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Does chronic hepatitis B infection have an impact on fasting blood glucose levels and fatty liver development?

Kronik Hepatit B enfeksiyonu açlık kan şekeri düzeylerini ve yağlı karaciğeri etkiler mi?

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Abstract

Aim: The relationship between hepatitis B virus (HBV) infection and insulin resistance (IR) appears to be confusing. In this study, the goal was to compare fasting blood glucose (FBG) levels and fatty liver (FL) frequency as a reflection of IR in patients with chronic active HBV infection and to determine whether there is a relationship between liver fibrosis, FBG and FL.

Methods: In this case-control study, the study group consisted of 116 chronic HBV patients with HBV DNA levels above 2000 IU/ml. The control group included 120 healthy individuals with matching age, gender, and body mass indexes.

Results: There was no difference in FBG levels between the groups (P=0.15), but FL rates were significantly higher in patients with HBV (P=0.01; OR: 2.13, 95% CI 1.26-3.61). Although the FBG levels of groups with regards to severity of fibrosis were similar, there was a significant difference in terms of FL (P=0.07 and P<0.001, respectively). A positive correlation was found between the development of FL and the severity of fibrosis (r_s=0.216, P=0.01).

Conclusion: While FBG level appears to be unaffected by chronic active HBV infection, the frequency of FL is markedly increased in these patients. Viral factors are likely responsible for the development of FL rather than metabolic factors.

Keywords: Fatty liver, Hepatitis B, Insulin resistance, NAFLD

Öz

Amaç: Hepatit B virüsü (HBV) enfeksiyonu ile insülin direnci (ID) arasındaki ilişki kafa karıştırıcı görünmektedir. Bu çalışmada amaç, kronik aktif HBV enfeksiyonu olan hastalarda açlık kan şekeri (AKŞ) düzeyleri ile yağlı karaciğer (YK) sıklığını ID'nin bir yansıması olarak karşılaştırmak ve karaciğer fibrozunun AKŞ ve YK ile bir ilişkisi olup olmadığını belirlemekti.

Yöntemler: Bu çalışma vaka kontrol çalışması olarak planlandı. Çalışma grubu, 2000 IU/ml'nin üzerinde HBV DNA seviyesi olan 116 kronik HBV hastasından oluşturuldu. Yaş, cinsiyet ve vücut kitle indeksi uyumlu 120 sağlıklı bireyden bir kontrol grubu oluşturuldu.

Bulgular: Gruplar arasında AKŞ düzeyleri arasında fark yoktu (P=0,15), HBV'li hastalarda YK oranları anlamlı olarak daha yüksekti (P=0,01; OR: 2,13, %95 GA 1,26-3,61). Fibrozis şiddetine göre gruplar arasında AKŞ düzeyleri arasında anlamlı bir fark olmamasına rağmen, YK açısından anlamlı bir fark vardı (sırasıyla P=0,07 ve P<0,001). YK gelişimi ile fibrozisin şiddeti arasında pozitif bir korelasyon bulundu (r_s=0,216, P=0,01).

Sonuç: AKŞ düzeyi kronik aktif HBV enfeksiyonundan etkilenmemiş gibi görünse de, bu hastalarda YK sıklığı belirgin şekilde artmaktadır. Metabolik faktörlerden ziyade viral faktörlerin YK gelişiminden sorumlu olması muhtemeldir.

Anahtar kelimeler: Yağlı karaciğer, Hepatit B, İnsülin direnci, NAFLD

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Introduction

Hepatitis B, an infection of the liver, is caused by a virus (Hepatitis B virus (HBV)) that is spread through blood and body fluids. Estimations are that 350 million people worldwide are affected by the disease [1,2]. Hence, it is a major global health problem. The vast majority of people infected with HBV in adulthood are able to fight off the virus and fully recover within 1 to 3 months, although occasionally the infection can last for 6 months or more (chronic hepatitis B). In 2015, HBV resulted in an estimated 887,000 deaths, due mainly to progression to cirrhosis and hepatocellular carcinoma (HCC) [3].

Insulin resistance (IR) is when cells in muscles, body fat and liver start resisting or ignoring the signal that the hormone insulin is trying to send out. There is a worldwide rapid increase in its prevalence, and it can have serious health consequences such as metabolic syndrome (MS), fatty liver disease (FL), type 2 diabetes, cardiovascular disorders, and cancer [4]. Chronic HCV infection is linked with higher risk of diabetes mellitus and insulin resistance [5]. On the other hand, the effect of chronic HBV infection is different from chronic hepatitis C virus (HCV) infection. An experimental study indicated that the hepatitis B X protein hinders the pathway for hepatic insulin signaling, and it showed an association between HBV infection and IR [6]. The association between HBV infection and IR was further confirmed by a Korean study, which also showed that chronic HBV infected patients may require monitoring for IR and diabetes onset [7]. Many studies, however, have not shown a difference between chronic HBV infected and post-inspection healthy patients with regards to IR [8,9].

FL or hepatosteatosis, is an accumulation of fat in the liver above 5% of liver weight and it is the most common cause of chronic liver disease worldwide [11]. Many studies are investigating the link between FL and chronic HBV infection with unclear and conflicting results. Some publications report that chronic HBV infection is preventive against FL, whereas other publications report an increase in FL with HBV infection [12,13].

Considering the foregoing, the link between insulin resistance and HBV is not conclusive. Additional studies are needed on this subject, and in this study, the aim was to compare FL frequency and fasting blood glucose (FBG) levels to gain an impression of IR in patients with chronic active HBV (CAHB) infection. An additional aim was to find out whether there is a relationship between FL and liver fibrosis with FBG.

Materials and methods

This was a case control study whereby HBV patient files were reviewed for those admitting themselves into the territorial hospital gastroenterology outpatient clinic between September 2017 to March 2020. Inclusion criteria comprised HBsAg positive patients for more than 6 months, having HBV DNA > 2000 IU/ml and a liver biopsy obtained. Exclusion criteria included patients with other viral agents (such as HIV, Delta hepatitis, hepatitis C), malignancy, known diabetes, metabolic and genetic liver diseases (Wilson disease, hereditary hemochromatosis, history of hyperlipidemia, alpha-1 antitrypsin deficiency), chronic systemic disease (kidney failure, heart failure, etc.), body mass index (BMI) of 30 and above, alcohol use, and a history of drug use influencing blood sugar regulation (steroid, thiazide etc.). A control group was formed from 120 healthy individuals with matching compatible age, gender, and BMIs. Demographic data and laboratory parameters were recorded from the files of the cases.

Histopathological findings

Using the Knodell scoring between 0-6, liver biopsies in 116 patients with CAHB were noted [14]. Using the fibrosis scoring, patients with scores between 1 and 3 were classified as mild fibrosis, and above 4, as severe fibrosis.

Ultrasonography

Fatty liver was widely diagnosed with liver ultrasonography, and detection was based on thin echoes in liver parenchyma in comparison to splenic or kidney parenchyma [15]. Liver fat was classified in four groups: No liver fat, mild (G1), moderate (G2) and severe (G3) liver fat.

Ethical approval

The ethical committee of our hospital approved the study (19-2020) and it was conducted according to the Helsinki Declaration. All participants gave written informed consents prior to biopsies.

Statistical analysis

SPSS IBM 22.0 software was used for analysis, and descriptive statistics were developed for the groups. Normally distributed continuous variables were presented as mean (standard deviation), and non-normally distributed variables were given as medium (min.-max.) using categorical data and sorting via percentages and number. Group differences were analyzed with Mann-Whitney U tests and Student t-tests while multiple group comparison was performed with the Kruskal-Wallis test. Variable correlation was performed using Spearman correlation analysis and statistical significance was considered as $P<0.05$.

Results

The study and control groups consisted of 116 patients with CAHB and 120 healthy individuals. The general characteristics of the groups are presented in Table 1. The mean ages of the study and control groups were 49.60 (17.41) and 49,63(15,26) years, respectively, which were similar ($P=0.93$). While there were 72 men (62.1%) and 44 women (37.9%) in the study group, there were 62 men (51.7%) and 58 women (48.3%) in the control group. There was no difference in terms of gender distribution between the groups ($P=0.11$). Aspartate transaminase (AST) and alanine transaminase (ALT) levels were significantly higher in the study group compared to the control group (49.99 (76.14) and 27.76 (24.97), $P<0.001$; 57.02 (97.62) and 28.84 (29.55), $P<0.001$). There was no difference between the groups in terms of BMI ($P=0.31$). FBG levels in the study and control groups were 100.42 (22.76) and 102.34 (20.90), respectively ($P=0.15$).

FL rates of the groups are presented in Table 2. The frequency of FL was significantly higher in the study group compared to the control group (41.7% vs 60.3%, $P=0.01$, OR: 2.13, 95% CI 1.26-3.61).

Patients with CAHB were divided into groups according to their levels of fibrosis (absent, mild fibrosis and severe

fibrosis). Groups were compared in terms of age, gender, AST, ALT, FBG and FL (Table 3). While there was no significant difference between the FBG levels, there was a significant difference in terms of FL (P=0.07 and P<0.001, respectively).

In the correlation analysis, no relation was found between the severity of fibrosis and FBG (r_s=-0.76, P=0.27), while there was a positive correlation between the severity of fibrosis and the development of FL (r_s=0.216, P=0.01).

Table 1: General characteristics of the groups

		Control group	Study group	*P*-value
Age		49.63(15.26)	49.60(17.41)	0.93
Gender	Male	62 (51.7%)	72 (62.1%)	0.11
	Female	58 (48.3%)	44 (37.9%)	
AST		27.76(24.97)	49.99(76.14)	<0.001
ALT		28.84(29.55)	57.02(97.62)	<0.001
FBG		102.34(20.90)	100.42(22.76)	0.15
BMI		27.17(3.06)	27.78(3.10)	0.31

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, FBG: Fasting blood glucose, BMI: Body mass index

Table 2: Hepatosteatosis rates of the groups

		n	%
Control group	No FL	70	58.3
	G1	32	26.7
	G2	14	11.7
	G3	4	3.3
Study group	No FL	46	39.7
	G1	33	28.4
	G2	7	6.0
	G3	30	25.9

FL: Fatty liver

Table 3: Comparison of the groups in terms of variables according to the severity of fibrosis

	FBG	FL	AST	ALT	Age	Gender
Chi-Square	5.476	16.649	41.392	25.995	4.232	8.228
[a]*P*-value	0.065	<0.001	<0.001	<0.001	0.121	0.016

a: Kruskal Wallis Test, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, FBG: Fasting blood glucose, FL: Fatty liver

Discussion

IR is regarded as the main cause for MS and FL development and characterized by hindered insulin-mediated glucose utilization in target tissues. More studies show that IR and its related diabetes are more prevalent in chronic HBV infection [17-20]. This study's goal was to compare FBG levels and the development of FL between the control group and the CAHB group, in terms of IR. No difference could be detected between the control and study groups with regards to FBG levels or fibrosis severity. FL frequency on the other hand was higher in the CAHB group. Furthermore, a positive correlation was detected with fibrosis severity.

Important risk factor for IR is reportedly chronic hepatitis C. Hepatitis C accelerates fibrogenesis in the liver, and it is reported to cause an elevated risk of diabetes mellitus [5-21]. On the other hand, chronic HBV infections behave differently and the relationship to IR is complex. An increasing number of studies indicate that there is a positive relationship between chronic HBV infection and IR, and its underlying mechanism is that hepatitis B X protein impairs the hepatic insulin signaling path [6,7,17-20,22]. However, a study by Wang et al. [8] showed no correlation between IR in HBsAg positive patients. A meta-analysis involving 15 studies showed no risk increase for type 2 diabetes mellitus which may be due to chronic HBV infection without cirrhosis. Chronic HBV infection has been reported to elevate the risk of type 2 diabetes mellitus with cirrhosis (OR=1.74, 95% CI: 1.43-2.13), therefore the authors deduce that HBV alone may not be diabetic [23]. In their 10-year study consisting of 1233 adults, Huang et al. [9] determined that asymptomatic chronic HBV infection was not correlated with diabetes mellitus after compensation for sex, age, and BMI. In the initial medical examination of 296 non-diabetic patients, the incidence of diabetes or glucose intolerance over 10 years was not different between HBV carriers and individuals without HBV. It can be concluded that asymptomatic chronic HBV infection does not elevate the risk of diabetes. This study showed no statistically significant difference in FBG levels between the groups.

Among healthy individuals, the liver plays a particularly significant role in maintaining glucose homeostasis. Disorders in glucose metabolism, called hepatogenous diabetes, are well defined in patients with advanced cirrhosis [24]. There is also a strong relationship between the components of IR syndrome and the stage of liver fibrosis [25,26]. Therefore, as the severity of fibrosis increases, changes in the level of FBG can be expected. However, in this study, we did not find a relationship between FBG levels and the severity of fibrosis.

It is generally believed that chronic HBV infection is preventive against the development of FL [12,27]. However, the frequency of FL was higher in chronic HBV patients compared to the control group in our study. It was compatible with few other studies in the literature that gave similar results [13,28].

Limitations

Our study has various limitations, including its single center and retrospective nature, along with the small number of cases involved.

Conclusion

Our study revealed that FBG levels were similar to that of the control group as a reflection of IR in patients with CAHB, but the frequency of FL was higher. The groups were similar in terms of age, gender, and BMI; therefore, we believe that HBV infection rather than metabolic factors may play a role in the development of FL. In addition, we think that hepatic fibrosis may be associated with the development of FL, but it may not have an effect on FBG. Large-scale studies are needed for further deduction.

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