metabolism, such as a high prevalence of insulin resistance and glucose intolerance, have been reported.[12,13] Nearly all patients with LC are insulin resistant, 60–80% are glucose intolerant, and about 20% develop clinical manifestations of diabetes mellitus.[12,13] However,

**Table 1** Clinical characteristics of the patients with liver cirrhosis

| Characteristics | Control ($n = 31$) | Liver cirrhosis ($n = 79$) | *P*-value |
|---|---|---|---|
| Sex (male: female) | 20:11 | 47:32 | NS |
| Age (years) | 63.0 ± 14.1 | 66.6 ± 8.9 | NS |
| Bodyweight (kg) | 59.1 ± 12.9 | 55.1 ± 11.0 | NS |
| Body mass index (kg/m$^2$) | 23.0 ± 3.7 | 22.3 ± 2.9 | NS |
| Child's A: Child's B: Child's C | – | 34:30:15 | |
| Total bilirubin (mg/dL) | 0.83 ± 0.24 | 1.64 ± 1.36 | $P < 0.01$ |
| AST (IU/L) | 25.3 ± 6.8 | 58.8 ± 26.2 | $P < 0.01$ |
| ALT (IU/L) | 27.8 ± 9.4 | 45.4 ± 33.0 | $P < 0.05$ |
| Platelets (x10$^4$/μL) | 26.6 ± 5.9 | 9.1 ± 5.0 | $P < 0.01$ |
| Fasting plasma glucose (mg/dL) | 98.0 ± 11.2 | 101.9 ± 23.0 | NS |
| Fasting plasma insulin (μU/mL) | 4.88 ± 2.63 | 16.2 ± 24.8 | $P < 0.05$ |
| HOMA-IR | 1.23 ± 0.70 | 4.44 ± 8.20 | $P < 0.05$ |
| QUICKI | 0.391 ± 0.055 | 0.338 ± 0.047 | $P < 0.01$ |
| Log adiponectin (μg/mL) | 0.36 ± 0.10 | 0.90 ± 0.44 | $P < 0.01$ |
| Resistin (ng/mL) | 3.38 ± 1.68 | 7.61 ± 6.70 | $P < 0.01$ |
| Log resistin (ng/mL) | 0.486 ± 0.189 | 0.776 ± 0.289 | $P < 0.01$ |

AST, aspartate aminotransferase; ALT, alanine aminotransferase; HOMA-IR, homeostatic model assessment insulin resistance; NS, not significant; QUICKI, quantitative insulin sensitivity check index.

the etiological mechanism of impaired insulin-mediated glucose utilization in LC remains unknown.

The plasma or serum concentrations of some adipocytokines such as adiponectin and leptin in chronic liver diseases have been studied and are reported to be elevated in patients with LC.[14–17] However, there is little information regarding resistin regulation in LC. The above background suggests a possible link between insulin resistance, liver function and the circulating resistin levels. The present study was designed to define the relationship between circulating resistin levels and LC.

## Methods

Subjects were LC patients that were followed up at Gunma University and three affiliated hospitals, and age-matched normal volunteers served as controls. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, was approved by the local ethical committee, and informed consent was obtained from each participant. All blood samples were obtained in the morning after an overnight fast. Table 1 summarizes the clinical background of 31 control subjects and 79 LC patients who were enrolled in this study. LC was diagnosed based on clinical features, laboratory tests and computed tomographic findings. Patients with a fasting plasma glucose (FPG) ≥140 mg/dL were excluded from this study. Patients complicated by renal dysfunction, infection, thyroid dysfunction or any other endocrine diseases were also excluded. Patients with LC due to hepatitis C virus (HCV) infection were selected for this study. The plasma resistin concentrations were determined by an enzyme-linked immunosorbent assay (ELISA) (Human resistin ELISA, BioVender Laboratory Medicine, Brno, Czech Republic). The plasma adiponectin concentrations were determined by ELISA (Adiponectin ELISA kit, Otsuka Pharmaceutical, Tokyo, Japan). Total bilirubin (T-Bil), aspartate aminotransferase (AST), alanine aminotransferase (ALT), FPG, fasting blood insulin (FIRI) and platelet counts were measured using standard techniques. BMI was calculated as weight divided by the square of height in meters. The homeostasis model assessment insulin resistance (HOMA-IR) index was calculated by the formula: glucose (mg/dL) × insulin (μU/mL)/405, and was used as an index of insulin resistance. The quantitative insulin sensitivity check index (QUICKI) was calculated based on the FPG and FIRI levels according to the report by Katz *et al.*[18] using the formula QUICKI = 1/(log [FIRI in μU/mL] + log [FPG in mg/dL]), and was used as an index of insulin sensitivity.

### Statistical methods

Data were expressed as mean ± SD. Differences between groups were analyzed by Student's *t*-test, Fischer's exact probability test, and multiple comparisons used the Kruskal–Wallis analysis of variances (ANOVA). Comparisons between the subgroups are illustrated with box-plot graphics, where the dotted line within the box indicates the median value, and the box boundaries represent 50% of the values of non-outliners. The plasma resistin and adiponectin levels were logarithmically transformed to obtain a distribution resembling a normal distribution. The relationships between variables were analyzed by Spearman's rank correlation coefficients and by linear regression analysis with forward selection. The threshold for significance was set at $P < 0.05$.

## Results

### Clinical characteristics and plasma resistin levels in liver cirrhosis patients and controls

This study comprised 110 subjects, including 31 controls (20 males/11 females, mean age 63.0 ± 14.1 years) and 79 patients with LC (47 males/32 females, mean age 66.6 ± 8.9 years). None of the patients received a blood transfusion or were on high-dose steroids at the time of the study. The severity of LC, defined by Child–Pugh classification, in our patients is summarized in


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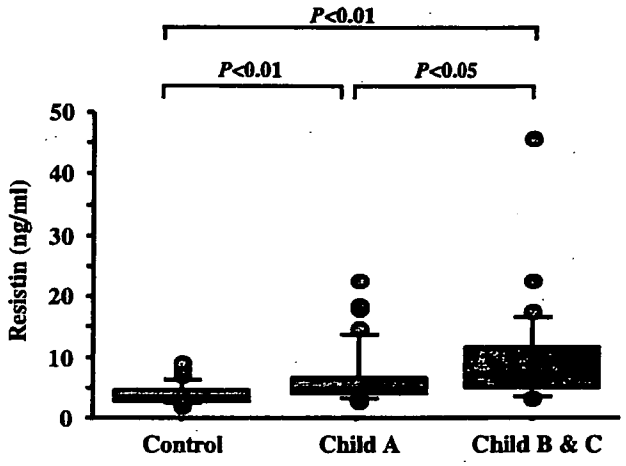


**Figure 1** Plasma resistin levels in liver cirrhosis. Resistin is elevated in Child–Pugh grade A (6.11 ± 4.68 ng/mL, $P < 0.01$) and Child's B and C (9.28 ± 8.16 ng/mL, $P < 0.01$) cirrhosis in comparison to controls (3.38 ± 1.68 ng/mL).

Table 1. The underlying causes of liver disease were all HCV infection. The patients with LC were similar to the controls with regard to sex, age, bodyweight and BMI. Serum T-Bil, AST and ALT were significantly higher in LC patients than in controls (T-Bil, AST, $P < 0.01$; ALT, $P < 0.05$). Platelet counts were significantly lower in LC patients than in controls ($P < 0.01$). Because patients with FPG ≥ 140 mg/dL were excluded from this study, there was no difference in the mean FPG value between LC patients and the controls. Resistin and insulin levels were significantly elevated in patients with LC in comparison to controls ($P < 0.01$). Plasma log adiponectin levels were also significantly elevated in patients with LC in comparison to controls ($P < 0.01$), consist with previous studies.[14,16,17] Furthermore, the plasma log adiponectin levels were significantly elevated in patients with Child's B and C (1.02 ± 0.46 μg/mL, $n = 45$) in comparison to those with Child's A (0.79 ± 0.39 μg/mL, $n = 34$, $P < 0.05$). The plasma log adiponectin levels increased in a stepwise fashion in line with a higher grade according to Child–Pugh classification. HOMA-IR was significantly elevated while QUICKI was significantly decreased in the patients with LC in comparison to the controls ($P < 0.01$).

### Plasma resistin levels and liver damage

The plasma resistin levels were significantly elevated in the patients with Child–Pugh grade A (6.11 ± 4.68 ng/mL, $n = 34$, $P < 0.01$), Child's B (7.27 ± 4.10 ng/mL, $n = 30$, $P < 0.01$) and Child's C (14.09 ± 12.83 ng/mL, $n = 15$, $P < 0.01$) LC in comparison to the controls (3.38 ± 1.68 ng/mL, $n = 31$). Plasma resistin levels were significantly elevated in the patients with Child's B and C (9.28 ± 8.16 ng/mL, $n = 45$, $P < 0.05$) in comparison to those with Child's A (Fig. 1).

### Correlation between resistin and clinical data

In the controls, there were no correlations between the plasma resistin levels and the observed parameters according to

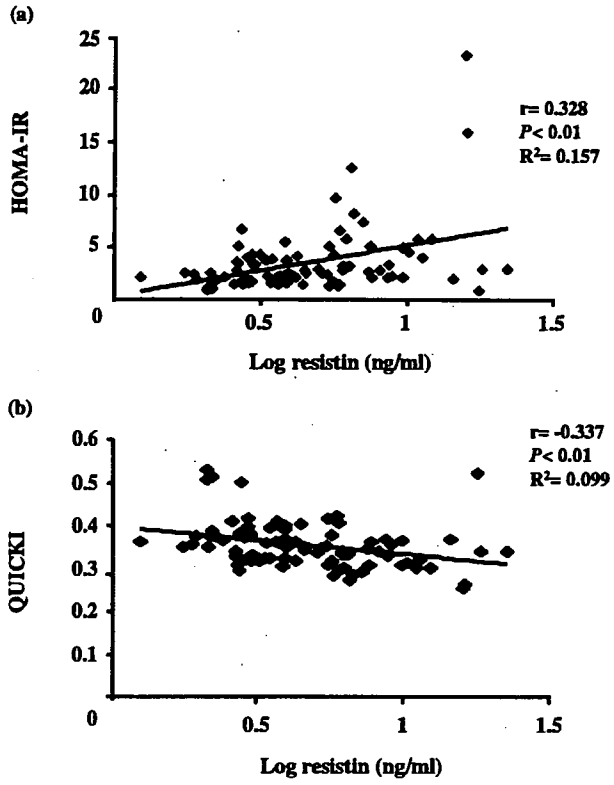


**Figure 2** Correlation between resistin and indices of insulin resistance. (a) Plasma resistin levels correlated positively with homeostatic model assessment insulin resistance (HOMA-IR) ($r = 0.328$, $P < 0.01$). (b) Plasma resistin levels correlated inversely with quantitative insulin sensitivity check index (QUICKI) ($r = -0.337$, $P < 0.01$).

Spearman's rank correlation (Table 2). In the LC group, the log plasma resistin levels were positively correlated with age ($r = 0.300$, $P < 0.05$) and the log plasma adiponectin levels ($r = 0.399$, $P < 0.01$). We did not find any correlation between the log plasma resistin levels and sex, BMI, T-Bil, AST, ALT, platelet, FPG, FIRI, HOMA-IR and QUICKI for both groups. According to Spearman's rank correlation for all subjects, the plasma resistin levels correlated positively with age ($r = 0.320$, $P < 0.01$), AST ($r = 0.309$, $P < 0.01$), FIRI ($r = 0.350$, $P < 0.01$), HOMA-IR ($r = 0.328$, $P < 0.01$), and log adiponectin ($r = 0.418$, $P < 0.01$), but were inversely correlated with QUICKI ($r = -0.337$, $P < 0.01$) and platelet counts ($r = -0.383$, $P < 0.01$). Figure 2 shows the correlation between resistin and indices of insulin resistance.

## Discussion

The major findings of the present study were: (i) the presence of high plasma resistin levels in patients with LC relative to controls; (ii) these levels increased in proportion to the severity of LC; and (iii) the plasma resistin levels significantly correlated with FIRI, adiponectin and HOMA-IR index, while showing a

**Table 2** Correlation with Spearman's rank test between log resistin and other parameters

| Variables | Controls | | Liver cirrhosis | | Total subjects | |
|---|---|---|---|---|---|---|
| | *r*-value | *P*-value | *r*-value | *P*-value | *r*-value | *P*-value |
| Age | 0.303 | NS | 0.3 | $P<0.05$ | 0.320 | $P<0.01$ |
| Sex | –0.071 | NS | 0.102 | NS | –0.153 | NS |
| BMI | 0.109 | NS | –0.139 | NS | –0.099 | NS |
| T-Bil | –0.066 | NS | –0.033 | NS | 0.140 | NS |
| AST | –0.220 | NS | –0.029 | NS | 0.309 | $P<0.01$ |
| ALT | –0.335 | NS | –0.078 | NS | 0.028 | NS |
| Platelet | –0.048 | NS | –0.050 | NS | –0.383 | $P<0.01$ |
| Fasting plasma glucose | 0.013 | NS | 0.210 | NS | 0.136 | NS |
| Fasting plasma insulin | 0.244 | NS | 0.134 | NS | 0.350 | $P<0.01$ |
| HOMA-IR | 0.192 | NS | 0.154 | NS | 0.328 | $P<0.01$ |
| QUICKI | –0.227 | NS | –0.155 | NS | –0.337 | $P<0.01$ |
| Log adiponectin | –0.094 | NS | 0.399 | $P<0.01$ | 0.418 | $P<0.01$ |

NS, not significant; BMI, body mass index; T-Bil, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HOMA-IR, the homeostatic model assessment insulin resistance; QUICKI, Quantitative insulin sensitivity check index

negative correlation with QUICKI and platelet counts in all subjects examined.

Although the role of resistin in humans is still controversial, resistin may represent a potential role in the pathomechanism of insulin resistance.[1,2] Conversely, adiponectin is considered to upregulate insulin sensitivity.[19] Therefore, adiponectin and resistin have opposite physiological functions. As a result, the finding in this study that they had a positive correlation in LC appears to be somewhat strange. The plasma adiponectin levels were previously reported to increase in a stepwise fashion in line with a higher grade of liver damage,[14,16,17] consistent with this study. The liver is a major source of adiponectin extraction and reduced liver function and hepatic hemodynamics have been reported to cause hyperadiponectinemia in LC.[16] Plasma resistin levels also increased with a higher grade of liver damage in this study. Therefore, both the plasma adiponectin levels and the resistin levels increase in a stepwise fashion in line with a higher grade of liver damage. The correlation between adiponectin and resistin may result from the impaired liver damage. Otherwise, the feedback mechanism between the networks of cytokines may result in this correlation.

Severe liver dysfunction is known to cause insulin resistance.[12,13] The positive correlation between resistin and HOMA-IR and the negative correlation between resistin and QUICKI seemed to be somewhat rational. However, regarding the elevation of resistin in LC, it is not clear at this time if this is the cause of insulin resistance in LC or the result of impaired liver function. The cytokine induction of resistin may contribute to insulin resistance in inflammatory states.[20,21] Further studies are thus necessary to elucidate the pathophysiological roles of resistin in LC.

HCV can itself induce insulin resistance via disturbance of the insulin signaling pathway by hepatitis C protein.[22] Therefore, we selected LC due to HCV infection in this study. Adiponectin correlated with hepatitis C viral factors such as genotype and viral load.[23] Further study of the correlation between resistin and HCV may reveal a new aspect of the pathological roles of resistin. We preliminarily evaluated the plasma resistin levels in LC with etiologies other than HCV infection with small numbers of patients. The plasma resistin levels were also significantly elevated in LC with other etiologic factors such as hepatitis B infection or alcoholic liver injury in comparison with controls. However, there were no differences between the etiologies of LC. Further evaluation of plasma resistin in metabolic disorders, such as nonalcoholic steatohepatitis, with large numbers of patients would thus likely provide interesting findings.

In conclusion, in the present study we demonstrated the presence of higher plasma resistin concentrations in patients with LC. Resistin may contribute to insulin resistance in patients with LC, although the pathophysiological roles of resistin in LC still require further investigation.

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