Turk J Gastroenterol 2008; 19 (4): 254-257

The relationship between chronic HCV infection and the level of plasma adiponectin

Kronik HCV enfeksiyonu ile plazma adiponektin düzeyleri arasındaki ilişki

Kadir AKSÖZ, Belkıs ÜNSAL, Adnan KIRCI, Emrah ALPER, Zafer BUYRAÇ, Fatih ASLAN, Cem ÇEKİÇ, Onur CENGİZ, Fulya ÖZCAN ARI, Zehra AKPINAR

Department of Gastroenterology, İzmir Atatürk Training and Research Hospital, İzmir

Background/aims: *Metabolic products (TNFα, adiponectin, resistin, etc.), which are effective in insulin sensitivity and in the regulation of inflammation, play an important role in the development of metabolic disorders and fatty liver disease. The aim of this study was to evaluate the effect of HCV infection alone on plasma adiponectin levels and insulin sensitivity when metabolic factors are minimized and to determine whether chronic HCV infection causes hepatosteatosis through its effect on these factors.* ***Methods:*** *This study was carried out between 2006-2007, at the Gastroenterology Clinic of İzmir Atatürk Training and Research Hospital, in 30 non-diabetic patients with chronic HCV infection and 30 healthy subjects as controls. BMI (<26 kg/m²), fasting plasma glucose level, and ultrasonography were normal in both groups. In the patient group, HCV RNA was ≥1.90x10³ IU/ml, ALT and AST were two times normal, and histological fibrosis scores were 1-2 in liver biopsy. Serum adiponectin levels and HOMA-IR were compared.* ***Results:*** *Fasting blood glucose levels, body mass index and HOMA-IR of the two groups were similar and normal. The mean ALT value was significantly higher in the patient group [61.8 U/L vs 28.17 U/L (p<0.05)]. The mean viral load was determined as 5.6x10⁵ IU/ml in the chronic HCV patient group. The mean plasma adiponectin concentrations were 71.07 µg/ml in chronic HCV patients and 82.07 µg/ml in the control group, and the difference was statistically insignificant (p>0.05).* ***Conclusions:*** *In the absence of metabolic disorders such as obesity, diabetes mellitus and hepatosteatosis, chronic HCV infection does not affect insulin sensitivity or adiponectin concentration.*

Key words: Chronic HCV, adiponectin level, HOMA-IR, metabolic disorders

Amaç: *İnsülin sensivitesinde ve inflamasyon regülasyonunda etkili olan metabolik ürünler (TNFα, adiponectin, resistin vb) kronik Hepatit C'deki metabolik bozuklukların ve karaciğer yağlanmasının oluşmasında önemli rol oynarlar. Bu çalışmanın amacı metabolik faktörler minimal düzeylerde iken HCV enfeksiyonunun plazma adiponectin düzeyleri ve insülin sensivitesi üzerine olan etkisini, ayrıca bu faktörleri etkileyerek tek başına hepatosteatoz nedeni olup olmadığını araştırmaktır.* ***Yöntem:*** *Bu çalışma 2006-2007 yıllarında İzmir Atatürk Eğitim ve Araştırma Hastanesi Gastroenteroloji kliniğinde yürütülmüştür. Çalışma kapsamına hasta grubu olarak diabeti olmayan 30 kronik HCV hastası ve kontrol grubu olarak 30 sağlıklı kişi alınmıştır. Beden kütle indeksi (<26 kg/m²), açlık kan şekeri, ultrasonografik inceleme her iki grupta normal idi. Hasta grubunda ALT ve AST normalin iki katı yüksek, karaciğer biyopsisinde histolojik fibrozis skoru 1-2 idi. Her iki grupta serum adiponectin ve HOMA IR düzeyleri karşılaştırıldı.* ***Bulgular:*** *Açlık kan şekeri düzeyleri, beden kütle indeksi and HOMA IR her iki grupta birbirlerine benzer ve normal düzeylerde idi. Ortalama ALT değerleri hasta grubunda belirgin düzeyde yüksek idi [61.8 U/L vs 28.17 U/L (p<0.05)]. Kronik HCV grubunda ortalama viral yük 5.6x10⁵ IU/mL olarak saptandı. Ortalama plazma adiponectin konsantrasyonları kronik HCV hastalarında 71.07µg/ml ve kontrol grubunda 82.07 µg/ml olarak saptandı, ki bu sonuç istatistiksel olarak anlamlı bulunmadı (p>0.05).* ***Sonuç:*** *Obezite, diabetes mellitus ve hepatosteatoz gibi metabolik bozuklukların bulunmaması durumunda kronik HCV enfeksiyonunun varlığı insülin sensivitesini ve adiponectin düzeylerini etkilememektedir.*

Anahtar kelimeler: Kronik HCV, adiponektin düzeyi, HOMA IR, metabolik bozukluklar

INTRODUCTION

In hepatitis C virus (HCV) infection, there is a decrease in host metabolic factors and/or insulin sensitivity due to the direct action of the virus; abnormality in glucose metabolism; and independent increase in the frequency of fatty liver disease (1). In recent years, various studies have demonstrated that metabolic products such as tumor necrosis factor (TNF)-alpha, leptin, adiponectin, and resistin, which are effective in insulin sensitivity and in the regulation of inflammation, play an im-

Address for correspondence: Kadir AKSÖZ
İzmir Atatürk Eğitim ve Araştırma Hastanesi
Basın Sitesi 35360 İzmir, Turkey
Phone: + 90 232 464 42 22 • Fax: + 90 232 244 61 17
E-mail: kadiraksoz@gmail.com

Manuscript received: 14.07.2008 **Accepted:** 25.09.2008

portant role in the development of these metabolic disorders and non-alcoholic fatty liver disease (NAFLD). These products are mostly secreted from adipose tissues and lead to decrease in insulin sensitivity or increase in glucose metabolism abnormalities, together with a substantial increase in NAFLD frequency (2-5). Adiponectin is a molecule, protein in nature, which is present in the circulation as a low- and high-molecular weight multimer and is secreted only from adipose tissues (5). The high molecular weight form acts on insulin sensitivity and possesses anti-inflammatory properties (6). 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 (7). The levels of serum adiponectin are inversely proportional to the amount of body fat, body mass index (BMI), and fasting insulin concentration (8, 9). It is considered that adiponectin inhibits triglyceride accumulation in the hepatocytes by reducing their free fatty acids production and increasing beta-oxidation (10). It is known that when metabolic factors are present, HCV infection has an effect on adiponectin levels. Our aim in this study was to evaluate the effect of HCV infection alone on plasma adiponectin levels and insulin sensitivity. We planned this study in a setting eliminating the metabolic factors that can affect the adiponectin levels in order to find out whether chronic HCV infection causes hepatosteatosis through its effect on adiponectin.

MATERIALS AND METHODS

The present study was carried out between 2006-2007, at the Gastroenterology Clinic of İzmir Atatürk Training and Research Hospital, by evaluating the results of 30 patients with chronic HCV infection and 30 control subjects. Informed consent was obtained from each patient and the study was approved by the İzmir Atatürk Training and Research Hospital Ethical Committee.

The 30 patients with chronic HCV infection enrolled in the study were selected based on the following required criteria: follow-up in our clinic for at least one year, no antiviral treatment before or during the study, anti HCV (+), with HCV RNA of $1.90x10^3$ IU/ml (Cobas Amplicor) and above, more than normal alanine aminotransferase (ALT) values (>40 U/L), BMI ≤26 kg/m^2, non-diabetic status, histological fibrosis scores of 1-2 in liver biopsy, histological activity index (HAI) scores of 3-7 (according to Isaac score) and no fat accumulation, and finally, no findings of hepatosteatosis on ultrasonography (USG) evaluation. The mean viral load detected by HCV RNA was determined as $5.6x10^5$ IU/ml (± $4.5x10^4$) (Cobas Amplicor) in the chronic HCV patient group. Patients who previously received or were receiving antiviral treatment, diabetic patients or patients with a BMI above 26 kg/m^2 were excluded in order to minimize the effects caused by metabolic diseases. The control group consisted of 30 healthy volunteers who were anti HCV(-), had ALT levels within normal ranges (<40 U/L), were non-diabetic, had BMI ≤26 kg/m^2 and no findings of hepatosteatosis in the USG. The fasting blood glucose (FBG) (mg/dl), postprandial 2nd hour plasma glucose (PBG) (mg/dl) after 75-gram glucose consumption, and fasting plasma insulin (mIU/ml) levels were measured in both groups, and the homeostasis model assessment 1 of insulin resistance (HOMA 1-IR) index was calculated from the fasting glucose x fasting insulin / 22.5 formula. The FBG and the PBG after 75-gram glucose consumption were analyzed in the biochemistry laboratory of our hospital, by using the Clinical Chemistry Abbott kit and the Aeroset Abbott Toshiba equipment. Insulin values were analyzed in the same laboratory by using the Bayer HealthCare ADVIA Centaur kit and the Bayer ADVIA Centaur Immunoassay System equipment. Individuals who qualified as non-diabetic according to the oral glucose tolerance test (OGTT) results were included in the study. Plasma adiponectin concentration was measured using the enzyme linked immunosorbent assay (ELISA) method, from the samples obtained for FBG and insulin measurements. The means, minimum – maximum values and the standard deviations of HOMA 1-IR and adiponectin concentrations were statistically analyzed. The Student's t test was used to compare the values of both independent groups. P values of less than 0.05 were considered as significant.

RESULTS

There was no significant difference between the demographic data of the two groups. The mean age of the chronic HCV group was 50.8 (±15.75) years and of the control group was 49.6 (±14.47) years. The chronic HCV group consisted of 14 women and 16 men, whereas the control group consisted of 16 women and 14 men. The mean ALT values were 61.8 U/L (±21.5) in the chronic HCV patient group and 28.17 U/L (±6.22) in the control

group, showing a statistically significant difference between the two groups ($p<0.05$). The FBG, HOMA-IR, and the plasma adiponectin concentration of both groups were evaluated. In the chronic HCV patient group, the mean FBG level was 98.2, whereas it was determined as 94.0 in the control group, and there was no statistically significant difference between the two groups ($p>0.05$). This same result was also verified in the comparison of HOMA-IR values (HCV HOMA IR 2.8, control HOMA IR 2.4, $p>0.05$) and plasma adiponectin concentrations (mean plasma adiponectin concentration 71.07µg/ml in chronic HCV patients and 82.07 µg/ml in controls, $p>0.05$), with statistically insignificant differences between the groups (data shown in Table 1).

DISCUSSION

The results of this study demonstrated that in the absence of hepatosteatosis, overt diabetes, and obesity, the HOMA-IR values in the control and chronic HCV patient groups were similar, and there was no decrease in plasma adiponectin levels or insulin sensitivity in either group. There was no statistically significant difference between the groups. Most studies regarding adiponectin and other adipokines in chronic HCV patients have demonstrated that the BMI of both groups was not within normal limits and hepatosteatosis was present at a high percentage in HCV patients. In this study, we evaluated the effect of chronic HCV infection alone on adiponectin levels and whether chronic HCV infection indirectly affects adiponectin release leading to hepatosteatosis, by minimizing the metabolic factors that could be effective on adiponectin levels.

Table 1. Epidemiologic and laboratory data of the patient and the control group

	N	Mean	Standard Deviation	P Value
Gender				
HCV	30	F 14 M 16		
Control	30	F 16 M 14		
Age				
HCV	30	50.8	15.7	
Control	30	49.6	14.4	
ALT (U/L)				
HCV	30	61.80	31.5	0.0047
Control	30	28.12	6.22	
BMI (kg/m²)				
HCV	30	25.1	3.1	0.059
Control	30	24.3	3.4	
HCV RNA (IU/mL)				
HCV	30	5.6x10 5	4.5x10 4	
Control	30	0	0	
FBG (mg/dL)				
HCV	30	99.2	19.3	0.098
Control	30	94.0	10.2	
HOMA IR				
HCV	30	2.8	1.5	0.34
Control	30	2.4	1.9	
Adiponectin (Ug/ml)				
HCV	30	71.06	83.02	0.74
Control	30	82.07	96.41	

F: Female. M: Male. FBG: Fasting blood glucose. HOMA-IR: Homeostasis model assessment of insulin resistance.

In related studies, the relationship of hepatosteatosis, insulin resistance and adiponectin levels was evaluated. Different results were obtained regarding the correlation between hepatosteatosis and the level of adiponectin. In a study performed on 161 non-diabetic patients with HCV infection, Durante-Mangoni et al. (11) stated that there was a significant decrease in the serum adiponectin levels and a significant increase in the TNF-alpha levels of chronic HCV patients with hepatosteatosis. Low serum adiponectin was associated with hepatosteatosis, but it was not associated with the degree of steatosis. It was suggested that low serum adiponectin concentration has a role in the development of hepatosteatosis. Petit *et al*. (12) reported that 42% of the included patients had steatosis. An association was observed between steatosis and the HCV genotype, high BMI, increased insulin and leptin levels and decreased adiponectin levels. Low levels of adiponectin were determined to have a role in the development of steatosis, and it has been suggested that treatment alternatives increasing the levels of adiponectin may prevent steatosis. On the other hand, in a study performed by Kara et al. (13) in 50 patients with HCV infection and 30 healthy controls, although hepatosteatosis was present in 41 patients (82%) of the HCV infection group, the levels of adiponectin were similar between the groups. There was no statistically significant association between the levels of adiponectin and hepatosteatosis. In a case-controlled study performed by Cua et al. (14), 154 patients untreated for HCV infection and 75 healthy controls were examined. The HOMA-IR, TNF-alpha, and interleukin (IL)-6 levels were significantly increased in the HCV infection group, whereas there was no significant difference compared with the control group regarding leptin and adiponectin concentrations. No relation was thought to exist between HCV-associated insulin resistance and adipocytokines. In this study, we found that insulin sensitivity and adiponectin levels in HCV patients with normal BMI and with no hepatosteatosis

were similar to those of the healthy control group. Lo Iacono *et al*. (15) demonstrated that there was a relationship between visceral obesity and the levels of steatosis and fibrosis. In these patients, there was a decreased adiponectin concentration together with a significant insulin resistance, and these conditions were significantly improved following antiviral treatment. In this study, we tried to investigate the effects of the virus in patients without visceral obesity by minimizing the metabolic factors of the interaction between adiponectin and insulin sensitivity. We demonstrated that the presence of HCV alone did not alter adiponectin concentration or insulin sensitivity.

In conclusion, it can be suggested that, in the absence of metabolic disorders such as obesity, diabetes mellitus and hepatosteatosis, chronic HCV infection alone does not affect insulin sensitivity and adiponectin concentration. According to our findings, a decrease in the level of adiponectin may be associated with host metabolic disorders, independent from chronic HCV infection. In order to evaluate these perspectives, extensive prospective case-control studies are required.

REFERENCES

1. Adinolfi LE, Gambardella M, Andreana A, et al. Steatosis accelerates the progression of liver damage of chronic hepatitis C patients and correlates with specific HCV genotype and visceral obesity. Hepatology 2001;33:1358-64.
2. Monto A, Alonzo J, Watson JJ, et al. Steatosis in chronic hepatitis C: relative contributions of obesity, diabetes mellitus, and alcohol. Hepatology 2002;36:729-36.
3. Marchesini G, Brizi M, Bianchi G, et al. Nonalcoholic fatty liver disease: a feature of the metabolic syndrome. Diabetes 2001;50:1844-50.
4. Cohen B, Novick D, Rubinstein M. Modulation of insulin activities by leptin. Science 1996;274:1185-8.
5. Pajvani UB, Du X, Combs TP, et al. Structure-function studies of the adipocyte-secreted hormone Acrp30/adiponectin. Implications for metabolic regulation and bioactivity. J Biol Chem 2003;278:9073-85.
6. Waki H, Yamauchi T, Kamon J, et al. Impaired multimerization of human adiponectin mutants associated with diabetes. Molecular structure and multimer formation of adinopectin. J Biol Chem 2003;278:40352-63.
7. Yamauchi T, Kamon J, Ito Y, et al. Cloning of adiponectin receptors that mediate antidiabetic metabolic effects. Nature 2003;423:762-9.
8. Shklyaev S, Aslanidi G, Tennant M, et al. Sustained peripheral expression of transgene adiponectin offsets the development of diet-induced obesity in rats. Proc Natl Acad Sci USA 2003;100:14217-22.
9. Fruebis J, Tsao TS, Javorschi S, et al. Proteolytic cleavage product of 30-kDa adipocyte complement-related protein increases fatty acid oxidation in muscle and causes weight loss in mice. Proc Natl Acad Sci USA 2001;98:2005-10.
10. You M, Considine RV, Leone TC, et al. Role of adiponectin in the protective action of dietary saturated fat against alcoholic fatty liver in mice. Hepatology 2005;42:568-77.
11. Durante-Mangoni E, Zampino R, Marrone A, et al. Hepatic steatosis and insulin resistance are associated with serum imbalance of adiponectin/tumour necrosis factor-alpha in chronic hepatitis C patients. Aliment Pharmacol Ther 2006; 24:1349-57.
12. Petit JM, Minello A, Jooste V, et al. Decreased plasma adiponectin concentrations are closely related to steatosis in hepatitis C virus-infected patients. J Clin Endocrinol Metab 2005;90:2240-3.
13. Kara B, Gunesacar R, Doran F, et al. Correlation of serum adiponectin levels and hepatic steatosis in hepatitis C virus genotype 1 infection. Adv Ther 2007;24:972-82.
14. Cua IH, Hui JM, Bandara P, et al. Insulin resistance and liver injury in hepatitis C is not associated with virus-specific changes in adipocytokines. Hepatology 2007;46:66-73.
15. Lo Iacono O, Venezia G, Petta S, et al. The impact of insulin resistance, serum adipocytokines and visceral obesity on steatosis and fibrosis in patients with chronic hepatitis C. Aliment Pharmacol Ther 2007;25:1181-91.