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Original Article

Biochemistry Section

Association of Insulin Resistance with Hepatitis B and Hepatitis C Infection: A Cross-sectional Study

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ABSTRACT

Introduction: Hepatitis B and C viruses (HBV and HCV) are the most common causes of chronic viral hepatitis in the United States and worldwide. As several studies have shown that some viral infections promote Insulin Resistance (IR), it becomes imperative to investigate the effect of HBV and HCV on the same.

Aim: To investigate the association between IR and Hepatitis C and Hepatitis B infection.

Materials and Methods: The present cross-sectional study was conducted in the Department of Paramedical and Health Sciences, Parul Institute of Paramedical and Health Sciences, Faculty of Medicine, Parul University, Vadodara, Gujarat, India, from November 2022 to June 2023. The study comprised 100 consecutive patients, with 55% testing positive for Hepatitis B and 45% for Hepatitis C. Biochemical parameters such as fasting blood sugar, fasting insulin and IR via the Homeostasis Model Assessment (HOMA-IR) were determined. Statistical analysis was performed using International Business Machines (IBM) Statistical Package for Social Sciences (SPSS) software version 26.0. The z-test of proportion was calculated and a Z-score calculator was used for p-value.

Results: In the present study, out of 100 consecutive patients, 76 were males and 24 were females. The mean insulin level for HBV patients was found to be high, with values of 28.94±2.22 mU/L in 23.63% of cases, whereas in HCV cases, 68.8% of patients were found to have higher levels, with mean values of 34.52±9.00 mU/L. The mean HOMA-IR values for HBV patients were found to be high, at 4.84±2.32 in 47.27% of cases, whereas in HCV cases, 77.7% of patients were found to have higher values of HOMA-IR, with a mean of 7.94±4.83.

Conclusion: Insulin resistance can be a consequence of the inability of insulin to induce the appropriate effect on glucose metabolism and is the principal indication for the development of metabolic syndrome and diabetes mellitus. In the current study, HCV-positive patients showed more IR compared to HBV-positive cases.

Keywords: Blood glucose, Homeostasis model assessment, Liver disease, Viral infection

INTRODUCTION

World Health Organisation (WHO) estimates that in 2019, 296 million people worldwide were living with hepatitis B and 58 million people were living with hepatitis C. Additionally, 1.5 million people were newly diagnosed with HBV and HCV infection [1,2]. HBV and HCV are the most common causes of chronic viral hepatitis in the United States and worldwide [3]. Viral hepatitis is an inflammation of the liver that causes liver damage. There are different types of hepatitis viruses, including HBV and HCV, which are separate viruses with some similarities. Recent studies have confirmed a close relationship between IR and other liver diseases [4-6]. IR and Type 2 Diabetes Mellitus (T2DM) are associated with complications similar to those associated with chronic hepatitis caused by HBV and HCV infection, such as cirrhosis and Hepatocellular Carcinoma (HCC) [7].

According to the US Department of Health and Human Services, the rates of new HBV infections are highest among adults aged 30-59 years, reflecting low hepatitis B vaccination coverage among adults at risk [8,9]. For 2019, the reported number and rate of HCV infections were highest among persons aged 30-39 years followed by those 20-29 years of age; the lowest number and rate was among those 0-19 years of age [8,10].

Insulin resistance appears as a result of the inability of insulin to induce the proper effect on glucose metabolism. Exceedingly large amounts of insulin are required to achieve a normal response in a state of IR [6]. HOMA-IR is one of the most commonly used methods to determine IR in large population-based studies, because it is mathematically derived from individual fasting glucose and insulin measurements. HOMA-IR is based on the feedback loop between glucose and insulin after it has been taken up by cells [7]. A hyperinsulinemic state causes several clinical abnormalities to appear in the blood vessels, kidneys and liver. These represent the major features of metabolic syndrome [11].

Metabolic disorders associated with IR are related to a worse prognosis in Chronic Hepatitis C (CHC) virus infection or Non Alcoholic Fatty Liver Disease (NAFLD) [12,13]. IR also plays an important role in the development of various complications associated with HBV infection. Recent evidence indicates that HCV-related IR can lead to liver fibrosis, steatosis, HCC and resistance to antiviral drugs [14]. Moreover, there is evidence suggesting that hepatitis C promotes IR and IR, in turn, induces interferon resistance, steatosis and fibrosis progression [15].

As mentioned above, several studies have shown that some viral infections promote IR, which is still unclear [16,17]. This relationship is likely found mainly in chronic hepatitis because acute infections promote liver damage instead of metabolic changes due to the extended duration of the damage. The reports on the relationship between IR and viral hepatitis, such as HBV and HCV infection, are inconsistent. Some authors have found glycaemic abnormalities in HBV-infected patients similar to those associated with HCV infection [18,19]. However, others have reported that IR and HBV infection are not related [20]. Due to the lack of substantial evidence, it still remains controversial. Hence, it becomes important to analyse the association of IR in the cases of HCV and HBV infections, respectively.

The current study focused on evaluating IR using the HOMA-IR method to examine the association of the same parameter in HBV and HCV patients. These results can indicate that patients with HBV and HCV may need to be carefully monitored for the occurrence of IR and, hence, diabetes mellitus in the future.

MATERIALS AND METHODS

The present cross-sectional study was conducted in the Department of Paramedical and Health Sciences, Parul Institute of Paramedical and Health Sciences, Faculty of Medicine, Parul University, Vadodara, Gujarat, India, from November 2022 to June 2023. The study subjects were counselled separately about the study and an informed consent form was obtained from each patient. The present study was approved by the Ethics Committee of the Parul University-Institutional Ethics Committee for Human Research (PU-IECHR), Vadodara (PUIECHR/PIMSR/00/081734/5311).

Inclusion criteria: Patients aged >30 years who had been clinically diagnosed with HCV and HBV, encompassing both males and females were included in the study. HBV testing was performed using the Meriscreen one step HBsAg test strip and HCV testing was conducted using the TREDRO HCV Ab kit method [21,22].

Exclusion criteria: Patients with type 1 diabetes, pregnant women, smokers and alcoholics were excluded from the study.

Sample size calculation: The sample size was determined using a non probability, characteristic and convenient sampling method with a 95% confidence level, using the online statistical tool OpenEpi. The sample size of the present study comprised a total of 100 individuals.

Study Procedure

Demographic data such as age and gender were recorded using a semistructured questionnaire. The information concerning the patients was obtained under strict confidentiality and their identities were not disclosed.

Blood samples of the subjects were collected using the sterile vein-puncture technique in grey (fluoride) vials for Fasting Blood Glucose (FBS) (2 mL) and red (plain) vials (2 mL) for Insulin (IF) following eight hours of fasting. FBS levels were estimated using an automated analyser (Fully automatic Erba Macchine EM 200) with the normal range being 70-100 mg/dL [23].

Insulin fasting was analysed using the ADVIA Centaur XP system by Chemiluminescent Immunoassays (CLIA) method, with the normal value being 0-25 mU/L. Further, FBS and insulin fasting were calculated using the OMNI Homeostatic Model Assessment (HOMA-IR) calculator:

HOMA-IR=(Insulin×Glucose)/405 [24,25]

The normal range of HOMA-IR values was taken as (0-2) and higher values of HOMA-IR, which indicate positive IR, were taken as >2 [25].

STATISTICAL ANALYSIS

The authors investigated the presence of an independent association between IR and HBV/HCV status. Statistical analysis was carried out using IBM SPSS software version 26.0, and Microsoft Excel 2013 was used for the analysis. The Chi-square test method was employed. The z-test of proportion was manually calculated and a z-score calculator was used for the p-value. A p-value less than 0.05 was considered statistically significant.

RESULTS

The study comprised 100 patients, including 76 males and 24 females. The total number of HBV-positive patients was 55, with 51 males (mean age: 48.5±12.25 years) and four females (mean age: 35.25±4.71 years). The total number of HCV-positive patients was 45, with 25 males (mean age: 49.32±12.37 years) and 20 females (mean age: 46.45±9.63 years) [Table/Fig-1].

Among the HBV-positive patients, 14 (25.45%) had higher fasting blood sugar levels. Similarly, for HCV-positive cases, 11 (24.4%) out of 45 patients were found to have higher fasting blood sugar levels. Almost 75% of patients were non diabetic in both cases. In HBV patients, out of 55, 13 (23.63%) were found to have high insulin fasting levels. Conversely, in HCV patients, out of 45, 31 (68.8%) were found with higher insulin fasting levels. There was a significant difference in the proportion of patients with high FBS, high insulin fasting and HOMA-IR [Table/Fig-2].

In HBV cases, the mean value for FBS was 85.34±8.02 mg/dL in normal cases and for higher levels, the mean values were 126.14±19.33 mg/dL. IF levels were 7.32±5.33 mU/L and 28.94±2.22 mU/L for lower and higher values, respectively. The HOMA-IR values were 1.13±0.42 and 4.84±2.32 for normal and higher values, respectively in HBV patients [Table/Fig-3].

In HCV cases, the mean values for FBS were 86.73±9.0 mg/dL for normal and 130.09±22.44 mg/dL for higher levels. The normal insulin fasting values were 6.58±3.89 mU/L and 34.52±9.0 mU/L for higher values of insulin fasting in HCV-positive patients. The tests indicated normal values of HOMA-IR as 1.08±0.43 and 7.94±4.83 for higher values of the same [Table/Fig-4].

Variables	HBV (n=55)		Statistics	p-value	HCV (n=45)		Statistics	p-value
	Male	Female			Male	Female		
n	51	4	z-value: 8.96	**0.0001**	25	20	z-value: 1.05	0.293
Mean age (years)	48.5±12.25	35.25±4.71	t-value: 2.13	**0.037**	49.32±12.37	46.45±9.63	t-value: 0.85	0.39

[Table/Fig-1]: Demographic data among HBV and HCV groups.
Z-test, Two-sampled Independent t-test
The p-value in bold font indicates statistically significant value

Parameters	HBV (n=55)		HCV (n=45)		Comparitive ratio of higher values of various parameters HCV/HBV	z-value	p-value
	Normal	High	Normal	High			
FBS, n (%)	41 (74.54)	14 (25.45)	34 (75.5)	11 (24.4)	0.78	24.0	**0.001**
Insulin Fasting, n (%)	42 (76.36)	13 (23.63)	14 (31.1)	31 (68.8)	2.38	23.12	**0.00001**
HOMA-IR, n (%)	29 (52.72)	26 (47.27)	10 (22.2)	35 (77.7)	1.34	46.06	**0.002**

[Table/Fig-2]: Comparison of FBS, insulin fasting and HOMA-IR associated with HCV/HBV patients.
z-score calculator

Parameters	HBV (n=55)		Statistics t value	p-value
	Normal	High		
FBS in mg/dL (Mean±SD)	85.34±8.02	126.14±19.33	-11.132	**0.00001**
IF in mU/L (Mean±SD)	7.32±5.33	28.94±2.22	14.17	**0.00001**
Homa-IR (Mean±SD)	1.13±0.42	4.84±2.32	-8.46	**0.00001**

[Table/Fig-3]: Mean values of low and high levels of parameters in HBV.
Two-sampled Independent t-test

Parameters	HCV (n=45)		Statistics t-value	p-value
	Normal	High		
FBS in mg/dL (Mean±SD)	86.73±9.0	130.09±22.44	-9.33	**0.00001**
IF in mU/L (Mean±SD)	6.58±3.89	34.52±9.0	-11.10	**0.00001**
Homa-IR (Mean ±SD)	1.08±0.43	7.94±4.83	-4.44	**0.0006**

[Table/Fig-4]: Mean values of low and high levels of parameters in HCV.
Two-sampled Independent t-test

The Pearson's Chi-square test was used to check the association between all three parameters in both HBV and HCV. The FBS levels were non significant, whereas IF and HOMA-IR were highly significant [Table/Fig-5].

Name of parameters	FBS	IF	HOMA-IR
Test significant value	0.013	20.59	9.681
p-value	0.548	**<0.0001**	**0.002**

[Table/Fig-5]: Association between different parameters of HBV and HCV. Pearson's Chi-square test

DISCUSSION

Many studies indicate that some viral infections encourage Insulin Resistance (IR) [26]. This association is more likely to occur in chronic hepatitis because acute infections promote liver damage [27,28]. It is believed that IR and T2DM are linked to complications such as cirrhosis and HCC, which are primarily linked to chronic hepatitis caused by HBV and HCV infections [29,30]. However, due to a lack of information related to the manifestation of IR in both viral hepatitis types, i.e., HBV and HCV, it is difficult to ascertain whether it plays a prominent role in the aetiology of complications occurring in both cases to the same extent. HOMA-IR, an IR index test, is used for prediction diabetes in patients and was utilised in the current study, where a value greater than 2.0 is considered indicative of the presence of IR [31]. The association between IR and hepatitis caused by HBV and HCV is crucial for preventing patients from future T2DM complications of which they might be unaware.

The present study revealed that out of a total of 100 patients, 55% (51 males with a mean age of 48.5±12.25 years and four females with a mean age of 35.25±4.71 years) were found to be HBV positive. The total number of HCV-positive patients were 45 (45%) with 25 males (mean age of 49.32±12.37 years) and 20 females (mean age of 46.45±9.63 years). In a population-based study, Wang S et al., found that among all study participants, 3.8% and 0.36% tested positive for hepatitis B and anti HCV, respectively. The HBsAg and anti-HCV-positive rates were significantly higher in male participants (4.58% and 0.43%) than in female individuals (3.0% and 0.33%) [32].

A hospital-based study related to the prevalence of HBV and HCV infection among patients with Chronic Liver Disease (CLD) in South India by Saravanan S et al., found that out of the 69 CLD cases screened for possible markers of HBV and HCV infection, 39 (57%) were positive for HBV and 30 (43%) were HCV infected [33].

In the current study, almost 75% of patients were non diabetic in both cases. However, the fasting insulin levels were high in 23.63% of HBV cases and it is quite interesting to note that 68.8% of HCV patients showed high values of fasting insulin, as well as with the HOMA-IR index. 47.27% of HBV patients were found to have high values and surprisingly, 77.7% of HCV patients were found to have high HOMA-IR values.

According to Kumar M et al., a total of 69 chronic HBV-positive patients were examined to study the relationship between histological findings and anthropometric and biochemical data, including IR determined by the HOMA-IR. They concluded that IR in Chronic HBV (CHBV) infected patients is a reflection of the host metabolic profile and CHBV infection is not in itself correlated with IR [26]. According to a review article, glucose abnormalities (DM/IR) are strongly associated with HCV infection [34]. On the contrary, Lee JG et al., demonstrated that chronic HBV is associated with IR. It may need to be monitored for the occurrence of IR and diabetes mellitus [12].

The mean FBS levels did not show a significant difference in both cases. It was found to be 126 mg/dL and 130 mg/dL, respectively, whereas the mean fasting insulin and HOMA-IR values were remarkably higher in HCV patients. The test results indicated 28.94±2.22 for higher values of fasting insulin for HBV-positive patients and 34.52±9.00 mU/L for HCV patients. A study conducted by Alizadeh AM et al., aimed to determine whether IR occurs in patients with Chronic Hepatitis B and CHC. According to the results, the mean fasting serum insulin and IR were found to be higher in HBV-positive cases as compared to HCV [35].

Although approximately, 74% of patients were found to be non diabetic in both cases, the fasting insulin and HOMA-IR were found to be higher, indicating an alarming condition for the patients regarding high IR and the future development of T2DM. It is noteworthy that HCV is a prominent connection to IR sensitivity. Hence, it is not an exaggeration to say that HCV-infected patients are more likely to develop IR and, as a result, T2DM.

The present study indicated that almost 75% of non diabetic patients in both HBV and HCV cases, hence approximately 25-26% of cases were found to be diabetic (T2DM). In other findings, such as Ryu JK et al., 24% of T2DM patients were found in the HCV-positive group and 10.4% T2DM in the HBV-positive group [36]. Several investigations related to CLD also showed that diabetes was observed in 24% to 26% of patients in the case of HCV infection, while it was observed in 9% to 13% of patients with HBV infection [36-38].

The mechanisms underlying IR are considered multifactorial. The development of IR involves glucose consumption in skeletal muscle and glucose production in liver cells. Thus, HCV can be considered a metabolic disease which can further complicate the infection and eventually, the onset of T2DM may occur due to this [39-41]. According to Bose SK and Ray R, HCV infection interferes with the insulin signaling pathway resulting in IR [42]. Many studies indicate the involvement of HCV as a risk factor for IR [4,43]. The relationship between T2DM and the development of cirrhosis and HCC has been reported in several studies [44,45]. Hence, screening for IR becomes important in patients with viral hepatitis [46]. In the current findings, HBV was not seen to be linked with high fasting insulin and HOMA-IR sensitivity. Similar findings were observed in other research, as well [26,47]. Due to a lack of adequate information, prospective studies on a larger scale are much needed to confirm the outcomes for HBV cases.

Limitation(s)

Although the present study needs to be conducted prospectively in a larger group and for a longer period of time to evaluate the long-term effects, additional parameters like Body Mass Index (BMI), lipid profile, Alanine Transaminase (ALT)/Aspartate Aminotransferase (AST) etc., can be further investigated to predict the occurrence of complications beforehand.

CONCLUSION(S)

In the current study, the Hepatitis B and C patients were checked for IR sensitivity. HCV-positive patients showed more IR compared to that of HBV-positive cases. In fact, IR is the principal indication for the development of metabolic syndrome and T2DM. IR can be a consequence of the inability of insulin to induce the appropriate effect on glucose metabolism. Hence, the evaluation of IR in viral hepatitis patients, especially in HCV cases, stands prominent in the prediction of T2DM much before and the patients can be saved from future complications like Non Alcoholic Fatty Liver Disease (NAFLD), hepatic steatosis and even hepatic carcinoma. The association of hepatitis B with IR is still uncertain. Further studies are warranted in the future for unraveling many hidden aspects.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
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- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

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