Research Article/ Araştırma Makalesi

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Comparison of non-invasive biochemical fibrosis markers according to obesity-based metabolic profile in chronic liver disease with chronic hepatitis B etiology

Kronik hepatit B etyolojili kronik karaciğer hastalığında obezite bazlı metabolik profile göre non-invaziv biyokimyasal fibrozis belirteçlerinin karşılaştırılması

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ABSTRACT

Aim: The aim of this study is to investigate the impact of obesity on fibrosis by comparing fibrosis markers between obese and non-obese patients with Chronic Hepatitis B (CHB).

Material and Method: A total of 172 CHB (50.6±9.4 mean aged) patients were included in this retrospective study. The patients were divided into two groups: Obese (n=72) and Non-obese (n=100). Inclusion criteria were those diagnosed with chronic hepatitis B and ≤ 50 IU/mL or undetectable HBV-DNA, and exclusion criteria were other chronic diseases other than CHB and pregnancy. The height, body weight, and waist circumferences were measured. BMI ≥30 kg/m2 was classified as the obese group. Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Gamma-glutamyl transferase, albumin, bilirubin, and prothrombin time were analyzed. Fibrosis-4 score (FIB-4) was calculated with the formula Age x AST / platelet count x √(ALT), and AST-Platelet Ratio Index (APRI) was calculated with the formula [AST/AST (upper limit of normal)]/ platelet count.

Results: AST levels were significantly higher in obese patients (p<0.001). FIB-4 (p=0.002) and APRI (p=0.007) scores were higher in the obese group. The length of the right lobe of the liver was also significantly enlarged in the obese group (p=0.035).

Conclusion: Obesity is associated withz increased fibrosis progression in CHB patients. These findings suggest that obesity may exacerbate liver damage in CHB patients and highlight the importance of managing obesity in this population to slow fibrosis progression. Further research is warranted to manage therapeutic strategies to mitigate the impact of obesity on fibrosis in CHB.

Key Words: Chronic Hepatitis B, Obesity, APRI, FIB-4

ÖZ

Amaç: Bu çalışmanın amacı, obez ve obez olmayan Kronik Hepatit B (KHB) hastalarında fibrozis belirteçlerini karşılaştırarak obezitenin fibroz üzerindeki etkisini araştırmaktır.

Gereç ve Yöntem: Bu çalışmaya toplam 172 KHB'li (ortalama yaşı 50,6 ± 9,4 olan) hasta dahil edildi. Hastalar iki gruba ayrıldı: Obez (n=72) ve Obez Olmayan (n=100). Dahil etme kriterlerini kronik hepatit B tanısı almış ve ≤ 50 IU/mL veya saptanamayan HBV-DNA'sı olanlar, dışlama kriterlerini ise CHB dışında diğer kronik hastalık ve gebelik oluşturmaktaydı. Boy, vücut ağırlığı ve bel çevreleri ölçüldü. BKİ ≥30 kg/m2 obez olarak sınıflandırıldı. Alanin Aminotransferaz (ALT), Aspartat Aminotransferaz (AST), Gama glutamil transferaz, albümin, bilirubin ve protrombin zamanı analiz edildi. Fibrozis-4 skoru (FIB-4), Yaş x AST / trombosit sayısı x √(ALT) formülüyle hesaplandı ve AST-Trombosit Oranı İndeksi (APRI), [AST/AST (normalin üst sınırı)]/trombosit sayısı formülüyle hesaplandı.

Bulgular: AST obez hastalarda anlamlı olarak daha yüksekti (p<0.001). FIB-4 (p=0.002) ve APRI (p=0.007) skorları obez grupta daha yüksekti. Karaciğerin sağ lobunun uzunluğu obez grupta anlamlı şekilde fazlaydı (p=0.035).

Sonuç: Obezite, KHB hastalarında artmış fibrozis progresyonuyla ilişkilidir.Bu bulgular, obezitenin KHB hastalarında karaciğer hasarını şiddetlendirebileceğini ve fibrozis ilerlemesini yavaşlatmak için bu popülasyonda obezitenin tedavisinin önemini vurgulamaktadır. Obezitenin fibrozis üzerindeki etkisini hafifletmeye yönelik tedavi stratejilerini yönetmek için daha fazla araştırmaya ihtiyaç vardır.

Anahtar Kelimeler: Kronik Hepatit B, Obezite, APRI, FIB-4

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Introduction

Chronic Hepatitis B (CHB) is a persistent viral infection that affects approximately 4.1% of the global population and is a public health problem leading to high morbidity and mortality rates (1). Hepatitis B virus (HBV) infection can lead to severe consequences such as liver cirrhosis, hepatocellular cancer, and liver failure in the long term (2). The course of liver diseases resulting from HBV infection is affected by various factors (3), the most important of which is obesity. It is of great importance to evaluate the effects of obesity in these patients because of the possibility that fibrosis progression may be more rapid and severe in the presence of CHB and obesity.

Obesity, a growing epidemic, is defined as abnormal and excessive fat accumulation with a body mass index (BMI) over 30 kg/m2. It is estimated that 1.02 billion adults will be obese by 2030 (4). Beyond being an aesthetic problem, obesity is a detrimental risk factor for many chronic diseases such as hyperlipidemia, type 2 diabetes mellitus, metabolic dysfunction associated fatty liver disease (MAFLD), and atherosclerotic cardiovascular disease. In addition to the metabolic consequences of obesity, it is also being investigated that it increases the risk of fibrosis development and progression in the liver. It has been shown to accelerate liver fibrosis progression in various chronic liver diseases (5). Studies have shown that chronic liver diseases such as MAFLD progress more rapidly in obese individuals. The relationship between obesity and fibrosis markers plays an essential role in the management of chronic liver diseases due to the more significant fat accumulation and increased oxidative stress in the liver tissue of obese individuals.

Fibrosis markers such as FIB-4 (Fibrosis-4 score) and APRI (Aspartate Aminotransferase-Platelet Ratio Index) are frequently used non-invasive methods to evaluate liver fibrosis without resorting to liver biopsy (6). The FIB-4 score is calculated based on age, AST (Aspartate Aminotransferase), ALT (Alanine Aminotransferase), and platelet count parameters, while the APRI score is calculated based on AST level and platelet ratio. These markers are considered reliable tools in the first step in determining the presence of fibrosis, especially in patients with chronic hepatitis B. They can identify individuals who need a biopsy, lowering the need for liver biopsy in the first step (7). However, the effect of obesity on these markers is a subject that has not been sufficiently investigated in the literature.

This study aims to compare fibrosis markers (FIB-4 and APRI) in obese and non-obese CHB patients and to investigate the effect of obesity on fibrosis progression. In addition, differences in liver function tests and biochemical parameters were also evaluated to reveal the impact of obesity on liver health. A better understanding of the relationship between obesity and fibrosis markers may help develop potential strategies to improve the clinical management of obesity and slow down fibrosis progression in CHB patients.

Material and Method

A total of 172 patients (50.6±9.4 mean age), 80 female and 92 male, with CHB diagnosis who applied to the gastroenterology clinic in the last six months, were included in our retrospective single-center study. Height, weight, waist, hip circumferences, and HBV durations of the patients were measured, and ALT, AST, bilirubin, albumin, International Normalized Ratio (INR), and hemogram tests were studied. BMI was calculated as follows: BMI= Weight (kg)/ Height squared (m2). BMI ≥30 kg/m2 was classified as the obese group. The vertical length of the spleen and right liver lobe were measured. The presence and grade of hepatic steatosis were determined through Liver ultrasonography (US) according to the criteria in Table 1.

Table 1. Hepatosteatosis grades according to ultrasonographic signs (8)

Hepatosteatosis Grade	Ultrasonographic Signs
Grade 0	Liver echogenicity is normal, and the diaphragm and vascular structures are clearly visible.
Grade 1	Echogenicity is slightly increased, but the diaphragm and intrahepatic vascular structures can still be distinguished.
Grade 2	Echogenicity is increased further, intrahepatic vascular structures and diaphragm are blurred.
Grade 3	Echogenicity has increased significantly and the diaphragm and intrahepatic vascular structures have become indistinguishable.

The FIB-4 score and APRI were calculated according to the following formulas:

FIB-4 index: Age (year) X AST (IU/L) / platelet count (10^9/L) X √(ALT(IU/L))

APRI= [AST (IU/L)/AST (upper limit of normal)(IU/L)/ platelet count (10^9/L) (9).

Inclusion criteria were male and female patients aged 18-65 years with chronic hepatitis B diagnosis and ≤ 50 IU/mL or nondetectable HBV-DNA.

Exclusion criteria: History of diabetes mellitus or other chronic disease except CHB, pregnancy.

The study was approved by the Erzurum Health Science University local Ethics Committee (Decision KAEK 2024/08-152, 14.08.2024). It was performed in accordance with the Declaration of Helsinki.

Statistical analysis

The Statistical Package for Social Sciences (SPSS) version 22.0 (IBM Corp., Armonk, NY, USA) was used for all statistical analyses. The Kolmogorov-Smirnov test was applied to check whether the measured variables conformed to a normal distribution. Since the continuous variables did not follow a normal distribution, they were reported as medians with minimum and maximum values. The Kruskal-Wallis test was employed to compare continuous variables across groups, while the Pearson chi-square test was used to analyze categorical variables. A p-value of less than 0.05 was deemed statistically significant. Spearman Correlation Analysis was used for correlations.

Results

A total of 172 patients with CHB were included in the study. Of these, 100 (58.1%) were non-obese, and 72 (41.9%) were obese. 64% of the non-obese individuals were overweight, and 36% had normal BMI levels. The mean age of the obese patients was 52.2±9.9, while it was 49.4±8.8 in the non-obese patients (p=0.500), and there was no significant difference between groups. The female rate was 51.4%, and the male rate was 48.6% in the obese group, while the female rate was 43.0% and the male rate was 57.0% in the non-obese group (p=0.277), and there was no significant difference in terms of gender distribution. No differences were found in terms of HBV durations (p=650). The mean weight in the obese group was 92.0±13.5 kg, while it was 73.5±10.2 kg in the non-obese group (p<0.001). The mean BMI was 34.4±4.4 kg/m2, and the waist circumference was 109±12.5 cm in the obese group. No significant difference was found between the groups in ALT levels (p=0.498); AST levelswere significantly higher in the obese group (p<0.001). No significant difference was found between the groups in GGT and albumin values (p=0.937 and p=0.493). Direct bilirubin levels were statistically significantly lower in obese patients (p<0.001). No significant difference was found in indirect bilirubin levels

(p=0.487). No significant difference was found in platelet count between the groups (p=0.249). PT (Prothrombin Time) values were lower in the obese group (p=0.009). Both FIB-4 (p=0.002) and APRI (p=0.007) values were significantly higher in obese patients. Liver diameters were more enlarged in obese patients (p=0.035), but no significant difference was found between spleen diameters (p=0.268) (Table 2).

Table 2. Demographic and Laboratory Parameters in Chronic Hepatitis B Patients in terms of Obesity

	Nonobese (n=100)	Obese (72)	Total (n=172)	P values
Age	49.4±8.8	52.2±9.9	50.6±9.4	0.500*
Gender n(%)				
Female	43(43.0)	37(51.4)	80(46.5)	0.277
Male	57(57.0)	35(48.6)	92(53.5)	
HBV duration (year)	6.6±2.3	6.2±2.7	6.4±2.4	0.650*
Weight (kg)	73.5±10.2	92.0±13.5	81±14.8)	<0.001*
Height (cm)	168±7.7	163±10.5	166±9.3	0.001*
Waist (cm)	93.2±12.2	109±12.5	99.8±14.6	<0.001*
BMI (kg/m2)	25.7±2.9	34.4±4.4	29.4±5.6	<0.001*
ALT (IU/L)	27(8-146)	28(9-574)	27.5(8-574)(	0.498**
AST (IU/L)	19(5-64)	25(10-607)	21(5-607)	<0.001**
GGT (IU/L)	23(7-250)	24(4-1233)	23(4-1233)	0.937**
Albumine (mg/dl)	43(30-50)	44(26-55)	44(26-55)	0.493**
D.BIL (mg/dl)	0.20(0.05-0.7)	0.13(0.05-2.4)	0.19(0.05-2.4)	<0.001**
ID.BIL (mg/dl)	0.5(0.1-2.25)	0.5(0.15-1.96)	0.5(0.1-2.25)	0.487*
PLT (10^9/L)	241±60	227±90	235±74.5)	0.249*
PT (sec)	13(11-18)	12(10-18)	12(10-18)	0.009**
INR	1.00(0.80-1.4)	1.01(0.90-1.5)	1.00(0.80-1.50)	0.638**
FIB4	0.88±0.45	1.78±2.34	1.2±1.6	0.002*
APRI	0.26±0.11	0.63±0.5	0.41±0.757	0.007*
Spleen (mm)	127(100-195)	130(106-180)	128(100-195)	0.268**
Liver (mm)	160(120-200)	160(135-230)	160(120-230)	0.035**

Values are expressed as Median(Q1-Q3) in Mann Whitney U test (**)and mean± SD in Student's T test (*), Abbreviations: HBV: Hepatitis B virus, AST: aspartate aminotransferase, ALT: alanine aminotransferase, PLT: platelet, DBIL: Direct Bilirubin, ID.BIL: Indirect Bilirubin, TG: triglyceride, GGT: gamma-glutamyl transpeptidase, PT: Prothrombin time, INR: International Normalized Ratio, FIB-4: Fibrosis-4 score and APRI Aspartate Aminotransferase-Platelet Ratio Index

While the frequency of Hepatosteatosis (HS) in nonobese individuals was 87.0%, the frequency of HS in obese individuals was found to be 81.9%. The prevalence of HS in our CHB population was 84.8%. Low-grade steatosis was found to be less common in obese individuals, while high-grade steatosis was found to be more common (grade 2: 36.1%, grade 3: 23.6%) (Table 3).

A positive correlation was found between BMI and AST, APRI and FIB-4, and a negative correlation was found between direct bilirubin and BMI (Table 4).

Table 3. Categorical Distribution of BMI in Patients with Chronic Hepatitis B.

Patient Groups	BMI (kg/m2)	n (%)	Hepatosteatosis n(%) Grade			
			0	1	2	3
Nonobese		100 (58.1)				
Normal weight	18.5-24.9	36 (20.9)	13(13)	43(43)	25(25)	19(19)
Overweight	25-29.9	64 (37.2)				
Obese	≥30	72 (41.9)	13(18.1)	16(22.2)	26(36.1)	17(23.6)
Total		172(100)	26(15.2)	59(34.3)	51(29.6)	36(20.9)

BMI: Body Mass Index

Table 4. Spearman's Correlation Analyses with Body Mass Index

	r	R	p
AST	0.316	0.022	<0.001
D.BIL	-0.310	0.016	<0.001
APRI	0.291	0.035	<0.001
FIB-4	0.341	0.054	<0.001

AST: Aspartate Aminotransferase, D.BIL: Direct Bilirubin, APRI: Aspartate Aminotransferase,-Platelet Ratio Index, FIB-4: Fibrosis-4 score,

Discussion

In this study, fibrosis markers (FIB-4 and APRI) and liver function tests were compared in obese and non-obese patients with CHB. The findings show that fibrosis markers are significantly higher in obese CHB patients and reveal the potential effect of obesity on liver fibrosis. The fact that FIB-4 and APRI scores, used as fibrosis predictors in clinical practice (10), are significantly higher in CHB accompanied by obesity suggests that obesity may accelerate fibrosis progression in CHB. There are findings in the literature that obesity is a significant risk factor for the progression of liver diseases, and this study supports these findings. In a recent study conducted on CHB patients, it was reported that abdominal obesity, in particular, increased the level of fibrosis measured by the Fibroscan method (11).

There are higher HS rates in CHB patients compared to the general healthy population. In our study, the prevalence of HS in CHB patients was determined to be 84.8% with US imaging, and this rate was higher than that of the literature studies in our country (12). In addition, the fact that HS grade 1 was detected less frequently in obese individuals than in nonobese HS grade 1 patients suggests that the presence of only Hepatitis B causes more low-grade steatosis. In contrast, the presence of obesity is associated with higher steatosis grades. This finding supports the idea that obesity increases the severity of HS. Increased oxidative stress in obese patients is an essential factor that causes liver damage to reach more progressive levels (13).

The mechanisms that increase liver fibrosis due to obesity are associated with various factors. The most critical factors are increased hepatocyte fat accumulation, insulin resistance, and oxidative stress. It is known that liver steatosis in obese individuals damages liver cells and accelerates the formation of fibrotic changes. In this study, the higher FIB-4 and APRI scores in obese patients suggest that obesity seen together with CHB may have a more pronounced effect on fibrosis. In particular, the FIB-4 score was used as a reliable indicator to determine the degree of fibrosis in obese patients.

The AST level, known to increase more significantly than ALT

as fibrosis progresses (14), was considerably higher in the obese group in our study, which is, therefore, a finding supporting fibrosis. This finding suggests that obesity may increase the damage and inflammatory effects on the liver. In addition, the fact that direct bilirubin levels are lower in obese patients indicates that further studies are needed to investigate the possible relationship between obesity and bile metabolism. Indeed, some studies in the literature have shown an inverse relationship between metabolic syndrome and obesity and bilirubin (15). The antioxidant and anti-inflammatory activity of bilirubin may be an essential factor underlying this relationship (16). While FIB-4 and APRI scores were higher in the obese group, the fact that there was no difference in components such as age, INR, albumin, and platelets, except for AST, suggests that evaluating these parameters as a whole rather than individually is a more rational approach in clinical practice.

Our findings are in line with previous research in the literature. Previous studies have shown that obesity increases liver fibrosis and inflammation in CHB patients. For example, in the study by Younossi et al. (17), it was reported that obesity is associated with liver fibrosis and may accelerate fibrotic progression in CHB patients. Similarly, in this study, it was observed that liver fibrosis was at more advanced grades in obese patients.

One of the most significant contributions of our research is that it demonstrates the effect of obesity on fibrosis development in CHB patients using noninvasive methods. These findings suggest that obese CHB patients should be monitored more closely in terms of fibrosis progression in clinical practice and that early interventions may be necessary in this patient group. It can be suggested that obesity management, in particular, may slow down liver damage and reduce the risk of fibrosis in CHB patients.

Some limitations of this study should also be noted. First, our study has a retrospective design and a limited patient sample. In addition, a liver biopsy was not performed in our study, which does not allow a direct assessment of the degree of fibrosis. However, the fact that noninvasive markers of fibrosis, such as FIB-4 and APRI, can be easily applied to clinical practice increases the importance of this study.

Conclusion

This study showed that obesity may increase liver fibrosis in CHB patients, and fibrosis markers are higher in obese patients. In clinical practice, more rigorous follow-up of obese CHB patients in the early period and control of obesity may be essential to slow down disease progression and develop effective treatment strategies.

Data availability statement

The corresponding author may provide the data sets used in this work upon reasonable request.

Conflict of Interest

There is no conflict of interest.

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