Study of adiponectin in chronic liver disease and cholestasis

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Abstract

Purpose Adiponectin is an adipocytokine suggested to have a hepatoprotective effect. To date, little information is available in the literature regarding changes in serum adiponectin levels in cirrhosis and cholestasis and the associated metabolic disturbances. In order to elucidate the role of adiponectin in chronic liver disease our aim was to determine serum adiponectin in patients with different grades of cirrhosis and cholestasis and to correlate it with markers of liver injury, inflammation and cholestasis. We also aimed to correlate adiponectin with markers of metabolic syndrome such as body mass index and insulin resistance.

Methods Forty patients with cirrhosis; 30 patients with cirrhosis and cholestasis; and 20 matched controls were studied. They were subjected to clinical assessment, laboratory investigations: serum bilirubin, ALT, AST, alkaline phosphatase, GGT, albumin, C-reactive protein, prothrombin activity, fasting blood sugar, insulin. HOMA index was calculated. Abdominal ultrasonography and upper GI endoscopy were performed.

Results Adiponectin was elevated in patients with cirrhosis and cirrhosis/cholestasis and was significantly higher in Child A and B. Adiponectin showed correlation with liver cell injury, marker of inflammation, synthetic liver function and markers of cholestasis. Adiponectin did not correlate with complications of cirrhosis as ascites and

esophageal varices nor did it correlate with BMI or HOMA.

Conclusions Adiponectin is elevated in cirrhosis and shows correlation with degree of hepatocellular injury and cholestasis. Finally, adiponectin levels in cirrhosis do not correlate with parameters of body composition or metabolism but exclusively with reduced liver function.

Keywords Serum adiponectin · Cirrhosis and cholestasis

Introduction

Until recently, the white adipose tissue has been considered an inert tissue, mainly devoted to energy storage. Currently, it is regarded as an active endocrine organ acting in the regulation of metabolism [1].

Recent advances in cell biology have shown that adipocytes produce and secrete several bioactive molecules which are collectively referred to as adipocytokines. An adipocyte-specific secretory protein, adiponectin, the gene transcript of which was most abundant in the expression profiles of human adipose tissue was previously identified. Adiponectin is composed of 244 amino acid residues containing a short non-collagenous N terminal segment followed by a collagen-like sequence. It belongs to the family of proteins that include C1q and the collectins which play important roles in the innate humoral immune system [2]. Adiponectin is the most abundant circulating adipokine and modulates a wide array of biological functions. It was demonstrated to improve insulin resistance [3, 4] and play a role in the prevention of atherosclerosis [5]. In addition to the above actions, adiponectin has several anti-inflammatory effects. It facilitates the removal of early apoptotic cells by macrophages; it reduces TNF- α

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production in response to various stresses and antagonizes several of its inflammatory effects; it reduces monocyte attachment to endothelial cells by inhibiting expression of vascular cell adhesion molecules; intercellular adhesion molecules and E-selectin [6]; it inhibits the production of interleukin (IL)-6 and enhances the production of IL-10 and acts as a tissue inhibitor of metalloproteinase 1 [7, 8].

Adiponectin is reported to exert its effects by interaction with specific receptors, termed AdipoR1 and AdipoR2. AdipoR1 is abundantly expressed in skeletal muscles and has a prominent action to promote lipid oxidation. AdipoR2 is primarily transcribed in liver, where it enhances insulin sensitivity and reduces steatosis. The expression of AdipoR1 and AdipoR2 has been reported to be regulated by insulin in animal models and cell culture systems [9, 10].

Growing evidence suggests that adiponectin can regulate lipid and glucose metabolism and lipid fat content in hepatocytes. Adiponectin is also known to protect hepatocytes from injury [3, 7].

There has been evidence that this hormone critically influences several components of the metabolic syndrome. Lately, it was proposed to include nonalcoholic fatty liver disease (NAFLD) in the complex picture of the metabolic syndrome and it was proved that low circulating adiponectin had a role in the pathogenesis of NAFLD [11, 12]. AdipoR2 is a specific receptor transcript in hepatocytes and can also act as an anti-apoptotic agent in a variety of cell types [13–16].

To date, there is minimal information available in the literature regarding changes in serum adiponectin levels in cirrhosis and cholestasis and the associated metabolic disturbances. Therefore, in order to elucidate the role of adiponectin in chronic liver disease, we set out to determine circulating serum adiponectin level in patients with different grades of cirrhosis and cholestasis and to correlate it with markers of liver injury, inflammation and cholestasis. We also aimed to correlate adiponectin with markers of the metabolic syndrome as body mass index and insulin resistance in these patients.

Materials and methods

The present study was conducted at the National Liver Institute, Menoufyia University. Seventy patients with liver cirrhosis were recruited, 30 of whom suffered from cholestasis. Patients with sepsis, gastrointestinal bleeding or abnormal renal function were excluded. The control group comprised 20 apparently healthy non-obese individuals who were age and gender matched to the study group. An

informed consent was taken from all participants and the study respected the local official ethical rules.

All subjects were subjected to thorough history taking, medical and anthropometric examination with emphasis on body mass index, splenomegaly and ascites. The body mass index (BMI) for Child C patients was calculated using the patients' height and a corrected weight, in which the amount of ascites and/or pleural effusion estimated by ultrasound was subtracted from the measured total body weight. Child–Turcotte–Pugh score was calculated for the patients.

Laboratory investigations

Liver function tests including serum bilirubin, ALT, AST, alkaline phosphatase, gamma-glutamyl transpeptidase (GGT), serum albumin (using Integra 800, Roche) and prothrombin activity (by Quick one stage method, Thromborel S human thromboplastin containing calcium, Behring, 1991, Germany) were performed. High sensitive C-reactive protein was measured using a Beckman highly sensitive CRP kit. Fasting blood sugar was measured and fasting insulin was determined using a two-site, solid-phase, chemiluminescent, enzyme immunoassay intended for use on the IMMULITE immunoassay analyzer (Chemiluminescence Elycos 2010). Serum adiponectin was measured using Human Adiponectin/Acrp 30 Quantikine ELISA kit (R & D System Europe Ltd. Abingdon, UK).

The degree of insulin resistance was calculated from the homeostasis model assessment (HOMA). The HOMA-IR was calculated according to the report by Matthews [17] with the formula:

$$\frac{\text{Fasting plasma insulin } (\mu\text{U/ml}) \times \text{Fasting plasma glucose (mg/dl)}}{405}$$

- Abdominal ultrasound examination and upper GI endoscopy were also performed.
- Liver biopsy was performed for Child A patients.

Statistical analysis

The data were statistically analyzed using SPSS statistical package, release 13 for windows. Data were expressed as mean $\pm$ SD. Differences between two groups were analyzed by Mann–Whitney *U* test. Multiple comparisons were performed by one way ANOVA tests (*F* test) and Scheffe test was used for post hoc analysis. Spearman rank correlation was calculated to quantify the degree of linear

association between two variables. A p value < 0.05 was considered statistically significant.

Results

The present study was conducted on 70 Egyptian patients: 40 cirrhotic patients; 30 cirrhotic and cholestatic patients; and 20 age and gender-matched individuals acting as control. The underlying etiology of liver cirrhosis in all patients was hepatitis C. Participants were grouped as follows: group I, 20 subjects as control, 14 (70%) of them were males, with a mean age of 50.10 ± 9.339 years; group II, 40 patients with cirrhosis, 30 (75%) of them were males and 10 (25%) were females, their mean age was 53.34 ± 8.182 years; group III, 30 cirrhotic and cholestatic patients, 21 (70%) males and 9 (30%) females, with a mean age of 53.72 ± 8.231 years.

There was a statistically significant difference when comparing liver function tests as well as adiponectin between the studied groups (Table 1).

Serum adiponectin levels in the studied groups

In the patients' groups, adiponectin levels were not different between male and female patients ($p = 0.739$) (Table 1; Fig. 1). Adiponectin serum levels were elevated in patients with cirrhosis and cirrhosis/cholestasis compared to healthy controls. In the 20 healthy controls, serum adiponectin had a mean of 4.7 ± 4.48 $\mu\text{g/ml}$ (range 0.9–15.6; median 3.07).

In the 40 cirrhotic patients, adiponectin values ranged from 1.3 to 34.5 with a mean of 15.1 ± 12.14 $\mu\text{g/ml}$ and a median of 8.49. Serum adiponectin levels were significantly elevated compared with the control group ($p < 0.05$). In the 30 cirrhotic patients with associated cholestasis, mean adiponectin value was 21.28 ± 10.2 $\mu\text{g/ml}$

Fig. 1 Adiponectin level in studied cases

(range 2.8–34.1; median 25.11). Serum adiponectin levels were significantly elevated compared with the control group ($p < 0.001$). Adiponectin values showed no significant difference between patients with cirrhosis when compared to cirrhotic patients with cholestasis.

Relation between adiponectin and degree of liver cirrhosis

Among all cirrhotic patients 15 (21.43%) were classified as Child A, 10 (25%) and 5 (16.67%) from group II and III, respectively; 29 (41.43%) were classified as Child B, 16 (40%) and 13 (43.33%) from group II and III, respectively; and 26 (37.14%) were classified as Child C, 14 (35%) and 12 (40%) from group II and III, respectively (Fig. 2). Serum adiponectin levels were significantly elevated in Child A and Child B cirrhosis compared with the control group ($p < 0.05$), whereas levels in patients with Child C did not differ significantly from control, Child A, or Child B groups.

Table 1 Comparison between studied groups regarding different parameters

	I: Controls	II: Cirrhotics	III: Cholestatics	<i>F</i>	<i>p</i>
Age (years)	50.10 ± 9.339	53.34 ± 8.182	53.72 ± 8.231	0.682	0.51
BMI (kg/m^2)	26.92 ± 4.29	27.94 ± 4.29	26.46 ± 4.52	0.701	0.501
ALT (U/L)	19.4 ± 6.69	56.71 ± 58.63	102.72 ± 140.03	3.039	0.56
AST (U/L)	22.6 ± 7.52	71.06 ± 60.06	105.94 ± 79.66	5.8	0.005*
ALP (U/L)	68.1 ± 19.66	116.34 ± 46.36	277 ± 339.8	5.14	0.009*
GGT (U/L)	33.1 ± 6.79	58.63 ± 33.62	187.72 ± 277.49	4.66	0.014*
Bilirubin (mg/dl)	0.88 ± 0.103	2.48 ± 2.55	16.62 ± 9.7	38.83	$<0.001^*$
Albumin (g/dl)	4.23 ± 0.38	2.92 ± 0.77	2.569 ± 0.64	18.56	$<0.001^*$
Prothrombin time	12.4 ± 1.04	16.3 ± 5.2	17.61 ± 4.9	17.65	$<0.001^*$
HOMA index	2.96 ± 1.03	2.96 ± 1.03	3.96 ± 2.41	0.681	0.51
Adiponectin ($\mu\text{g/ml}$)	4.7 ± 4.48	15.1 ± 12.14	21.28 ± 10.2	8.033	0.001*

Fig. 2 Adiponectin value in different grades of cirrhosis

Relation between adiponectin and markers of hepatic injury

Adiponectin levels are closely correlated with markers of hepatic injury and hepatic inflammation, such as aspartate-aminotransferase ($r = 0.367$, $p < 0.05$), and alanine aminotransferase ($r = 0.283$, $p < 0.05$) (Fig. 3a–c).

Moreover, adiponectin is positively correlated with C-reactive protein as one of the inflammatory parameters ($r = 0.406$, $p < 0.05$).

Relation between adiponectin and parameters of hepatic protein synthesis

Adiponectin levels are inversely correlated with serum albumin ($r = -0.287$, $p < 0.05$) (Fig. 3d). On the other hand, adiponectin did not correlate with prothrombin time ($r = 0.278$, $p = 0.053$).

Relation between adiponectin and markers of cholestasis

Adiponectin is significantly correlated with indicators of cholestasis, e.g., serum alkaline phosphatase ($r = 0.394$, $p < 0.005$) and gamma-glutamyl transpeptidase ($r = 0.298$, $p < 0.05$) (Fig. 3e, f). Similarly, adiponectin is correlated significantly with bilirubin ($r = 0.369$, $p < 0.05$) (Fig. 4).

Relation between adiponectin and complications

From the studied cirrhotic patients, 29 (41.43%) patients had ascites, 14 (35%) were from the cirrhotic group and 15 (50%) from the cirrhotic cholestatic group. Adiponectin values showed no significant difference between patients

with ascites when compared to patients without ascites (167.53 ± 112.15 , 166.86 ± 118.44 , respectively, $p = 0.79$). Esophageal/gastric varices were present in 11 (15.71%) of the cases, 6 (15%) from the cirrhotic group and 5 (16.67%) from the cirrhotic cholestatic group. Similarly, no significant difference was observed between patients with esophageal/gastric varices when compared to patients without varices (204.01 ± 106.01 , 168.48 ± 118.32 , respectively, $p = 0.39$).

Relation between adiponectin and insulin sensitivity

Adiponectin did not correlate with BMI (corrected for the amount of ascites and pleural effusion) ($r = 0.024$, $p = 0.858$) or HOMA index ($r = -0.002$, $p = 0.99$) in cirrhotic patients.

Discussion

In the present study, adiponectin was significantly elevated in chronic liver disease compared to control. Likewise, this was reported in other studies [18–20]. In fact, data indicate that adiponectin plays an anti-inflammatory role in both acute and chronic inflammatory liver diseases [21, 22]. The observed high plasma adiponectin could reflect an imbalance between its production by adipocytes and metabolism in the liver [20]. Kaser [23] suggested that high adiponectin levels in chronic liver disease might reflect one of the body's anti-inflammatory mechanisms in this condition. The liver may play an important role in its catabolism and thus the elevated plasma levels in cirrhosis are, at least in part, due to decreased hepatic catabolism [18, 19]. Even true hepatic production might be another impact, since studies demonstrated that hepatocytes express significant amounts of adiponectin mRNA after injury [23, 24]. Similarly, Ding et al. [25] reported that quiescent hepatic stellate cells (HSC) synthesize adiponectin, which in turn can induce activated HSC apoptosis and inhibit their proliferation. Another suggested impact for the increased adiponectin in liver cirrhosis is altered hepatic extraction [18, 19]. The increased level of circulating adiponectin in cirrhosis seems to be independent of the underlying etiology. Previous studies demonstrated its elevation in cirrhosis due to hepatitis B, hepatitis C and primary biliary cirrhosis [23, 26, 27]. In the present study, all patients suffered from hepatitis C-related cirrhosis.

Moreover, the elevated adiponectin level showed correlation with the stage of liver cirrhosis as there was a significant increase in Child A and B but not C compared to control. Tietge et al. and Kaser et al. [18, 23] stated that the increases in circulating adiponectin depended on the clinical stage in cirrhosis compared with controls. Furthermore,

Fig. 3 Correlation between adiponectin and studied parameters. Adiponectin is positively correlated with **a** AST, **b** ALT, **c** CRP, **e** alkaline phosphatase, **f** GGT and inversely correlated with serum albumin (**d**)

adiponectin paradoxically increased with aminotransferase activities as markers of liver cell injury. Similar results were reported by Tacke et al. [28]. Jonsson [10] related the increment of adiponectin in chronic liver disease to increased inflammation and increased hepatic adiponectin immunoreactivity. Several clinical studies documented the relationship between low-plasma adiponectin concentrations in healthy individuals and high levels of CRP, an established inflammatory marker in various populations [29, 30]. Although the liver is considered the main source of CRP, serum levels of this acute-phase protein are not diminished in cirrhotics [31]. Kazumi et al. [32] reported an association

between marker of liver injury, alanine aminotransferase and the inflammatory marker, CRP. In the present study, adiponectin is correlated positively with CRP in cirrhotic patients in contrast to the inverse association present in healthy persons. This may represent a regulatory role of adiponectin in the chronic inflammatory state associated with liver cirrhosis, or alternatively it may be just a reflection of rising adiponectin level in cirrhosis, rather than a true relationship with inflammation.

In the present study, as well as that of Tietge [18], adiponectin is correlated with synthetic liver function, as there was an inverse correlation with albumin. Clinical

Fig. 4 Correlation between adiponectin and bilirubin

complications of cirrhosis such as ascites and development of esophageal varices did not affect the levels of adiponectin. Similar results were reported by Tacke et al. [28].

In addition to the fact that adiponectin was significantly higher in patients with cirrhosis and cholestasis than patients with cirrhosis, it was also associated with laboratory markers of cholestasis (bilirubin, alkaline phosphatase and GGT). This raises the suggestion that adiponectin might be elevated in cholestasis due to decreased biliary excretion. Although kidneys have been proposed to play a role in adiponectin biodegradation and/or elimination [33, 34], Tacke et al. [28] showed very high adiponectin levels in human bile in biliary obstruction suggesting that biliary excretion contributes to its clearance. Floreani et al. [35] observed that the high levels of adiponectin in patients with primary biliary cirrhosis is correlated with GGT as observed in the current study.

Hypermetabolism may occur in patients with liver cirrhosis regardless of the clinical, laboratory or histologic features of the disease or of its duration and severity, suggesting that extrahepatic factors are the major determinants of hypermetabolism [36]. Data from animal studies support the idea that adiponectin affects the metabolic rate, because adiponectin has been shown to attenuate weight gain [37]. In previous studies, adiponectin levels were invariably negatively correlated with body mass index [27]. Although adiponectin has been proposed to play important roles in the regulation of energy homeostasis, surprisingly there was no correlation between adiponectin and BMI in cirrhotic patients in the present study, in accordance with others [18, 27, 28]. Portal hypertension and portosystemic shunting in addition to the effects of the systemic inflammatory condition, which is mediated by increased concentrations of various cytokines,

and the effects of an increased β -adrenergic activity were suggested to cause hypermetabolism in clinically stable patients with liver cirrhosis. However, circulating adiponectin in cirrhosis increased without association with other metabolic items [36].

A strong association between adiponectin and insulin resistance has been extensively demonstrated [11, 38]. But the striking result of the current study is the lack of a correlation between insulin resistance, when tested by HOMA, and adiponectin levels in cirrhotic patients. Our findings might indicate that the pathogenesis of insulin resistance in cirrhosis differs from that in patients without liver disease, as consistent with previous reports [39, 40]. Tacke et al. [28] suggested that the physiological adiponectin regulation is significantly affected in patients with liver diseases compared with healthy volunteers. However, circulating adiponectin in cirrhosis increased notably and completely independently of all metabolic parameters [18].

To conclude, adiponectin level is elevated in cirrhosis and is correlated with degree of hepatocellular injury. Cholestasis may add a further factor by decreasing adiponectin clearance. Levels do not show correlation with parameters of body composition or metabolism but exclusively with reduced liver function.

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