Original Article

The Impact of Viral Hepatitis B on Insulin Resistance in Iraqi Patients

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Abstract

Background: Chronic hepatitis B (CHB), which can lead to cirrhosis and liver cancer, is probably triggered due to hepatitis B virus (HBV) contagion. Even it had been given medical care, Infections with some viruses, particularly persistent infections, can harm the liver and result in insulin resistance (IR). The onset of type 2 diabetes mellitus is one of the top 10 causes of morbidity and the leading cause of mortality. **Objective:** In this study, we investigated the correlation between hepatitis B and IR in patients infected with HBV. **Materials and Methods:** A total of 203 patients, the mean age of patients with hepatitis B was 40.05 ± 14.87 years (range 14–83 years), were enrolled. A real-time PCR technique was used to investigate HBV-DNA levels with a kit provided by Roche company (Germany), and HOMA-IR (Homeostatic Model Assessment for Insulin Resistance) was used to calculate IR. Human insulin and blood glucose were measured using the sandwich enzyme-linked immunosorbent assay (ELISA) method with kits provided by the Sunlong Company (China). **Results:** The fasting insulin and fasting blood sugar levels were higher in the patients when compared to the controls (6.73 ± 2.23 mIU/mL vs. 5.01 ± 1.83 mIU/mL and 5.49 ± 0.62 mg/dL vs. 5.45 ± 0.41 mg/dL, respectively). Likewise, HOMA-IR was higher in the patients when compared to the controls (1.71 ± 0.55 relative to 1.07 ± 0.32). Levels of HOMA-IR were significantly higher in insulin-resistant patients than insulin-sensitive patients (2.29 ± 0.17 vs. 1.44 ± 0.46, respectively). Viral load was markedly greater in IR than in insulin-sensitive patients, with a significant *P* value of <0.001. **Conclusion:** The levels of fasting blood sugar, fasting insulin, and HOMA-IR were significantly higher than usual. A high viral load of HBV is significantly associated with IR.

Keywords: Fasting blood sugar, fasting insulin, HBV, HOMA-IR, insulin resistance, viral load

Introduction

Insulin resistance (IR) is an inadequate physiological response of tissues that are targeted to insulin stimulation, particularity the liver, muscle, and adipose tissue. Due to poor glucose disposal brought on by IR, hyperinsulinemia and increased beta-cell insulin production ensue.[1] IR is considered the main cause of type 2 diabetes (T2DM). According to estimates, IR appears many years before T2DM.[2] Muscles, the liver, and adipose tissue are the three main areas where IR occurs. Free fatty acid overproduction and immune-mediated inflammation in muscle tissue are believed to be the first steps in developing IR.[3] The main clinical sign of T2DM is non-physiologic high plasma glucose levels preceded by IR. To satisfy standard insulin requirements, insulin levels rise in the prediabetic condition, which ultimately results in T2DM, chronic hyperinsulinemia, and hyperglycemia-induced cell death.[4]

When fasting, the liver secretes glucose into the blood to stabilize your blood sugar levels and nourish your body's glucose-consuming tissues. Hepatic glucose production (HGP) is the term for this procedure, which entails glycolysis, a decomposition of hepatic glycogen, and the creation of glucose (gluconeogenesis) from scratch utilizing

Access this article online

Quick Response Code:

Website: https://journals.lww.com/mjby

DOI: 10.4103/MJBL.MJBL_1018_23

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Submission: 16-Jul-2023 **Accepted:** 07-Dec-2023 **Published:** 30-Apr-2026

How to cite this article: Hasan HS, Gaidan AM. The impact of viral hepatitis B on insulin resistance in Iraqi patients: The effects of viral hepatitis B on patients' insulin resistance. Med J Babylon 2026;23:272-8.

adipose-derived fatty acids and glycerol.[5] Additionally, insulin reduces HGP by preventing gluconeogenic gene expression and lipolysis in adipose tissue.[6] Since insulin does not have the ability to regulate hepatic glycogen production or glucose generation in people with T2DM, elevated hepatic metabolism of glucose is the major cause of their fasting hyperglycemia.[7] IR also affects the insulin-induced increase in glycogen creation, for instance, is decreased in those suffering from T2DM. amounts of postprandial and fasting hepatic glycogen.[8] Hepatic IR also reduces the quantity of hepatic glycogen metabolism produced by fasting and eating.[9] Type 2 diabetics (T2D) and many obese people who have collapsed insulin-stimulated glucose assimilation and stored it across muscle and adipocytes with ineffective insulin repression of hepatic glucose output are examples of insulin-resistant people. IR was first used to describe the wide variation in insulin doses needed to decrease elevated blood glucose amounts in those with type 2 diabetes type 1 (T2D1), and then it was used to describe how much blood glucose levels changed after a specific amount of both glucose and insulin was administered.[10] Hyperglycemia serves as one of the manifestations of type 2 diabetes mellitus (DM), which is caused by an inability to produce insulin.[11]

Hepatitis is an inflammation of the liver's cells (similar to hepatocyte infection or malfunction). While some people experience jaundice (yellow skin), diarrhea, vomiting, headache, decreased appetite, and nausea, some patients with hepatitis show no symptoms at all. Acute hepatitis is the term used to describe hepatitis that returns within six months, while chronic hepatitis is used to describe hepatitis that lasts longer than 6 months.[12] Hepatitis B virus (HBV), the prototypical virus belonging to the extended family Hepadnaviridae, is a non-cytopathic DNA virus that infects the liver and produces conditions varying in seriousness and length. It is spread through contact with contaminated blood and bodily exudate. The pathogenic virion is a nucleocapsid that penetrates the hepatocyte only after delivering a fragmented circular DNA genome, which starts a difficult viral replication process.[13] Several authors documented the average frequency variation in HBV genotypes in Iraqi cases.[14] Recently, an experimental investigation revealed that HBV infection is linked to IR and that hepatitis B X protein (HBx) affects the hepatic insulin signaling system. Notably, IR can exist in people who do not have diabetes or obesity.[15]

The purpose of the current study is to detect the effect of viral Hepatitis B infection on IR and study the linkage between viral load and IR.

Materials and Methods

Subjects and study design

Subjects of this study were collected randomly from 203 patients (117 males and 86 females) infected with hepatitis B and 38 healthy individuals (18 females and 20 males). Our study focused on cases that were infected with chronic hepatitis B patients. Ninety-four patients were randomly designated of 203 (51 males and 43 females) who sustained HBV-DNA based on their infection with type B virus, had no diabetes, had no other virus or coinfection were in the chronic phase [Figure 1]. Throughout the interval between September 2022 to April 2023 from the subsequent institute Hepatology and Gastroenterology Teaching Hospital (Baghdad, Iraq). The investigation was carried out in the Hepatology and Gastroenterology Teaching Hospital—Ministry of Health (Iraq) laboratory.

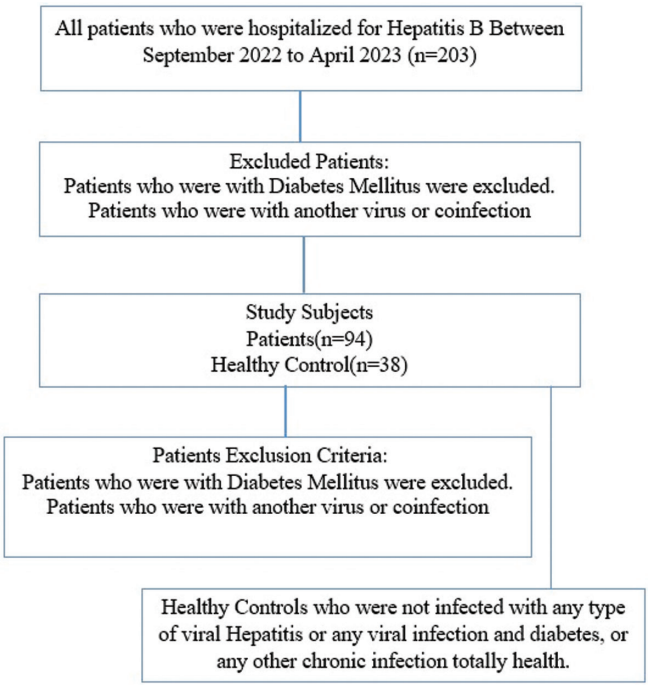

Figure 1: Flowchart of selection of study patients

Sample collection

Antecubital vein blood samples were taken after a minimum 10-h fast. Enzyme-linked immunosorbent assay (ELISA) was used to assess the levels of fasting blood sugar, and human insulin with kits provided by the Sunlong Company (China). Fully automated real-time PCR techniques were used for molecular detection of HBV and to evaluate the amount of HBV viral load in the serum of patients (COBAS TaqMan 48/ COBAS AmpliPrep) with kit COBAS AmpliPrep/COBAS TaqMan HBV Assay, v2.0 provided by (Roche, Germany) is based on two primary processes: (1) sample preparation for HBV-DNA separation and (2) simultaneous PCR amplification[16] of target DNA and detection of a cleaved, double-labeled target-specific oligonucleotide detection probe.

HOMA-IR estimation

A homeostasis model of evaluation of insulin resistance (HOMA-IR) was used to measure IR and was based on the following equation[17]:

$$\text{HOMA-IR}=\frac{\text{Glucose (mg/dL)}\times\text{Insulin }(\mu\text{ IU/mL})}{405}$$

Statistical analysis

Statistical analyses were performed by using SPSS software version 25.0 (SPSS, Chicago). Continuous data were subjected to a normality test (Shapiro–Wilk test). Data with normally distribution were presented as mean and standard deviation and analyzed with Student *t* test. Data with non-normal distribution were presented as median and range and analyzed with Mann–Whitney *U* test. Categorical variables were expressed as numbers and percentages and analyzed with Chi square test. Pearson's correlation test was used to explore the possible correlation between different variables. A *P* value less than 0.05 was considered to indicate a statistically significant difference.[18,19]

Ethical approval

This study was carried out in conformity with the ethical standards outlined in the Helsinki Declaration. Before taking the sample, the patient's verbal and analytical consent were obtained. To obtain this permission, a local ethics committee evaluated and approved the study protocol, subject information, and consent form using document number 31898 (containing the number and date of August 11, 2022).

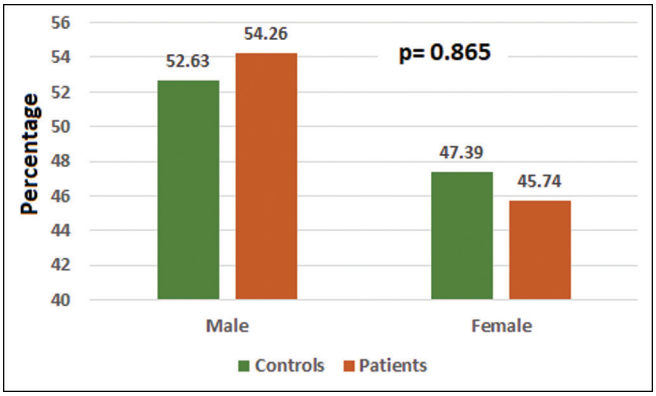

Figure 2: Gender distribution in patients and controls

Results

The mean age of patients with hepatitis was 40.05 ± 14.87 years (range 14–83 years) which was higher than the controls (36.82 ± 6.93 years, range 25–54 years) with a significant difference.

There were 20 male (54.53%) and 18 female (47.39%) among controls compared with 51 male (54.26%) and 43 female (45.74%) among patients with no significant difference [Figure 2].

Biochemical data of the study population

The fasting insulin and FBS levels were higher in the patients when compared to the controls (6.73 ± 2.23 mIU/mL vs. 5.01 ± 1.83 mIU/mL and 5.49 ± 0.62 mg/dL vs. 5.45 ± 0.41 mg/dL, respectively). Likewise, HOMA-IR was higher in the patients when compared to the controls (1.71 ± 0.55 relative to 1.07 ± 0.32), as shown in Table 1

Clinical characteristics of the patients

There was a very high diversity in viral load with a median level of 6.0×10^4 copy/mL (range $2.0–270\times10^6$ copy/mL). Half of the patients (50%) were under anti-HBV medications [Table 2].

Incidence of IR

Considering 2.1 as a cutoff value for HOMA-IR to determine the presence of IR, there were 21 patients with IR (31.82%) compared with 4 subjects among the control group (10.53%) with a highly significant difference [Figure 3].

Association of gender and anti-HBV medications with viral load

No significant difference was demonstrated between insulin-resistant and insulin-sensitive patients with regard

Table 1: Biochemical data of the study population

Variable	Controls (*n* = 38)	Patients (*n* = 94)	*P* value
Fasting insulin (mIU/mL)			
Mean ± SD	5.01 ± 1.83	6.73 ± 2.23	**0.037**
Range	2.39–10.4		
FBS (mg/dL)			
Mean ± SD	5.45 ± 0.41	5.49 ± 0.62	**0.033**
Range	4.67–6.8	3.81–6.74	
HOMA_IR			
Mean ± SD	1.07 ± 0.32	1.71 ± 0.55	**0.001**
Range	0.59–2.41	0.66–2.80	

FBS = fasting blood sugar, independent *t* test

The significance of bold *p*-value ≤ 0.05

to age, gender, and type of medication. On the contrary, the viral load was markedly higher in insulin-resistant patients than those who are insulin-sensitive, with a significant *P* value of less than 0.001, as demonstrated in Table 3.

Association of gender and anti-HBV medications with viral load

Although males had higher viral load than females, the difference was not significant. In contrast, patients receiving medication had a much lower viral load (median = 751×10^4 copy/mL (range $3.0–170 \times 10^6$ copy/mL) than those without such drugs (751×10^4 copy/mL (range $3.0–170 \times 10^6$ copy/mL) with highly significant difference [Table 4].

Table 2: Clinical characteristics of the patients

Variable	Value
Viral load, copy/mL	
Mean ± SD	$45.47 \times 10^4 \pm 252.45 \times 10^5$
Median	6.0×10^4
Range	$2.0–270 \times 10^6$
Anti-hepatitis B medication	
Yes	47 (50%)
No	47 (50%)
Descriptive statistics	

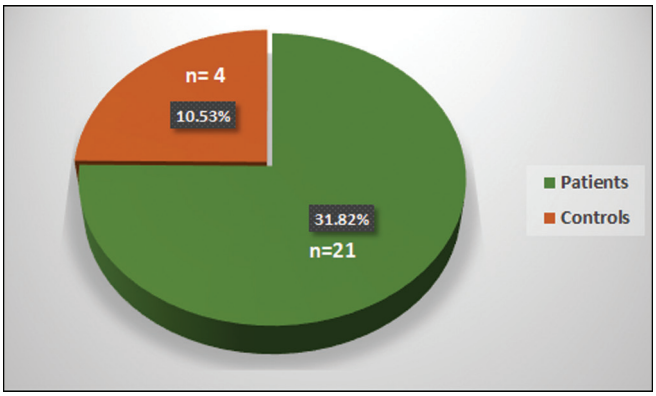

Figure 3: Incidence of insulin resistance in patients and controls

Discussion

The results demonstrate that there is a presence of HOMA-IR cutoffs implying established IR. This is one of the principal pathogenetic mechanisms underlying type 2 diabetes, atherosclerosis the syndrome of metabolic disorders, influencing the morbidity and mortality of prosperous societies.[20]

IR is one of the essential pathophysiological mechanisms underlying metabolic syndrome (MS). As calculated by HOMA-IR, IR is considerably higher in hepatitis B patients with fatty liver, and serum triglyceride levels are an independent risk factor for steatosis development, according to an Indian study.[21] Another study reported that chronic Hepatitis B (CHB) is correlated with insulin resistance, as detected by fast insulin, fast blood sugar, HOMA-IR, and other methods, in the absence of a prior history of DM. Patients with severe cirrhosis and liver injury exhibited more excellent insulin resistance.[22] The subsequent are putative insulin resistance strategies in cirrhosis: (1) Hyperinsulinemia is caused by liver failure in cirrhotic patients with insulin breakdown, which can decrease portal blood flow to the liver cells and insulin assimilation. Data showed that diversion could improve patients' glucose tolerance after a blockage. (2) Impaired glucose tolerance in cirrhosis patients has been linked to insulin receptor alterations. In liver, muscle, and fat cells, the number and affinity of insulin receptors decreased, reducing the repercussions of peripheral insulin and promoting the emergence of insulin resistance. Additionally, it was noted that patients with liver cirrhosis

Table 3: Association of demographic data of patients with insulin-resistant patients with CHB

Variable	Insulin-resistant (n = 21)	Insulin-sensitive (n = 45)	*P* value
Age, years			
Mean ± SD	43.0 ± 18.2	39.09 ± 13.84	0.270†
Range	28–83	15–68	
Gender			
Male	11 (52.38%)	20 (44.44%)	0.547‡
Female	10 (47.62%)	25 (55.56%)	
Medication			
Yes	10 (47.62%)	21 (46.67%)	0.942‡
No	11 (52.38%)	24 (53.33%)	
Viral load			
Mean ± SD	751 × 104	227 × 104	**<0.001**††
Range	3.0–170 × 106	2.0–143 × 106	

†: independent t test, ‡: Chi square, ††: Mann–Whitney *U* test

The significance of bold *p*-value ≤ 0.05

Table 4: Association of gender and medication with viral load

Variable	Median viral load (copy/mL)	*P* value
Gender		
Male	47 × 104 (2.0–144 × 106)	0.077
Female	231 × 104 (2.0–133 × 106)	
Medication		
Yes	104 × 104 (2.0–111 × 106)	**<0.001**
No	751 × 104 (3.0–170 × 106)	

Mann–Whitney *U* test

The significance of bold *p*-value ≤ 0.05

and insulin resistance had greater serum levels of tumor necrosis factor receptors, suggesting the tumornecrosis factor system may exert a substantial role in controlling insulin action.[23] In fact polymerase, a surface protein, a core protein, and the HBx protein are the four proteins that the HBV genome generates. Among these proteins, the contents of HBx may have the greatest linkage alongside hepatic steatosis, inflammation, and HBV-associated illnesses.[24]

The FBS levels of the patients were higher than those of the control individuals in accordance with Abdulhakeem *et al*.[11] The investigation revealed that the patients' serum levels of fasting insulin and FBS were greater than those of the controls (*P* value is 0.002). In a comparable manner HOMA-IR was more elevated in patients than in normal people (*P* value is 0.001) similar to the research that demonstrated HOMA-IR levels to be significant in HBV-infected patients, this study came to the conclusion IR had no connection with fibrosis.[25] Likewise, another study involving 7880 individuals who were not diabetic identified that CHB cases exhibit higher fasting blood sugar, fasting insulin, and HOMA-IR values, and that CHB corresponds with IR; their findings suggest which CVHB is conjointly linked with IR.[22] This outcome is based on the same hypothesis as our study: that HBX protein may significantly contribute to fatty liver and inflammation by conflicting with the insulin signal pathway.[26]

Additionally, an investigation revealed individuals with CHB had considerably higher fasting blood sugar, fasting insulin, and HOMA-IR.[27] The current study findings were in line with those of Ghenea *et al*.,[28] who found that patients with fatty liver disease had considerably greater demonstrate levels of fasting insulin, fasting glucose, and HOMA-IR than patients without steatosis, whereas HBV-DNA levels were significantly lower.

For all patient groups, there was a distinct correlation between fasting insulin levels and the presence of hepatic steatosis as determined by fibro scan, and fasting insulin and IR as evaluated by HOMA-IR were significantly higher in patients. These outcomes are in line with the research.[29-31]

In consistent with our results, a study stated that the relationship was stronger for HCV than HBV.[32] The connection between HBV infection and diabetes has been the subject of debate. In some studies, the prevalence of diabetes was more significant in HBsAg+ than in HBsAg− patients.[33,34]

On the other hand, metabolic disorder was less frequently seen in HBV patients, according to a meta-analysis.[35] However, in contrast with chronic HCV infection, the link between HBV and IR is still ambiguous. It is well established that having both CHB and MS raises your chance of getting cirrhosis and HCC.[36]

Our study findings showed that there is a connection between viral load and IR with a significant *P* value of less than 0.001, and these findings were consistent with an investigation that demonstrated that cases with significant HBV-DNA were more likely to have IR.[37]

A high viral burden, a prolonged CHB infection, the existence of cirrhosis, alcoholic steatosis, and a variety of other risk factors may be predictive of the development of T2DM in CHB-infected cases, as proposed via further studies. Individuals at high risk for CHB require vigilant glucose surveillance and aggressive management of modifiable risk factors.[38] Also, according to another study, IR is definitely correlated with viral burden.[39] IR is intermittently similar to chronic moderate inflammation, and numerous immune cell-derived mediators contribute to its development, as demonstrated by a study that was approved alongside our own.[40] Infection with HBV was most commonly linked with problems with metabolism, especially obesity, IR, and dyslipidemia, rather than viral factors, according to additional research[41]

Similarly, a recent study determined that IR coincides with the presence of HBV, as measured by HOMA-IR. Reportedly, HBV viral burdens, the severity of liver disease, and the degree of liver fibrosis are all indicative of IR.[42]

In contrast, a previous study indicated that HBV carriers were not associated with IR.[24] Nonetheless, another study suggested that extreme and centrally obese people were associated with a mild occurrence of abundant HBV viral load in HBeAg seropositive, particularly in men.[43] Another investigation reported that diabetes patients (T1DM and T2DM) have extremely low rates of HBV and HCV infections.[44]

Nonetheless, a different study reported that there is a significant incidence of people with moderate hepatitis and chronic HBV infection having IR. In these patients, IR is associated with diminished liver function but not with viral load.[45] Unlike our findings, a Turkish study showed that the amounts of IR and HBV-DNA were not significantly associated. Compared to the general population, these patients experienced IR more frequently.[27] Likewise, it was approved that IR levels were not statistically different depending on the patient's DNA levels.[46]

Conclusion

In individuals with CHB infections, fasting blood sugar, fasting insulin, and HOMA-IR were all raised. In CHB patients, the prevalence of IR is 31.82%, compared to 10.53 in healthy controls. IR has a strong relationship with a high HBV viral load.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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