Research Article

International Journal of Tumor Research

Level of the Serum Adiponectin as a Biochemical Marker of Liver Fibrosis in Hepatitis C Patients

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Received: 02 Oct 2025; **Accepted:** 10 Nov 2025; **Published:** 25 Nov 2025

Citation: Mahmoud Saad Berengy, Abd El- Monem Gaballah, Abd El- Mohsen Shaheen, et al. Level of the Serum Adiponectin as a Biochemical Marker of Liver Fibrosis in Hepatitis C Patients. Int J Tumor Res. 2025; 1(1): 1-6.

ABSTRACT

Background: *Adiponectin is a protein hormone secreted by adipose tissue. There is no data about the secretion of adiponectin during hepatitis C infection; some studies revealed that hyperadiponectinemia found with chronic HCV infection is significantly associated with the development of liver fibrosis. Nonetheless, the action of adiponectin in chronic HCV infection is still controversial.*

Objective: *measurement of the serum adiponectin as a biochemical marker of liver fibrosis in hepatitis C patients.*

Subjects and Methods*: The present study was conducted on sixty patients suffering from chronic hepatitis C and twenty eight healthy volunteers served as controls.*

Results: *The significant finding of this study is that chronic HCV patients have increased circulating adiponectin levels than healthy controls (9.16 ± 6.72 for HCV vs. 4.12 ± 1.78 for control, p <0.05) and it can be used as a biochemical marker for grade 4 fibrosis in metavir score which indicate cirrhosis while no significant difference between non cirrhotic grades and control group, also, adiponectin correlates positively with grade of fibrosis.*

Conclusion: *This study demonstrated that hyperadiponectinaemia in HCV-infected patients correlate with hepatic fibrosis and it can be used as a biochemical marker for grade 4 fibrosis in metavir score which indicates cirrhosis.*

Keywords

AdiponectI in – HCV – fibrosis, Hepatitis C, Liver diseases.

Introduction

Hepatitis C virus (HCV) infection is a major global health issue. Estimates indicate that three to four million persons are newly infected each year, 170 million people are chronically infected and death rate is about 20-25% of cirrhotic cases [1]. Egypt has the highest prevalence of HCV in the world, estimated nationally about 14.7% [2]. Left untreated, chronic HCV infection can cause liver fibrosis ending in cirrhosis and hepatocellular carcinoma. Of those with chronic HCV infection, the risk of cirrhosis of the liver is 15–30% within 20 years. The risk of HCC in persons with cirrhosis is approximately 2–4% per year [3].

The classical view of adipose tissue as just a passive reservoir for

energy storage has radically changed [4]. Besides its function as an energy reservoir, white adipose tissue plays a key role as an organ secreting numerous bioactive molecules collectively called adipokines or adipocytokines [5].

Adiponectin is a protein product of 244 amino acids consisting of four domains, an amino-terminal signal sequence, a variable region, a collagenous domain (cAd) and a carboxyterminal globular domain (gAd). Adiponectin automatically self-associates into larger structures. Initially, three adiponectin molecules bind together to form a homotrimer. The trimers continue to self-associate and form a hexamer or dodecamer [6].

Adiponectin has two isoforms in the circulation: full length adiponectin (fAd); and a globular fragment (a proteolytically cleaved fragment consisting of gAd) [7]. The globular fragment is present in small amounts in plasma and increases free fatty acid oxidation in muscle tissue, an important mechanism for the control of energy homoeostasis, while full length adiponectin has the capacity to group globular domains into three isoforms: trimeric (low molecular weight); hexameric (middle molecular weight); and multimeric (high-molecular-weight). Each oligomeric form has distinct biological properties and activates different cellular signaling pathways in several tissues [7].

Both globular and full length adiponectin exert their effects via transmembrane G-protein coupled receptors, adiponectin receptor-1 (Adipo-R1), and adiponectin receptor-2 (Adipo-R2) and has the following functions; insulin sensitizing, hepatoprotective and anti-atherosclerotic actions [9].

Our aim in this study was to measure the serum adiponectin as a biochemical marker of liver fibrosis in hepatitis C patients.

Subjects and Methods

Sixty patients suffering from chronic hepatitis C and twenty eight healthy volunteers served as controls were enrolled in the study. The following criteria were excluded from this study:

- Subjects suffering from any systemic diseases like diabetes mellitus, hypertension, cardiovascular system diseases, and renal dysfunction.
- Smokers, alcoholics and drug addicts.
- Subjects with positive HBV.
- Subjects who are known to have any auto-immune disease or those taking any medication that affect the immune system.
- Subjects who are known to have hormonal treatment.

Only patients with HCV hepatitis were included in this study.

The subjects selected from out patients clinic of Damietta Tropical Hospital and New Damietta hospital Al-Azhar University. All patients have presented to the hospital by positive HCV antibody and they are coming to be assessed as potential candidate for anti-viral therapy. An informed consent was obtained from the patients prior to their enrollment in this study. This study protocol was approved by the hospital's ethical committee.

Laboratory investigations including liver function tests, hepatitis C virus (HCV) antibody, HCV RNA viral load (PCR), serum creatinine, fasting blood glucose lipid profile and adiponectin were done. BMI was calculated as body weight in kilograms divided by the square of height in meters (kg/m^2).

Abdominal ultrasonography: It aimed at establishing the diagnosis by imaging the liver; spleen; portal, splenic and hepatic veins; detection of ascites; and hepatic focal lesion.

Liver biopsy: The biopsy was done for histopathological examination. The biopsies were examined by Metavir score.

Statistical analysis: Patient's data were tabulated and analyzed using SPSS 23.0 for Windows 8 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. p value was considered significant in when less than 0.05.

Results

The main clinical and laboratory data are summarized in Table 1. As shown in Table 2, the mean adiponectin levels is 9.16 ± 6.72 µg/mL in the chronic HCV group and 4.12 ± 1.78 µg / mL in the control group and this difference is highly significant (p<0.001) (Figure 1).

	CONTROL (n=28) Mean ± SD	HCV (n =60) Mean ± SD	Significance & *p* value
Age (years)	46.71 ± 5.93	51.06 ± 7.07	S (0.006)
BMI (weight/ height^2)	27.14 ± 4.35	27.97 ± 3.81	NS (0.3)
TG (mg/dl)	108.57 ± 56.21	84.73 ± 41.30	NS (0.02)
T.Cholest. (mg/dL)	183.28 ± 32.92	185.91 ± 74.08	NS (0.8)
LDL (mg/dL)	114.35 ± 30.74	126.23 ± 73.61	NS (0.2)
HDL (mg/dL)	46.75 ± 9.51	42.48 ± 9.04	S (0.04)
AST (IU /L)	26.17 ± 7.69	42.40 ± 20.40	HS (< 0.001)
ALT (IU /L)	21.92 ± 7.13	40.91 ± 21.01	HS (< 0.001)
T. Bil. (mg/dL)	0.68 ± 0.16	0.937 ± 0.234	HS (< 0.001)
Albumin (g/dL)	3.69 ± 0.39	3.67 ± 0.523	NS (0.8)

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

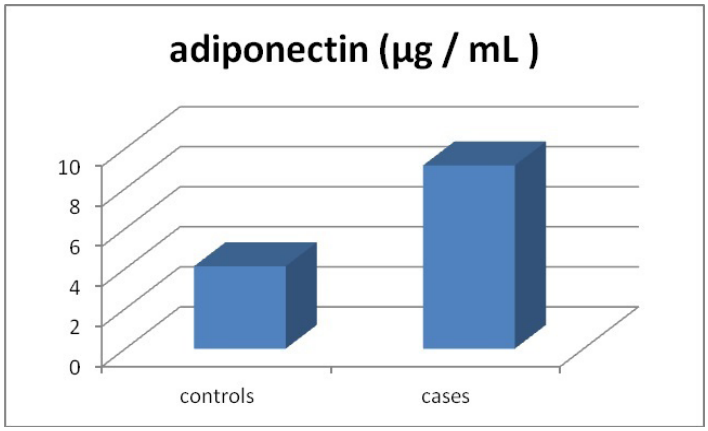

Figure 1: Mean adiponectin levels among the studied groups.

	Controls (n=28) Mean ± SD	HCV (n=60) Mean ± SD	Significance & *p* value
Adiponectin (µg / mL)	4.12 ± 1.78	9.16 ± 6.72	HS (< 0.001)

Table 2: Mean serum adiponectin levels of the studied groups.
HS: Highly significant.

Table 3 show the correlation between adiponectin and the various parameters performed in the study among HCV group. There is no significant correlation found between adiponectin and ALT, AST, total bilirubin or viral load. On the contrary, there is highly significant and negative correlation between adiponectin and BMI (r = -0.479, p <0.001), albumin (r = -0.714, p <0.001), total cholesterol (r = -0.609, p <0.001) and LDL (r = -0.635, p <0.001). Also, no significant correlation found between adiponectin and TG or HDL.

Adiponectin & other parameters	Pearson's correlation coefficient "r"	Significance & *p* value
BMI	-0.479	HS (<0.001)
ALT	0.066	NS (0.615)
AST	0.162	NS (0.217)
T. Bilirubin	-0.062	NS (0.638)
Viral load	0.252	NS (0.052)
Albumin	-0.714	HS (<0.001)
T. Cholesterol	-0.609	HS (<0.001)
LDL	-0.635	HS (<0.001)
TG	-0.006	NS (0.963)
HDL	0.174	NS (0.183)

Table 3: Correlation between serum adiponectin and various parameters among the HCV group.
HS: Highly significant; NS: Non-significant.

In the present study we categorized HCV group into cirrhotic group represented by F4 in metavir score which examine liver biopsy and non-cirrhotic group represented by F1, F2 and F3.

Table 4 shows the comparison between adiponectin levels in control, non-cirrhotic group (F1, F2 and F3) and cirrhotic group (F4).

	Control (n=28) Mean ± SD	Non cirrhotic (F1,F2,F3) (n=40) Mean ± SD	Cirrhotic (F4) (n=20) Mean ± SD	Significance & *p* value
Adiponectin (µg / mL)	4.12 ± 1.7	5.09 ± 2.1	17.31 ± 5.1	HS (< 0.001)

Table 4: Comparison between mean adiponectin levels in control, non-cirrhotic group and cirrhotic groups. HS: Highly significant.

There is no significant difference between control and non-cirrhotic groups as regard adiponectin but, there is highly significant difference between cirrhotic and non-cirrhotic or control groups. So we make receiver operating characteristic (ROC) curve analysis which conducted to identify the optimal adiponectin levels for potential prediction of development of cirrhosis within CHC patients (Figure 2).

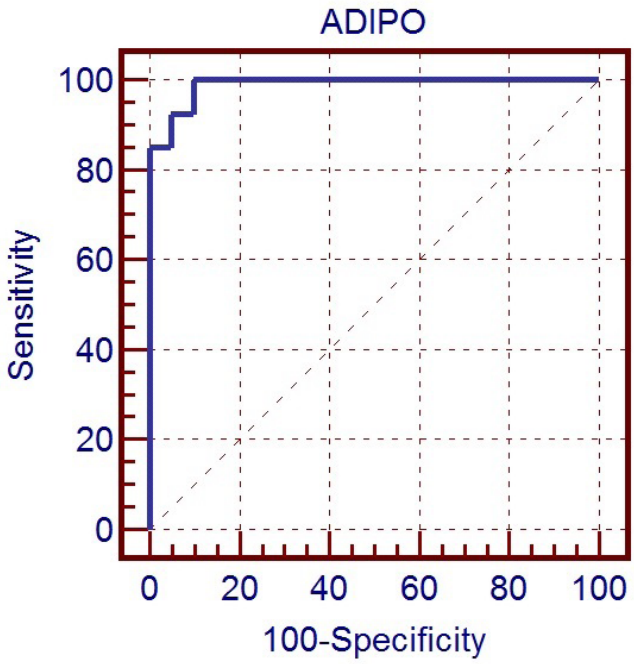

Figure 2: A receiver operating curve (ROC) analysis of Adiponectin levels for the prediction of development of cirrhosis in CHC patients. Adiponectin cut off 11.21 sensitivity = 100%, specificity = 90%, PPV = 95.2, NPV = 100, Accuracy = 99% and area under the curve (AUC) is 0.989.

Discussion

Hepatitis C virus (HCV) infection is a common liver disease with an estimated 3% of the world's population chronically infected with this viral pathogen. The majority of the infected individuals (60-80%) develop chronic hepatitis C (CHC), which is associated with progressive liver fibrosis and a risk of cirrhosis after 20 years [10].

Egypt has the highest prevalence of HCV worldwide (15%) and the highest prevalence of HCV-4, which is responsible for almost 90 % of infections and is considered a major cause of chronic hepatitis, liver cirrhosis, hepatocellular carcinoma, and liver transplantation in the country [11].

The liver is the major organ responsible for mediating the whole body metabolic effects generated by adiponectin through the activation of specific receptors [12]. In the hepatocytes, adiponectin regulates two metabolic pathways, anti-inflammatory peroxisome proliferator-activated receptor alpha and fatty acid oxidation, which has been shown to be reduced in chronic HCV-infected liver [13].

Circulating adiponectin levels have been reported to be elevated in CHC independently of age, body mass, diabetes, and severity of liver fibrosis [14]. In addition, hypoadiponectinemia has been

reported to enhance hepatic steatosis, inflammation, fibrosis, and hepatocarcinogenesis in animal models of liver diseases [15]. Indeed, reduced adiponectin levels were found in patients with nonalcoholic steatohepatitis (NASH) and were associated with increased steatosis and necroinflammation in the liver. However, the role of adiponectin in hepatitis C virus (HCV)-induced chronic hepatitis is still not understood and the relationship between adiponectin level and disease severity remains controversial [16].

The aim of this study was to define the potential role of adipocyte derived adiponectin as a marker for liver fibrosis in patients with chronic hepatitis C infection in Egypt. Hypothesized that dysregulation of adiponectin and adiponectin receptor system could contribute to the development of fibrosis in chronic hepatitis C virus patients. This hypothesis is supported by results of several recent studies. Corbetta et al. [17], said that in patients with chronic HCV hepatitis, fibrosis was associated with hyperadiponectinemia, suggesting a state of adiponectin resistance and Canavesi et al. [14], stated that CHC is associated with increased serum adiponectin independently of age, body mass, diabetes, and of severe liver fibrosis, particularly in men.

The significant finding of this study is that chronic HCV patients have increased circulating adiponectin levels than healthy controls (9.16 ± 6.72 for HCV vs. 4.12 ± 1.78 for control, $p < 0.05$) and it can be used as a biochemical marker for grade 4 fibrosis in metavir score which indicate cirrhosis while no significant difference between non cirrhotic grades and control group, also, adiponectin correlate positively with grade of fibrosis.

On comparing the mean adiponectin levels in both groups under study as regard the gender, it was found that, mean adiponectin level is increased in the females than males in the control group without statistical significant difference (4.3 ± 1.9 for females & 3.8 ± 1.6 for males, $p = 0.394$). The same result in HCV group (9.6 ± 7.8 for females, and 8.8 ± 6.1for males, $p = 0.665$).

This disagrees with Corbetta et al. [5], who revealed that there is significant difference between male and females as regard serum adiponectin in chronic HCV patients and controls.

The present study revealed that there is significant correlation between adiponectin and BMI in both cases and controls (r= -,497 , p< 0.001for cases & r=-,557 , p< 0.01 for controls). This agrees with other study which revealed that there is significant negative correlation between serum adiponectin and BMI in both cases and controls [18].

On the contrary, Liu et al. [19], reported that serum adiponectin did not correlate with BMI. The present study revealed that ALT, AST and total bilirubin are highly significantly higher in HCV group than controls, and there is no significant correlation found between adiponectin and liver enzymes or total bilirubin in the HCV studied group ($p = 0.615$, 0.217, 0.638 respectively).

These results coincide with that of the studies done by others who reported that no significant correlation between serum adiponectin and ALT levels could be found in chronic HCV-infected patients [17].

Yokoyama et al. [20], 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 non-alcoholic fatty liver disease concluding that hypoadiponectinaemia may worsen liver disease associated with metabolic disease.

Also, the same result was reported by Derbala et al. [21], who said that there is a significant negative correlation between serum adiponectin and ALT, which implies that hypoadiponectinaemia contributes to an increase in transaminase activity and attributed that to possible triglyceride accumulation but, hypoadiponectinaemia causes liver injury independently from hyperlipidaemia, insulin resistance and obesity.

In the present study, there was significant and negative correlation seen between serum adiponectin levels and albumin which represent synthetic liver function in HCV group ($r = -0.714$, $p < 0.001$). These results coincide with that of the study which reported that there is significant correlation between serum adiponectin and albumin [22]. In the present study there was no significant correlation seen between serum adiponectin levels and viral load ($p = 0.052$). This agrees with study by Khattab et al. [23], who reported that neither serum adipocytokines nor homeostasis model assessment estimated insulin resistance (HOMA-IR) was correlated with viral load. Also, Derbala et al. [21], concluded that adiponectin changes are not related to viral load, insulin resistance or other demographic data, suggesting that this change is histologically related.

On the other hand, a study by Liu et al. [19], reported that high HCV load was significantly associated with lower serum adiponectin levels, but serum adiponectin levels did not correlate with other clinical parameters. This may be attributed to HCV genotype-specific differences in hepatic mRNA expression of adiponectin receptors.

Furthermore, in HCV group we found a highly significant negative correlation between adiponectin and both total cholesterol and LDL ($r = -0.609$, $p<0.001$ & $r = -0.635$, $p<0.001$) respectively, also, there is an inverse correlation seen with TG and positive correlation with HDL but, without important significance.

On the contrary, in control group there is no significant negative correlation between adiponectin and both total cholesterol and LDL ($r = -.361$, $p>0.01$ & $r = -.374$, $p>0.01$) respectively, whereas a highly significant correlation between adiponectin and both TG and HDL ($r = -.584$, $p= 0.001$ & $r = .650$, $p <0.001$) respectively.

These results coincide with that of the study done by Komatsu et al. [24], on apparently healthy subjects, it was reported that serum adiponectin was positively correlated with HDL and inversely correlates with triglycerides. This disagrees with study

by Corbetta et al. [17], who revealed that Serum HDL cholesterol and triglycerides levels were significantly correlated with serum adiponectin levels in both cases and controls.

The main finding of this study was that there is no significant difference between control and non-cirrhotic groups as regard adiponectin but, there is highly significant difference between cirrhotic and non-cirrhotic or control groups ($p < 0.001$). So we make receiver operating characteristic (ROC) curve analysis which conducted to identify the optimal adiponectin level for potential prediction of development of cirrhosis within CHC patients. Adiponectin best cut-off value was 11.21µg/mL, with a sensitivity of 100% and a specificity of 90%. The area under the curve was 0.98. The PPV was 95.2% and the NPV was 100% with an accuracy of 99%.

This agrees with study by Corbetta et al. [17], reported that severe stages of fibrosis were characterized by serum adiponectin levels significantly higher than those in healthy controls and mild to moderate fibrosis.

Also, Salman et al. [22], stated that Adiponectin is elevated in cirrhosis and shows correlation with degree of hepatocellular injury and do not correlate with parameters of body composition or metabolism but exclusively with reduced liver function.

The significant increase of the serum adiponectin levels may be explained by the impaired biliary secretion in the cirrhotic liver as biliary excretion has previously been shown to be involved in the clearance of adiponectin [21]. Since CHC is associated with insulin resistance, it would be expected to be also linked to decreased circulating adiponectin. Increased adiponectin levels in the presence of insulin resistance have thus led Corbetta et al. [17], to hypothesize a state of adiponectin resistance that would account for the association of high adiponectin levels with the risk of hepatocellular carcinoma and overall mortality in CHC [14].

Other Various mechanisms have been proposed to explain the raised levels of adiponectin with fibrosis progression, such as an imbalance between the production of adiponectin by adipocytes and its excretion by the liver, an increase in adiponectin production by hepatic stellate cells (HSC) [7]. Masaki et al. [25], proposed that the significant increase of the serum adiponectin levels might reflect one of the body anti-inflammatory mechanisms in chronic liver disease. Canavesi et al. [14], said that the significant increase of the serum adiponectin levels may be explained by a feedback mechanism to counteract insulin resistance, which would be consistent with the negative correlation between adiponectin and insulin levels in CHC patients.

Conclusion

This study demonstrated that hyperadiponectinaemia in HCV-infected patients correlate with hepatic fibrosis and it can be used as a biochemical marker for grade 4 fibrosis in metavir score which indicates cirrhosis.

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