Elevated circulating adiponectin levels in liver cirrhosis are associated with reduced liver function and altered hepatic hemodynamics

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Tietge, Uwe J. F., Klaus H. W. Böker, Michael P. Manns, and Matthias J. Bahr. Elevated circulating adiponectin levels in liver cirrhosis are associated with reduced liver function and altered hepatic hemodynamics. Am J Physiol Endocrinol Metab 287: E82–E89, 2004.—Adiponectin is a novel adipokine negatively correlated with parameters of the metabolic syndrome, such as body mass index (BMI), body fat mass (BFM), and circulating insulin levels. Furthermore, metabolic actions directly on the liver have been described. The aim of the present study was to characterize circulating adiponectin levels and hepatic turnover in 20 patients with advanced cirrhosis. Hepatic catabolic disease. Circulating adiponectin levels and hepatic turnover were investigated in 20 patients with advanced cirrhosis. Hepatic hemodynamics [portal pressure, liver blood flow, hepatic vascular resistance, indocyanine green (ICG) half-life], body composition, resting energy expenditure, hepatic free fatty acids (FFA) and glucose turnover, and circulating levels of hormones (catecholamines, insulin, glucagon) and proinflammatory cytokines (IL-1β, TNF-α, IL-6) were also assessed. Circulating adiponectin increased dependently on the clinical stage in cirrhosis compared with controls (15.2 ± 1.7 vs. 8.2 ± 1.1 μg/ml, respectively, P < 0.01), whereas hepatic extraction decreased. Adiponectin was negatively correlated with parameters of hepatic protein synthesis (prothrombin time; r = −0.62, P = 0.003; albumin: r = −0.72, P < 0.001) but not with transaminases or parameters of lipid metabolism. In addition, circulating adiponectin increased with portal pressure (r = 0.67, P = 0.003), hepatic vascular resistance (r = 0.60, P = 0.008), and effective hepatic blood flow (ICG half-life: r = 0.69, P = 0.001). Adiponectin in cirrhosis was not correlated with BMI, BFM, parameters of energy metabolism, insulin levels, hepatic FFA and glucose turnover, and circulating proinflammatory cytokines. These results demonstrate that 1) adiponectin plasma levels in cirrhosis are significantly elevated, 2) the liver is a major source of adiponectin extraction, and 3) adiponectin levels in cirrhosis do not correlate with parameters of body composition or metabolism but exclusively with reduced liver function and altered hepatic hemodynamics.

hepatic turnover; hepatic venous pressure gradient; calorimetry; body composition

ADIPONECTIN IS A RECENTLY DISCOVERED 244 amino acid-containing molecule that belongs to the group of adipocytokines. It has been identified by several different groups and is thus also referred to as adipocyte complement-related protein 30 (ACRP30) (38), adipose most abundant gene transcript (apM1) (19), adipoQ (13), and gelatin-binding protein (GBP28) (29). Notably, adiponectin plasma levels in humans are in the microgram-per-milliliter range and therefore several orders of magnitude higher than most other hormones (6). In normal humans and mice, adiponectin expression is restricted to adipose tissue (6, 10) or adipocytic cells within, for example, the liver (51). However, carbon tetrachloride-treated mice have been reported to show a dramatic increase in the expression of adiponectin protein as well as mRNA within hepatocytes, possibly implicating adiponectin in contributing to the various metabolic abnormalities observed in patients with liver cirrhosis (51). Most recently, specific adiponectin receptors have been cloned, that, among other tissues, are expressed in the liver (48).

Although the physiological role of adiponectin has not been fully established (6), recent data have provided evidence that this hormone critically influences several components of the metabolic syndrome. In previous studies in humans, adiponectin plasma levels were invariably negatively correlated with body mass index and body fat mass, fasting plasma glucose and insulin, the degree of insulin resistance, systolic and diastolic blood pressure, and plasma total cholesterol and triglycerides (3, 6, 10, 41).

Studies in experimental animals have greatly contributed to an understanding of the metabolic functions of adiponectin. Circulating adiponectin levels are reduced in obese mice (29, 49) and rhesus monkeys (12). Administration of adiponectin to mice resulted in a decrease in plasma glucose (2) and free fatty acid (FFA) and triglyceride levels (9). In addition, hepatic glucose production decreased (9, 49). Adiponectin knockout mice were reported to develop insulin resistance either when chow fed (16) or after feeding a high-fat, high-sucrose diet (20). However, homozygous knockout mice generated by a different group did not exhibit insulin resistance (18).

The regulation of adiponectin gene expression is to date only incompletely understood. However, most relevant for our current study are the findings that adiponectin expression and secretion in adipocytes are significantly reduced by treatment with TNF-α (15, 21) or with β-adrenergic agonists (5, 7).

Liver cirrhosis is a catabolic disease. Patients with cirrhosis are characterized by a series of severe metabolic alterations: they have increased resting energy expenditure, suffer a loss of body fat mass as well as body cell mass, and exhibit a striking elevation in the percentage of energy derived from fat (23–25). Hormonal alterations comprise elevated levels of fasting glucose, insulin, and catecholamines and the development of insulin resistance (31, 33, 37). In addition, patients with cirrhosis are characterized by a chronic inflammatory state with elevated plasma levels of IL-6, IL-1β, and TNF-α (17, 46).
To date, there is no information available in the literature regarding changes in adiponectin plasma levels in cirrhosis and associated metabolic disturbances. We therefore investigated circulating adiponectin as well as hepatic turnover of adiponectin in a collective of patients with established cirrhosis in different clinical stages. In parallel, several key parameters of hepatic hemodynamics and systemic as well as local hepatic metabolism were assessed. Our data demonstrate that 1) adiponectin plasma levels in cirrhosis are significantly elevated, 2) the liver is a major source of adiponectin extraction, and 3) adiponectin levels in cirrhosis do not correlate with parameters of body composition or metabolism but exclusively with reduced liver function and altered hepatic hemodynamics.

MATERIALS AND METHODS

Patients. Twenty patients with liver cirrhosis were studied. In each case, diagnosis was confirmed by liver histology following liver biopsy. They were graded according to the Child-Pugh classification (36): four patients were classified as CHILD A, nine as CHILD B, and seven as CHILD C. Six patients each suffered from alcoholic liver disease, virus-induced cirrhosis (hepatitis B or C), and biliary cirrhosis (primary biliary cirrhosis, primary sclerosing cholangitis), and in two patients liver disease was of cryptogenic origin. Detailed clinical data of the patients are given in Table 1. The cirrhotic patients were studied while they were hospitalized to be evaluated for liver transplantation. All were in a stable clinical condition before entering the study and had been following a weight-maintaining diet containing 80 g of protein daily for at least 1 wk. Patients with renal insufficiency, proteinuria, suspected infections, clinically overt diabetes mellitus, thyroid dysfunction, or any other endocrine disorder were excluded from the study. No hormone or thyroid-regulatory medication was administered. Patency of portal vein and hepatic artery was documented by Doppler ultrasound before patients entered the study. Patients with a significant amount of ascites or peripheral edema were excluded from the study to avoid methodological inconsistencies with the body composition measurement.

Controls were matched to the patient population by sex (male = 15, female = 5), age (46.2 ± 2.5 vs. 47.6 ± 2.4 yr, respectively) and body mass index (BMI; 23.6 ± 0.9 vs. 23.0 ± 0.6 kg/m², respectively). None of them had a history of endocrine disorders or hepatic disease; all had completely normal liver function tests, normal ultrasound of the liver and biliary system, and negative serological findings for viral and autoimmune liver disease. None of the controls had a first-degree relative with type 2 diabetes.

All patients were thoroughly informed about the rationale and the possible risks of all investigational procedures and gave written consent before entering the study. The study protocol was approved by the Ethics Committee of the Medizinische Hochschule Hannover.

Assessment of hepatic hemodynamics. Hepatic vein catheterization to collect hepatic venous blood samples was performed after an overnight fast by means of a balloon catheter essentially as described (43). Arterial blood was drawn from a line placed in the right femoral artery. No complications were encountered during or after the procedure. Quantitative hepatic blood flow (HBF) was determined by the indocyanine green (ICG, Cardio-Green, Paesel & Lorei, Frankfurt/M, Germany) steady-state infusion technique according to a previously published protocol (43). Briefly, on the day before hepatic venous catheterization, individual ICG half-life (ICGt1/2), as a measure of effective HBF, was determined by ICG bolus injection (43). From these data the individual ICG infusion rate was calculated according to the formula (43): $I_{\text{ICG}} = I_0/\text{ICG}_{t1/2} \times 60$, with $I_{\text{ICG}}$ representing the individual ICG infusion rate (mg/h), and $\text{ICG}_{t1/2}$ representing the ICG half-life (min).

Patients received an intravenous loading dose of 0.3 mg ICG/kg body wt followed by a constant infusion of ICG through a forearm cannula with the infusion rate calculated according to the formula above. After steady-state conditions were achieved, HBF was calculated as: HBF = $I_{\text{ICG}}/(\text{ICG}_{a} - \text{ICG}_{v})(1 - \text{Hct})$, with $I_{\text{ICG}}$ representing the individual ICG infusion rate (mg/min), $\text{ICG}_{a}$ representing the arterial ICG concentration (mg/l), $\text{ICG}_{v}$ representing the hepatic venous ICG concentration (mg/l), and Hct representing the hematocrit. If the arteriohepatic venous ICG concentration difference was below 0.1 mg/l, no HBF calculation was performed (4). Hepatic vascular resistance (dyne-s·cm⁻²) was calculated from these data as 80 times hepatic venous pressure gradient (mmHg) divided by HBF (l/min) (43).

Percent hepatic extraction was calculated by dividing the arteriohepatic venous concentration difference by the respective arterial concentration. Hepatic production/extraction rates per minute were calculated by multiplying the respective arteriohepatic venous concentration differences with the HBF; this parameter is therefore dependent on HBF, and the proportions of the results obtained might differ from the values of the percent hepatic extraction when different patients are compared among one another.

Table 1. Clinical details of the patients with liver cirrhosis and the controls studied

<table>
<thead>
<tr>
<th></th>
<th>Cirrhosis (all)</th>
<th>CHILD A</th>
<th>CHILD B</th>
<th>CHILD C</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>47.6 ± 2.4</td>
<td>39.8 ± 7.3</td>
<td>49.7 ± 3.0</td>
<td>49.3 ± 3.5</td>
<td>46.2 ± 2.5</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.0 ± 0.6</td>
<td>22.7 ± 1.1</td>
<td>23.1 ± 0.87</td>
<td>23.0 ± 1.2</td>
<td>23.6 ± 0.9</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>70 ± 2</td>
<td>71 ± 4</td>
<td>71 ± 2</td>
<td>69 ± 4</td>
<td>82 ± 3*</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>113 ± 3</td>
<td>116 ± 6</td>
<td>110 ± 3</td>
<td>109 ± 6</td>
<td>122 ± 3*</td>
</tr>
<tr>
<td>Bilirubin, μmol/l</td>
<td>39.7 ± 5.4</td>
<td>22.5 ± 3.9</td>
<td>49.2 ± 10.1</td>
<td>37.3 ± 6.0</td>
<td>9.8 ± 3.1*</td>
</tr>
<tr>
<td>Albumin, g/l</td>
<td>31.6 ± 1.5</td>
<td>40.3 ± 2.7</td>
<td>29.8 ± 2.2</td>
<td>29.0 ± 1.3</td>
<td>42.2 ± 1.2*</td>
</tr>
<tr>
<td>Prothrombin time, %</td>
<td>71 ± 3</td>
<td>86 ± 6</td>
<td>73 ± 5</td>
<td>59 ± 1</td>
<td>98 ± 2*</td>
</tr>
<tr>
<td>Cholesterol, mmol/l</td>
<td>4.68 ± 0.43</td>
<td>6.08 ± 0.78</td>
<td>4.83 ± 0.57</td>
<td>3.69 ± 0.78</td>
<td>5.12 ± 0.34</td>
</tr>
<tr>
<td>Triglycerides, mmol/l</td>
<td>0.95 ± 0.09</td>
<td>1.07 ± 0.04</td>
<td>1.13 ± 0.16</td>
<td>0.66 ± 0.07</td>
<td>1.00 ± 0.05</td>
</tr>
<tr>
<td>Glucose, mmol/l</td>
<td>6.15 ± 0.25</td>
<td>5.50 ± 0.23</td>
<td>6.11 ± 0.43</td>
<td>6.57 ± 0.39</td>
<td>4.74 ± 0.12*</td>
</tr>
<tr>
<td>AST, U/l</td>
<td>31 ± 4</td>
<td>16 ± 3</td>
<td>39 ± 5</td>
<td>28 ± 7</td>
<td>14 ± 1*</td>
</tr>
<tr>
<td>ALT, U/l</td>
<td>33 ± 5</td>
<td>26 ± 8</td>
<td>42 ± 8</td>
<td>26 ± 7</td>
<td>16 ± 1*</td>
</tr>
<tr>
<td>G1DH, U/l</td>
<td>6 ± 1</td>
<td>7 ± 2</td>
<td>5 ± 1</td>
<td>4 ± 1</td>
<td>2 ± 1*</td>
</tr>
<tr>
<td>AP, U/l</td>
<td>362 ± 77</td>
<td>217 ± 67</td>
<td>552 ± 144</td>
<td>202 ± 44</td>
<td>105 ± 6*</td>
</tr>
<tr>
<td>γ-GT, U/l</td>
<td>79 ± 13</td>
<td>57 ± 10</td>
<td>108 ± 24</td>
<td>54 ± 12</td>
<td>18 ± 2*</td>
</tr>
<tr>
<td>Cholinesterase, kU/l</td>
<td>2.56 ± 0.27</td>
<td>4.30 ± 0.30</td>
<td>2.56 ± 0.26</td>
<td>1.55 ± 0.21</td>
<td>4.57 ± 0.19*</td>
</tr>
</tbody>
</table>

Data are given as means ± SE. CHILD, Child-Pugh classification; AST, aspartate aminotransferase; ALT, alanine aminotransferase; G1DH, glutamate dehydrogenase; AP, alkaline phosphatase; γ-GT, γ-glutamyltransferase. Results significantly different from cirrhosis: *P < 0.05 or less.
**Blood sampling and laboratory analyses.** All blood samples were immediately placed on crushed ice and processed without delay. ICG was measured spectrophotometrically at 800 nm wavelength (DU 6 Beckmann Photometer; Beckmann Instruments, Munich, Germany). FFA and glucose levels were measured enzymatically using a commercially available assay kit (Boehringer Mannheim, Mannheim, Germany). Aliquots for hormone and cytokine analyses were stored at −80°C. Commercially available radioimmunosassays were used to determine plasma concentrations of insulin (Pharmacia Insulin RIA 100; Pharmacia Diagnostics, Uppsala, Sweden), C-peptide (C-Peptide 1251 RIA Kit; Incstar, Stillwater, MN), glucagon [Glugagon-RIA DAK/PEG (E-125); Hermann Biermann, Bad Nauheim, Germany]. Plasma concentrations of catecholamines (epinephrine and norepinephrine) were measured by high-performance liquid chromatography (HPLC) as described (45). All these hormone measurements represent standard clinical chemistry parameters at our institution with established large reference collections of normal controls and subsequently derived normal values as presented in the RESULTS tables. Adiponectin was measured with a commercially available ELISA according to the manufacturer’s instructions (B-Bridge International, San Jose, CA). Concentrations of TNF-α, IL-6, and IL-1β were assessed with commercially available ELISAs (Medegenix Diagnostics, Brussels, Belgium).

**Indirect calorimetry and body composition analysis.** Resting energy expenditure was measured by indirect calorimetry using a ventilated open hood as described [Deltatrac Metabolic Monitor; Datex Instruments, Helsinki, Finland (44)]. The calculation of substrate oxidation rates was carried out as described (26). To calculate protein oxidation, urea nitrogen excretion was measured in urine collected overnight. Bioelectrical impedance analysis (BIA) was performed to assess body composition using a radio frequency current of 800 μA at 50 kHz between a set of electrodes attached to the dorsum of the hand and foot (BIA 101; RJL Systems, Detroit, MI). Calculations were performed using previously described formulas (42).

**Statistics.** Statistical analysis was performed using the statistical package for social sciences (SPSS). Data are expressed as means ± SE. Nonparametric statistical tests were used. Kruskal-Wallis analysis of variance was used to compare values of three or more different groups. Values showing significant intergroup differences were then compared using the Mann-Whitney U-test. Spearman’s rank correlation coefficient was used to assess possible associations between different parameters. P values < 0.05 were considered statistically significant.

**RESULTS**

**Circulating adiponectin levels increase dependently on the clinical stage of cirrhosis, whereas hepatic extraction is decreased.** Plasma adiponectin levels in cirrhosis were significantly elevated compared with an age-, sex-, and BMI-matched control group (15.2 ± 1.7 vs. 8.2 ± 1.1 μg/ml, respectively, P < 0.01; Fig. 1). Among the patients with liver cirrhosis, patients graded CHILD A (7.3 ± 0.9 μg/ml, P < 0.05; Fig. 2A) had significantly lower adiponectin plasma levels than patients in the CHILD B (17.2 ± 2.2 μg/ml) or CHILD C (17.2 ± 3.1) clinical stages. There was no statistically significant difference in circulating adiponectin between patients suffering from different etiologies of liver cirrhosis (alcoholic, biliary, post-hepatic). However, there were not enough female patients in our study to establish a reliable assessment of sex differences of circulating adiponectin in patients with liver cirrhosis. Hepatic percent adiponectin extraction as well as hepatic adiponectin extraction per minute decreased from CHILD A (38 ± 6%, 2.48 ± 0.47 mg/min, respectively, Fig. 2, B and C) to CHILD B (14 ± 17%, 0.50 ± 0.95 mg/min, respectively) and CHILD C patients (−10 ± 13%, 0.28 ± 1.11 mg/min, respectively), although this trend was not statistically significant.

**Circulating adiponectin levels in cirrhosis increase with decreasing hepatic protein synthesis.** Next, we asked whether circulating adiponectin levels in cirrhosis were associated with transaminase levels or parameters of cholestasis and lipid metabolism or indicators of hepatic protein synthesis. Plasma adiponectin was not correlated with aspartate aminotransferase (r = 0.37, not significant (NS)), alanine aminotransferase (r = 0.07, NS), glutamate dehydrogenase (GIDH; r = −0.11, NS), and γ-glutamyltransferase (γ-GT; r = 0.17, NS). Also, no association was found with plasma bilirubin (r = 0.31, NS) or alkaline phosphatase (r = 0.21, NS) levels. In contrast to data obtained in obese populations, circulating adiponectin in cirrhosis did not correlate with plasma total cholesterol (r = −0.28, NS) or triglyceride levels (r = −0.38, NS). Strikingly, plasma adiponectin was significantly correlated with prothrombin time (r = −0.62, P = 0.003; Fig. 3A), albumin (r = −0.72, P < 0.001; Fig. 3B), and cholinesterase (r = −0.61, P = 0.004), all parameters of hepatic protein synthesis capacity.

**Circulating adiponectin levels in cirrhosis are not associated with parameters of body composition or energy expenditure.** In contrast to other patient collectives reported in the literature, in our patients with liver cirrhosis, circulating adiponectin was not associated with BMI (r = −0.03, NS). Neither did it correlate with body fat mass (r = 0.23, NS), fat-free mass (r = −0.07, NS), body cell mass (r = −0.06, NS), extracellular mass (r = −0.11), or lean body mass (r = −0.06, NS). Arterial adiponectin levels were also not associated with resting energy expenditure (r = −0.15, NS). In addition, adiponectin showed no correlation with the substrate oxidation rates of carbohydrates (r = 0.06, NS), fat (r = −0.19, NS), or protein (r = 0.13, NS) in patients with cirrhosis.

**Circulating adiponectin levels in cirrhosis increase with deteriorating hepatic hemodynamics.** Next, we investigated the relationship between the increased arterial adiponectin levels in cirrhosis and systemic as well as hepatic hemodynamics (Table 2). Adiponectin was not associated with diastolic blood pressure (r = 0.01, NS) or systolic blood pressure (r = −0.10, NS). Interestingly, hepatic venous pressure gradient as measure
of portal pressure was positively correlated with circulating adiponectin \( (r = 0.67, P = 0.003; \text{Fig. 4A}) \). In addition, arterial adiponectin levels increased with increasing hepatic vascular resistance \( (r = 0.60, P = 0.008; \text{Fig. 4B}) \). Adiponectin levels were also significantly positively associated with ICG half-life, a measure of effective hepatic blood flow \( (r = 0.69, P = 0.001, \text{Fig. 4C}) \).

**Circulating adiponectin levels are not associated with hepatic glucose or FFA metabolism in cirrhosis.** To test the hypothesis that adiponectin impacts on hepatic glucose production or FFA extraction, we correlated circulating adiponectin levels with parameters of hepatic glucose and FFA metabolism. Adiponectin was associated neither with circulating glucose plasma levels \( (r = 0.01, \text{NS}) \) nor with hepatic percent \( (r = 0.22, \text{NS}) \) or per minute \( (r = 0.31, \text{NS}) \) glucose production. There was also no statistically significant correlation between arterial adiponectin levels and circulating plasma FFA \( (r = 0.28, \text{NS}) \) or hepatic percent \( (r = 0.08, \text{NS}) \) or per minute \( (r = 0.19, \text{NS}) \) FFA extraction.

**Adiponectin in cirrhosis is not associated with insulin or proinflammatory cytokines.** Data in the literature indicate that adiponectin plasma levels are inversely correlated with plasma

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**Table 2. Parameters of hepatic hemodynamics in the patients with liver cirrhosis investigated**

<table>
<thead>
<tr>
<th></th>
<th>Cirrhosis (all)</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICG half-life, min</td>
<td>12.8 ± 1.5 (3.6–26.7)</td>
<td>&lt; 4</td>
</tr>
<tr>
<td>Hepatic venous pressure gradient, mmHg</td>
<td>16 ± 2 (4–28)</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Hepatic vascular resistance, dyn·s·cm⁻¹</td>
<td>1.701 ± 0.282 (152–4113)</td>
<td>&lt; 250</td>
</tr>
</tbody>
</table>

Data are given as means ± SE; the ranges of the respective values are also indicated (min-max). ICG, indocyanine green.
be altered in cirrhosis on the other hand (Table 4). Arterial adiponectin was significantly associated with arterial glucagon levels \((r = 0.56, P = 0.01)\). Otherwise, no statistically significant correlations were observed.

**DISCUSSION**

This study demonstrates that 1) adiponectin plasma levels in cirrhosis are significantly elevated, 2) there is a significant exchange of adiponectin in the hepatic vascular bed, and 3) adiponectin levels in cirrhosis do not correlate with parameters of body composition or metabolism, but exclusively with reduced liver function and altered hepatic hemodynamics.

Adiponectin is the only adipocytokine to date with decreased expression in obesity (6, 10). In all studies reported so far, plasma adiponectin levels were consistently correlated with BMI and body fat mass (1, 11, 22, 40, 47). This relation is thought to be dynamic, because weight loss resulted in an increase in plasma adiponectin levels in humans (11, 50). Liver cirrhosis is a catabolic disease, with patients exhibiting increased resting energy expenditure, loss of body fat mass, and increased lipid oxidation for energy generation (23–25). Therefore, under these circumstances, adiponectin levels would have been predicted to increase. However, circulating adiponectin in cirrhosis increased completely independently of all metabolic parameters, and notably also independently of body fat mass. Instead, a close correlation with parameters of hepatic metabolism and hemodynamics was observed.

To reach a valid conclusion on the absence of a correlation of adiponectin with parameters of body composition, a reliable

<table>
<thead>
<tr>
<th>C-peptide</th>
<th>Glucagon</th>
<th>Epinephrine</th>
<th>Norepinephrine</th>
<th>TNF-α</th>
<th>IL-6</th>
<th>IL-1B</th>
</tr>
</thead>
<tbody>
<tr>
<td>r = 0.36, NS</td>
<td>r = 0.56, P = 0.01</td>
<td>r = 0.21, NS</td>
<td>r = 0.26, NS</td>
<td>r = 0.17, NS</td>
<td>r = 0.24, NS</td>
<td>r = 0.07, NS</td>
</tr>
<tr>
<td>NS</td>
<td>r = 0.14, NS</td>
<td>r = 0.01, NS</td>
<td>r = 0.36, NS</td>
<td>r = 0.32, NS</td>
<td>r = 0.05, NS</td>
<td>r = 0.25, NS</td>
</tr>
</tbody>
</table>

Spearman’s rank correlation coefficients are given. NS, not statistically significant.

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**Table 3. Circulating hormone and proinflammatory cytokine levels in the patients with liver cirrhosis investigated**

<table>
<thead>
<tr>
<th>CIRRHOSIS (ALL)</th>
<th>NORMAL RANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine, ng/l</td>
<td>160±10 (77–238)</td>
</tr>
<tr>
<td>Norepinephrine, ng/l</td>
<td>545±38 (313–962)</td>
</tr>
<tr>
<td>Insulin, mU/l</td>
<td>18.0±2.5 (6.0–53.1)</td>
</tr>
<tr>
<td>C-peptide, μg/l</td>
<td>3.61±0.40 (1.65–7.39)</td>
</tr>
<tr>
<td>Glucagon, ng/l</td>
<td>233±30 (79±656)</td>
</tr>
<tr>
<td>IL-1β, pg/ml</td>
<td>8.7±3.3 (2.0–28.5)</td>
</tr>
<tr>
<td>IL-6, pg/ml</td>
<td>6.1±0.5 (4.1–11.0)</td>
</tr>
<tr>
<td>TNF-α, pg/ml</td>
<td>15.8±2.0 (4.3–33.9)</td>
</tr>
</tbody>
</table>

Data are given as means ± SE; the range of the respective values is also indicated (min-max).
method to measure these parameters is necessary. In the past, BIA has been questioned to represent such a method when applied to the assessment of body composition in patients with liver cirrhosis. However, recent studies demonstrated that, at least in patients without clinically significant fluid overload, such as in our patient collective, there is an excellent correlation between body composition parameters calculated from BIA and those derived from total potassium counting (27, 34, 35). We therefore believe that the absence of a correlation between adiponectin plasma levels and body fat mass or BMI in cirrhosis is valid and not due to methodological problems.

The pathogenesis of body fat mass loss in cirrhosis has not been entirely clarified (23, 25). However, current data indicate that chronic endotoxemia due to reduced clearance of gut-derived bacteria by the diseased liver leads to a persistent macrophage activation state (17, 24). Cytokines are released from activated macrophages into the circulation, impacting on the wasting syndrome in liver cirrhosis (46). TNF-α has been implicated in this process, and preliminary data from our group indicate that circulating TNF-α levels are inversely correlated with body fat mass in cirrhosis (Bahr MJ and Tietge UJF, unpublished observations). However, TNF-α levels did not correlate with circulating adiponectin in the present study.

In addition to measuring circulating adiponectin levels in cirrhosis, we also assessed hepatic turnover. Interestingly, in all CHILD A patients, who had the lowest circulating adiponectin levels, there was a significant percent as well as per minute hepatic extraction of adiponectin, whereas in CHILD B and C patients extraction was decreased and some patients even showed adiponectin production. Patients with CHILD A cirrhosis in the present study had normal circulating adiponectin levels comparable with patients with liver fibrosis (Tietge UJF and Bahr MJ, unpublished observations). These findings suggest that adiponectin metabolism remains normal in patients with liver disease until the decompensation of manifest cirrhosis. To strengthen the role of the liver in adiponectin catabolism, we further demonstrate a number of interesting correlations. Circulating adiponectin was negatively related to markers of hepatic protein synthesis, such as albumin, coagulation factors (prothrombin time), and cholinesterase. It further correlated negatively with the degree of portal hypertension. Importantly, circulating adiponectin was positively associated with ICG half-life, meaning that adiponectin levels increase with decreasing effective hepatic blood flow (30). The term effective hepatic blood flow comprises the combination of hepatocellular metabolic functions, the amount of intra- as well as extrahepatic shunts, and the degree of capillarization. Capillarization of the hepatic sinusoids is a key feature of cirrhosis complicating the contact between blood components and the hepatocytes, and ICG is an established test substance to assess effective hepatic blood flow (4, 30, 43). An increase in the ICG half-life thereby represents a decrease in ICG clearance per time, reflecting decreased effective hepatic blood flow. Our data suggest that the liver may play an important role in the catabolism of adiponectin and that the elevated plasma levels in cirrhosis are, at least in part, due to decreased hepatic catabolism. Even true hepatic production might impact on our findings, since a recent study demonstrated that hepatocytes express significant amounts of adiponectin mRNA as well as protein in vivo when challenged with the fibrotic stimulus carbon tetrachloride (51). To our knowledge, the only other study dealing with possible sites of adiponectin catabolism so far proposed a role of the kidney in adiponectin catabolism due to the finding that patients with chronic renal failure have elevated circulating adiponectin levels (52).

Another surprising result of our current study is the lack of a correlation between circulating insulin and adiponectin levels in patients with cirrhosis. Adiponectin has been proposed to be involved in the development of insulin resistance and type 2 diabetes, and in studies conducted so far a close negative correlation between plasma insulin and plasma adiponectin was reported (11, 22, 47). In agreement with these findings, plasma adiponectin was elevated in patients with type 1 diabetes, although insulin substitution did not alter plasma adiponectin (14). Furthermore, in vitro studies demonstrated that treatment of 3T3-L1 adipocytes with insulin reduced adiponectin expression levels in a time- and dose-dependent fashion (8), pointing to a direct, causative role of insulin in the regulation of adiponectin. However, our patients with liver cirrhosis had increased circulating insulin levels on the one hand and increased adiponectin levels on the other. A large number of patients with liver cirrhosis develop insulin resistance (up to 80%) and diabetes (up to 15%) (28, 31, 39). Our findings, although not investigated directly in the present study, might indicate that the pathogenesis of insulin resistance and diabetes in cirrhosis differs from the mechanisms in patients without liver disease, consistent with previous reports (31, 33, 37).

However, the impact of increased adiponectin in cirrhosis on insulin resistance and diabetes in patients with liver disease requires further investigation. Similar to what occurs with other hormones, patients with cirrhosis might develop a state of adiponectin resistance. Notably, other circulating hormone and cytokine levels also, especially catecholamines and TNF-α, did not correlate with parameters of adiponectin metabolism. Only glucagon was associated with arterial adiponectin levels. This relationship might not be causal, since glucagon is a hormone with a known high hepatic extraction rate (32) and is with a high likelihood eliminated from the bloodstream similarly to adiponectin.

In summary, elevated plasma adiponectin levels in cirrhosis do not correlate with any of the established parameters influencing adiponectin levels in normal controls or obese or diabetic populations. Instead, liver function seems to be a major determinant of the circulating adiponectin levels in patients with established liver cirrhosis. This finding warrants further study, especially of the metabolic consequences of raised adiponectin in terms of insulin resistance in patients with liver disease. These results might further indicate that the proposed use of adiponectin as a novel treatment strategy of insulin resistance and diabetes might be limited to patients without liver disease.

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