

## PREVALENCE OF CHOLELITHIASIS IN IRAQI PATIENTS WITH HEPATITIS B INFECTION

Ali Abdul Hussan, Athraa Zaidan Hassan, Luma Ghaeb Al- Saadi, Istabreq Muhammed Ali Salman

<sup>1</sup>College of Health & Medical Technology (MTU), Iraq, <sup>2</sup>College of Science, Al-Mustansiryah University, Iraq. E. mail: lmas\_73@yahoo.com

Article received 14.4.2018, Received 27.5.2018, Accepted 6.6.2018

### ABSTRACT

Liver Cirrhosis is a strong and a common, known risk factor for Cholelithiasis. The aim of this study is to determine the frequency of cholelithiasis in patients with hepatitis B virus infection and determine gall stone and their association with hepatitis B virus infection in Iraqi patients.

Patients and Methods: study, involved 131 patients with chronic liver disease according to clinical, laboratory' and Ultrasonographic findings. in addition, 45-individual with no evidence with hepatitis B virus infection as control groups alkaline phosphatase (ALP), hepatitis B surface antigen (HBsAg) were analyzed. ELISA test used to detect hepatitis B surface antigen (HBsAg) and sonography, was done to determine presence or absence of gallstones.

Results: The results showed that Hepatitis B (HBV) was present in 77.8% with a highly significant' difference ( $p < 0.001$ ) between patient groups when compared' to control groups. Also, increase in Alkaline phosphates in 31.2% with highly significant difference ( $p < 0.001$ ) between patient groups and control group. The prevalence of cholelithiasis was 79.4% as significantly higher ( $P < 0.001$ ) in the patients subjects as compared with control subject. In this study was observed that 33.3% of the patients infected with hepatitis B virus were show increase in alkaline phosphates. Statistically highly significant association was found between abnormal increase in alkaline phosphates and hepatitis B virus positive results ( $P < 0.001$ ). In study appeared that 82.4% of the patients infected with hepatitis B infection (84 of 102 cases) were positive for stone formation (cholelithiasis) as Highly significant association between HBV status and gallbladder stones ( $P < 0.001$ ).

Conclusion: Cholelithiasis' tends to' occur more frequently' in patients with hepatitis B virus infection. There is a strong, association, between HBV infection and gallstones. So, HBV infection is definitely 'a risk factor' for gallstone disease.

Keyword: Hepatitis B virus infection, ALP, Gallstone.

### INTRODUCTION

Gallstone disease (GSD) is one of the most prevalent and costly gastrointestinal tract disorders in the world with prevalence of 10–20% in adults in developed countries (Xu *et al.*, 2017). Gallstones (GS) are a major cause of morbidity and mortality throughout the world (Zhang *et al.*, 2006). Gallstone disease, (GSD) is responsible for about 10,000 deaths per year in the United States. About, 7000 deaths are attributed to acute gallstone complications, such as acute pancreatitis. About 2000-3000 deaths are caused by gallbladder cancers (80% of which appear in the setting of gallstone disease with chronic cholecystitis) (Lammert and Sauerbruch, 2005). The prevalence of GS in patients with chronic liver disease (CLD) is 20 - 40%, while it is 10-15% among the general population (Almani *et al.*, 2007).

Gallstone disease is a multifactorial disease based on a complex interaction of environmental and genetic factors. Gallstones are principally formed, due to abnormal bile constituents such as cholesterol, phospholipids and bile salts (Bajwa *et al.*, 2011). When bile is concentrated in the gallbladder,

it can become, supersaturated with such substances which then precipitate as microscopic crystals. The crystals are trapped in gallbladder mucus, producing gallbladder sludge. Over time, the crystals grow, aggregate and fuse to form macroscopic stones (Ponsioen, 2015). Moreover, the increase in gall bladder wall thickness by hyperemia, edema, decreased contractility or impaired gallbladder emptying contributes to gallstone formation (Acalovschi *et al.*, 2004).

The most accurate predicting gallstone' disease was achieved by ultrasound, which has a sensitivity' and a specificity of more than 95% which can help to confirm the presence of gallstones in the gallbladder and may be indicate a thickening of the gallbladder wall (Estrada *et al.*, 2007; Erdem *et al.*, 2010).

Acute inflammation of the liver is most commonly caused by viruses A, B and C. B and C viruses are very dangerous, because upon acute, commonly, unrecognized attacks of illness, chronicity is appeared, and chronic liver disease caused by viruses is one of the leading causes of death. Hepa-

titis B virus (HBV) is known world-wide as a cause of both acute and chronic hepatitis. Acute HBV infection is usually asymptomatic (60% infected), as a self-limiting disease, with complete curing in 90-95% of patients, on average, after 2-3 months of treatment (Miodrag *et al.*, 2012). Hepatitis B virus (HBV) infection is a global health problem, which causes noncytotoxic, chronic infection to hepatocytes and this is one of the reasons for chronic HBV infections (Porth, 2002).

Two biochemical markers of hepatocellular damage are AST (also termed as SGOT) and ALT (also called SGPT) (Jose *et al.*, 2012). Another important biochemical marker of hepatocellular damage is serum alkaline phosphatase (AP), involved in transport of metabolites across cell membranes. It is found in a decreasing order of abundance, in placenta, ileal mucosa, kidney, bone, and liver (Pattullo, 2015). Association of gallstones with chronic liver disease is documented in medical literature (Acalovschi *et al.*, 2009; Chang *et al.*, 2005; Bini and Gready, 2005), but study hasn't been carried out in Iraq. This study aimed to shed light on the frequency of cholelithiasis in patients with hepatitis B virus infection as well as to determine association between gallstone and hepatitis B virus infection in Iraqi patients.

## MATERIALS AND METHODS

A total of 176 cases are included in this study. 131 patients with chronic liver disease the patient groups and 45 subjects with no evidence of infection with hepatitis B virus or any chronic liver diseases control groups who attended to the Alkadimiya hospital in Baghdad city during the period from April 2015 to June 2016. Each patient and control groups were tested for Alkaline phosphates (ALP) by Alkaline Phosphatase Assay Kit (Colorimetric endpoint) (abcam, UK, cat. Number ab83369) which Hepatitis B surface antigen (HBsAg) was analyzed by Cell Biolabs' QuickTiteR HBsAg ELISA Kit (cat. number VPK-5004, USA) in addition Gallstones have been determined by ultrasonography.

**Statistical analysis:** Data were analyzed by SPSS version 18.0. Chi-square test was used to determine the association of HBV infection with alkaline phosphates and gallstones. p-value of <0.05 was considered significant.

## RESULTS

This study involved 131 patients with chronic liver disease. Chronic HBV infection was found in 77.8% (102 out of 131 patients) and 22.1% (29 out of 131 patients) were negative for HBV infection with highly significant difference ( $p < 0.001$ ) between patient groups and control groups as shown in Table 1. Also, it was cleared from this table that alkaline phosphates increased (abnormal) in 31.2% (41 out of 131 patients) while 68.7% (90 out of 131 patients) were negative for alkaline phosphates. Statistically Highly significant difference ( $p < 0.001$ ) between patient groups and control groups on comparison of alkaline phosphates.

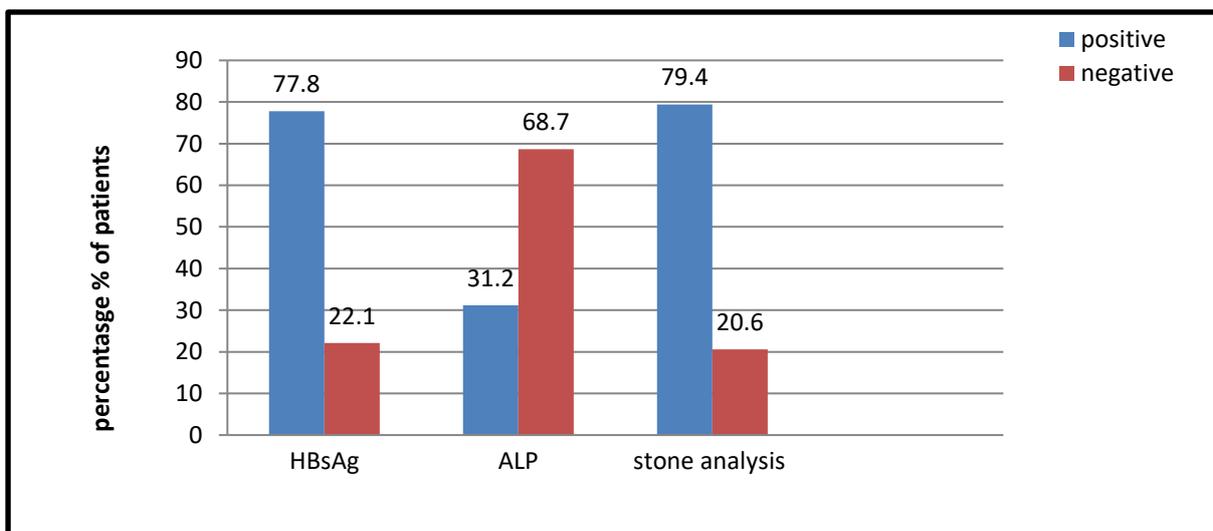
Stone analysis was determined in the current study by sonography. It was found that the prevalence of cholelithiasis in the examined patients was 79.4% (104 out of 131 patients) and negative in 20.6% (27 out of 131 patients). There was Highly Significant difference ( $p < 0.001$ ) in comparison the results according to the stone analysis between patient groups and control groups as shown in Table 1.

Stratification on the basis relationship between HBsAg and ALP results revealed that 33.3% (34 out of 102 patients) of HBsAg positive results were increase (abnormal) for ALP Whereas 24.13% (7 out of 29 patients) of HBsAg negative were abnormal for ALP. while 66.7% (68 out of 102 patients) of HBsAg positive results were normal for ALP. Whereas 75.8% (22 out of 29 patients) of HBsAg negative results were normal for ALP. There are obvious Statistically Highly Significant association ( $p < 0.001$ ) in rate of ALP results between HBsAg positive and HBsAg negative results as seen in Table 2.

In the present study, the association between HBsAg results and stone analysis were listed in Table 3. It was observed that 82.3% (84 out of 102 patients) of HBsAg positive results were positive for stone analysis. Whereas 17.6% (18 out of 102 patients) of HBsAg positive results were negative for stone analysis. while 68.9% (20 out of 29 patients) of HBsAg negative results were positive for stone analysis. Whereas 31.0% (9 out of 29 patients) of HBsAg negative were revealed also negative results for stone analysis. Statistically Highly significant association ( $p < 0.001$ ) between cholelithiasis (stone analysis) and positive or negative infection with hepatitis B virus as shown in Table 3.

**Table 1: Distribution of HBs-Ag, ALP level, Stone analysis between patient groups and control groups.**

Parameters		Patients	Control	P-value
HBsV-Ag	Negative	29 22.13%	45 100 %	P < 0.001 HS*
	Positive	102 77.8%	0 0.0%	
ALP Levels	Abnormal	41 31.2%	0 0.0%	P < 0.001 HS*
	Normal	90 68.7%	45 100%	
Stone analysis	Negative	27 20.6%	45 100 %	P < 0.001 HS*
	Positive	104 79.4%	0 0.0%	



HS\* = Highly Significant

**Figure 1: distribution of patients according to parameters (HBsAg ALP, Stone analysis).**

**Table 2: Relationship between HBV-Ag and ALP level among studies groups.**

HBVs-Ag	ALP Level			P-value
	Abnormal	Normal	Total	
Negative	7 24.1%	22 75.8%	29 100%	P < 0.001 HS*
Positive	34 33.3%	68 66.7%	102 100%	

HS\*= Highly Significant

**Table 3: Association between HBV-Ag and stone analysis among studies groups.**

HBVs-Ag	Stone analysis			P-value
	Negative	Positive	Total	
Negative	9 31.0%	20 68.9%	29 100%	P < 0.001 HS*
Positive	18 17.6%	84 82.3%	102 100%	

HS\*= Highly Significant

## DISCUSSION

Hepatitis B is a major public health problem worldwide (Previsani and Lavanchy, 2002). This infection with global burden due to its link with the development of liver cirrhosis and hepatocellular carcinoma (HCC), which forms around 2% of all death and is, expected to increase over the next decades (Mathers and Loncar, 2006) were attributed to HBV infections (Perz et al., 2006). In the current study we detected the presence of HBsAg in patients with chronic liver disease. We showed that 77.8% of the patients were positive results for HBsAg these results were comparable with other studies (Miodrag et al., 2012; Rui et al., 2015). In this respect, Globally, it was found that high incidence of chronic hepatitis B virus infection which comprised 90% seen in China and other Asia-Pacific countries this result in keeping with our data (Zhang et al., 2008). HBV infections, are among the most prevalent infectious diseases in humans worldwide. The infections are associated with a broad range of clinical presentations ranging from acute or fulminant hepatitis to chronic infection that may be clinically asymptomatic or may progress to chronic hepatitis and liver cirrhosis (Dasarathy et al., 1992). The prevalence of infection with HBV varies from one country to another depending upon a complex mixture of behavioral, environmental and host factor. However, the result of the current study shows high percentage than other studies in Iraqi population (Ataallah et al., 2013; Ataallah et al., 2011; AL-Hammieary, 2009). In addition, the reported global studies indicated a wide variation in HBsAg seroprevalence between countries and in different regions of the same country. HBsAg seroprevalence was 0.2%-8.5% in Brazil (Scaraveli et al., 2011; Bertolini et al., 2006), 0.4% in Canada (Rotermann et al., 2013) 1 %-2.28% in Pakistan (Jafri et al., 2006), 3.58% in Poland (Hartleb et al., 2012), 6.71% - 9.8% in China (Xia et al., 1995), 4.8%-18% in Asian American (Sheikh et al., 2011). Awan et al (2010) reported ~38% prevalence of different hepatitis B markers, with a 4% HBs Ag carrier rate and 32% with anti-HBV surface antibodies (Anti HBs Ab) by natural conversion. Our data indicated an increase in the prevalence of the disease during study period (2015-2016). This phenomenon was a reflection of many underlying etiology, such as the disruption of health care providing system, improper surveillance of infectious disease, disruption of prevention and control

program of notifiable communicable diseases, all of these' may lead to unsafe<parenteral injection, blood and blood product transfusion. A national effective prevention and control programs application is required, and new research community-based studies is warranted' to clarify the health impact of HBV on community (Abdulghani et al., 2016).

Our investigation showed that 31.2% of patients were increase in Alkaline phosphate. This results in line with other study (Goni et al., 2013). While the present study disagreement with other study (Disha et al., 2013) which shows that 54.1% of patients with hepatitis B infection were elevated in alkaline phosphates. Variation in the alkaline phosphate level in various studies could be attributed to differences in patient selection well as clinical characteristics of the study populations involved.

In this respect, it was found that Elevation of ALP in the setting of liver disease results from increased synthesis and release of the enzyme into serum rather than from impaired biliary secretion. The cholestasis liver diseases primarily cause elevation of serum alkaline phosphatase values, while in about 90% of those patients with HBV; the AP value is fond normal (Doumas et al., 2004). The current study revealed that 79% of patients with chronic liver disease were formed gallstone (cholelithiasis). On the other hand, Eljaky et al., (2012) revealed that 21.8% of patients with cholelithiasis were have chronic liver disease. Also, several studies (Hsing et al., 2007; Acalovschi et al., 2004; Buzas et al., 2011) observed that relation between liver cirrhosis and gallstone with varying percentage (23-40%). This different in the percentage among studies attributed to the differed in the sample size, patient characters and the stage of liver disease.

It showed that 33.3% of patients with hepatitis B infection were have abnormal or increase in alkaline phosphates. This is in keeping with other study (Goni et al., 2013). Furthermore, Ugwuja and Ugwu (2008) who observed that significant increase of alkaline phosphates in positive HBsAg patients. These results deal with the present study. The association between hepatic viral infection and gall stone disease has been evaluated in several studies (Wu et al., 2010; Sulaberidze et al., 2009). In the current study we discussed the association between HBV infection and gallstone formation and results of our study were showed highly significant associated between HBV infection and cholithiasis. The results of this study are in harmony with that done by Shih et al., (2011)

and Shao et al., (2014) who demonstrated that the hepatitis B contribute a significant risk for cholelithiasis (Shih et al., 2011; Shao et al., 2014).

On the other hand, in the present study we found that 82% of HBV patients had gallstone as compared to previous studies done by Miodrag, et al., (2012) who reported that 63% and 13.6% respectively comprised the incidence of gallstones in HBV positive patients. The prevalence in our study is higher from these studies. Explanation for this variation may be related to sample size, genetic background, geographical distribution, ethnicity factors and the selection of subjects studied. In this respect, it was found that increased prevalence of gallstone diseases was associated with the duration and severity of HBV-related liver disease (Sheen and Liaw, 1989). This means that the risk of cholelithiasis increases over time in patients with HBV. In addition, the high prevalence of gallstone in our study may be due to direct infection of the gallbladder by the hepatitis B VIRUS. Sulaberidze et al., (2009) reported that the cholecystopathogenic caused by hepatitis B virus leads to structural and functional changes of the gallbladder. It is possible that viral infection of the gallbladder may be increase the risk of gallstone formation by causing altered gallbladder mucosal function or gallbladder motility. Further studies in large samples to shed light on this hypothesis are needed. In conclusion Cholelithiasis tends to occur more frequently in patients with hepatitis B virus infection. There is a strong association between HBV infection and gallstones. So, HBV infection is definitely a risk factor for gallstone disease.

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