The relationship between serum adiponectin and steatosis in patients with chronic hepatitis C genotype-4

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Abstract: The mechanisms underlying steatosis during hepatitis C virus (HCV) infection are complex and multifactorial. The aim of our study was to assess whether host metabolic factors influence the degree of hepatic steatosis and fibrosis in patients infected with hepatitis C virus genotype 4 by investigating the role of adiponectin, leptin and insulin resistance. **Methods:** Adiponectin and leptin levels, HCV genotypes, HCV-RNA, IR (HOMA-IR), body mass index and liver steatosis and fibrosis were assessed in 74 chronic patients with HCV genotype 4. **Results:** Chronic HCV patients with steatosis showed lower serum adiponectin levels and higher levels of leptin, HOMA, alanine aminotransferase, γ glutamiltransferase and fibrosis scores. Low adiponectin levels were independently associated with grades of steatosis and HOMA-IR. Adiponectin levels showed significant inverse correlation between adiponectin and steatosis grade, BMI, HOMA and fibrosis stage. The multivariate analysis of factors showed that steatosis was significantly associated with low adiponectin concentration while, leptin, Insulin, HOMA, ALT, γ-GT and cholesterol were positively associated with steatosis. **Conclusion:** This study stated that Egyptian patients with HCV genotype-4 suffering from steatosis had lower adiponectin level that is inversely correlated with insulin resistance. These data support a role for adiponectin in protection against liver injury and that hypoadiponectinemia may contribute to hepatic steatosis progression. Further molecular and genetic studies with larger numbers of patients are required to confirm these results. [Nature and Science 2010;8(2):109-120]. (ISSN: 1545-0740).

Key words: Adiponectin, steatosis, hepatitis C, leptin

1. Introduction

Infection with hepatitis C virus (HCV) is a leading cause of chronic liver disease worldwide **(Alter and Seeff, 2000)** Genotype 4 is the most common genotype of HCV in Egypt and its response to treatment is still a controversy **(Zekri et al., 2000).** Steatosis is a common histological feature of hepatitis C virus (HCV) infection but the relative importance of host and viral factors remains unclear **(Tsochatziz et al.,2009)**. Hepatic steatosis is considered to be mostly associated with viral factors in genotype 3 namely viral steatosis while host factors seem to play the major pathogenic role in HCV genotype non-3 infection, namely metabolic steatosis **(Tsochatziz et al., 2007).**

Non-alcoholic fatty liver disease (NAFLD) represents a spectrum of liver diseases characterized mainly by macrovesicular steatosis that occurs in the absence of alcoholic consumption. The hepatic histology varies from isolated hepatic steatosis alone "first hit" to fatty liver accompanied by hepatocellular damage plus inflammation known as steatohepatitis "second hit" which is followed by the development of fibrosis. Steatosis is associated with risk factors for nonalcoholic steatohepatitis (NASH), particularly obesity, rather than with alcohol consumption (**Monto et al., 2002).** Obesity is a well-recognized risk factor for the development of steatosis and of fibrosis in HCV infected patients **(Lonardo et al., 2004).** Visceral fat distribution rather than body mass index (BMI) proved to be associated with HCV related steatosis. 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.. It secretes variety of hormones including adiponectin and leptin, which may contribute to the development of metabolic abnormalities **(Adinolfi et al., 2001).**

There are few data on adipocytokines and liver function. There are some controversial data about the relationship between serum leptin levels and HCV-related steatosis **(Giannini et al., 2000).** Regarding adiponectin, its levels are associated in healthy humans with plasma concentrations of

various liver function tests; however, there is no data about the secretion of adiponectin during hepatitis C infection **(Lopez-Bermejo et al., 2004)**. Although the deleterious association between obesity and HCV infection is well recognized, it has not been ascertained whether adipocytokines and, in particular, adiponectin may have a role in the development of steatosis in chronic hepatitis C. Adiponectin modulates hepatic fat content and has an antiseatotic effect on liver. Moreover, adiponectin is a hepatic insulin sensitizer and has anti-inflammatory and antifibrotic effect in experimental murine models of liver damage **(Kamada et al., 2003).**

Leptin is an adipocyte-derived antiobesity hormone that in rodents prevents "lipotoxicity" by limiting triglyceride accumulation and also regulates matrix deposition (fibrosis) during wound healing **(Chitturi et al., 2002).** Leptin has been suggested to play a role in the pathogenesis of hepatic steatosis and steatohepatitis in the absence of viral infection **(Tungtrongchitr et al., 2006).** Leptin and adiponectin have been implicated in the pathogenesis and progression of non-alcoholic steatohepatitis (NASH) and chronic hepatitis C **(Tsochatzis et al., 2008).**

Insulin resistance is a frequent feature of chronic hepatitis C. Whether insulin resistance could be the cause or consequence of steatosis and fibrosis is unknown **(Fartoux et al., 2005),** the interaction between insulin resistance (IR), steatosis and genotype to fibrosis in chronic hepatitis C virus (HCV) infection has not been comprehensively assessed. In chronic hepatitis C (CHC), there is a close association between insulin resistance (IR), hepatic steatosis **(Moucari et al., 2008),** progression of fibrosis **(Camma et al., 2006)**, adipocytokine profile **(Hui et al., 2003)** and a lower rate of sustained virological response (**Conjeevaram et al., 2007).**

The objective of this study was to assess whether host metabolic factors influence the degree of hepatic steatosis and fibrosis in patients infected with hepatitis C virus genotype 4 by investigating the role of adiponectin, leptin and insulin resistance.

2. Patients and methods

Seventy four patients were enrolled in this study, they were admitted to division of Internal Medicine and Hepatology Ain shams University hospital with a diagnosis of chronic hepatitis C (CHC) genotype 4. All patients were evaluated with physical examination, laboratory tests and underwent pretreatment liver biopsy. Entry criteria included patients aged 42–63 year, with elevated alanine aminotransferase (ALT) levels for at least 6 months on at least 3 occasions, positive for HCV-RNA and liver histology compatible with chronic hepatitis C. Patients were divided into two groups according to presence or absence of steatosis.

We excluded patients with: (a) Other causes of chronic liver disease, Wilson's disease, haemochromatosis, autoimmune hepatitis and alcoholics, (b) Decompensated liver disease (c) History of heart failure, diabetes, thyroid diseases, abnormal renal function and cancer (d) Previous treatment with antiviral agents, metformin, vitamin E, or thiazolidinedione and (e) The use of drugs known to induce liver steatosis (corticosteroids, amiodarone, tamoxifen, valproic acid) within the last 6 months. The study protocol had been approved by the Ethics Committee and subjects gave written consent to participate in the present study.

2.1 Clinical, laboratory and virological parameters:

(1) Clinical Assessment:

Complete clinical evaluation was performed for all patients. Baseline characteristics collected at the time of liver biopsy included the age, ethnicity, height, weight and waist circumference.

Body mass index (BMI; kg/m2) and waist circumference were calculated.

BMI= body weight (kilograms) / the square of height (meters).

Visceral obesity was defined as a waist circumference $\geq$102 cm in males and $\geq$88 cm in females.

(2) **Liver Histopathology:**

Liver biopsy was done for all patients for diagnostic purposes. Liver specimens were formalin-fixed and paraffin-embedded for histological evaluation. Stained sections were evaluated according to a scoring system that includes the semi-quantitative assessment of liver disease grading and staging **(METAVIR study, 1994, Brunt et al., 1999).**

(3) Grading:

Steatosis was graded by percentage of cells showing fatty changes. Grading was made according to macrovesicular steatosis and necroinflammatory activity Macrovesicular steatosis was graded as:

- Grade 0: Absent or minimal (less than 5% of hepatocytes involved)

- Grade 1: Mild (5-30% of hepatocytes involved)
- Grade 2: Moderate (30- 60% of hepatocytes involved)
- Grade 3: Severe (60% of hepatocytes involved)

- Necroinflammatory activity. Grade 1: mild; Grade 2: moderate; Grade 3: severe.

(4) Staging:

According to the METAVIR system [20], fibrosis was staged on a scale from F0 to F4, as follows;

- F0: no fibrosis;
- Stage 1(F1): portal fibrosis, without septa.
- Stage 2(F2): few septa.
- Stage 3(F3): many septa without cirrhosis.
- Stage 4(F4): cirrhosis.
-

The stages of fibrosis were modified to two categories as follows: mild fibrosis (stages 0 to 2) and advanced fibrosis (stages 3 and 4).

- Blood assays: At the time of liver biopsy, assays were carried out on plasma and serum samples collected after overnight fasting and stored at -70°C until use. Routine blood tests were performed at University hospital laboratory.

A) Virology

All serum samples were tested by ELISA for the presence of a hepatitis C antibody (anti-HCV). Serological testing for anti-HCV was carried out using a commercial microparticle enzyme immunoassay {a line immunoassay (INNO-LIA HCV Ab III; Innogenetics, Ghent, Belgium)}.

- **HCV RNA**

All ELISA anti-HCV-positive samples were submitted to RNA extraction, reverse transcription and a nested PCR with primers complementary to the conserved area of the 5'_ NC region of HCV, essentially as described by **(Ginabreda et al., 1997).** HCV genotyping was determined in all HCV RNA-positive samples. A line probe assay (Inno-LiPA HCV II; Innogenetics) was used to determine the genotype in the amplicons of the 5_ NC region according to the procedure described by the manufacturer.

- **HCV genotyping**

In order to ascertain the presence of HCV genotype 4 in clinical specimen, HCV-RNA isolated from each HCV-infected patient was amplified in the 5′-untranslated region (UTR) by nested reverse transcription–polymerase chain reaction (RT-PCR) using previously described primers and conditions **(Holland et al., 1994).** The amplified HCV-RNA PCR products were purified using the Wizard SV GEL and PCR Clean-Up System kit (Promega Corporation, Madison, WI, USA), and the nucleotide sequences were then determined by direct double-strand DNA cycle sequencing using the DTCS Quick Start master mix (Beckman Coulter) with each of the internal HCV primers, according to the manufacturer's instructions. Electrophoresis and analysis of DNA sequence reactions were done using the CEQ 8000 sequencer (Beckman Coulter). The derived sequences were then analyzed using the CEQ8000 software (Beckman Coulter), and compared to sequences available from the GenBank database. Only patients with HCV genotype 4 infection were included in this study.

B) Adipocytokines

Serum adiponectin and leptin concentrations were measured by using commercial ELISA (human adiponectin ELISA kit and human leptin ELISA kit; Quantikine, R&D Systems, Wiesbaden, Germany).

C) Serum Insulin levels and HOMA-IR calculation

- **Plasma glucose** concentration was measured by God-PAP enzymatic colorimetric method using Biomerieux test kit, Cat. No. 5127.
- **Serum levels of insulin** were assayed by commercially available radio-immunoassay (Abbott IMx Insulin assay) which is a micro-particle Enzyme Immunoassay for the quantitative measurement of human insulin

The degree of insulin resistance was calculated according to the homeostasis model assessment for insulin resistance [HOMA-IR] measured by multiplying fasting serum insulin (microunits per milliliter) and fasting plasma glucose (micromoles per liter) divided by 22.5 **(Matthews et al., 1985).**

3. Statistical analysis

Statistical analyses were performed with STATISTICA software. All text and table values are expressed as means ± S.D. For analysis of parameters, analysis of variance (ANOVA) was used to address differences between groups. Univariate analysis was made by chi-square test for frequencies and by Mann–Whitney rank-sum test for means. For multivariable analysis, when steatosis was used as dependent variable (i.e.

absence vs. presence of steatosis), we considered as possibly independent variables as body mass index (BMI), HOMA score, plasma adiponectin level, leptin level, ALT, γ-GT, cholesterol and liver fibrosis scores. The sensitivity (Sn), specificity (Sp), positive predicative value (PPV), negative predictive value (NPV) and accuracy calculated for adiponectin, leptin and HOMA by using ROC curves. Pearson's correlation coefficients were used to test the correlation between variables. (P values less than 0.05 were considered to be statistically significant).

4. Results

The baseline characteristics of the study population are shown in Table 1; univariate analysis of factors associated with steatosis showed that there was no significant difference in the age between patients with and without steatosis. Patients with steatosis showed significant increase in BMI, HOMA index, ALT, γ-GT and cholesterol when compared with patients without steatosis.

Patients with steatosis showed significantly lower serum adiponectin and significantly higher serum leptin levels compared to those without steatosis. Serum levels of adiponectin and leptin showed no significant differences between male and female in both studied groups, also, there was no significant difference in the levels of these adipocytokines between CHC patients with mild and moderate steatosis (grade 1 &2) or between different stages of fibrosis. (Fig. 1, 2, 3, 4).

Table 2 shows the sensitivity (Sn), specificity (Sp), positive predicative value (PPV), negative predictive value (NPV) and accuracy calculated for adiponectin, leptin and HOMA. At adiponectin value of 11.6 (ug/ml), the sensitivity and NPV values were (100%) but the specificity (84.1%) and PPV (40.5%) decreased. At the leptin value of 7.5 (pg/ml), the sensitivity was further increased to 90%, but the specificity 84.1 and PPV (79.4%) decreased. In ROC analysis, the area under the receiver characteristic curve for HOMA index (0.997+0.003) was greater than for adiponectin values (0.988+0.009) or Leptin values (0.936+0.029) indicating a greater ability of HOMA index for distinguishing steatosis from non-steatosis group(Fig5a-c).

Table 3 shows the correlation between serum adiponectin and other parameters in patients with steatosis, adiponectin levels showed significant inverse correlation with steatosis grade, BMI and HOMA. It was poorly associated with leptin, insulin, ALT, γGT, cholesterol and triglyceride.

The analysis of factors independently associated with the presence of steatosis according to HCV genotype4 is presented in Table 4.The multivariate analysis of factors showed that steatosis was significantly associated with low adiponectin concentration while, leptin, Insulin, HOMA, ALT, γ-GT and cholesterol were positively associated with steatosis.

Table (1) Univariate analysis of the factors associated with liver steatosis in 74 non diabetic chronic hepatitis C genotype 4 patients

Patients characterization	With steatosis (n =30)	Without steatosis (n = 44)	P-value
Age(mean±SD)	52±0.5	54.5±0.2	0.471
BMI(mean±SD)	26±1.2	23±0.2	0.0001*
No. Male sex	21	33	
No. Female sex	9	11	
Grade of Steatosis ❖ *Macrovesicular steatosis* (no. &%) • Grade 0: (no steatosis) • Grade 1: steatosis up to 30% • Grade 2: steatosis between 30 and 60%; ❖ *Necroinflammatory activity* • . Grade 1: mild • Grade 2: moderate • Grade 3: severe	 0 20(66.7%) 10(33.3%) 20(66.7%) 10(33.3%) 0	 44 (100%) 0 0 40(91%) 4(9%) 0	
Stage of Fibrosis (no. &%) • mild fibrosis (stages 0 to 2) • advanced fibrosis (stages3 to 4)	 24(80%) 6(20%)	 39(88.6%) 5(11.4%)	
HOMA-IR(mean±SD)	4.67	2.59	0.003*
ALT (IU/L)(mean±SD)	97	73	0.0001*
γ-GT (IU/L) (mean±SD)	88	45	0.001*
Cholesterol (mg/dL) (mean±SD)	230	188	0.001*
Triglycerides(mg/dL) (mean±SD)	125	122	0.103

* Significant p<0.05, BMI: body mass index; ALT, alanine aminotransferase; -γGT:gamma-glutamyltransferase

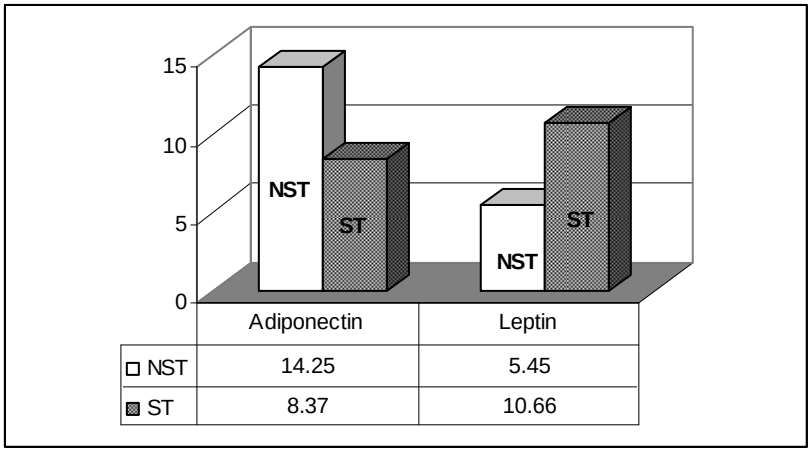

Fig (1) Serum levels of Adiponectin (ug/ml) and leptin (pg/ml) among chronic hepatitis C patients with (ST) and without steatosis (NST)

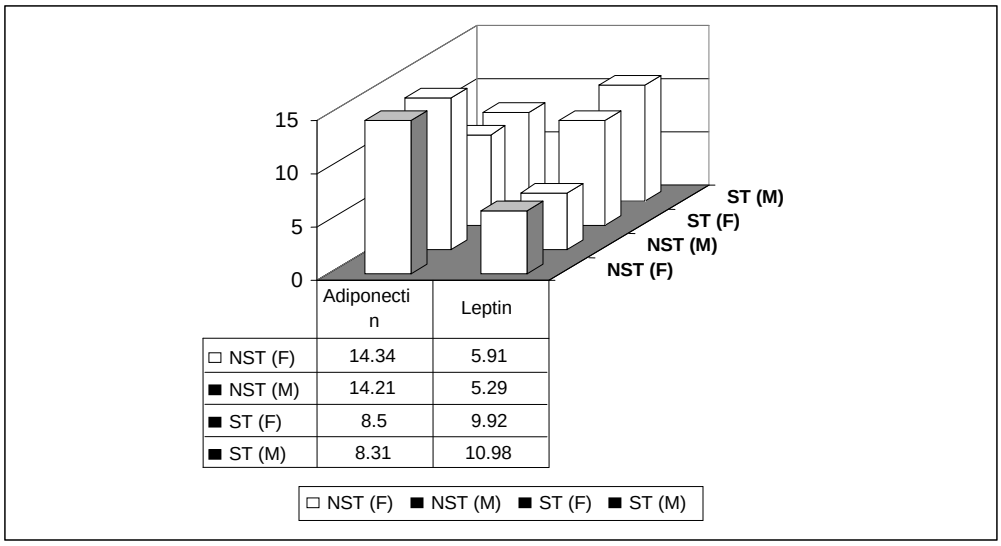

Fig (2) Serum levels of Adiponectin (ug/ml) and leptin (pg/ml) in different Sex (female & Male) among chronic hepatitis C patients with (ST) and without steatosis (NST)

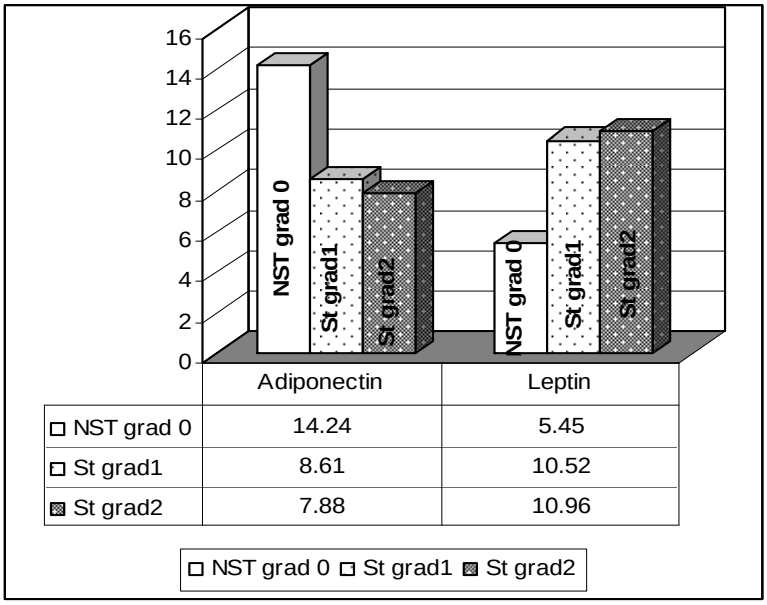

Fig (3) Serum levels of Adiponectin (ug/ml) and leptin (pg/ml) among chronic hepatitis C patients with and without steatosis (According to grade of Steatosis)

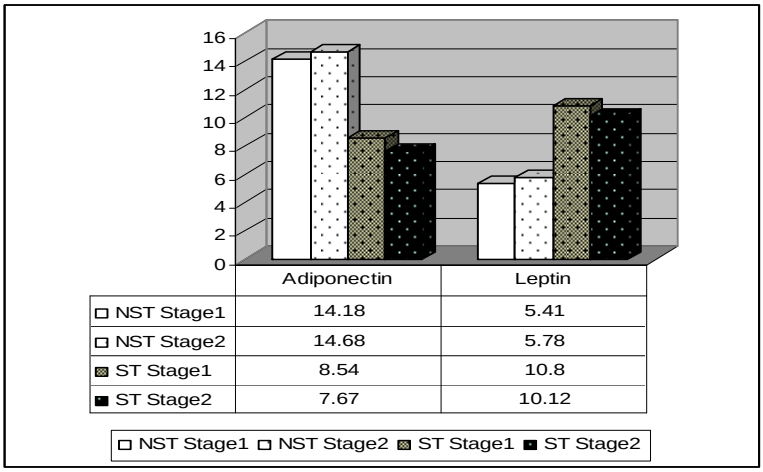

Fig (4) Serum levels of Adiponectin (ug/ml) and leptin (pg/ml) among chronic hepatitis C patients with and without steatosis (According to stage of fibrosis)

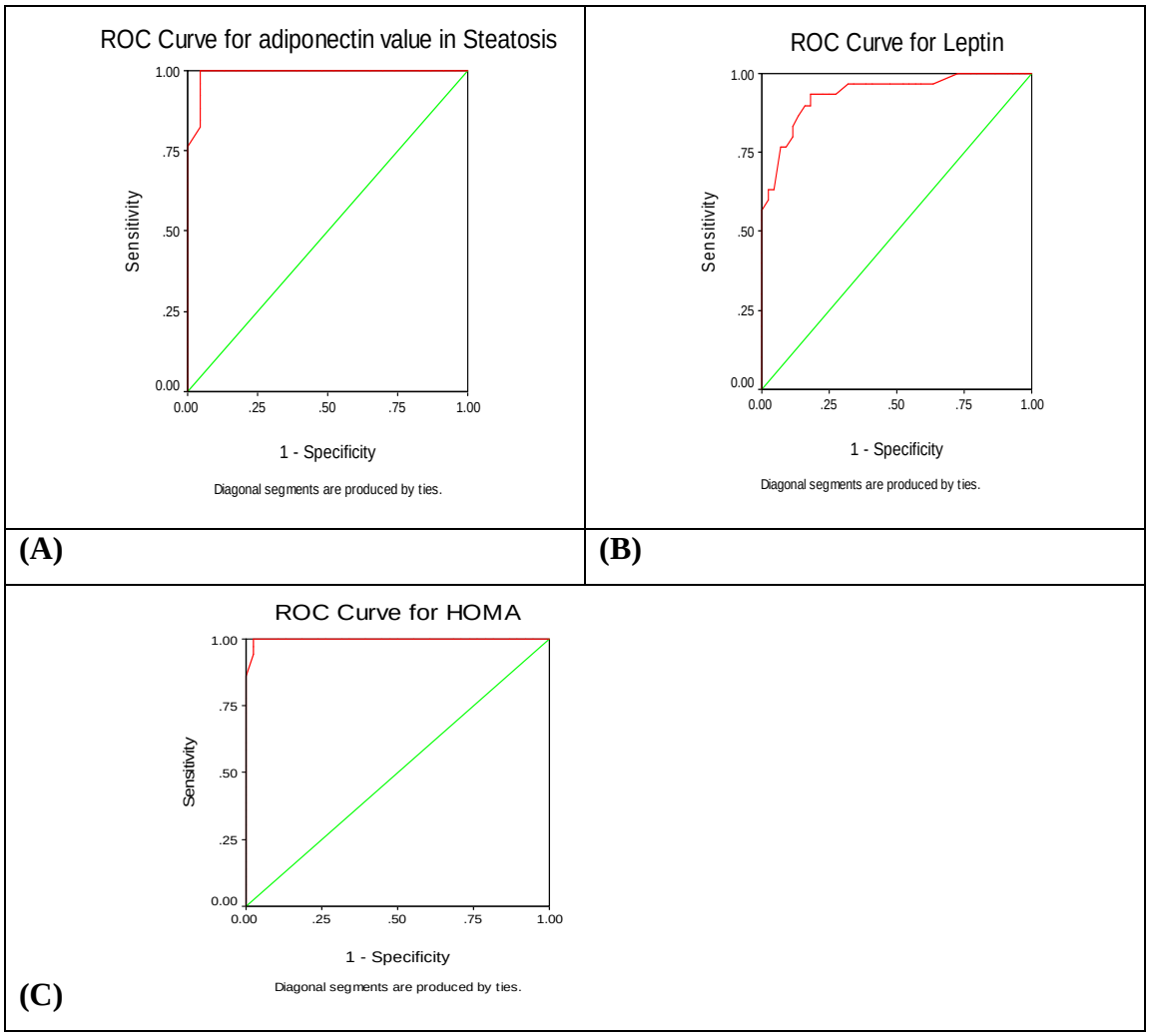

Fig (5) Receiver operating characteristic curve for Adiponectin (A), receiver operating characteristic curve for Leptin (B) and receiver operating characteristic curve for HOMA index (C)

Table (2) Sensitivity, Specificity, PPV, NPV, and Accuracy According to Steatosis

Parameter	Sensitivity	Specificity	PPV*	+NPV	Accuracy
(1)Adiponectin	30/30(100%)	37/44(84.1%)	40.5%	50%	90.5%
(2)leptin	27/30(90%)	37/44(84.1%)	79.4%	92.5%	86.5%
Combined (1)&(2)	30/30(100%)	36/44(81.8%)	78.9%	48.6%	89.2%
(3)HOMA	18/30(60.0%)	26/44(59.1%)	50.0%	68.4%	59.5%
Combined (1)&(3)	30/30(100%)	37/44(84.1%)	81.1%	100%	90.5%
Combined (2)&(3)	27/30(90%)	37/44(81.1%)	79.4%	92.5%	86.6%

Data expressed in percentages *PPV=Positive predicative value, +NPV= Negative predicative

Table (3) Correlation between adiponectin and other variables in patients with steatosis

	Serum adiponectin	
parameters	**r**	**P value**
Age	-0.162	0.394
BMI	-0.334	0.001*
Fibrosis	-0343	0.063
Steatosis grade	-0.372	0.001*
Leptin	0.066	0.729
Insulin	0.019	0.922
HOMA	-0.341	0.001*
ALT	-0.256	0.172
γ GT	-0.221	0.240
Cholesterol	-0.276	0.139
Triglyceride	-0.240	0.201

* Significant p<0.05

Table (4) Multivariate analysis of factors independently associated with steatosis in chronic hepatitis C patients

Dependent Variable	(I) steot.	(J) steot.	Mean Difference (I-J)	Std. Error	95% Confidence Interval for Difference[(a)]	Sig.
BMI	**ST**	**NST**	1.840*	.320	1.202/ 2.478	.000
Adiponectin	**ST**	**NST**	-6.329*	.706	-7.738 /-4.920	.000
Leptin	**ST**	**NST**	4.866*	.798	3.273 /6.458	.000
Iinsluin	**ST**	**NST**	3.581*	.792	2.001/5.161	.000
HOMA	**ST**	**NST**	.928*	.438	5.429E-02/1.801	.038
Cholesterol	**ST**	**NST**	10.308*	4.784	.766/19.850	.035
Triglyceride	**ST**	**NST**	3.040	4.399	-5.734/11.814	.492
ALT	**ST**	**NST**	41.317*	5.929	29.492/53.141	.000
γGT	**ST**	**NST**	40.003*	3.739	32.545/ 47.460	.000

ST; steatosis group, NST; non-steatosis group

* The mean difference is significant at the .05 level.

5. Discussion

Steatosis is an established risk factor for disease progression in chronic hepatitis C. The reported prevalence of steatosis in patients with chronic hepatitis C varies between 40% and 80%, this figure represents an approximately 2-fold increase compared to the prevalence of steatosis in another common chronic liver disease like hepatitis B (20%). This evidence suggests that HCV may directly cause steatosis, at least in some patients **(Monto et al., 2002).**

Cytokines are mediators of cellular communication produced by multiple liver cell types such as Kupffer cells, stellate cells, hepatocytes and endothelial cells. Cytokines can directly induce necrosis or apoptosis. There are also beneficial cytokines, such as adiponectin, which is one of the beneficial cytokines, made outside the liver and appear to protect against liver damage. Adiponectin is specifically secreted by adipocytes that circulate at relatively high levels in the bloodstream **(Kershaw and Flier, 2004).**

The results of this study demonstrated that CHC patients with steatosis had reduced serum levels of adiponectin, with significant inverse correlation between adiponectin level and steatosis grade, HOMA index, BMI and fibrosis stage. These results were in agreement with **Petit et al., 2005** who reported an association between serum levels of adiponectin and HCV related steatosis, they stated that adiponectin is a cytokine secreted by adipocytes with antilipogenic effects that may protect nonadipocyte tissues, such as liver from fat accumulation. Chronic hepatitis C patients have the lowest levels of adiponectin that inversely correlated with steatosis which lead to increased serum free fatty acids, which are then taken up by hepatocytes. In a study done by **Lopez-Bermejo et al., 2004** they found that adiponectin is inversely correlated with BMI, intraabdominal fat and indices of insulin resistance. Two receptors of adiponectin have been cloned; adiponectin receptor 1 is abundantly expressed in skeletal muscle, whereas adiponectin receptor 2 is predominantly expressed in the liver **(Yamauchi et al., 2003).** Growing evidence suggests that adiponectin can regulate lipid and glucose metabolism and lipid fat content in hepatocyte **(Yamauchi et al., 2001).**

Tsochatzis et al, 2007 declared that hepatic steatosis in genotype 4 is mostly associated with metabolic factors, similarly to those in genotype 1 CHC patients and that the actions of adiponectin on the liver are to oppose fatty acid synthesis, and promote mitochondrial oxidation, these actions are exerted through activation of the cyclic-AMP dependent protein kinase (AMPK). Adiponectin also exerts anti-inflammatory effects by opposing the synthesis and release of TNFα from macrophages within adipose tissue. In addition, hypoadiponectinaemia is independently associated with IR and this, in turn, is strictly associated with the development of steatosis. **Dixon et al, 2001** stated that whether hepatic steatosis is a consequence of hepatic or peripheral insulin resistance or whether hepatic steatosis causes hepatic insulin resistance remains unclear. It is likely that excess free fatty acid flux due to peripheral insulin resistance may induce hepatic steatosis. On the other hand, excess fat deposition in the liver may render hepatocytes less sensitive to insulin action and lead to hepatic insulin resistance which occur in early stages of course of HCV infection before the development of cirrhosis **(Petit et al.,2001)**

In our study the result of ROC curve indicated greater ability of HOMA index for distinguishing steatosis from non-steatosis group, studies supported this association suggesting that IR enhances progression to fibrosis by inducing steatosis, implying a complex mechanism in which inflammatory activity and modified cytokine profile have a distinct role **(Lo Iacono et al., 2007),** other studies were not able to demonstrate this association **(Hsu et al., 2008, Papatheodoridis et al., 2006).**

Insulin resistance in chronic HCV infection could be caused by an interplay between viral and host factors. HCV infection per se generates multiple defects in hepatic insulin signaling pathways. The major role of HCV in IR development is also supported by the identification of IR in patients with normal BMI and without significant fibrosis **(Yaneda et al., 2007).** Recently, a study was able to demonstrate a direct role of viral replication in IR development, establishing a significant correlation between HOMA-IR and HCV-RNA levels even after adjustment for age, gender and BMI as known factors which might be confounders **(Pittas et al., 2004).**

In this study serum leptin showed significant increase in patients with steatosis compared with patients without steatosis, also there was no correlation between leptin levels and adiponectin levels. Several studies have evaluated the role of leptin in HCV steatosis. However, some controversial data were obtained; leptin was found associated with steatosis in some studies but not all (**Giannini et al., 2000**, **Manolakopoulos et al., 2007). Giannini et al., 2000** found no relationship

between leptin levels and severity of steatosis. In contrast, another study observed that hepatic steatosis was associated with leptin, BMI, percentage of body fat, and visceral obesity **(Manolakopoulos et al., 2007**). Serum leptin levels were found increased in proportion to the severity of steatosis **(Testa et al., 2000, Lin et al., 2002).** It has been proposed that the liver becomes refractory to the 'anti-steatotic' effects of leptin, a state of 'hepatic leptin resistance' that accompanies hepatic insulin resistance rather than correcting it **(Testa et al., 2000).** There is also a possibility that the relationship of adipose tissue disorders including regional and generalized obesity and lipodystrophies to hepatic steatosis may be due to reduced central or peripheral actions of leptin, an adipocyte derived hormone. High plasma levels of leptin have been related to liver steatosis and steatohepatitis in the obese and nonobese patients [38-39] **(Tobe et al., 1999, Uygun et al., 2000).** In these subjects, leptin resistance may occur centrally or at the level of liver. Patients with severe generalized lipodystrophies who have reduced blood leptin levels are also susceptible to hepatic steatosis. Hepatic steatosis is also observed in *ob/ob* and *db/db* mice that have leptin and leptin receptor mutations, respectively. Similarly, patients with congenital leptin deficiency due to leptin mutations and those with leptin resistance due to leptin receptor mutations should also have marked hepatic steatosis, however, none of the patients described so far have been reported to have liver enlargement or hepatic steatosis **(Ozata et al., 1999)**

In conclusion, our study reported that Egyptian patients with HCV genotype-4 suffering from steatosis had a lower adiponectin level that is inversely correlated with insulin resistance. These data support a role for adiponectin in protection against liver injury and that hypoadiponectinemia may contribute to hepatic steatosis progression. Further molecular and genetic studies with larger numbers of patients are required to confirm these results.

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