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Significance of serum adiponectin levels in patients with chronic liver disease

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ABSTRACT

Adiponectin, which plays a pivotal role in metabolic liver diseases, is reduced in concentration in patients with NASH (non-alcoholic steatohepatitis). The aim of the present study was to determine adiponectin concentrations in patients with different forms and stages of chronic liver diseases. Serum adiponectin concentrations were measured in 232 fasting patients with chronic liver disease: 64 with NAFLD (non-alcoholic fatty liver disease), 123 with other chronic liver disease (e.g. viral hepatitis, $n = 71$; autoimmune disease, $n = 18$; alcohol-induced liver disease, $n = 3$; or elevated liver enzymes of unknown origin, $n = 31$) and 45 with cirrhosis. Circulating adiponectin levels were significantly lower in patients with NAFLD in comparison with patients with other chronic liver disease (4.8 ± 3.5 compared with 10.4 ± 6.3 μg/ml respectively; $P < 0.0001$). Circulating adiponectin levels were significantly higher in patients with cirrhosis in comparison with patients without cirrhosis (18.6 ± 14.5 compared with 8.4 ± 6.1 μg/ml respectively; $P < 0.0001$). Adiponectin concentrations correlated negatively with body weight ($P < 0.001$), serum triacylglycerols (triglycerides) ($P < 0.001$) and, in women, with BMI (body mass index) ($P < 0.001$). Adiponectin concentrations correlated positively with serum bile acids ($P < 0.001$), serum hyaluronic acid ($P < 0.001$) and elastography values ($P < 0.001$). Adiponectin levels were decreased in patients with NAFLD. In conclusion, adiponectin levels correlate positively with surrogate markers of hepatic fibrosis (transient elastography, fasting serum bile acids and hyaluronate) and are significantly elevated in cases of cirrhosis.

INTRODUCTION

Adiponectin is a 244-amino-acid adipocytokine that plays a pivotal role in metabolic liver diseases. Adiponectin is produced by adipocytes [1,2] and circulates at high concentrations (0.5–30 μg/ml) in plasma under normal physiological conditions. Adiponectin levels are hormonally regulated: the hormone testosterone inhibits adiponectin secretion, triggering lower levels of adiponectin in men [3]. In the liver, adiponectin increases fatty acid β-oxidation, thereby decreasing hepatic TG [triacylglycerol (triglyceride)] content and hepatic insulin resistance. Adiponectin-associated metabolic effects are exerted via corresponding receptors, AdipoR1 (adiponectin receptor 1) and AdipoR2 (adiponectin receptor 2). Although AdipoR1 is considered important for

Key words: adiponectin, chronic liver disease, cirrhosis, hepatic fibrosis, metabolic syndrome, non-alcoholic fatty liver disease (NAFLD).

Abbreviations: AdipoR, adiponectin receptor; ALT, alanine aminotransferase; ANCOVA, analysis of covariance; AST, aspartate aminotransferase; BMI, body mass index; HOMA, homoeostasis model assessment; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; TG, triacylglycerol.

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mediating adiponectin effects in skeletal muscle, AdipoR2 appears to be the predominant player in liver [4,5].

Adiponectin plasma levels correlate negatively with BMI (body mass index) and body fat mass, and fasting plasma glucose, insulin and TG levels [1,2,6,7]. Patients with NASH (non-alcoholic steatohepatitis) have reduced circulating adiponectin levels [5,8–10]. The ease with which the levels of adiponectin can be measured, owing to its high abundance, small diurnal variation and high stability in plasma, has made it an attractive target for measurements in clinical settings. It has emerged as a valuable biomarker to monitor insulin sensitivity, cardiovascular risk and inflammation; however, its significance in the setting of other chronic liver diseases still remains unknown.

Therefore the aim of the present study was to assess the value of measuring adiponectin concentrations in patients with NAFLD (non-alcoholic fatty liver disease) in comparison with patients with non-metabolic chronic liver diseases and patients with cirrhosis.

MATERIALS AND METHODS

Study design and patients

From 1 January 2006 to 31 December 2007, patients referred to a tertiary liver outpatient clinic were enrolled prospectively after signing an informed consent form and following the approval by the local ethics committee. For each patient, the following information was collected: age, BMI, diagnosis, serum fasting levels of TGs, bile acids, hyaluronate, aminotransferases, glucose and insulin, transient elastography, measured using FibroScan®, co-morbidities and current medication. We assigned all patients to one of three groups: (i) NAFLD, (ii) chronic liver diseases other than NAFLD (including viral hepatitis, $n=71$; autoimmune disease, $n=18$; alcohol-induced liver disease, $n=3$; or elevated liver enzymes of unknown origin, $n=31$) and (iii) cirrhosis (whatever its cause). The allocation was based on the following criteria: cirrhosis, biopsy-proven or complications of cirrhosis (oesophageal varices, ascites); and NAFLD, biopsy-proven or clinical presentation [adiposity, hyperlipidaemia in combination with elevated ALT (alanine aminotransferase) after exclusion of other liver disease and hyperechogenic appearance of liver parenchyma at sonography].

Adiponectin serum levels of 20 healthy control subjects were measured from 1 January 2006 to 31 December 2006. Prior to measurement, all control subjects underwent a detailed interview, a clinical examination, and serum CRP (C-reactive protein), creatinine and albumin were measured to exclude chronic diseases. At the time of blood sampling, all controls were free of pharmacological treatments.

Biochemical assays

Fasting serum adiponectin levels were determined with a human colorimetric sandwich ELISA kit (Mediagnost). Insulin levels were quantified by electrochemiluminescence. Hyaluronate was determined using the Corgenix protein binding assay. Bile acids were monitored enzymatically using the reagents from Trinity Biotech on a Mira plus chemistry analyser (Roche Diagnostics). Briefly, bile acids were first oxidized to 3-oxo bile acids in the reaction catalysed by 3α-HSD (3α-hydroxysteroid dehydrogenase). During this oxidative reaction, an equimolar quantity of NAD [11] is reduced to NADH. The NADH is subsequently oxidized to NAD with concomitant reduction of NBT (Nitro Blue Tetrazolium) salt to formazan by the catalytic action of diaphorase. The formazan has an absorbance maximum at 530 nm. The intensity of the colour produced is directly proportional to the concentration of the bile acids in the sample. Glucose, TGs, ALT and AST (aspartate aminotransferase) were determined in the Clinical Chemistry Laboratory of the Inselpital (Bern, Switzerland). HOMA (homoeostasis model assessment) scores were calculated with the HOMA index formula [insulin (μ-units/ml)$\times$glucose (mmol/l)/22.5]. All measurements were made according to the manufacturer's protocol. Elastography was assessed using FibroScan® by an experienced investigator.

Statistical analysis

Q-Q (quantitle-quantile) plots were made to confirm the parametric distribution of the data. Pair-wise comparisons of the serum concentrations of adiponectin with AST, ALT, bile acids, hyaluronate, insulin, glucose, TG, elastography, fibrosis and HOMA index were performed by correlation matrices. One-way ANOVA, χ^2 tests and independent Student's t tests were used to compare the groups. Data were adjusted for age, gender and BMI using ANCOVA (analysis of co-variance). All tests were performed using SAS/STAT or Prism5 Software.

RESULTS

A total of 232 patients (136 men and 96 women) and 20 healthy controls (11 men and 9 women) were included: 64 patients with NAFLD, 123 with other chronic liver disease and 45 with cirrhosis. Of these, 101 patients had a liver biopsy (40 with NAFLD, 42 with other chronic liver disease and 19 with cirrhosis). The anthropometric data are shown in Table 1 and Supplementary Figure S1 (at http://www.clinsci.org/cs/119/cs1190431add.htm). ANOVA revealed differences between the patient groups for adiponectin, BMI, transient elastography, AST, glucose, insulin, HOMA index, bile acids, TGs and hyaluronic acids, whereas there was no significant difference for ALT (Table 1). BMI and the HOMA index were significantly higher in patients with NAFLD

Table 1 Anthropometric data and laboratory values of the three different patient groups and the controls

Values are presented as means. *P* values were obtained with one-way ANOVA and χ^2 tests comparing the three patient groups.

	Patients with				
Characteristic	Cirrhosis ($n = 45$)	NAFLD ($n = 64$)	Other liver disease ($n = 123$)	Controls ($n = 20$)	*P* value
Gender (*n*) (male/female)	29/16	49/15	58/65	11/9	0.001
Diabetes/treated (*n*)	7/6	15/13	5/3	—	0.39
Age (years)	57	52	49	37	0.01
BMI (kg/m^2)	28.1	30.5	25.8	23.7	<0.001
ALT (units/l)	59.1	73.2	61.2	—	0.12
AST (units/l)	82.9	51.6	50.3	—	<0.001
Bile acids (μmol/l)	68.7	23.8	24.7	—	<0.001
Hyaluronate (μg/l)	340	41	47	—	<0.001
FibroScan® (kPa)	40.3	8.9	7.7	—	<0.001
TG (mmol/l)	1.5	2.4	1.2	—	0.001
Insulin (μ-units/ml)	16.4	18.8	8.4	—	<0.001
Glucose (mmol/l)	5.8	6.0	5.0	—	<0.001
HOMA	3.6	5.1	2.0	—	<0.001
Adiponectin (μg/ml)	18.6	4.8	10.4	9.1	<0.001

($P < 0.001$), whereas hyaluronate, bile acids and elastography values were significantly higher in patients with cirrhosis ($P < 0.001$).

Fasting serum adiponectin levels were higher in patients with cirrhosis compared with patients without cirrhosis (18.6 ± 14.5 compared with 8.4 ± 6.1 μg/ml respectively; $P < 0.0001$; Figure 1A). This difference remained after adjustment for age, gender and BMI ($P = 0.0001$). In patients with NAFLD, serum adiponectin levels were significantly decreased compared with those with other liver disease (4.8 ± 3.5 compared with 10.4 ± 6.3 μg/ml respectively; $P < 0.0001$; Figure 1B). Separating patients with simple steatosis from patients with NASH did not reveal a significant difference in serum adiponectin levels (Supplementary Figure S2 at http://www.clinsci.org/cs/119/cs1190431add.htm), and patients with NAFLD had decreased levels independently of age, gender or BMI ($P = 0.0001$). There was a significant correlation between serum adiponectin levels and bile acids ($r = 0.51$, $P < 0.001$), serum hyaluronate levels ($r = 0.52$, $P < 0.001$) and elastography values ($r = 0.45$, $P < 0.001$), consistent with the higher adiponectin levels observed in patients with cirrhosis (Figure 2).

Serum adiponectin levels significantly correlated with body weight and serum TG levels ($P < 0.001$) (Figure 3). Analysis according to gender revealed that adiponectin levels correlated with body weight in men and women ($r = -0.22$, $P = 0.024$ compared with $r = -0.29$, $P = 0.004$ respectively), whereas the correlation with BMI was lost in men ($r = -0.34$, $P < 0.001$ in women compared with $P = 0.22$ in men). No correlation was observed with markers of glucose metabolism (fasting glucose, insulin or HOMA index; results not shown).

Our healthy controls had adiponectin levels with the typical gender- and BMI-specific variations that have been reported previously ([10] and Supplementary Figure S3 at http://www.clinsci.org/cs/119/cs1190431add.htm) and that are in accordance with the validation study performed in 226 healthy subjects by Professor J. Kratzsch (Institute of Laboratory Medicine, Clinical Chemistry and Molecular Diagnostics, University of Leipzig, Leipzig, Germany) published in the ELISA kit manufacturer's protocol (http://search.cosmobio.co.jp/cosmo_search_p/search_gate2/docs/MDA_/E09.20081120.pdf).

DISCUSSION

The main findings of the present study are that BMI-, gender- and age-corrected serum adiponectin levels are low in patients with NAFLD, but are elevated in patients with cirrhosis. This has implications for its interpretation in the clinic.

Serum adiponectin levels are significantly lower in patients with NAFLD compared with patients with other chronic liver diseases. NAFLD is viewed as the hepatic manifestation of the metabolic syndrome and adiponectin measurement can help to identify patients with this condition. Others have suggested that the sensitivity of serum adiponectin levels in the diagnosis of NASH was 68 %, which was higher than for any other marker, while its specificity was 79 % [13]. Adiponectin prevents steatosis by stimulating mitochondrial β-oxidation via activation of AMPK (AMP-activated protein kinase) and PPAR-α (peroxisome-proliferator-activated receptor-α) and down-regulation of SREBP-1c (sterol-regulatory-element-binding protein-1c), a master regulator of fatty

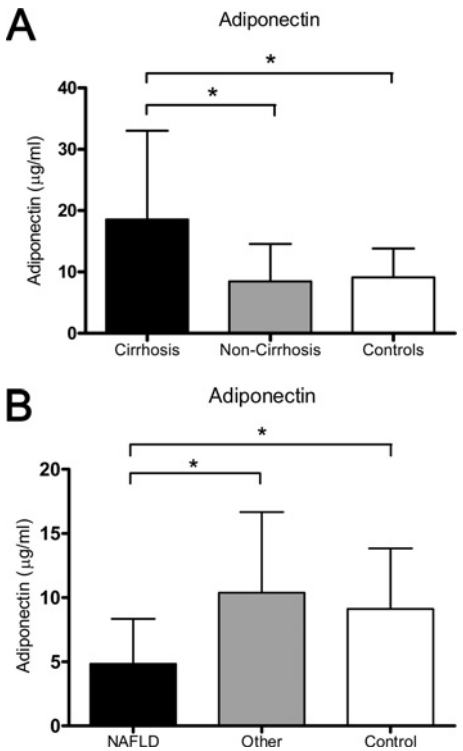

Figure 1 Adiponectin levels in the study groups

Adiponectin levels were significantly increased in patients with liver cirrhosis compared with patients without cirrhosis (non-cirrhosis) (A), whereas they were decreased in patients with NAFLD (B). Serum adiponectin levels are presented as means+S.D. $^*P < 0.001$ as determined by ANCOVA with adjustment for age, gender and BMI.

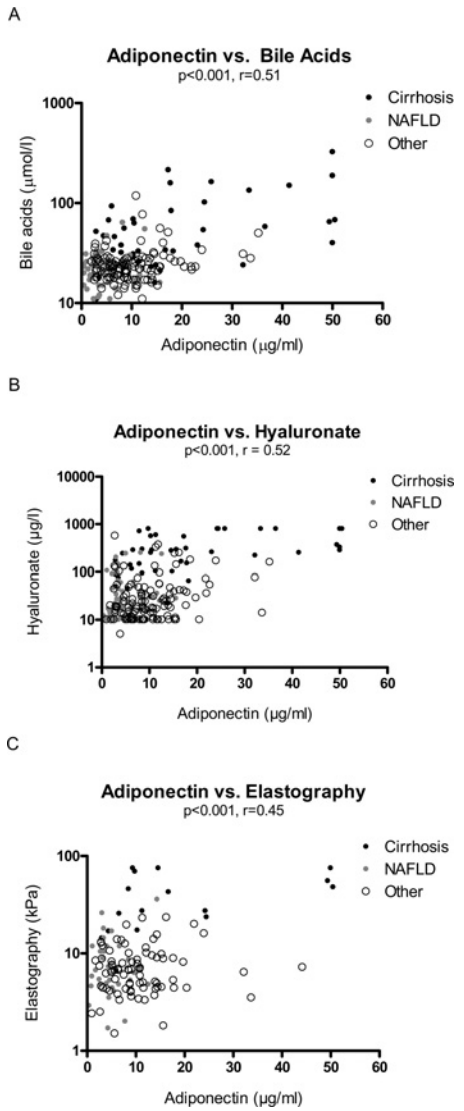

Figure 2 Correlation of serum adiponectin with bile acids, hyaluronate and elastography

Serum adiponectin levels were significantly correlated with bile acids, hyaluronate and elastography. Patients from all groups were considered together.

acid synthesis [14,15]. Moreover, adiponectin attenuates oxidative stress, pro-inflammatory cytokine production and ameliorates liver fibrosis via suppression of activated hepatic stellate cell function. Therefore low circulating levels of adiponectin may be associated with the development of NASH in patients with steatosis and in the progression of NASH towards cirrhosis. Outside the liver, decreased adiponectin concentrations are associated not only with increased coronary risk, but also with the progression of atherosclerosis in coronary vessels [11]. Thus adiponectin levels have a strong impact on disease-related morbidity and mortality in a variety of diseases associated with the metabolic syndrome.

Importantly, we found that adiponectin levels correlated well with markers of hepatic fibrosis, including serum fasting bile acids, hyaluronate and transient elastography, even in the presence of elevated BMI. It has been shown that serum bile acids are elevated in patients with NASH and increase with disease progression [16]. We demonstrated that adiponectin levels correlate significantly with serum bile acids and thus accompany disease progression. One may speculate that this increase is due to less clearance of adiponectin in the liver of patients with cirrhosis. In fact, high adiponectin levels after bile-duct ligation in mice and in human bile from patients with cholestasis suggest that biliary secretion is involved in adiponectin clearance [17]. However, a recent study has shown that the serum adiponectin concentration was negatively associated with higher levels of fibrosis and that low adiponectin levels are an independent risk factor for advanced fibrosis in patients with NAFLD [18]. Thus, in interpreting adiponectin levels in patients with NAFLD, one has to take into account the stage of the disease: if characteristically low in early stages, it will increase with the progression of the disease to actually be elevated in patients with cirrhosis. In our

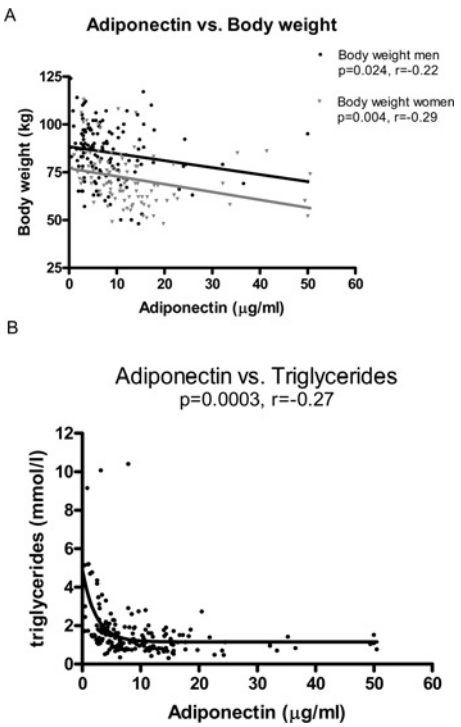

Figure 3 Correlation of serum adiponectin with body weight and TG

Serum adiponectin significantly correlates with body weight and serum TG (triglyceride) levels. Patients of all groups were considered together.

patient cohort, patients with NASH-induced cirrhosis had adiponectin concentrations similar to patients with cirrhosis of other causes (see Supplementary Figure S4 at http://www.clinsci.org/cs/119/cs1190431add.htm). This is in line with the observation that patients with NAFLD-induced cirrhosis frequently lose the histological features of NASH, such as steatosis.

Moreover, our present findings show a correlation between serum adiponectin levels and the body weight of patients. It has been shown that plasma adiponectin levels are lower in obese than in non-obese subjects, and weight reduction significantly raises plasma adiponectin levels [19,20]. Treating patients with NASH with vitamin E and UDCA (ursodeoxycholic acid) also significantly increased serum adiponectin levels [21]. Therefore adiponectin is the only fat protein that shows down-regulation in relation to weight gain, and it has been proposed that an accumulation of visceral fat might produce inhibiting factors for adiponectin synthesis or secretion [22]. Adiponectin levels significantly correlated with serum TG concentrations, another important parameter of the metabolic syndrome.

Thus serum adiponectin levels not only accompany markers of hepatic fibrosis, but also correlate with parameters involved in metabolic disease.

The present study is limited by its relatively small number of patients; many of them did not have a liver biopsy. However, it is a cross-sectional study, which represents the real situation of an outpatient clinic and shows the value of adiponectin monitoring in this setting. Cohort studies will be necessary to document the increase in circulating levels of adiponectin in patients with NASH when they develop cirrhosis. In our group of patients with NAFLD, we observed a male predominance (49 men/15 female). Adiponectin levels are known to be lower in males compared with females; however, analysis of the data adjusted for gender revealed no significant difference in the reduction in adiponectin levels in this patient subgroup.

In conclusion, adiponectin levels show a two-phase distribution in liver disease. In steatosis and NASH, adiponectin levels are low, in keeping with a proposed protective effect in these conditions and suggesting elevation of adiponectin as a desirable therapeutic target in NAFLD. In advanced liver disease, however, adiponectin is elevated. Therefore in the context of negative elastography, and serum hyluronate and bile acids, abnormally low adiponectin may be a good additional marker for NAFLD.

AUTHOR CONTRIBUTION

Maria Luisa Balmer redacted the manuscript; Jeannine Joneli determined the adiponectin levels; Alain Schoepfer recruited the patients and provided the samples; Felix Stickel recruited the patients and provided the samples; Wolfgang Thormann supervised the determination of the adiponectin levels; and Jean-François Dufour recruited the patients and provided the samples, designed and supervised the study.

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SUPPLEMENTARY ONLINE DATA

Significance of serum adiponectin levels in patients with chronic liver disease

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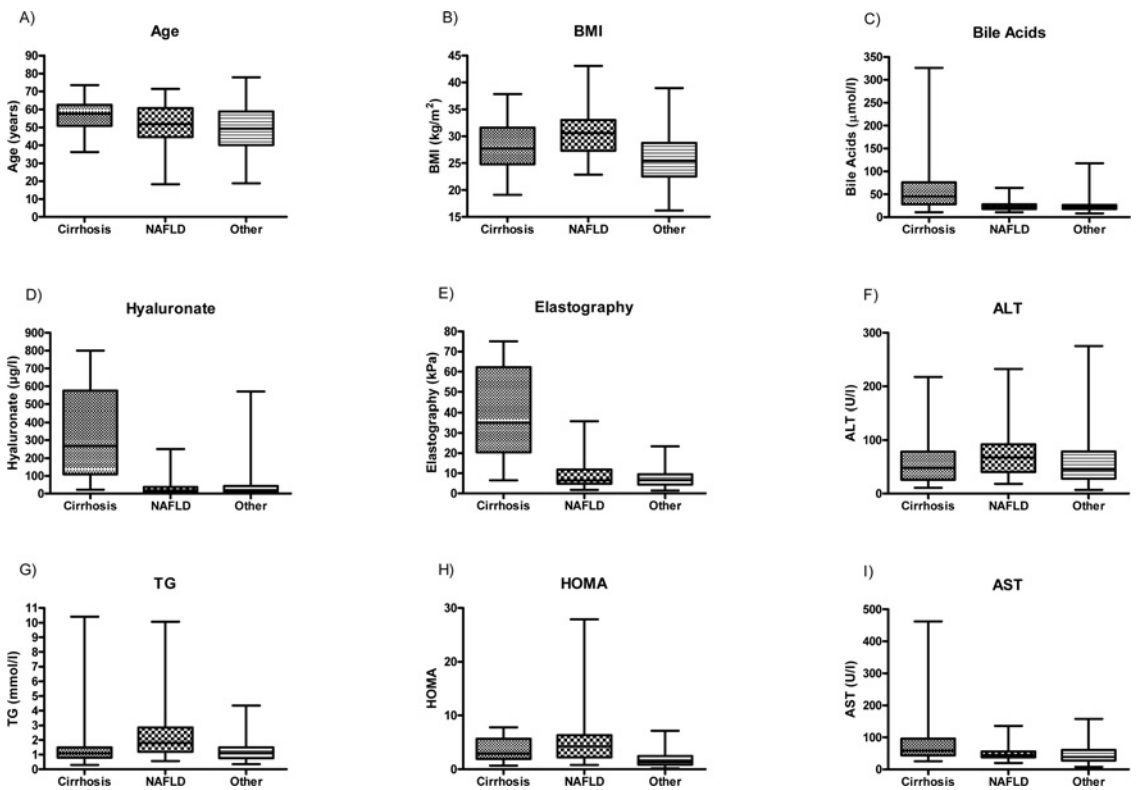

Figure S1 Distribution of anthropometric data and laboratory values in the three patient groups

The values shown are those presented in Table 1 of the main text.

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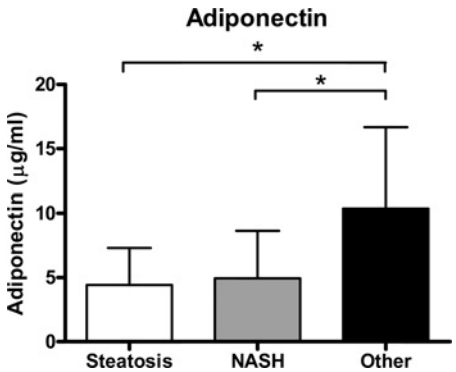

Figure S2 Serum adiponectin levels in patients with NAFLD and other chronic liver disease

Values are presented as means + S.D. No significant difference ($P = 0.62$) was observed between patients with simple steatosis ($n = 14$) and NASH ($n = 52$). *$P < 0.001$.

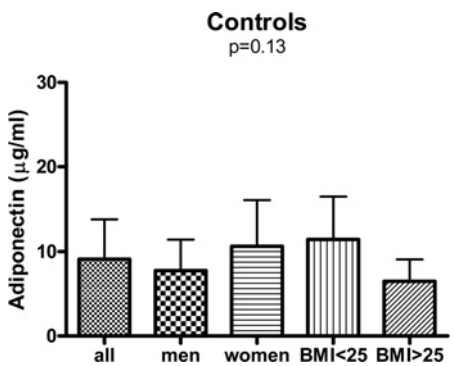

Figure S3 Serum adiponectin levels of healthy control subjects reflecting the typical gender- and BMI-related alterations

Values are presented as means + S.D.

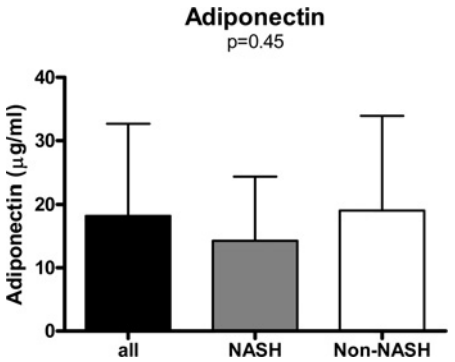

Figure S4 Serum adiponectin levels in patients with liver cirrhosis stratified by its origin

Values are presented as means + S.D. all, $n = 45$; NASH-related, $n = 7$; Non-NASH, $n = 38$.

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