



# Insulin Resistance in Patients with Chronic Hepatitis B Virus Infection: A Case-control Study

Kronik Hepatit B Virüsü Enfeksiyonu Olan Hastalarda İnsülin Direnci: Bir Olgu Kontrol Çalışması

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## ABSTRACT

**Objectives:** It was aimed to compare the rate of insulin resistance (IR) in patients with chronic hepatitis B virus (CHB) infection with the general population.

**Materials and Methods:** The files of the patients were retrospectively examined. Patients testing for insulin and fasting blood glucose were included. For detecting IR, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) index was used. All patients were divided into 2 groups in terms of HOMA-IR. All data were compared between two groups. The rate of IR was compared with the general population.

**Results:** Forty-seven were female and the mean age was 38. Seventy-one had hepatitis B e antigen (HBeAg)-negative CHB infection, 44 had CHB and 5 had HBeAg-positive CHB infection. IR was detected in 47 patients. The rates of IR were similar between females and males. The rates of IR was 38% in HBeAg negative CHB infection, 36.4% in CHB and 80% in HBeAg positive CHB infection. The rate of IR in patients with CHB infection was found to be 39% in our study.

**Conclusion:** This study showed higher rate of IR in patients with CHB infection than in the general population and thus these patients should be carefully monitored in terms of the occurrence of IR and diabetes mellitus.

**Keywords:** Insulin resistance, hepatitis B, metabolic syndrome

## ÖZ

**Amaç:** Kronik hepatit B virüsü (KHB) enfeksiyonu olan hastalarda insülin direnci (İR) oranının genel popülasyonla karşılaştırılması amaçlanmaktadır.

**Gereç ve Yöntemler:** KHB enfeksiyonu olan hastaların dosyaları geriye dönük olarak incelendi. Çalışmaya insülin ve açlık kan şekeri düzeyleri ölçülen hastalar dahil edildi. İR'yi tespit etmek için Homeostatik Model Değerlendirmesi (HOMA-İR) indeksi kullanıldı. Tüm hastalar HOMA-İR açısından 2 gruba ayrıldı. Tüm veriler iki grup arasında karşılaştırıldı. KHB enfeksiyonu olan hastalardaki İR oranı genel popülasyon ile karşılaştırıldı.

**Bulgular:** Hastaların 47'si kadındı ve ortalama yaş 38 (aralık: 20-65) idi. Yetmiş bir hastada hepatit B e antijeni (HBeAg) negatif KHB enfeksiyonu, 44'ünde KHB ve 5'inde HBeAg pozitif KHB enfeksiyonu vardı. Kırk yedi hastada İR tespit edildi. İR oranları kadın ve erkek arasında benzerdi. İR oranları; HBeAg negatif KHB enfeksiyonu olanlarda %38, KHB olanlarda %36,4 ve HBeAg pozitif KHB enfeksiyonu olanlarda %80 bulundu ve bunlar istatistiksel olarak anlamlı değildi. Çalışmamızda KHB enfeksiyonu olan hastalarda İR oranı %39 olarak bulundu.

**Sonuç:** Bu çalışma, İR'nin KHB enfeksiyonu olan olgularda genel popülasyona göre daha yüksek oranlara sahip olduğunu ve bu nedenle bu hastalarda İR ve diabetes mellitus oluşumunun dikkatle izlenmesi gerektiğini göstermiştir.

**Anahtar Kelimeler:** İnsülin direnci, hepatit B, metabolik sendrom

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## Introduction

Metabolic syndrome (MS) is a cluster of conditions including central obesity, hypertension, glucose abnormality and dyslipidemia (1). It is associated with an increased risk of heart diseases, diabetes mellitus (DM) and the development of cancer (2). Though the pathogenesis of MS remains uncertain, insulin resistance (IR) has been considered a key mechanism (3). Also, IR is a main contributing factor of MS and DM.

Hepatitis B is one of the most common infection in the world and may cause complications including cirrhosis, liver failure and hepatocellular carcinoma (HCC) (4). Both hepatitis B and MS are common health problems. In general population, the prevalence of combined chronic hepatitis B (CHB) infection and MS is around 0.99%-1.74% (5,6,7). However, this rate varies depending on whether the area is endemic for HBV infection or MS. Furthermore, the coexistence of both diseases increases the risk of cirrhosis and HCC.

Recently, an experimental study showed that hepatitis B X protein impairs the hepatic insulin signaling pathway and that CHB infection is found to be related to IR (8). A clinical study also suggest that hyperinsulinemia develops in CHB infection and CHC virus (CHC) infection (9). This association has been understood in CHC infection but the relationship between CHB infection and IR is still remained unclear (10,11). In this study, the rate of IR in patients with CHB infection is compared with that in the general population.

## Materials and Methods

This study was conducted between December 2016 and January 2018 in infectious diseases and clinical microbiology department. Of cases with CHB infection, the files of the patients were retrospectively examined. Since our study was a retrospective design, ethical approval and patient consent were not obtained. Patients testing for insulin and fasting blood glucose (FBG) were included. Their age, sex, height, body weight and body mass index (BMI), hepatitis B virus (HBV) DNA level, FBG, fibrosis score, hepatitis activity index (HAI), alanine aminotransferase, insulin level were determined. The height and weight of all patients were recorded and BMI was calculated. For detecting IR, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) index was calculated by using FBG and insulin values and "FBG (mg/dL) X fasting insulin ( $\mu$ U/mL)/405" formula of 120 patients. All patients were divided into the 2 groups in terms of IR; 1) case group (HOMA-IR  $\geq$ 2.5 mg/dL) and 2) control group (HOMA-IR <2.5 mg/dL). HBV infection was defined according to European Association for the Study of the Liver 2017 Clinical Practice Guidelines (12). Patients with known DM, cirrhosis and HCC were excluded from the study. All subjects were also negative for anti-hepatitis C virus (HCV), delta infection and human immunodeficiency virus. All data were compared between two groups. The rate of IR in the patients included in our study was compared with that in the general population.

## Statistical Analysis

SPSS 21.0 program was used for all statistical analysis. Chi-square test was used for categorical data. Pearson's chi-square test results were accepted. In order to determine the presence of parametric data, normal distribution was examined by Kolmogorov-

Smirnov test. For data showing normal distribution, Student's t-test was used and  $p < 0.05$  was considered statistically significant.

## Results

Of the 120 patients, 47 were female and the mean age was 38 (range: 20-65). Detailed characteristics of the patients shown in Table 1. Seventy-one had hepatitis B e antigen (HBeAg)-negative CHB infection, 44 had CHB; 9 patients had HBeAg positive and 25 patients were on anti-viral treatment) and only five had HBeAg-positive CHB infection. IR was detected in 47 patients. The rates of IR were similar between female (38.4%) and male (40.4%). The rates of IR; 38% in HBeAg-negative CHB infection, 36.4% of CHB and 80% of patients in HBeAg-positive CHB infection were found and these were not statistically significant. There was no statistically significant in IR according to the DNA levels of the patients. Five patients were weak (BMI: <18.5), 44 were normal weight (BMI: 18.5-24.9), 47 were overweight (BMI: 25-29.9) and 24 were obese (BMI >30). The rates of IR were 40% in weak patients, 25% in normal weight, 47% in overweight, and 50% in obese patients. The results were statistically significant between the groups. Of the 38 patients underwent biopsy, moderate-to-advanced fibrosis (F: 3-6) was detected in 8 patients and mild fibrosis (F: 0-2) was observed in the remaining 30 patients. HAI and fibrosis score were not statistically significant for IR. All statistical results were shown in Table 2.

## Discussion

IR is an important factor for MS and DM. CHC infection is well known to be associated with IR and increased risk of DM. In contrast, IR in CHB infection has not been clearly defined. Previous studies showed that IR in CHB infection was not different from healthy controls (13,14). In 296 non-diabetic subjects, at the first health examination, the incidence of DM or glucose intolerance was found to be similar between HBV carriers and non-HBV controls,

**Table 1.** Detailed characteristics of the patients according to insuline resistance

<b>Sex (female, n)</b>	<b>47</b>
<b>Age (year)</b>	<b>38.96<math>\pm</math>11.57</b>
<b>Body weight (kg)</b>	<b>74.04<math>\pm</math>18.60</b>
<b>Body height (cm)</b>	<b>167<math>\pm</math>8.82</b>
<b>Body mass index (kg/m<sup>2</sup>)</b>	<b>26.47<math>\pm</math>6.26</b>
<b>Hepatitis activity index</b>	<b>5 (1-12)</b>
<b>Fibrosis score</b>	<b>2 (0-4)</b>
<b>Alanine aminotransferase (U/L)</b>	<b>38.30<math>\pm</math>20.10</b>
<b>Fasting blood glucose (mg/dL)</b>	<b>89.19<math>\pm</math>20.72</b>
<b>Insulin level (mU/L)</b>	<b>12.47<math>\pm</math>6.68</b>
<b>HbA1C (%)</b>	<b>5.60<math>\pm</math>0.82</b>
<b>HbeAg negativity (n)</b>	<b>110</b>
<b>HOMA-IR</b>	<b>2.96<math>\pm</math>2.16</b>
<b>HBV-DNA level (IU/mL)</b>	<b>57 (0-1140000000)</b>
HbA1C: Hemoglobin A1C, HbeAg: Hepatitis B e antigen, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, HBV: Hepatitis B virus	

**Table 2.** All results according to insuline resistance

	HOMA-IR $\geq 2.5$ (47)	HOMA-IR $< 2.5$ (73)	p
<b>Sex (Female)</b>	<b>19</b>	<b>28</b>	<b>0.48</b>
Age (year)	39.82 $\pm$ 13.53	38.82 $\pm$ 10.44	0.94
Body weight (kg)	75.38 $\pm$ 12.47	73.13 $\pm$ 22.22	0.02
Body height (cm)	165.64 $\pm$ 8.82	168.51 $\pm$ 8.94	0.83
Body mass index (kg/m <sup>2</sup> )	27.37 $\pm$ 3.54	25.84 $\pm$ 7.66	0.01
Hepatitis activity index	7 (1-11)	4 (2-12)	0.06
Fibrosis score	2 (0-4)	2 (0-4)	0.76
Alanine aminotransferase (U/L)	39.45 $\pm$ 17.90	37.50 $\pm$ 22.03	0.08
Fasting blood glucose (mg/dL)	98.82 $\pm$ 28.32	82.56 $\pm$ 9.92	0.001
Insulin level (mU/L)	18.47 $\pm$ 6.80	8.80 $\pm$ 2.43	0.001
HbA1C (%)	6.15 $\pm$ 1.01	5.22 $\pm$ 0.34	0.001
HbeAg negativity (n)	42	68	0.34
HBV-DNA level (IU/mL)	1470 (0-1140000000)	15 (0-156000)	0.08
HbA1C: Hemoglobin A1C, HbeAg: Hepatitis B e antigen, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, HBV: Hepatitis B virus			

showing that asymptomatic CHB infection did not increase the risk of DM but unlike our study, IR was not investigated among the subjects (15). Contrary to relevant study comparing subjects with recovery from hepatitis B and CHB infection with those of disease-free, a study showed that CHB infection was correlated with IR and has shown that patients with CHB infection may need to monitor the development of IR and DM (16). Also, in a systematic review examining chronic viral hepatitis and metabolic derangement, HCV infection is positively associated with IR and hepatic steatosis (17). In contrast, in this article, HBV infection is inversely associated with lipid metabolism, and exhibits no conclusive association with IR or the risk of DM. Taken together, the relationship between HBV and IR is uncertain (14).

Similar to our results, in a study from Turkey, no significant relationship was seen between IR and HBV-DNA levels and IR was observed more frequently in these patients compared to the general population (18). In a study from south Korea reviewing hepatitis B surface antigen (HBsAg) and anti-HCV Ab among study participants, unlike our study, IR was not evaluated, and it found that serologic evidence of HBV and HCV infection was associated with the prevalence of diabetes (19). Furthermore, Ye et al. (20) found CHB had a risk of developing IR, especially higher in CHB patients with non-alcoholic fatty liver disease.

IR is defined as a subnormal biological response to normal insulin concentrations (21). It most frequently occurs in association with obesity, but can result from many causes including stress, medications, pregnancy. As consequences of obesity-related IR, it includes impaired glucose tolerance, impaired fasting glucose, type 2 DM, and increased insulin requirements in type 1 DM (22). As expected, in this study, increased weight and BMI, high FBG, elevated insulin level and high hemoglobin A1C were found statistically significant for IR.

IR is seen in 25% of healthy population, 60% of those with impaired glucose tolerance and 60-75% of patients with type 2 DM (23). The rate of IR was found to be 39% in our study. This rate was slightly higher than the healthy population.

### Study Limitations

The study has some limitations. It was a retrospective study and had low number of patients and some data were missing. Because this study was cross-sectional, it was difficult to conclude a causal relationship between HBV infection and IR. For valuable clinical data, this study may be generalized across Turkey.

### Conclusion

This study showed IR has higher rate in cases with chronic HBV infection than in the general population and thus these patients should be carefully monitored the occurrence of IR and DM but further studies are needed to clarify this challenge.

### Ethics

**Ethics Committee Approval:** Retrospective study.

**Informed Consent:** It was obtained.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Concept: Ö.F.T., Desing: B.M., İ.İ.B., Data Collection or Processing: S.Y.K., Analysis or Interpretation: N.S., Literature Search: A.K., Writing: A.K.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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