Evaluation of Serum Levels of Adiponectin in Egyptian Patients with Chronic Hepatitis C

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Abstract

Introduction: Adiponectin is a protein hormone secreted by the adipose tissue. There is no data about the secretion of adiponectin during hepatitis C infection, some studies revealed that hypoadiponectinemia found with chronic HCV infection is significantly associated with the development of liver steatosis. Adiponectin may be an attractive therapy for fatty liver disease.

Aim of the Work: The aim of this study is to define a potential role of adiponectin in Egyptian patients with chronic hepatitis C virus infection and to investigate its role in HCV-related steatosis.

Subjects and Methods: The present study was conducted on thirty seven patients suffering from chronic hepatitis C and sixteen healthy volunteers served as controls.

Results: The significant finding of this study is that chronic HCV patients have reduced circulating adiponectin levels than healthy controls (12.7 ± 8.2 for HCV Vs. 19.5 ± 11.6 for control, p=0.04). However, there is no significant correlation seen between serum adiponectin level and steatosis as well as the grades of steatosis as mean adiponectin level is 9.00 ± 7.45 in steatosis <30% while it was 14.50 ± 2.12 in steatosis ≥30% (p=0.29).

Conclusion: This study demonstrated hypoadiponectinemia in HCV-infected patients, but this did not correlate with hepatic steatosis.

Key Words: Adiponectin – HCV – Steatosis.

Introduction

STEATOSIS is a common histological feature of HCV infection [1]. The prevalence of steatosis in liver biopsy specimens from patients with chronic HCV infection has been reported at around 50% [1]. Recent studies found a role for steatosis in the progression of chronic HCV [1-3]. The pathogenesis of steatosis in patients with HCV is not well understood [4]. Moreover, HCV-related steatosis is not always virally related and other factors may coexist [5]. Obesity is a well-recognized risk factor for the development of steatosis and of fibrosis in HCV-infected patients [1-3, 6]. Adipose tissue has traditionally been considered an energy storage organ, but over the last decade, a new role has emerged for the adipose tissue as an endocrine organ [7, 8]. Adipose tissues secrete a variety of hormones including adiponectin, and leptin which may contribute to the development of metabolic abnormalities [9].

It has also been documented that viral genotype is a major factor associated with steatosis in HCV infection. Traditionally, two types of hepatic steatosis are distinct in HCV infection: Virus-induced steatosis and metabolic steatosis. Virus-induced steatosis is related to genotype 3 infection, the degree of steatosis is related to viral load [8]. The antiviral therapy leads to complete reversal of lipid alterations and steatosis [10], but the virological relapse leads to the reappearance of steatosis [11]. Numerous studies indentified the metabolic intracellular pathways that mediate “viral steatosis” [7, 12].

Adiponectin is a molecule, protein in nature, which is present in the circulation as a low- and high-molecular weight forms and is secreted only from adipose tissues [13-15]. The high molecular weight form acts on insulin sensitivity and possesses anti-inflammatory properties [16]. It carries out its metabolic function by binding to Adipo R1 and Adipo R2 receptors, which are expressed in many tissues, particularly liver and muscle cells [17, 18]. Our aim in this study was to define a potential role of adiponectin in Egyptian patients with chronic hepatitis C.
hepatitis C virus infection and t investigate its role in HCV-related steatosis.

Patients and Methods

Thirty seven untreated chronic hepatitis C patients and Sixteen healthy volunteers serving as controls were enrolled in the study. The study was done in the Tropical Medicine Department, Faculty of Medicine, Cairo University and National Research Institute for Tropical Medicine and Liver Disease from 2008-2010.

Collected data included age, gender, past history of diabetes mellitus and alcohol use. BMI was calculated as body weight in kilograms divided by the square of height in meters (kg/m2). Subjects with BMI (<26kg/m2), were enrolled in the study.

Subjects who gave written consent to participate in the present study were subjected to Laboratory investigations including liver biochemical profile, anti-HCV antibody measured in serum samples by enzyme linked immunosorbant assay (ELISA) second and third generation. HCV RNA viral load were analyzed by serum real time polymerase chain reaction (PCR) and real time quantitative RT-PCR was performed in international units (IU)/ml.

All biochemical data were collected after an overnight fasting (12 hours) in both patients and controls.

Abdominal ultrasonography using an ultrasound scanner with a 3.5MHZ convex transducer was done to all patients.

Patients underwent an ultrasound-guided liver biopsy with true cut needle 16- or 14- gauge. The inter-costal technique is the method used. The biopsies were examined by single pathologist and the histological activity index (HAI), also called modified Knodell’s score was used to score the liver biopsies.

Statistics:

Patient’s data were tabulated and analyzed using SPSS 10.0 for Windows xp Quantitative data were expressed by mean and standard deviation (SD) and analyzed using t-student, Pearson or Spearman correlation whenever appropriate. Qualitative data were expressed by number and percent and compared by Chi-square test. p value was considered significant in all tests when less than 0.05.

Results

Both groups are age and sex matched. The main clinical and laboratory data are summarized in Table (1):

As shown in Table (2), the mean adiponectin levels is $12.73 \pm 8.17 \mu g/ml$ in the chronic HCV group and $19.50 \pm 11.57 \mu g/ml$ in the control group and this difference is a significant one ($p=0.043$).

Multivariate analysis, (Age versus adiponectin in the studied cases) shows that age was not a significant covariate with the level of adiponectin in cases and control in this study.

Adiponectin inversely correlated with FBS ($r=-0.043, p=0.78$) as well as serum Albumin, prothrombin time, total and direct bilirubin and it showed no significance by Pearson’s correlation.

There is an inverse correlation between adiponectin and serum triglycerides ($r=-0.22, p=0.16$); total cholesterol ($r=-0.16, p=0.29$) and high density lipoprotein (HDL) ($r=-0.14, p=0.35$) with no significance.

The low density lipoprotein (LDL) showed a non-significant positive correlation with adiponectin ($r=0.003, p=0.99$).

No significant correlation was found between adiponectin and ALT, AST and ALP. Correlation between adiponectin and other parameters among the HCV group under study were summarized in Table (3).

As for the histopathological activity index (HAI), the correlation is considered significant at the 0.01 level (2-tailed).

Table (1): Main clinical and laboratory data of the studied groups.

<table>
<thead>
<tr>
<th></th>
<th>HCV (No.=44)</th>
<th>Controls (No.=16)</th>
<th>Significance &amp; p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (weight/height²)</td>
<td>25.63±2.18</td>
<td>25.5±2.63</td>
<td>NS (0.9)</td>
</tr>
<tr>
<td>AST (IU/l)</td>
<td>61.09±35.51</td>
<td>27.94±9.02</td>
<td>HS (&lt;0.01)</td>
</tr>
<tr>
<td>ALT (IU/l)</td>
<td>77.82±54.34</td>
<td>30.31±9.024</td>
<td>HS (&lt;0.01)</td>
</tr>
<tr>
<td>ALP (IU/l)</td>
<td>130.45±57.51</td>
<td>95.31±21.97</td>
<td>HS (&lt;0.01)</td>
</tr>
<tr>
<td>T. BIL (mg/dl)</td>
<td>0.92±0.439</td>
<td>0.75±0.242</td>
<td>NS (0.139)</td>
</tr>
<tr>
<td>FBS (mg/dl)</td>
<td>98.59±17.68</td>
<td>99.38±18.44</td>
<td>NS (0.881)</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>160±84.76</td>
<td>137.13±75.9</td>
<td>NS (0.347)</td>
</tr>
<tr>
<td>Serum Cholesterol (mg/dl)</td>
<td>150.25±26.35</td>
<td>190.63±38.38</td>
<td>HS (0.01)</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>43.39±5.74</td>
<td>41.38±6.59</td>
<td>NS (0.235)</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>74.86±28.15</td>
<td>124±29.82</td>
<td>HS (&lt;0.01)</td>
</tr>
</tbody>
</table>

HS: Highly significant.
NS: Non significant.
Table (2): Mean serum adiponectin levels of the studied groups.

<table>
<thead>
<tr>
<th></th>
<th>HCV (No.=44)</th>
<th>Controls (No.=16)</th>
<th>Significance &amp; p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Adiponectin</td>
<td>12.73±8.17</td>
<td>190.50±11.57</td>
<td>S (0.04)</td>
</tr>
</tbody>
</table>

S: Significant.

Table (3): Correlation between serum adiponectin (mean ± SD) and various parameters among the HCV group.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Serum Adiponectin (mean±SD)</th>
<th>p value</th>
<th>Significance &amp; p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasonographic findings</td>
<td>0.5917</td>
<td>NS (0.5917)</td>
<td></td>
</tr>
<tr>
<td>Bright liver (No 27)</td>
<td>13.3±7.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NAD (No 17)</td>
<td>11.88±8.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spearman’s rho correlation coefficient for HAI</td>
<td></td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Activity score</td>
<td>0.24</td>
<td>0.156</td>
<td>(0.156)</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>0.18</td>
<td>0.295</td>
<td>(0.295)</td>
</tr>
<tr>
<td>Steatosis</td>
<td>0.3</td>
<td>NS (0.3)</td>
<td></td>
</tr>
<tr>
<td>&lt;30%</td>
<td>14.50±2.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥30%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viraemia</td>
<td>Low (No 26)</td>
<td>12.80±7.53</td>
<td>NS (0.56)</td>
</tr>
<tr>
<td></td>
<td>Moderate (No 15)</td>
<td>12.13±10.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High (No 3)</td>
<td>14.33±6.66</td>
<td></td>
</tr>
</tbody>
</table>

Discussion

The interaction of hepatitis C virus core protein with the lipoprotein secretion pathways causes the characteristic alterations of lipid metabolism observed in hepatitis C virus-related steatosis. Several pathogenic mechanisms are likely involved into the pathogenesis of hepatitis C virus-related steatosis, including hyper-homocysteinaemia, hypo-adiponectinemia and insulin resistance. Steatosis is a major determinant of the liver damage progression in chronic hepatitis C (CHC) and negatively affects the response rate to the interferon (IFN)-based antiviral treatment. Moreover, recent evidence suggests that steatosis may contribute to liver carcinogenesis [4].

There is no data about the secretion of adiponectin during hepatitis C infection, it has not been ascertained whether adipokines and in particular adiponectin may have a role in the development of steatosis in hepatitis C [19].

The aim of this study was to define the potential role of adipocyte derived adiponectin in patients with chronic hepatitis C infection in Egypt and to investigate its role in HCV-related steatosis. Hypothesized that dysregulation of adiponectin and adiponectin receptor system could contribute to the development of steatosis in chronic hepatitis C virus patients. The hypothesis is supported by results of several recent studies [20,21].

The results of our study indicate that hypoadiponectinemia is associated with the presence of chronic hepatitis C. These findings were independent of age, gender, and viral load. This result agree with a study which found that decreased serum adiponectin levels have been detected initially in patients with chronic hepatitis C infection [22].

There is no statistical significant difference of the mean adiponectin level for both genders in the HCV group (12.9±10.3 in females Vs. 12.7±7.6 in males) (p value: 0.94) This disagrees with other studies [23,24] which revealed that there is significant negative correlation between serum adiponectin and male gender in the chronic HCV patients. In addition, they concluded that the lower levels of serum adiponectin were associated with the presence of steatosis in males only. Thus, their results suggest that the role of adiponectin in chronic liver disease may be contingent with gender.

Further, the present study and another study [24] revealed by multivariate analysis, that age was not a significant covariate with level of adiponectin in cases and control groups.

Our study revealed that ALT, AST and ALP are highly significantly higher in HCV group than controls, yet there is no significant correlation found between adiponectin and liver enzymes in the HCV studied group.

Recently an association between plasma adiponectin and liver functions was found also in healthy subjects. Lopez, et al. reported that adiponectin levels were significantly correlated with ALT, γGT and ALP independently of sex, age and BMI suggesting a wider role for adiponectin in the maintenance of liver integrity [19].

Others demonstrated that the serum adiponectin level was inversely correlated with the levels of serum AST and ALT in a study done to assess the relation between adiponectin and nonalcoholic fatty liver disease concluding that hypoadiponectinemia may worsen liver disease associated with metabolic disease [25].
In this study, Adiponectin inversely correlated with FBS with no statistical significance. Another study was done to assess the role of adiponectin in the pathogenesis of hepatitis C virus-associated insulin resistance and reported that; HCV-associated insulin resistance is most likely an adipocytokine-independent effect of the virus to modulate insulin sensitivity \[26\].

Furthermore, this study found a non significant positive correlation between adiponectin and LDL \((r=0.003, p=0.99)\) and there is an inverse correlation seen with T.G, total cholesterol and HDL \((r=-0.22, p=0.16 \text{ and } r=-0.16, p=0.29 \text{ and } r=-0.14, p=0.35)\) respectively.

Notably, LDL and T. cholesterol are significantly lower in chronic HCV patients than controls while the mean total triglyceride level in the control group is lower than HCV group and mean adiponectin is higher in control group than HCV. This suggests that hypoadiponectinaemia reported in the HCV group disturb the lipid metabolism causing relative elevation of triglycerides, total cholesterol and HDL.

A study done on apparently healthy subjects, reported that serum adiponectin correlated with their lipid profile \[27\].

In our study there was no significant correlation seen between serum adiponectin levels and the presence of bright liver on ultrasonographic examination (US) \((13.3 \pm 7.8 \text{ in cases of bright liver on US Vs. 11.88} \pm \text{8.3 in cases without bright liver on US). The number of cases with low hepatitis C viraemia was 26, those with moderate and high viraemia was fifteen and three cases respectively.}\)

We observed that the viral load was not significantly correlated with the adiponectin level in chronic HCV \((12.80 \pm 7.53 \text{ in cases of low viraemia, } 12.13 \pm 10.01 \text{ in cases of moderate viraemia and } 14.33 \pm 6.66 \text{ in those with high viraemia). On the contrary, it was reported that high HCV load was significantly associated with a lower serum adiponectin levels }[24]\).

The results of the present study suggested that there is no significant relationship between adiponectin levels and liver biopsy result; necroinflammatory activity score \((r=0.23, p=0.15)\) and fibrosis grade \((r=0.17, p=0.29)\). Similarly, previous studies reported that there was no association between serum adiponectin level and stage of fibrosis. \[23,26\]. As for the histopathological activity index (HAI), the correlation is considered significant at the 0.01 level (2-tailed).

Histopathological examination shows steatosis in 8 cases. Our study suggest that there is no significant correlation between adiponectin and steatosis \((13.25 \pm 8.43 \text{ in cases without steatosis Vs. } 14.50 \pm 12.13 \text{ in those with steatosis)}. Similar findings were found in the study performed on similar groups of patient \[24\].

On the contrary, other studies concluded that the plasma levels of adiponectin inversely correlated with steatosis in HCV-infected subjects suggesting that hypoadiponectinemia is at least partly responsible for hepatic steatosis and liver injury in this population. The mechanism of this association needs to be clarified; however, it is probably related with the effect of adiponectin on lipid metabolism. This study gives new support to the argument that adiponectin, or treatment (such as thiazolidinedione) leading to an increase of the circulating adiponectin levels might represent a novel treatment strategy to decrease steatosis during HCV infection \[20\]. Moreover, adiponectin may act to reverse hepatic stellate cells activation or maintain its quiescence or significantly may have important therapeutic implications in liver fibrosis \[28\].

In conclusion, this study demonstrates that hypoadiponectinemia in HCV-infected patients did not correlate with hepatic steatosis. However further studies on a larger number of patients with different stages of hepatic affection are needed to explore the respective role of the adiponectin in the pathogenesis of HCV-related steatosis. The role of HCV genotype and its relation to hepatic steatosis should well studied because the most prevalent genotype in Egypt is HCV genotype 4 \[29\] and most of the western publications demonstrated that Liver steatosis is frequent in chronic hepatitis C, particularly in patients infected with hepatitis C virus (HCV) genotype 3 \[10\]. Baranova and his colleagues \[30\] concluded that analysis of adipokines associated with steatosis supports the hypothesis that steatogenic pathways differ in HCV genotype 3 from those infected with non-genotype 3 infections, they stated that HCV-related steatosis and fibrosis was predicted by IL-8 and resistin levels.

References


