Elevated resistin levels in cirrhosis are associated with the proinflammatory state and altered hepatic glucose metabolism but not with insulin resistance.

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Bahr, Matthias J., Johann Ockenga, Klaus H. W. Böker, Michael P. Manns, and Uwe J. F. Tietge. Elevated resistin levels in cirrhosis are associated with the proinflammatory state and altered hepatic glucose metabolism but not with insulin resistance. Am J Physiol Endocrinol Metab 291: E199–E206, 2006. First published February 14, 2005; doi:10.1152/ajpendo.00291.2005.—The adipokine resistin has been implicated in obesity and insulin resistance. Liver cirrhosis is associated with decreased body fat mass and insulin resistance. We determined plasma resistin levels in 57 patients with cirrhosis, 13 after liver transplantation, and 30 controls and correlated these with hemodynamic as well as hepatic and systemic metabolic parameters. Patients with cirrhosis had, dependent on the clinical stage, an overall 86% increase in resistin levels (P < 0.001) with hepatic venous resistin being higher than arterial levels (P < 0.001). Circulating resistin was significantly correlated with plasma TNF-α levels (r = 0.62, P < 0.001). No correlation was observed between resistin and hepatic hemodynamics, body fat mass, systemic energy metabolism, and the degree of insulin resistance. However, plasma resistin in cirrhosis was negatively associated with hepatic glucose production (r = -0.47, P < 0.01) and positively with circulating free fatty acids (FFA; r = 0.40, P < 0.01) and ketone bodies (r = 0.48, P < 0.001) as well as hepatic ketone body production (r = 0.40, P < 0.01). After liver transplantation, plasma resistin levels remained unchanged, whereas insulin resistance was significantly improved (P < 0.01). These data provide novel insights into the role of resistin in the pathophysiological background of a catabolic disease in humans and also indicate that resistin inhibition may not represent a suitable therapeutic strategy for the treatment of insulin resistance and diabetes in patients with liver cirrhosis.

hepatic turnover; body composition; liver; portal pressure

RESISTIN IS A RECENTLY IDENTIFIED ~12-kDa adipokine with a proposed role in obesity and insulin resistance, key features of the metabolic syndrome (9, 15, 42). In rodents, resistin is almost exclusively expressed in adipocytes (13, 43), whereas in humans resistin expression is hardly detectable in adipocytes and is mostly found in monocytes/macrophages (19, 37, 43). These different expression patterns possibly translate into different biological properties of resistin in rodents and humans (43). However, studies conducted so far (13, 43) implicate resistin in 1) the regulation of adipose tissue mass; 2) glucose homeostasis, particularly insulin resistance; and 3) inflammation.

Liver cirrhosis is a catabolic disease characterized by 1) decreased adipose tissue mass (24, 26), 2) a high incidence of insulin resistance and diabetes (31, 40, 48), and 3) a proinflammatory state as represented by elevated cytokine levels (22, 49). Patients with liver cirrhosis display disturbances of glucose metabolism with 60–80% having impaired glucose tolerance (IGT) and 10–15% developing overt diabetes (31, 40). Cirrhosis-associated IGT is characterized by hyperinsulinemia and peripheral insulin resistance (16, 25), whereas a reduced insulin secretory capacity appears to eventually cause the development of overt diabetes (31, 29). Shunting of insulin, caused by a decreased hepatic first pass insulin clearance due to capillarization of the hepatic sinusoids and extensive collateral blood flow (16), as well as β-cell hypersecretion (31), has been implicated in the pathophysiology of IGT in cirrhosis (34). In turn, increased insulin levels compensate at least partially for insulin resistance (31, 16). To date, no data are available on plasma resistin levels in human patients with liver cirrhosis and their relation to body composition as well as the metabolic and inflammatory state. We hypothesized that resistin might represent a link between the proinflammatory state and insulin resistance in cirrhosis.

Therefore, we determined arterial as well as hepatic venous resistin levels in patients with established liver cirrhosis and compared these with metabolic, hemodynamic, and inflammatory parameters. Our data demonstrate that plasma resistin levels in cirrhosis are elevated, depending on the clinical stage of the disease and the inflammatory state. Although resistin was associated with hepatic glucose and ketone body metabolism, no correlation was observed with hepatic hemodynamics, body fat mass, systemic metabolism, and the degree of insulin resistance. Thus, this study provides novel insights into the biological role of resistin in a human pathophysiological condition associated with a catabolic state and insulin resistance.

MATERIALS AND METHODS

Patients. We studied 57 patients with biopsy-proven liver cirrhosis and 30 controls without any liver or metabolic disease. Detailed clinical data of patients and controls are given in Table 1. Patients with cirrhosis were graded according to the Child-Pugh classification: 7 patients were classified as Child A, 23 as Child B, and 27 as Child C. Fourteen patients suffered from alcoholic liver disease, 22 had virus-induced cirrhosis (hepatitis B virus, hepatitis C virus, hepatitis B + hepatitis D virus), 15 suffered from biliary cirrhosis (primary biliary cirrhosis and primary sclerosing cholangitis), and in 6, liver disease was of cryptogenic origin. The cirrhotic patients were studied 14, 26), 60 – 80% having impaired glucose metabolism with 60–80% having impaired glucose tolerance (IGT) and 10–15% developing overt diabetes (31, 40). Cirrhosis-associated IGT is characterized by hyperinsulinemia and peripheral insulin resistance (16, 25), whereas a reduced insulin secretory capacity appears to eventually cause the development of overt diabetes (31, 29). Shunting of insulin, caused by a decreased hepatic first pass insulin clearance due to capillarization of the hepatic sinusoids and extensive collateral blood flow (16), as well as β-cell hypersecretion (31), has been implicated in the pathophysiology of IGT in cirrhosis (34). In turn, increased insulin levels compensate at least partially for insulin resistance (31, 16). To date, no data are available on plasma resistin levels in human patients with liver cirrhosis and their relation to body composition as well as the metabolic and inflammatory state. We hypothesized that resistin might represent a link between the proinflammatory state and insulin resistance in cirrhosis.

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stable long-term course following liver transplantation (>1 yr). They had normal liver function tests and no evidence of fibrosis or cirrhosis of the graft. The immunosuppressive medication consisted of cyclosporine A (adjusted to serum levels between 80 and 120 ng/ml) and prednisone (5 mg/day) in all patients. In these patients, circulating levels of resistin, glucose, and insulin were measured; they did not receive the hepatic vein catheterization protocol described below.

Arterial and hepatic venous glucose, FFA, acetocetate, and 3-hydroxybutyrate levels were measured enzymatically using commercially available assay kits (Boehringer Mannheim, Mannheim, Germany). Percent hepatic extraction was calculated by dividing the arteriohepatic venous concentration difference by the respective arterial concentration differences. Hepatic substrate production/extraction rates were calculated by multiplying the respective arteriohepatic venous concentration differences with the HBF.

Aliquots for hormone and cytokine analyses were stored at −80°C. Commercially available radioimmunoassays were used to determine plasma concentrations of insulin (Pharmacia Insulin RIA 100; Pharmacdia Diagnostics, Uppsala, Sweden), C-peptide (C-peptide 125I RIA kit; Incstar, Stillwater, MN), and glucagon (Glukagon-RIA DAK/PEG 125I; Hermann Biermann, Bad Nauheim, Germany). Plasma concentrations of epinephrine, norepinephrine, and dopamine were measured by high-performance liquid chromatography (HPLC) as described previously (45). Resistin was measured with a commercially available ELISA according to the manufacturer’s instructions (BioVendor Laboratory Medicine, Brno, Czech Republic). Concentrations of TNF-α, IL-6, and IL-1 (Medgenix Diagnostics, Brussels, Belgium), adiponectin (B-Bridge International, San Jose, CA), and leptin (Linco Research, St. Charles, MO) were assessed with commercially available ELISAs.

The quantitative insulin-sensitivity check index (QUICKI) and the homeostasis model assessment of insulin resistance (HOMA-IR), as indexes of insulin resistance, were calculated essentially as previously described (30).

Measurement of splanchnic oxygen uptake. To determine splanchnic oxygen uptake, arterial and hepatic venous blood samples were drawn simultaneously and immediately placed on ice. Oxygen saturation as well as oxygen and carbon dioxide partial pressures were determined immediately (NOVA 1 biomedical analyzer; NOVA Biomedical, Darmstadt, Germany). From these data, the oxygen concentrations of arterial and hepatic venous blood were calculated, and splanchnic oxygen uptake (ml/min) was calculated by multiplying the arteriohepatic venous oxygen concentration difference with the HBF (44).

Indirect calorimetry and body composition analysis. Resting energy expenditure was measured using indirect calorimetry with a ventilated open hood as described previously (Delta trac metabolic monitor; Datex Instruments, Helsinki, Finland) (46). Bioelectrical impedance analysis was performed to assess body cell mass, body fat mass, lean body mass, and fat free mass by using a radio frequency current of 800 μA at a 50-kHz frequency between a set of electrodes attached to the dorsum of the hand and foot (BIA 101; RJL Systems,

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**Table 1. Clinical data of patients with liver cirrhosis and of 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>n</td>
<td>57</td>
<td>7</td>
<td>23</td>
<td>27</td>
<td>30</td>
</tr>
<tr>
<td>Age, yr</td>
<td>47.5 ± 1.3</td>
<td>50.0 ± 3.1</td>
<td>48.5 ± 2.1</td>
<td>47.1 ± 1.9</td>
<td>46.8 ± 2.7</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.0 ± 0.4</td>
<td>23.6 ± 1.6</td>
<td>22.5 ± 0.7</td>
<td>23.2 ± 0.7</td>
<td>23.7 ± 1.0</td>
</tr>
<tr>
<td>Bilirubin, μmol/l</td>
<td>65.0 ± 10</td>
<td>26.3 ± 3.0</td>
<td>42.6 ± 3.0</td>
<td>39.3 ± 2.0</td>
<td>18.0 ± 2.3</td>
</tr>
<tr>
<td>Albumin, g/l</td>
<td>30.1 ± 1.0</td>
<td>37.2 ± 1.0</td>
<td>30.1 ± 1.0</td>
<td>28.1 ± 1.0</td>
<td>44.1 ± 1.0</td>
</tr>
<tr>
<td>Prothrombin time, %</td>
<td>64.2 ± 1.0</td>
<td>87.3 ± 1.0</td>
<td>65.3 ± 1.0</td>
<td>57.3 ± 1.0</td>
<td>98.2 ± 1.0</td>
</tr>
<tr>
<td>Cholesterol, mmol/l</td>
<td>4.7 ± 0.6</td>
<td>6.2 ± 0.6</td>
<td>4.7 ± 0.6</td>
<td>4.3 ± 0.6</td>
<td>5.0 ± 0.4</td>
</tr>
<tr>
<td>Triglycerides, mmol/l</td>
<td>1.0 ± 0.1</td>
<td>1.1 ± 0.1</td>
<td>1.1 ± 0.1</td>
<td>0.9 ± 0.1</td>
<td>1.0 ± 0.1</td>
</tr>
<tr>
<td>Glucose, mmol/l</td>
<td>6.3 ± 0.3</td>
<td>5.8 ± 0.3</td>
<td>6.3 ± 0.3</td>
<td>6.4 ± 0.3</td>
<td>4.6 ± 0.3</td>
</tr>
<tr>
<td>AST, U/l</td>
<td>37 ± 3.3</td>
<td>25.7 ± 3.3</td>
<td>35.4 ± 3.3</td>
<td>39.5 ± 3.3</td>
<td>15.1 ± 1.0</td>
</tr>
<tr>
<td>ALT, U/l</td>
<td>32 ± 3.3</td>
<td>31.8 ± 3.3</td>
<td>35.4 ± 3.3</td>
<td>39.5 ± 3.3</td>
<td>17.1 ± 1.0</td>
</tr>
<tr>
<td>γ-GT, U/l</td>
<td>89 ± 10</td>
<td>72 ± 10</td>
<td>86 ± 16</td>
<td>97 ± 14</td>
<td>18 ± 2.0</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>4.56 ± 0.43</td>
<td>3.03 ± 0.55</td>
<td>3.84 ± 0.45</td>
<td>5.78 ± 0.80</td>
<td>1.82 ± 0.28</td>
</tr>
<tr>
<td>QUICKI</td>
<td>0.315 ± 0.003</td>
<td>0.330 ± 0.009</td>
<td>0.320 ± 0.005</td>
<td>0.305 ± 0.005</td>
<td>0.378 ± 0.007</td>
</tr>
</tbody>
</table>

**Child A, Child B, and Child C** represent Child-Pugh classifications assigned to liver cirrhosis patients. BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GT, γ-glutamyltransferase; HOMA-IR, homeostasis model assessment of insulin resistance; QUICKI, quantitative insulin-sensitivity check index. Data are means ± SE. *P < 0.05, significantly different from cirrhosis.
Detroit, MI). Calculations were performed using previously described formulas (46).

Statistics. Statistical analysis was carried out using the statistical package for social sciences (SPSS). Data are expressed as means ± SE. Nonparametrical 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 Mann-Whitney’s 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 resistin levels are elevated in cirrhosis, dependent on clinical stage and etiology of liver disease. Patients with liver cirrhosis had 86% higher circulating resistin levels compared with controls (6.5 ± 0.4 vs. 3.5 ± 0.2 ng/ml, respectively, P < 0.001, Fig. 1). Whereas patients in clinically early stages of the disease exhibited already increased resistin levels but no difference between the Child A and Child B stages [5.6 ± 0.6 and 5.6 ± 0.6 ng/ml, respectively, not significant (NS); Fig. 2A], in Child C patients resistin was further significantly elevated (7.7 ± 0.7 ng/ml, P < 0.05; Fig. 2A). Plasma resistin levels did not differ between male and female patients with liver cirrhosis (6.5 ± 0.6 vs. 6.6 ± 0.6, respectively, NS).

Interestingly, in the stable long-term course after liver transplantation, circulating resistin levels remained elevated (6.8 ± 0.6 ng/ml, P < 0.001 compared with controls, NS compared with pretransplant levels; Fig. 1) with no difference between males and females (6.7 ± 1.1 vs. 6.8 ± 0.6 ng/ml, respectively, NS).

However, the underlying etiology of liver cirrhosis had an impact on circulating plasma resistin. Whereas patients with alcoholic and biliary liver disease displayed similar resistin levels (7.8 ± 1.0 and 7.0 ± 0.7 ng/ml, respectively, NS; Fig. 2B), these levels were significantly lower in patients with cirrhosis due to chronic hepatitis despite having a similar distribution of clinical severity as assessed by the Child-Pugh classification compared with the other groups (4.9 ± 0.5 ng/ml, P < 0.05; Fig. 2B).

Circulating adiponectin levels (17.2 ± 1.8 vs. 7.9 ± 1.0 μg/ml, respectively, P < 0.001) as well as circulating leptin levels (9.4 ± 1.7 vs. 5.6 ± 1.4 ng/ml, respectively, P < 0.01) were also increased in the patients with liver cirrhosis compared with the control group.

Circulating resistin levels in cirrhosis increase with increasing levels of proinflammatory cytokine TNF-α. Arterial and hepatic venous resistin levels were closely related in patients with cirrhosis (r = 0.88, P < 0.001; Fig. 3) with higher hepatic venous compared with arterial resistin concentrations (7.4 ± 0.5 vs. 6.5 ± 0.5 ng/ml, respectively, P < 0.001). Hepatic turnover data demonstrated a significant hepatic percent resistin production (18 ± 4%, P < 0.001) as well as resistin production per minute (543 ± 123 ng/min, P < 0.001) in patients with cirrhosis. However, hepatic production/extraction did not differ among patients in different Child stages or among patients with different underlying etiologies of the liver disease. Plasma resistin did not correlate with the hepatic venous pressure gradient as a measure of portal pressure (r =
0.10, NS), liver blood flow \((r = -0.17, NS)\), the ICG half-life \((r = -0.02, NS)\), and monoethylglycinexylidide formation \((r = -0.09, NS)\). These data indicate that, in contrast to adiponectin \((47)\), altered hepatic hemodynamics including deteriorated effective hepatic blood flow do not represent the underlying cause of elevated resistin in cirrhotic patients.

Because resistin expression has been reported to increase in response to proinflammatory cytokines \((12, 19, 21)\), we next assessed the relationship between plasma resistin in cirrhosis and parameters of the proinflammatory state in these patients. Circulating resistin was significantly correlated with plasma levels of TNF-\(\alpha\) \((r = 0.62, P < 0.001; \text{Fig. 4})\) but not with IL-1\(\beta\) \((r = 0.03, NS)\) and IL-6 \((r = -0.18, NS)\). It is important to note that circulating TNF-\(\alpha\) levels were significantly lower in the group of patients with chronic hepatitis as the underlying cause of elevated resistin in cirrhotic patients.

Interestingly, even in our patients with no evidence of renal failure, plasma levels of resistin were significantly positively correlated with plasma creatinine \((r = 0.40, P < 0.01)\), plasma urea \((r = 0.44, P = 0.001)\), and plasma uric acid levels \((r = 0.46, P < 0.001)\) in accordance with previous results obtained in patients with severe renal failure \((14)\).

\textbf{Circulating resistin levels in cirrhosis are not associated with circulating hormones and degree of insulin resistance.} In patients with liver cirrhosis, plasma resistin levels did not correlate with circulating levels of epinephrine \((r = -0.04, NS)\), norepinephrine \((r = -0.08, NS)\), dopamine \((r = -0.24, NS)\), insulin \((r = -0.01, NS)\), C-peptide \((r = 0.21, NS)\), and glucagon \((r = -0.14, NS)\).

Importantly, circulating resistin in cirrhosis also was not related to HOMA-IR \((r = 0.09, NS)\) and QUICKI \((r = -0.09, NS)\), established indexes of insulin resistance that have been validated for use in patient collectives with liver cirrhosis \((30)\). After liver transplantation, insulin resistance was improved as assessed using the indexes HOMA-IR \((2.56 \pm 0.42 \text{ vs. } 4.56 \pm 0.43, \text{respectively}, P < 0.01)\) and QUICKI \((0.352 \pm 0.009 \text{ vs. } 0.315 \pm 0.003, \text{respectively}, P < 0.01)\) but not normalized \((P < 0.05 \text{ compared with controls for both indexes})\). However, also after liver transplantation, plasma resistin levels were correlated with neither HOMA-IR \((r = 0.10, NS)\) nor QUICKI \((r = -0.11, NS)\).

\textbf{Circulating resistin levels in cirrhosis are not associated with parameters of body composition and whole body energy/substrate metabolism.} Patients with liver cirrhosis display a variety of systemic metabolic alterations \((24, 26)\). Because the underlying etiology of these is not unequivocally clarified, we next investigated whether resistin may have an impact on these conditions. However, body mass index \((r = 0.02, NS)\), systemic oxygen consumption \((r = 0.13, NS)\), respiratory quotient \((r = -0.04, NS)\), resting energy expenditure \((r = 0.13, NS)\), and the oxidation rates of carbohydrates \((r = -0.13, NS)\), fat \((r = 0.20, NS)\), and protein \((r = 0.04, NS)\) were not significantly correlated with circulating resistin concentrations. In addition, parameters of body composition such as body fat mass \((r = 0.17, NS)\), fat free mass \((r = 0.01, NS)\), body cell mass \((r = 0.07, NS)\), or lean body mass \((r = 0.15, NS)\) also had no statistically significant association with plasma resistin levels in cirrhosis. Furthermore, our data did not provide evidence for a correlation between plasma total cholesterol \((r = -0.10, NS)\) or triglycerides \((r = 0.06, NS)\) and circulating resistin.

\textbf{Circulating resistin levels in cirrhosis are associated with parameters of hepatic metabolism.} Plasma resistin in cirrhosis was not correlated with hepatic oxygen consumption, indicating no significant impact of resistin on global hepatic metabolic activity \((r = -0.02, NS)\). However, increasing resistin levels were linked with a decrease in hepatic glucose production \((r = -0.47, P < 0.01; \text{Fig. 5A})\), whereas resistin was not associated with blood glucose levels \((r = 0.15, NS)\). To compensate for decreased glucose production, ketogenesis from fatty acids is increased within the cirrhotic liver \((26)\). Interestingly, plasma resistin correlated with circulating FFA levels \((r = 0.40, P < 0.01; \text{Fig. 5B})\) as well as with circulating levels of 3-hydroxybutyrate \((r = 0.48, P < 0.001; \text{Fig. 5C})\) and acetoacetate \((r = 0.34, P < 0.05; \text{data not shown})\). Furthermore, circulating resistin levels were also positively associated with hepatic production of 3-hydroxybutyrate \((r = 0.40, P < 0.01; \text{Fig. 5D})\).
and acetoacetate \((r = 0.40, P < 0.01; \text{data not shown})\). Therefore, these data indicate that resistin may have an impact on the hepatic regulation of glucose production and ketogenesis in liver cirrhosis.

**DISCUSSION**

This study demonstrates that 1) plasma resistin levels are elevated in patients with liver cirrhosis, dependent on the clinical stage as well as on the etiology of the liver disease; 2) the increase in circulating resistin in cirrhosis may be due to an increased hepatic production and is related to the proinflammatory state of cirrhotic patients; and 3) elevated plasma resistin in cirrhosis is associated with hepatic glucose and ketone body metabolism but may not be an underlying factor of insulin resistance and the disturbed whole body metabolism.

It is important to point out that there are substantial differences regarding the tissues synthesizing resistin between rodents and humans. Whereas in rodents resistin is almost exclusively expressed in white adipose tissue, in humans the contribution of adipocytes to circulating resistin appears to be minor (43). Thus far, we are not aware of any human study reporting plasma resistin levels or resistin expression in cirrhosis. Consistent with our data, a recent study in rats with liver cirrhosis following bile duct ligation indicated that, in this condition, plasma resistin levels are elevated because of increased synthesis within adipose tissue (20). However, in humans, monocytes/macrophages rather than adipocytes have been reported as the major contributors to circulating resistin (19, 37). Resistin expression within these cells is increased in response to inflammatory stimuli, namely, TNF-\(\alpha\) (4, 12, 19, 21, 37). Our data are in line with these findings, showing a tight correlation between circulating resistin levels and elevated plasma TNF-\(\alpha\). The lack of a correlation between circulating resistin levels and altered hepatic hemodynamics, especially the ICG clearance as a measure of effective hepatic blood flow, indicates that in contrast to adiponectin (47), the metabolic basis for elevated resistin in cirrhosis is not decreased hepatic clearance. Because 10% of total liver cell mass consists of Kupffer cells, representing resident macrophages, the significant increase in hepatic resistin release in cirrhotic patients observed in our study conceivably may be due to increased resistin production by these cells in response to TNF-\(\alpha\), although this concept was not directly addressed in our current study. However, other liver cell types may not represent a likely source of resistin production: hepatocytes and endothelial cells do not express resistin, and although in rats resistin expression has been demonstrated in quiescent hepatic stellate cells, this was abolished when these cells became activated, as is the case in a fibrotic/cirrhotic liver (39).

In our study, patients with chronic hepatitis had significantly lower plasma resistin levels compared with patients with cirrhosis due to other etiologies. Because there was a tight correlation between plasma TNF-\(\alpha\) levels and plasma resistin levels, this observation might be explained in part by the lower TNF-\(\alpha\) levels in patients with chronic hepatitis. However, the underlying immunological basis of this finding remains un-
clear. It is important to point out that the inflammatory response underlying obesity and the metabolic syndrome may have a nature completely different from that of the inflammatory response associated with a chronic degenerative disease such as liver cirrhosis, and especially cirrhosis due to chronic viral infections (7, 13). Therefore, conceivably, the consequences in terms of effects on gene regulation and expression may also be different. In this respect, the observation of decreased circulating resistin levels in patients with chronic hepatitis as the underlying etiology of cirrhosis is striking and requires further mechanistic studies.

Liver cirrhosis is a catabolic disease with affected patients displaying increased resting energy expenditure and increased fat oxidation rates as well as decreased body fat mass and body cell mass (24, 26). Notably, in patients with cirrhosis, resistin was not associated with any of these parameters. In vitro studies in mouse 3T3-L1 adipocytes suggested that resistin inhibited adipogenesis (15). This was supported by an in vivo study in mice demonstrating that resistin mRNA decreased during the development of obesity (17). However, the resistin knockout mouse did not show differences in body weight and body fat mass compared with wild-type controls even when challenged with a high-fat diet (1). Also, resistin transgenic mice did not display changes in body weight compared with controls (33). In humans, adipose resistin mRNA levels and plasma resistin were increased in diverse obese patient populations (3, 28, 37, 41, 50, 51). In contrast, other studies did not find a correlation between plasma resistin levels and obesity (6, 18). Interestingly, in patients with genetic lipodystrophy that exhibit reduced adipose tissue mass, plasma resistin levels were unchanged compared with controls (5). Also, in patients with reduced body fat mass due to anorexia nervosa and bulimia nervosa, serum resistin was not altered (10).

Another important feature of resistin that is already implied by its name ("resistant to insulin") is the ability of this adipokine to induce insulin resistance (13, 43). However, in our study, plasma resistin levels were not correlated with HOMA-IR and QUICKI, indexes of insulin resistance that have been thoroughly validated for the use in patient collectives with liver cirrhosis (30). Interestingly, although HOMA-IR and QUICKI, as measures of insulin resistance, were significantly improved in the clinically stable long-term course after liver transplantation, plasma resistin levels remained unchanged. These data further stress that, at least in patients with liver disease, plasma resistin levels are not linked to insulin resistance. In rodents, administration of resistin to wild-type mice induced insulin resistance (42). However, in several different rodent models of insulin resistance and diabetes, resistin expression has been reported to be increased (2, 8, 42), decreased (11, 32), or unchanged (23) compared with wild-type controls. More conclusive evidence came from genetically modified mouse models: results in resistin knockout mice (1), mice with attenuated resistin expression by means of antisense oligonucleotides (27), and liver-specific resistin transgenic mice (33) all indicated that the main metabolic effect of resistin on glucose metabolism is to increase hepatic glucose production. In our study, however, high resistin levels were associated with decreased hepatic glucose production. In addition, increased hepatic glucose production does not seem to be the underlying cause of glucose intolerance and hepatojenous diabetes in patients with cirrhosis (31, 34, 36), because this condition is characterized by decreased hepatic glucose output. Furthermore, in contrast to the situation in patients with type II diabetes, e.g., associated with obesity, hepatic glucose production in patients with cirrhosis is suppressed by insulin to a degree similar to that in controls, suggesting that there is no significant hepatic insulin resistance in cirrhosis (31, 34).

In other human studies, insulin-resistant or type II diabetic patients were reported to have increased (52), unchanged (6, 18), or even decreased (38) circulating resistin levels. Overall, the correlation with insulin resistance appears to be poor in humans (6, 28, 52). In agreement with our study, two recent reports on patients not primarily selected for obesity and insulin resistance indicated that in subjects with cardiovascular disease (35) as well as in patients with terminal renal insufficiency (14), resistin is not associated with insulin resistance. These findings may indicate that human and rodent resistin have different biological functions. On the other hand, the role of resistin in disease models such as renal failure has not been investigated in experimental animals so far.

In our study, circulating resistin levels were correlated with the increased circulating FFA levels in patients with cirrhosis, indicating that resistin might contribute to FFA release by adipose tissue. In the livers of patients with cirrhosis, increased ketogenesis with FFA as a substrate has been reported, and ketone bodies contribute significantly to the energy supply of these patients in the fasted state (26). In our study, plasma resistin levels also were significantly positively associated with circulating ketone bodies as well as with the rate of hepatic ketogenesis in cirrhosis. However, further studies are required to address this point and to investigate the underlying basis of these findings on the molecular level.

In summary, we demonstrate that circulating resistin levels are elevated in liver cirrhosis, a catabolic disease characterized by reduced body fat mass and a proinflammatory state. Our data indicate that reducing resistin expression may not represent a suitable target for the treatment of hepatogenous insulin resistance and diabetes, because resistin in patients with cirrhosis was not associated with measures of insulin resistance. However, further studies are required to delineate the effects of elevated resistin in cirrhosis on key metabolic functions of the liver such as glucose production and ketogenesis.

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