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Study of golgi protein-7 levels associated cirrhosis in patients with infections hepatitis B virus

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Abstract--Background/Aims: Infection with the hepatitis B virus (HBV) is a major health concern that can lead to liver failure. The hepatitis B virus (HBV) infects humans in both acute and chronic forms. The transmission of this infectious illness is caused by several risk factors. The goal of this study was to look at the epidemiology and risk factors of HBV infection. HBV infection is associated with cirrhosis and/or hepatocellular cancer (HCC). Golgi protein 73(GP73) in human serum is a useful biomarker in the evaluation of hepatic fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) by hepatitis B virus (HBV). The purpose of this study was to evaluate the serum GP73 level's ability to predict HBV infection caused by cirrhosis and/or HCC. Methods: In serum samples, GP73 levels were determined using an enzyme-linked immunosorbent assay (ELISA). This study looked at the underlying function of HBV-induced GP73 in controlling cirrhosis and/or HCC development. ELISA was used to assess hepatitis B surface Antigen (HBsAg) and GP73 expression in HBV-related to cirrhosis and/or hepatocellular cancer (HCC). Results: This study included a total of 35 patients with HBsAg by ELISA technique and 18 persons as control group negative to (HBsAg, anti-HBc-Ab, anti-HCV-Ab, HIV). The distribution of HBV patients with age groups (45-55) years old was the highest prevalence, followed by those aged (34-44, 23-33, 56-66, 12-22 and more than 67) years old. And the concentration of serum GP-73 (pg/ml) in patients with HBV infection was in males (6.649pg/ml) more significantly than control male group and in females (9.605pg/ml) no significantly than control female group. Conclusion: Elevated age group (45-55) years old with HBV infection. Serum GP73 is a useful and important indicator to predict HBV infection, cirrhosis, and HCC, and increase GP73 levels in HBV patients (males and females) compared with the control group.

Keywords---Hepatitis B virus, Golgi protein73, Cirrhosis, HCC, ELISA.

Introduction

Hepatitis B virus (HBV) infection is still a significant public health issue everywhere in the globe. It presents certain challenges as a result of a number of factors, such as immigration and immunization regulations. Those who have chronic hepatitis B (CHB) (Hepatol, 2017). Hepatitis B virus (HBV) infection can be acute or chronic (Yuen *et al.*,2018).HBV has infected more than 2 billion individuals throughout the world(Schweitzer *et al.*,2015). Around 5-10% of people acquire chronic HBV infection after an acute infection, and up to 30% of chronic carriers get hepatitis, fibrosis, or cirrhosis, which can result in hepatocellular carcinoma (HCC) (Trépo *et al.*,2014). Cirrhosis and/or HCC can easily arise as a result of HBV infection (Arzumanya *et al.*,2013). However, Unknown molecular processes underlie HBV infection-induced cirrhosis and/or HCC. During an HBV infection, hepatocytes start to express a number of proteins improperly, with GP73 (Golgi protein 73) being one of the increased proteins (Sai *et al.*,2015). GP73 is a Golgi protein that has been discovered by (Kladney *et al.*,2000). Adult giant cell hepatitis was studied in a study. Normal liver tissues seldom include hepatocytes with the exception of the bile duct epithelial cells in the portal area, where GP73 is mostly expressed (Kladney *et al.*,2000). The concentration of serum GP73 is much greater in individuals with hepatocyte injury induced by viral invasion, according to clinical data (Kladney *et al.*,2002). However, The majority of research focuses on the link between aberrant GP73 expression and liver carcinogenesis (Jiang *et al.*,2016). Chronic hepatitis B virus (HBV) infection is a serious public health concern across the world (Neuveut *et al.*,2010). Globally, more than 240 million people have HBV infection that is chronic, and more than 780,000 people are expected to pass away each year as a result of this virus (WHO, 2014). HBV infection can result in serious liver diseases such cirrhosis and hepatocellular carcinoma (HCC) as well as hepatic necrosis, inflammation, and fibrosis (EASL, 2012). Antiviral medicine should be used to treat chronic HBV infection. Since HBV infection is seldom cured, the main goals of antiviral medicine are to decrease HBV replication, stop the progression of liver disease to cirrhosis, decompensated cirrhosis, or HCC, and delay the onset of end-stage liver disease (EASL, 2012; Keeffe *et al.*,2008). Golgi protein 73 (GP73) is a type II transmembrane glycoprotein that is generally found inside the Golgi complex (Ke *et al.*,2019). Shortened GP73 can be released into the bloodstream because it possesses a protease cleavage site (Block *et al.*,2005). Liver disorders such acute hepatitis, liver cirrhosis, and HCC are associated with the level of GP73 expression in liver tissue and blood. In those with recurrent HBV infections, GP73 is a reliable marker for predicting severe fibrosis, according to new research (Qiao *et al.*,2014). Many epithelial cells in human tissues express the Golgi protein 73 (GP73). The GP73 gene is found on chromosome 9 of the human genome (Kladney *et al.*,2000).GP73 has recently been proposed as a marker for hepatocellular carcinoma (HCC) and/or cirrhosis, with its serum levels correlating with CHB development (Riener *et al.*,2009). Hepatic GP73 expression was found to be higher in acute and chronic liver illness in subsequent research (Liu *et al.*,2011), and an increase in serum GP73 concentration was linked to the course of chronic liver

disease (Sun *et al.*,2011), fibrosis, and liver inflammation (Wright *et al.*,2009). Given that it was markedly amplified in injured livers, increased GP73 hepatocyte expression appears to be an important factor in the development of liver disease (Rockey *et al.*,2009). As a result, evidence points to serum GP73 as a potential HCC serum marker as well as a useful indicator of the progression of overall liver disease (Mao *et al.*,2010). The present study aimed to detect the change in serum level of Golgi protein-73 biomarker in patients with HBV infection as an indicator to determine the progression of liver damage and cirrhosis by hepatitis B virus.

Materials and Methods

This study included 35 patients with HBV infection in the age group (of 12-75)years old both sexes were accepted to the Department of Infectious Diseases and were collected from Main Blood Bank, Central Laboratory and Central of Digestive System in AL-Sader medical city in AL-Najaf Governorate through the period from December 2021 to June 2022. those patients were compared with 18 healthy control individuals, 5 ml of blood was drawn from each patient, placed in a gel tube were without anticoagulant then after centrifugation was drawn serum and placed in two Eppendorf tubes, for blood to be used for preparing sera for subsequent serological tests. . Each sample was labelled and given a serial number together with the patient name, the serum samples were frozen at (-80°C) Until used for Virological and serological biomarker Investigation. that detection by enzyme-linked immunosorbent assay technique (ELISA) Positivity for hepatitis B surface antigen (HBs -Ag) by Kit (Abia, Berlin, Germany) and the quantitative detection of human GP-73 in serum was used ELISA kit (Elabscience, USA).

Detection of HBsAg in human serum by ELISA kit (abia, Berlin, Germany)

Micro wells coated with antibodies to the HBs antigen are used in the "sandwich" test known as Abia HBs Ag. The conjugate is made up of streptavidin that has been HRP-labeled and biotin-labeled antibodies against the HBs antigen. If HBs antigens are present in the sample, they bind to antibodies immobilized on the wells to form stable complexes, which may be recognized by adding:

- (1) biotinylated antibodies and
- (2) HPR – labelled streptavidin

The unbound components are eliminated by washing. Following the addition of the TMB and hydrogen peroxide solution, the bound conjugate-containing wells had a blue colour that turned to yellow when the reaction was stopped using sulphuric acid. The color intensity is directly related to the amount of HBs antigens present in the samples at 450 nm or 450 and 620–680 nm.

Statistically analysis

All data were recorded as Means \pm Standard Error (SE). A statistical test was performed using (the Graph Pad prism ver.7) programme. Statistical significance was defined as a (P-value < 0.05).

Results

Based on the age ranges of the patients, sex groups were assigned. According to figure (1), the age groups with the highest prevalence of HBV were those between the ages of (45-55), followed by those between the ages of (34-44), (23-33), (56-66), (12-22), and those older than (67).

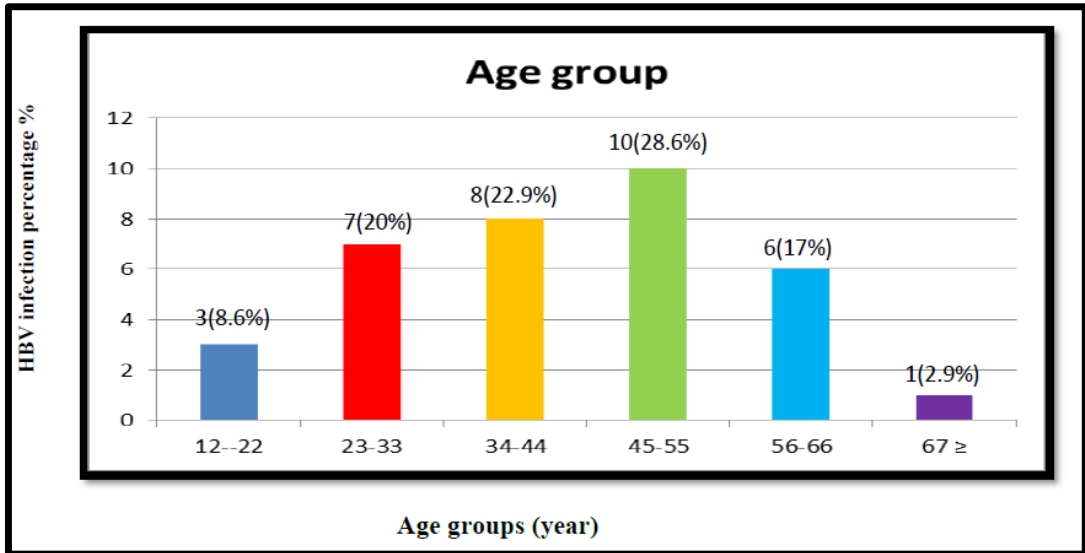


Figure 1: Distribution of HBV infection among patients according to age.

GP-73 distribution in hepatitis B virus and control by gender, As demonstrated in Table (1), and figure (2) the current study also discovered that the concentration of GP-73 (pg/ml) in hepatitis B virus infection in females (9.605 3.644 pg/ml) was not statistically different from that of control females (1.729 1.095 pg/ml).

Table 1: Serum GP-73 level hepatitis B virus in female

GP-73	HBV Female	Control female
Mean ± Std. Error	9.605 ± 3.644	1.729 ± 1.095
P value	0.1940 Ns	

Ns = no significant

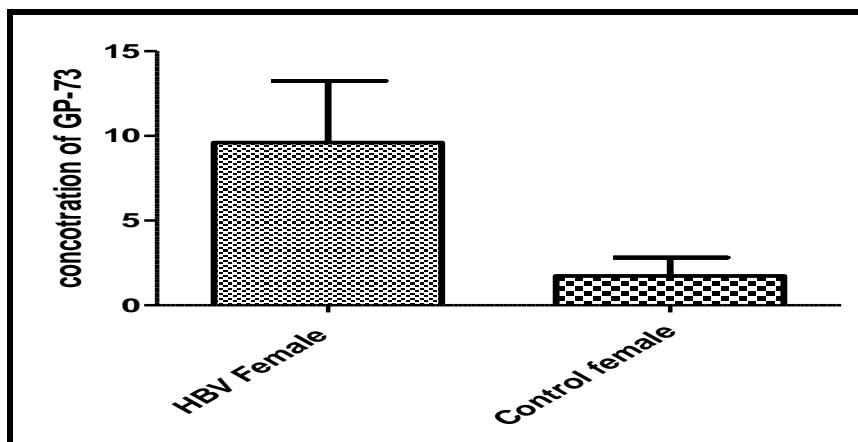


Figure 2: Serum GP-73 level hepatitis B virus in female

The current study also found that, as indicated in Table (2) and Figure (3), the concentration of GP-73 (pg/ml) in HBV infection in males was (6.649 1.141 pg/ml) was considerably higher than Control male individuals were (1.174 0.183 pg/ml).

Table 2: Serum GP-73 level hepatitis B virus in male

GP-73	HBV male	Control male
Mean \pm Std. Error	6.649 \pm 1.141	1.174 \pm 0.183
P value	**0.0011	
**= high significant		

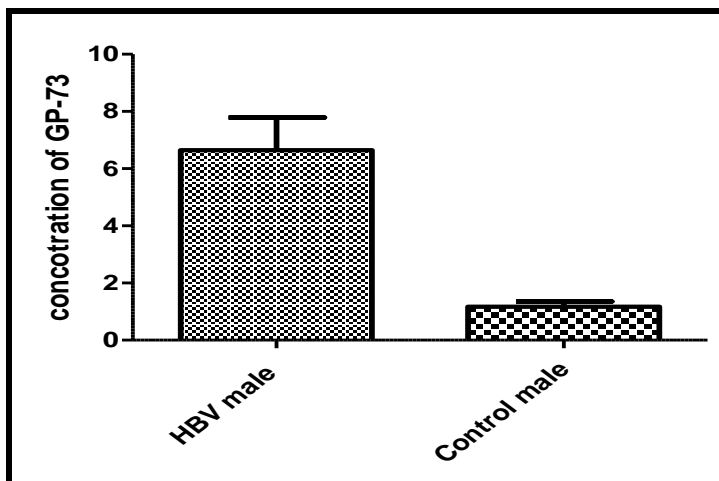


Figure 3: Serum GP-73 level hepatitis B virus in male

Discussion

Serum markers are an essential tool for identifying and forecasting liver damage, inflammation, fibrosis, and carcinogenesis in chronic HBV patients. Serum indicators are especially useful for determining whether or not the antiviral

medication is required, as well as monitoring the antiviral response of individuals who have received treatment. GP-73 is a current biomarker. This biomarker, as well as liver fibrosis serum indicators, are used to assess HBV infection patients (Xu *et al.*,2015). Patients with persistent HBV infection are at a greater risk of developing cirrhosis and HCC, depending on the host and viral variables. The goal of therapy is to slow or stop the course of the illness, which improves survival and quality of life. Furthermore, determining the degree of liver disease is necessary to identify which individuals should be treated (Hepato1, 2017). The clinical use of invasive liver biopsy has not been well-accepted due to its invasive nature, difficulties, and unfeasibility, even though CHB is a global concern and invasive liver biopsy has been regarded as the gold standard for assessing liver pathology (Xu *et al.*,2018). Golgi protein 73 (GP73) is a 73-kDa type-II Golgi transmembrane glycoprotein discovered in a variety of human epithelial cells. It is normally seen in lesser concentrations in serum and hepatocytes (Xu *et al.*,2015). Golgi protein 73 has been postulated as a viable biomarker for early detection of cirrhosis and/or HCC, and its blood concentration has been linked to chronic liver disease development (Yamamoto *et al.*,2010). Golgi protein 73 is expressed in biliary epithelial cells in normal liver but not in normal hepatocytes, even though its physiologic role is unknown (Bachert *et al.*,2007). In cases of advanced liver illness, GP73 expression has been found to rise in hepatocytes GP73 levels in the liver was shown to be substantially linked to disease progression, inflammation, and fibrosis (Liu *et al.*,2011; Xu *et al.*,2015). The researchers discovered that serum GP73 was linked with Child-Pugh scores in hepatic cirrhosis patients, implying that GP73 might be used to diagnose cirrhosis in people with persistent HBV infection (Qiao *et al.*,2014). Identified serum GP73 as a reliable biomarker that increased in individuals with chronic HBV infection as they progressed through the phases of fibrosis (Cao *et al.*, 2017). Chronic HBV carriers are more prone than non-carriers to develop cirrhosis and/or HCC(Nguyen *et al.*, 2009). HBV replicates in hepatocytes indefinitely without causing cell death or damage, implying that it is a non-cytopathic virus (Sells *et al.*,1987). However, Cirrhosis and/or HCC caused by ongoing HBV infection develop in an inflammatory environment, demonstrating that these conditions are immune-mediated (Rehermann and Nascimbeni 2005). Chronic inflammation and CLD (Chronic Liver Disease), the most prevalent cause of cirrhosis and/or HCC, are brought on by ongoing HBV replication in hepatocytes (Fattovich *et al.*, 2004). After HBV infection, several proteins are first expressed abnormally by hepatocytes. The activation of certain proteins that dampen the human immune response after HBV infection may lead to chronic infection. Studies have shown that virus infection causes the expression of GP73 in hepatocytes (Hu *et al.*, 2014). Despite the fact that research has linked aberrant GP73 expression to clinical viral liver injury (Jiang *et al.*,2016). The major finding of the study was that changes in hepatic necroinflammatory activity in CHB patients were positively correlated with changes in GP73 liver expression and serum levels. As hepatitis progressed from undetectable to moderate to severe, hepatic GP73 expression and blood GP73 levels rose in lockstep. This study supported earlier research that discovered GP73 expression in both acute and chronic liver conditions and connected elevated blood GP73 levels to hepatic fibrosis and inflammation (Sun *et al.*,2011). The approach showed that serum GP73 levels were significantly greater in patients with severe hepatitis, cirrhosis, and HCC (Wright *et al.*,2009). Recent studies have shown that the majority of the hepatocytes in livers with acute or

chronic hepatitis started to express GP73 (Liu *et al.*,2011). Recent studies have shown that the majority of the hepatocytes in livers with acute or chronic hepatitis started to express GP73 (Iftikhar *et al.*,2004). Injured hepatocytes and stimulated hepatic stellate cells greatly elevated their expressions of GP73 and end protease, increasing the amount of GP73 released into the bloodstream (xu *et al.*,2015). In line with data from Iraq, the current study discovered that adult young ageing groups (31-40) and (41-50) years had higher HBV prevalence rates than older age groups (Abdul-Hussian, 2013). The study revealed a higher significant prevalence of HBV among age groups in response to research by Lai *et al.* (2022) in Taiwan, which reported that the age group (45-54) years old (34.92%) was greater than other groups (45-55 years) (Lai *et al.*,2022). According to Wang *et al.* (2019) and El-Baky *et al.* (2020) investigations, patients with HBV infection were more likely to be in the 23-65 age range than in other age groups. This study's findings about this age group are comparable to those of earlier studies (Wang *et al.*, 2019; El-Baky *et al.*, 2020). A few of the potential reasons for the high frequency of HBV infection include sharing drinking cups, inadequate vaccination coverage, poor vaccine adherence, and particularly frequent unprotected sex transmission (ABUSAIBA ,2020) With ageing and stress, the immune system, and bodily cells may also weaken, and reviewing dental clinics and exposure to contaminated tools. In agreement with studies by Liu *et al.* (2022) in China that highlighted raised GP-73 levels in HBV infection patients compared with the control group, the current study revealed an increase in GP-73 levels in HBV infection patients than healthy control persons (Liu *et al.*, 2022) also in line with research conducted in Turkey (Atilla *et al.*, 2022). The current study found that HBV patients had higher blood levels of GP-73 than did controls, which was consistent with the findings (Xu *et al.*, 2015).

Conclusions

Our results revealed that HBV infection facilitates HCC development by activating GP-73 activation, and HBV infection stimulates GP73 expression. It was found that the age group (45-55) years old are more susceptible to infection with HBV. The level of GP-73 in HBV-infected males and females is higher than in the control.

Ethical Clearance

Before enrolment, all subjects submitted their written informed consent after the protocol was approved by the Ethical Review Board for human studies at the Faculty of Nursing/University of Kufa/Iraq (No. 10-04/01/2015).

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