Original Investigation

Relationship between the frequency of hepatitis B virus infections and levels of serum adipokines in patients with hepatosteatosis and insulin resistance

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ABSTRACT

Objective: Although the steatogenic effect of hepatitis B virus (HBV) has been established in several studies, it is not yet known whether it leads to hepatosteatosis in anti-HBc IgG-positive patients. This study aimed to investigate the relationship between the frequency of HBV and levels of serum adipokines in patients with hepatosteatosis and insulin resistance.

Methods: Eighty patients diagnosed with hepatosteatosis by ultrasonography, who were admitted to our polyclinic between July 2011 and June 2012 for various reasons, and who had insulin resistance were included. Homeostasis model assessment-insulin resistance of >2.7 was considered as insulin resistance, and these patients was investigated for anti-HBc IgG. The anti-HBc IgG level was analyzed by enzyme-linked immunosorbent assay. Levels of adiponectin, resistin, and leptin in serum samples were analyzed in anti-HBc IgG (+) and anti-HBc IgG (−) groups.

Results: Anti-HBc IgG was positive in 29 (36.2%) patients and negative in 51 (63.8%). While the level of leptin in the anti-HBc IgG (+) group was 31569.72±14027.64 ng/mL, it was 25410.73±10978.26 ng/mL in the anti-HBc IgG (−) group. The levels of leptin in the anti-HBc IgG (+) and anti-HBc IgG (−) groups were statistically significant (p=0.047). However, levels of adiponectin and resistin were not different between the groups.

Conclusion: These results suggest that anti-HBc IgG positivity is involved in the etiology of hepatosteatosis and insulin resistance as well.

Keywords: Hepatosteatosis, insulin resistance, adipokine, hepatitis B virus

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) has two clinical manifestations: 1) Steatosis (non-alcoholic fatty liver). 2) Non-alcoholic steatohepatitis (NASH). The rate of progression to cirrhosis is 20% in patients with NASH. Today, NASH is defined as an important cause of cryptogenic cirrhosis (1-3).

The prevalence of non-alcoholic fatty liver disease was found to be around 20% in studies using ultrasonography (USG) as a screening method, whereas this ratio can be increased 2 to 3 times in studies based on liver biopsy (4-6).

Many agents and conditions have been associated with hepatic steatosis. Factors such as acquired insulin resistance (metabolic syndrome), congenital and genetic metabolic disorders, medical or surgical conditions associated with weight loss, various medications and toxins can lead to NAFLD (7).

Insulin resistance is defined as a reduction in the endogenous and exogenous effects of insulin and the inability to perform its gluco-

regulatory role in target organs. Increases in visceral adipose tissue and intrahepatic fat mass are associated with increased gluconeogenesis, free fatty acid levels, and insulin resistance (8).

Adiponectin is a hormone released mainly from the adipose tissue, which provides both clearance of fat from the plasma and stimulation of beta-oxidation of fatty acids in the muscles. The decrease in the circulating amount of adiponectin correlates with the severity of liver histology in NAFLD patients (9). In a study, plasma adiponectin levels were found to be significantly associated with hepatic insulin sensitivity. In addition, exogenous administration of pioglitazone increases adiponectin levels, which in turn improves hepatic steatosis, necroinflammation and fibrosis (10).

Resistin is an adipose tissue-derived protein that is believed to play an important physiological role in the development of insulin resistance (11).

Leptin is a peptide produced mainly in adipose tissue, which is thought to contribute to the development of fibrosis in NAFLD,

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and increases the insulin resistance of hepatocytes by stimulating the dephosphorylation of insulin-receptor substrate 1. In patients with chronic hepatitis C, blood leptin levels correlate with the grade of fibrosis (12).

Patients with non-alcoholic fatty liver disease should be screened for biochemical findings of liver diseases and also for accompanying metabolic disorders. It is useful to investigate "Homeostasis Model Assessment-Insulin Resistance" (HOMA-IR) by measuring fasting blood glucose levels as well as fasting insulin levels in patients. In this method, insulin resistance; is calculated by the following formula; IR = fasting insulin level (µIU / mL) X fasting glucose level (mg / dL) / 405. An IR value of >2.7 supports the presence of hepatic steatosis (13).

There are very few studies on the prevalence of steatosis in hepatitis B virus infection. In these studies, the prevalence of steatosis in patients with chronic HBV was found to be similar to that of the general population. There was a correlation between the presence of steatosis and metabolic syndrome diagnostic criteria and BMI (body mass index), whereas no association was found between steatosis and viral genotype and viral load, and even between steatosis and fibrosis (14).

The clinical significance of the presence of isolated anti-HBc has not been fully elucidated. However, PCR analysis of sera from anti-HBc positive patients revealed a detection rate of 0 to 20% for HBV DNA (15). The evaluation of liver biopsies from patients with isolated anti-HBc positivity showed that more than 70% of these patients had HBV DNA in their liver tissues. Detailed examination of donors with isolated anti-HBc positivity in terms of blood or other organ donation suggests that these patients actually carry HBV infection and that the incidence of this condition may range from 0.4 to 78% (16).

In this study, it was aimed to investigate the correlation between the incidence of HBV and serum adipokine levels in patients with hepatosteatosis and insulin resistance.

METHODS

This study included 195 patients who were admitted to the outpatient clinic at Gaziantep University, School of Medicine, Department of Gastroenterology between July 2011 and June 2012 for various reasons and had USG findings of hepatosteatosis. However, among these patients, 80 patients with insulin resistance [Homeostasis Model Assessment-Insulin resistance (HOMA) ≥2.7] who gave consent were enrolled in the study. Informed consent of these patients was obtained. Demographic information of these patients was collected and they were subjected to biochemical and serological tests. The study was performed in accordance with the 1975 Declaration of Helsinki Principles as revised in 2008 and the Approval of the Ethics Committee Commission dated/numbered 30.06.2011/140. All patients signed the informed consent form and approved the study.

Patients
The inclusion criteria for the study are as follows: 1) Patients over 18 years old 2) Patients with steatosis detected on USG 3) Patients with insulin resistance (HOMA IR> 2.7).

The exclusion criteria were as follows: 1) Acute hepatitis 2) HBsAg (+) and anti-HCV (+) 3) Known liver cirrhosis 4) Alcohol use (> 20 gr / day) 5) Diabetes Mellitus (DM) 6) Pregnancy 7) Metabolic and genetic liver diseases (Wilson's disease, hereditary hemochromatosis, alpha-1 antitrypsin deficiency) 8) Autoimmune liver diseases 9) Patients with malignant disease 10) Drug use that can lead to hepatosteatosis (tetracycline, methotrexate, valproic acid etc.).

Laboratory examination
Patients' height and weight were recorded for calculation of body mass index (BMI) (kg / m^2). The history of alcohol consumption and medication use was surveyed for participants. Complete blood count was measured from fasting blood samples, and the following biochemical parameters were measured from serum samples: AST, ALT, bilirubin, albumin, lipid profile (total cholesterol, LDL, HDL, triglyceride), fasting blood glucose (FBG), PT / INR, ceruloplasmin, ANA, ASMA, alpha-1 antitrypsin, protein electrophoresis, serum iron, iron binding capacity and ferritin. In addition, adiponectin (ng / mL), resistin (ng / mL), leptin (ng / mL) and insulin (IU / mL) levels were measured from the serum samples. Insulin resistance was calculated by HOMA-IR score using fasting blood glucose (mg / dL) and insulin (IU / mL) levels.

USG Evaluation
Hepatocellular ultrasonography of the patients was performed using Siemens Antares equipment with a CH4-1 MHz transducer at Gaziantep University School of Medicine, Department of Radiology. The ultrasonographic diagnosis of steatosis was based on the appearance of "bright liver" and/or loss of echogenicity in the glisson capsule.

The following criteria were used to grade hepatosteatosis with USG: Grade 1: Mild steatosis. Minimal diffuse increase in hepatic echogenicity and clear visualization of intrahepatic (portal vein) vessel borders and diaphragm. Grade 2: Moderate steatosis. Moderate diffuse increase in hepatic echogenicity and loss of clarity in the appearance of intrahepatic vessel borders and diaphragm. Grade 3: Severe steatosis. Significant increase in hepatic echogenicity. Inability to visualize the Posterior segment of the liver, intrahepatic vessels and diaphragm.

Calculation of Insulin Resistance
The fasting insulin level required for the calculation of insulin resistance (HOMA-IR) was studied using the CMIA (chemiluminescent microparticle immunoassay) method with the Abbott Architect i2000SR analyser. The following formula was then used to calculate the HOMA-IR score.

HOMA-IR = fasting insulin level (µIU / mL) X fasting glucose level (mg / dL) / 405. HOMA-IR values of 2.7 and above were accepted as insulin resistance. Anti-HBc IgG was studied in patients with a HOMA-IR of >2.7. In cases with Anti-HBc IgG positivity, anti-HBs levels were studied by ELISA (Enzyme-Linked Immuno-Sorbent Assay) method.

Adiponectin, Resistin and Leptin Levels
In cases with anti-HBc IgG positivity (+) and anti-HBc IgG negativity (-), the plasma samples were evaluated by performing the following steps in sequence: 2 mL EDTA blood samples taken at the

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same time from the patient were kept at room temperature for 30-60 minutes. The incubated blood was centrifuged at 4000 rpm for 5-10 minutes. The resulting plasma samples were placed in Eppendorf tubes. Plasma samples in Eppendorf tubes were then placed in deep freezers at -80°C to study adipokine levels. After all the samples were collected, they were removed from the freezer at -80°C, first taken to -20°C, then the plasma samples at -20°C were allowed to stand at room temperature to reach + 4°C. This period lasted approximately 60 minutes. Adipokine (adiponectin, resistin, leptin) levels were then studied by ELISA method. Adiponectin levels (ng / mL) were obtained using the ELISA kit with ELx800 (Biotek Inc.; Ca, USA) device. Resistin levels (ng / mL) were obtained using AssayMa ELISA kit with ELx800 (Biotek Inc.; Ca, USA) device, whereas Leptin levels (ng / mL) were obtained using Invitrogen ELISA kit with ELx800 (Biotek Inc.; Ca, USA) device.

Statistical Analysis

The Statistical Package for Social Sciences 16.0 (SPSS Inc.; version 16.0, Chicago, IL, USA) was used for statistical analysis of the data obtained at the end of the study. The results are given as mean (±) standard deviation and percentage. Chi-square test was used for categorical variables, student-t test was used for the variables that can be averaged, Pearson correlation test was used for correlation analyses. The chi-square test was used for intra-group categorical comparisons. For all tests, p<0.05 was considered statistically significant.

RESULTS

The present study enrolled 80 patients with hepatosteatosis and insulin resistance. For all patients, the mean age was 44.73±13.17 years (21 to 78 years) and the mean BMI (kg / m^2) was 30.15±3.15. Of the patients, 47 were female (58.75%) with a mean age of 47.31±12.99 years, whereas the mean age of males was 41.06±12.72 years.

By ultrasonographic examination, steatosis was graded as grade 1 (mild), grade 2 (moderate), and grade 3 (severe). Ultrasonographic examination revealed that 31 patients had grade 1 steatosis, 43 patients had grade 2 steatosis, and 6 patients had grade 3 steatosis. Ultrasonographic examination of the patients with anti-HBc IgG positivity (+) revealed grade 1, 2 and 3 steatosis in 10, 17 and 2 patients, respectively, whereas USG examination of the patients with anti-HBc IgG negativity (-) revealed grade 1, 2 and 3 steatosis in 21, 26 and 4 patients, respectively.

Serological examination of the patients showed anti-HBc IgG positivity (+) in 29 (36.2%) patients. Of the patients with anti-HBc IgG positivity (+), 18 were female and 11 were male. The remaining 51 (63.8%) patients had anti-HBc IgG negativity (-). In Anti-HBc IgG (-) group, there were 29 females and 22 males. There was no gender difference between the two groups (p=0.327).
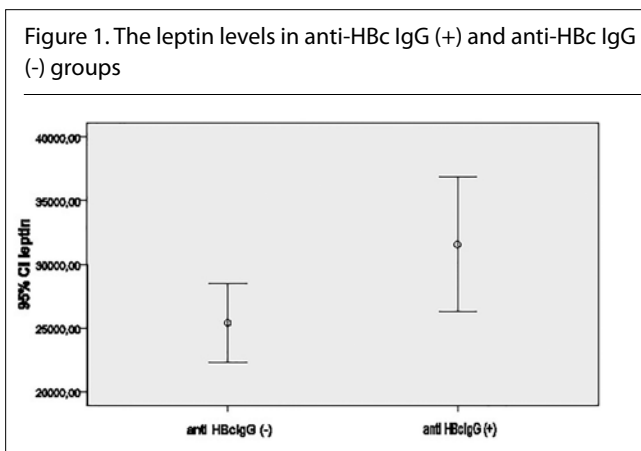
Of 29 patients with anti-HBc IgG positivity (+), 8 (27.5%) had anti-HBs negativity (-), which was accepted as isolated anti-HBc IgG positivity (+). Of these patients, 21 (72.5%) had anti-HBs positivity (+). On the other hand, anti-HBs negativity (-) was detected in 35 (68.6%) of 51 patients with anti-HBc IgG negativity (-). However, 16 patients (31.4%) had anti-HBs positivity (+), which was considered to be due to vaccination.

The comparison of the mean values for BMI (kg/m2) HOMA-IR, FBG (mg / dL), triglyceride (mg/dL), total cholesterol (mg/dL), LDL, HDL, insulin (IU/mL), resistin (ng/mL), adiponectin (ng/mL), ALT (U/L) values showed no statistically significant difference between two groups (p>0.05) (Table 1). However, the mean leptin level was 31569.72±14027.64 in anti-HBc IgG (+) group, whereas 25410.73±10978.26 in anti-HBc IgG (-) group. There was a statistically significant difference in mean leptin levels between the two groups (p=0.047) (Figure 1).

Table 1. Comparison of demographic and biochemical parameters between anti–HBc IgG (+) and anti–HBc IgG (–) groups

	Anti HBc IgG (+)	Anti HBc IgG (−)	p
BMI (kg/m^2)	30.67±4.33	29.86±3.00	ns
Age (Years)	45.96±12.19	44.03±13.76	ns
HOMA–IR	3.63±1.18	3.92±2.12	ns
Adiponectin (ng/mL)	26229.44±8497.45	26149.73±6868.67	ns
Resistin (ng/mL)	38.13±17.14	32.91±14.46	ns
Leptin (ng/mL)	31569.72±14027.64	25410.73±10978.26	0.047
Insulin (IU/mL)	16.37±5.42	17.31±8.28	ns
HDL (mg/dL)	46.55±19.95	43.45±10.71	ns
LDL (mg/dL)	132.76±23.37	126.08±35.96	ns
T. cholesterol (mg/dL)	201.14±29.07	197.04±40.66	ns
Triglyceride (mg/dL)	177±52.19	204.45±143.69	ns
ALT (U/L)	49.31±57.28	40.92±31.78	ns
FBG (mg/dL)	91.82±6.97	92.54±8.64	ns

ALT: alanine aminotransferase; FBG: fasting blood glucose; HDL: high density lipoprotein; HOMA–IR: homeostasis model assesment–insulin resistance; LDL: low density lipoprotein; T. cholesterol: total cholesterol; BMI: body mass index ns: p>0.05

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Figure 1. The leptin levels in anti-HBc IgG (+) and anti-HBc IgG (-) groups

Figure 2. Positive correlation between resistin and triglyceride levels in patients with hepatosteatosis (p=0.005)

The mean leptin levels in the patients with a BMI of <30 kg/m^2 were found to be significantly higher in anti-HBc IgG (+) group (31909±14618.63) compared to anti-HBc IgG (-) group (24072 ± 10240.53). Leptin levels were significantly higher in anti-HBc IgG (+) group (p<0.05). No statistically significant difference was found between leptin levels of anti-HBc IgG (+) and anti-HBc IgG (-) groups with a BMI of >30 kg/m^2 (p=0.695).

Correlation analyses were performed between adipokine levels and other biochemical parameters in both groups. There was a significant positive correlation between serum resistin and triglyceride levels in both groups (r=0.314, p=0.005) (Figure 2).

Although there was a positive correlation between resistin and triglyceride, no correlation was observed between resistin and FBG, HDL, LDL, total cholesterol, insulin, HOMA-IR and ALT levels.
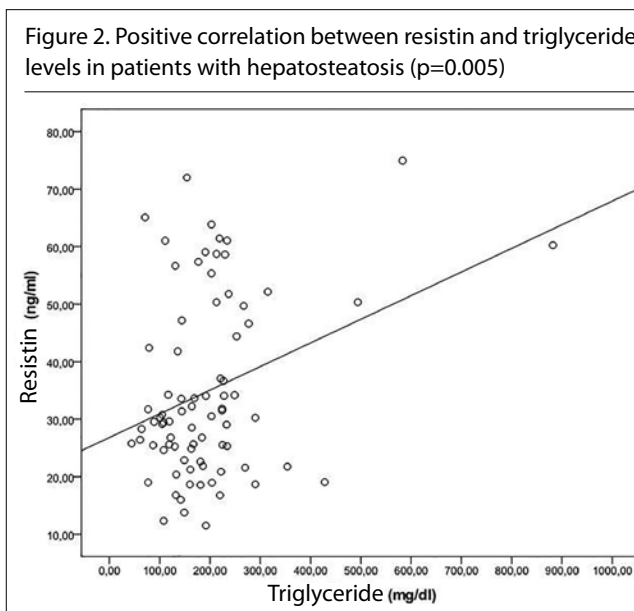
After the patients were divided into anti-HBc IgG (+) and anti-HBc IgG (-) groups, correlation analysis was performed between adipokine levels and other biochemical parameters.

In anti-HBc IgG (+), there was a significant negative correlation between adiponectin levels and BMI and between leptin and FBG levels (p=0.049) (p=0.017). In anti-HBc IgG (-) group, there was a significant positive correlation between resistin and triglyceride levels, while there was a significant negative correlation between leptin and insulin levels (p=0.001) (p=0.0419).

DISCUSSION

Nonalcoholic fatty liver disease is a disease that has been known for many years and is presenting with different etiologies. Although the exact diagnosis of NAFLD is established by liver biopsy, this method is not considered appropriate because it is an invasive and expensive method and requires special conditions. Therefore, radiological methods and biochemical tests are more frequently used for diagnosis (17).

Insulin resistance seems to play a key role in the etiopathogenesis of nonalcoholic fatty liver disease. It causes an inflammatory process leading to the development of steatohepatitis and fibrosis. Therefore, cytokines and adipokines that cause insulin resistance appear to be extremely important. Adipokines are pro-

teins secreted from adipocytes and from connective tissue cells between adipocytes. These proteins are known to have a role in proinflammatory process, increased immunoreactivity and systemic insulin resistance. In the literature, there are some studies on adipokine levels which can be considered as noninvasive methods investigating NAFLD and insulin resistance. In these studies, the relationship between leptin, adiponectin, TNF-alpha, resistin, IL-6 levels was investigated in many clinical cases. In this study, resistin levels were found to be elevated in hepatic steatosis, which was thought to cause insulin resistance leading to the development of NAFLD (18).

In clinical practice, it is quite practical to measure triglycerides by biochemical methods, whereas it is difficult to measure the resistin levels in laboratory methods due to the difficulties in supplying the kits and lack of widespread use. In our study, the positive correlation between triglyceride and resistin gave rise to the hope that triglyceride could be used as a substitute for resistin. Adiponectin, a hormone released mainly in the adipose tissue, has an anti-inflammatory effect, which suppresses the production of TNF-alpha in the liver and thus its increase reduces the development of NAFLD. An examination of studies conducted to date shows that the increase in serum IL-6 levels is significant for NAFLD. We investigated serum adiponectin, resistin, leptin levels instead of TNF-alpha and IL-6 levels in our study, considering that serum levels of TNF-alpha and IL-6 are parallel to levels of other adipokines. We found that leptin levels were significantly higher in the anti-HBc IgG (+) group. In a related study, there was a significant relationship between leptin levels and the brunt classification used in the pathologic grading of NAFLD. According to the Brunt classification, leptin levels increased as the pathological stage increased (19).

It has been suggested that increased production of leptin during the inflammatory period in chronic viral hepatitis induces cytokine release by stimulating CD4 T lymphocytes and macrophages (20). In some animal models, leptin-activated T cells have

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been found to damage hepatocytes either by exerting cytotoxic effects directly on hepatocytes or through mediators released from active T cells (21). In another study, it was shown that the leptin system plays a role in immunopathogenesis in patients with chronic viral hepatitis (22).

It is known that leptin may also increase in hepatic steatosis and chronic viral hepatitis. Therefore, we excluded the patients with chronic HBV and HCV, considering that the agent causing chronic hepatitis will cause liver damage by increasing leptin levels and that the increase in leptin levels may be due to a virus. Patients were included in the study by considering the presence of anti-HBc IgG. It is known that patients with anti-HBc IgG positivity (+) have already had contact with HBV but have no surface antigen (HBsAg) positivity, and therefore are not considered within the scope of chronic hepatitis. Therefore, neither a liver biopsy nor a treatment is applied in anti-HBc IgG (+) patients. Thus, increased leptin levels in the absence of or sometimes in the presence of undetectable levels of HBV, or if HBV is concealed in areas that cannot be detected by routine examinations (e.g.; HBV DNA detected by PCR after liver biopsy despite HBsAg negativity (-)) suggest that there may be a correlation between leptin and HBV levels as well as between leptin levels and anti-HBc IgG (+). We believe that leptin may also cause hepatic damage and hepatosteatosis by using the pathways it uses in the case of HBV also in the case of anti-HBc IgG (+).

However, studies have shown that leptin has a role in the development of chronic liver disease and hepatic fibrogenesis, whereas, unexpectedly, a study has shown that leptin levels decrease in chronic hepatitis (23). In another study, high serum leptin levels were found in patients with chronic HCV infection (24). However, further studies are needed to clarify this issue.

Studies on the physiopathogenesis of chronic HCV in hepatosteatosis have shown that lipid peroxidation occurs in the kupffer cells due to the increase of oxygen radicals through HCV core protein and NS3 (Non structural HCV protein 3). As a result, decreased adiponectin levels and increased TNF-alpha and leptin levels result in insulin resistance (25). On the other hand, the increase in free radicals leads to the clustering of triglycerides and the decrease in apo B lipoprotein levels leads to steatosis. If leptin levels had increased only because of steatosis, then increased leptin levels should have increased the insulin resistance as well as the insulin levels. However, in our study, as the leptin levels increased, insulin levels decreased inverse proportionally and showed a negative correlation in the anti-HBc IgG (-) group, while a similar negative correlation was observed in the anti-HBc IgG (+) group. However, this was not statistically significant. This suggests that the increase in leptin levels in the anti-HBc IgG (+) group is not directly due to steatosis, but perhaps due to concealed viruses.

It is not yet known whether anti-HBc IgG positivity (+), which is evidence of having contacted with hepatitis B virus, will cause hepatosteatosis and if so, how effective it can be. There are no studies on hepatosteatosis and insulin resistance in patients contacted with HBV and improved. In this study, which we de-

signed to find the answer to this question, we found that leptin levels in patients with anti-HBc IgG (+) were significantly higher than those with anti-HBc IgG negativity (-). There are also studies showing that leptin levels are elevated in relation to obesity (26). In our study, there was no difference in BMI between the two groups. The comparison of patients with VKI> 30 kg/m^2 in both groups showed higher leptin levels in anti-HBc IgG (+) group, but this result was not statistically significant. However, the comparison of patients with VKI> 30 kg/m^2 in both groups showed that leptin levels in the anti-HBc IgG (+) group were statistically higher than those of the anti-HBc IgG (-) group. This suggests that leptin levels were increased in the anti-HBc IgG (+) group due to a factor other than obesity.

In a study of patients with chronic hepatitis B who had evidence of hepatosteatosis in liver biopsy, a positive correlation was found between HBV DNA and adiponectin levels, whereas a negative correlation was found between insulin resistance (assessed by HOMA-IR) and adiponectin levels. There was a positive correlation between insulin resistance and leptin and IL-6 levels, but no correlation was found between HBV DNA levels and leptin and IL-6 levels. There was no significant relationship between adipokine levels and HBeAg positivity (+) and HBeAg negativity (-) (27). It would be ambitious to state that this leptin increase is due to HBV. In this study, if leptin levels were measured in two groups with and without HBV carriers, who had equal-grade of hepatic steatosis, it would be considered that HBV levels are directly correlated with leptin levels if the increase in leptin levels was greater in the HBV group. Unfortunately, there is no such study in the literature. In the light of literature, it is already known that leptin levels and insulin resistance are positively correlated in liver steatosis. Furthermore, in a study conducted in our country, obesity has been shown to be mainly due to the transport of serum leptin through the blood-brain barrier (28). A recent study conducted in our country included 119 patients with chronic hepatitis B and evidence of statosis in liver biopsy and found that hepatic steatosis does not affect the virological response to oral antiviral therapy (29). In our study, it is difficult to state that the patients have an equal level of hepatic steatosis by USG examination because of the lack of liver biopsy studies. However, since there is no significant difference between the two groups in terms of USG evidence of steatosis, BMI and blood lipid profiles, it can be stated that these two groups have a comparable level of hepatic steatosis. We therefore attributed high levels of leptin in the anti-HBc IgG (+) group to HBV infection. Therefore, we cannot attribute the increase in leptin levels only to steatosis. It can therefore be argued that this increase in leptin levels is related to having contacted with HBV.

In the light of these findings, in our study, increased leptin levels in patients contacted with HBV, who had ultrasonographic evidences of hepatosteatosis, suggest that anti-HBc IgG positivity (+) may also be involved in the etiology of NAFLD. The correlation of HBV burden with leptin levels and therefore with the grade of steatosis could be demonstrated more clearly by measuring HBV DNA levels in patients with anti-HBc IgG positivity (+). However, HBV DNA levels were not measured in our patients. Because there was a possibility of positivity of liver biopsy for HBV DNA

in patients who had negative results with blood measurements. Failure to perform liver biopsy for ethical reasons also impeded the HBV DNA analysis in the liver.

Although the measurement of leptin levels in the etiopathogenesis of non-alcoholic fatty liver disease appears to be a useful test, its limited industrial use and expensive and impractical nature limit its usability. However, it is very practical to measure anti-HBc IgG levels in patients found to have ultrasonographic evidences of steatosis in outpatient clinics. Anti-HBc IgG positivity (+) and elevated leptin levels in these patients suggest that leptin is a molecule that plays a role in the etiopathogenesis of hepatosteatosis. Therefore, our study demonstrates that anti-HBc IgG measurement may be an important laboratory analysis for the investigation of the etiopathogenesis of NAFLD. In clinical practice,-anti-HBc IgG levels as well as anti-HCV and HBsAg levels may be routinely analyzed in patients investigated for steatosis. However, it seems impossible to comment on the progression of steatosis with current information during follow-up nor during treatment of such patients.

CONCLUSION
In conclusion, anti-HBc IgG positivity (+) should be considered in the etiology of hepatosteatosis and insulin resistance. In addition, larger studies are needed to prove whether there will be a difference in the long term in terms of progression to cirrhosis between the patients with hepatosteatosis and insulin resistance who have anti-HBc IgG positivity (+) and who have anti-HBc IgG negativity (-).

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