Research Article **ISSN: 2393 – 9532**

International Journal of Arts and Science Research

Journal home page: www.ijasrjournal.com

https://doi.org/10.36673/IJASR.2020.v07.i01.A03

SERUM HBEAG AND HBV DNA MARKER LEVELS IN PATIENTS WITH CHRONIC HEPATITIS B INFECTION IN SANA'A CITY - YEMEN

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ABSTRACT

Hepatitis B virus (HBV) infection is one of the most worldwide health problems in the world, including Yemen. So, this study has been designed to explore the correlations between HBV DNA levels with biochemical and serological markers in patients during different stages of chronic hepatitis B to assess the infectivity of virus, during the period of study was from September 2016 to June 2017. A total of 108 serum samples of chronic hepatitis B patients who not treated with any antiviral drugs were analyzed by biochemical, serological and molecular assays. The age of CHB patients ranged between 8 and 72 years included males and females, with detectable hepatitis B surface antigen (HBsAg) and anti-core IgG antibody (anti-HBcAb IgG) in serum at the time of study. The hepatitis B virus markers of these patients were determined and expressed as geometric mean ± SD, (41.78 ± 46.77), (35 ± 43.5) IU/ml for ALT and AST respectively, while the mean ± SD for hepatitis B e antigen (HBeAg) was (50.5 ±0.68) *s/*co and the mean ± SD for HBV DNA viral load was (13037710.44±39003202.39) IU/ml. 34(31.5%) abnormal for ALT and 22(20.4%) abnormal for AST. Also, the distribution of HBV DNA viral load were 36 (33.3%) had HBV DNA viral load more than or equal to 2000 IU/ml while 72(66.7%) had HBV DNA viral load less than 2000 IU/ ml. High HBV DNA viral load (≥ 2000 IU/ml) found with 18(52.9%) abnormal ALT and 14(63.6%) abnormal AST levels while low HBV DNA viral load (< 2000 IU/ml) found in 16 (47.1 %) abnormal ALT and 8(36.4%) abnormal AST levels. The increase of ALT and AST levels in patients with high HBV DNA viral load was significantly higher than that in patients with low HBV DNA viral load, so there were significant correlations between levels of HBV DNA viral load and biochemical marker levels [ALT and AST ($p < 0.05$)]. Out of (108) CHB patients 17(15.7%). HBeAg positive and 91(84.3%) HBeAg negative. High HBV DNA viral load founded in all17 (100%) HBeAg positive patients. Out a total of (91) HBeAg negative patients, 19(20.9%) patients had high HBV DNA viral load, while 72(79.1%) had low HBV DNA viral load. The levels of HBV DNA viral load in HBeAg positive patients were significantly higher than those in HBeAg negative patients ($P < 0.05$), so there were significant correlation between levels of HBV DNA viral load and HBeAg marker ($P < 0.05$).

KEYWORDS

HBeAg positive, Chronic hepatitis B and HBV DNA levels.

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INTRODUCTION

Human hepatitis B virus (HBV) is a type of the hepadnavirus which is spread by contact with infected blood, body fluids and causes acute and chronic necro inflammatory liver diseases[1]. Globally, more than two billion people are estimated to have

been infected with HBV, about 240-400 million have chronic HBV infection. Approximately 600000 to 1 million people die every year from its consequences[2].

Chronic HBV infection is often asymptomatic and diagnosed late unless with risk individuals for this infection. These complications of chronic liver failure or HCC develop, they are often fatal[2,3]. The combination of viral, environmental and host genetic factors contribute to the heterogeneous outcome of CHB infection. Annually HBsAg seroclearance rate was reported between 0.1 and 2.3% depending on the endemicity of the area for HBV infection, mean age of participants, years of follow up and serum levels of HBV DNA and HBsAg[4].

The detection of HBV DNA in most hospitals is still only performed on a limited basis, due to its expensive cost. In contrast, detection of HBeAg and ALT is relatively simple and affordable. Therefore, when polymerase chain reaction (PCR) is not available to carry out HBV DNA quantitative detection and follow up CHB patients, assessing HBeAg together with serum ALT levels may be sufficient to describe HBV activity and infectiousness[5]. The understanding of the pathogenesis and natural history of CHB have been evolved due to improved sensitivity of HBV DNA viral load assays and recently, sensitive and reliable assays have been also developed to quantify both serum HBsAg and HBeAg[6]. In this cross-sectional study, we aimed to explore the correlations between HBV DNA levels with age, sex, biochemical markers (ALT and AST) and HBeAg status in patients from Sana'a city of Yemen with chronic HBV infection.

MATERIAL AND METHODS

Study Design

In this cross sectional study was based on collection of samples from 108 of patients (82 males, 26 females) with chronic hepatitis B virus attending the Gastroenterology and Hepatology Clinic at University of Science and Technology Hospital in Sana'a city between September 2016 to June 2017.

In our study, all patients had a positive hepatitis B surface antigen in their serum for more than six months and patients were excluded at screening if they had been taken interferon or antiviral; were co-infected with hepatitis C, hepatitis D (HDV) or human immunodeficiency virus (HIV), Cirrhosis or hepatocellular carcinoma and autoimmune hepatitis.

Biochemical Tests; Alanine Aminotransferase (ALT) and Aspartate Aminotransferase Levels

The biochemical test (ALT and AST) levels were performed using the Roche/Hitachi Cobas 6000 analyzer series (the Cobas c 501 analyzer, Roche Diagnostics, Hitachi, Japan) with cutoff value 40 U/L for ALT and 35 U/L for AST[7].

Serological markers

Separated serum was tested in Cobas e 411 analyzer (Roche Diagnostic GmbH, Mannheim, Germany) with electrochemiluminescence immunoassay (ECLIA) technique for detecting of HBsAg, HBeAg and anti-HBc IgG among patients with CHB infection according to manufacture's instruction.

Serum HBV DNA Levels by using Real-time PCR

Quantitative assessment for serum HBV DNA levels were detected based on level: high $\geq$ 2000 IU/mL and low < 2000 IU/mL (1IU/mL≈5,82 copies/mL) by the Cobas Amplicor HBV Monitor test (real-time Polymerase Chain Reaction, Roche Diagnostic Systems, COBAS® Ampli Prep® HBV Test, COBAS® Taq Man® 48).

The lower limit of detection was 4.63 IU/mL and the upper limits of detection was 220000000.0IU/mL[8,9].

Statistical Analyses

The data were analyzed using a statistical package of social science program (SPSS, version 21) and the results was presented as percentages, mean, stander division and tabulation. Chi-square X^2 test was used for categorical variables. A P value of <0.05 were considered statistically significant. Continuous variables are presented as mean ± standard deviation (SD).

RESULTS

PATIENT CHARACTERISTICS

A total of 108 chronic hepatitis B patients were examined. The age of patients ranged between 8 and 72 years old with mean ± SD (38.21±14.16). There were 82 males and 26 female patients in this study. The clinical, virological, biochemical data of the 108

chronic hepatitis B patients were shown in Table No.1.

Biochemical tests

The mean levels of ALT and AST were 41.78 ± 46.77 U/L (range 7 to 410 U/L), and 35.0±43.5U/L (range 10 to 342 U/L), respectively. Normal ALT (≤40 U/L) and AST (≤35 IU/L) levels were detected in 68.5% and 79.6% of the patients, respectively.

HBeAg status

All patients were anti-HBc IgG and HBsAg positive in this study. However, 17(15.7%) patients were HBeAg positive and 91(84.3%) patients were HBeAg negative.

Serum HBV DNA levels

The mean ± SD level of HBV DNA was 13037710.44 ± 39003202.39.4 IU/mL (range from 4.63 to 2.2×10^8 IU/mL). In our study, 36 patients (33.3 %) had HBV DNA level more than or equal to 2000 IU/mL while 72 patients (66.7%) had HBV DNA level less than 2000 IU/mL. The clinical, biochemical and virological data HBeAg Serostatus patients was shown in Table No.2.

Relationship of HBV DNA viral load with age, gender and biochemical markers (ALT and AST)

There were no statistical relationship between HBV DNA viral load and age and gender ($p > 0.05$). High HBV DNA viral load with abnormal ALT counted 18(52.9%) while high HBV DNA viral load with abnormal AST counted 14(63.6%). In low HBV DNA viral load, the number of patients with abnormal ALT was 16(47.1%) while the number of patients with abnormal AST counted 8(36.4%). Thus, there was high statistically significant association between ALT, AST and HBV DNA viral load which ($P < 0.05$).

Relationship of HBeAg status with ages, genders, ALT and AST

There was no significant difference in age groups and gender ($p \geq 0.05$). HBeAg Positive with abnormal ALT counted 10(29.4%) while abnormal AST counted 8 (36.4%). In HBeAg negative, the number of patients with abnormal ALT was 24(70.6%) while the number of patients with abnormal AST counted 14(63.6%). There were high statistically significant association between ALT and AST with HBeAg ($p < 0.05$).

Relationship of HBV DNA level with HBeAg status in CHB patients

The relationship between serum hepatitis B virus DNA viral load and the HBeAg serological status in CHB patients was studied. High HBV DNA viral load with HBeAg positive counted 17(100%) while high HBV DNA viral load with HBeAg negative counted 19(20.9%). There was no HBeAg positive patients with low HBV DNA viral load, while the number of HBeAg negative patients with low HBV DNA viral load were counted 72(79.1%). So, there were high statistically significant relationship between HBeAg and levels of HBV DNA viral load ($P < 0.05$).

DISCUSSION

Hepatitis B infection remain a major health problem having important effect on morbidity and mortality in Yemen. The chronic HBV infection can characteristically start with presence of HBsAg for more than 6 months[10], positive or negative HBeAg and infectivity with HBV DNA level, this infection may also develop and remain for months or years. The prevent progression to end-stage liver disease, cirrhosis and hepatocellular carcinoma remain the purpose for treatment of chronic hepatitis B[11]. Due to the high risk for HBV-related HCC, the Gastroenterology Society of Australia recommends that CHB patients with HBV DNA levels > 2000 IU/mL should receive treatment regardless of age[12].

The age at acquiring of HBV has a large impact factor effect on the likelihood of the disease becoming chronic. In our study, the mean age of patients was 38.21 years. Similar reported by Kirisci *et al.* Who reported that 173 patients with the mean age was 39.39 years[13]. In separate study by Demir *et al.* Reported the mean age of 456 patients was 36.7 years and Yalcin *et al.* were found that the mean age of 179 patients were 26.9 years[14,15]. According to previous studies, the most of patients were in the middle of their lives which manifested that HBV infection is an important health problem[16]. Our finding showed that HBV infection higher more in males than females. This may be related to the fact that males in Yemen are more socially active than female. Furthermore, they are more exposed to male

related risk factors for HBV than female (e.g. hairdressing and circumcision). This result is in agreement with other studies in general populations[17-19].

Monitoring of ALT levels is used to assess hepatocellular damage in patients with chronic hepatitis B virus infection[20]. Our finding showed that 31.5% of the patients were abnormal for ALT levels while 20.4% of the patients were abnormal for AST levels. This result matched with the observation of Bonacini *et al*. Who reported that the levels of abnormality ALT were consistently higher than AST with chronic hepatitis infection[21]. Also, our result was in closed to Myers *et al*. Who reported that serum ALT levels were constantly above the normal in 42.6% of the CHB patients[22]. These result were disagreement with Olut *et al*. Who found that 11% showed ALT above the normal levels[23]. Our results found that abnormal ALT and AST levels were higher among male patients compared to female, 30/82 (36.6%) vs 4/26 (15.3%) for ALT and 18/82 (21.9%) vs 4/26 (15.3%) for AST respectively with statistical significance ($p < 0.05$). This findings were agreement with another study by Kirisci *et al*[13]. This observation may be related to the male predominance in the development of chronic liver disease during chronic HBV infection. The mechanism of this male predominance is unknown[24].

Chronic infection may present either as HBeAg positive or negative form[9]. The presence of HBeAg in serum correlates with the presence of viral replication in the liver and the virus is highly infectious[25]. HBeAg positive infections are considered to be at higher risk for HCC development[26].

In our study, the prevalence of HBeAg was 15.7% among patients who were positive for HBsAg. These results were close to others of previous studies 10.5% by Lahiri *et al* and 18.5% by Chen *et al*[5,27], and much lower prevalence than that reported in a previous studies 35.6% by Babamahmoodi *et al* and 39 % by Yang *et al*[26,28]. This findings showed that the prevalence of CHB cases increases in HBeAg negative and decreases in HBeAg positive which may be due to several factors including the awareness of HBeAg negative CHB, decrease in new HBV infection, aging of existing carries, vaccination, mutations in the pre C region of the virus, and/or improved sensitivity of the detection method[5]. In our result, HBeAg negative patients were older and had a longer HBV infection duration than HBeAg positive patients. These results agreement with earlier studied by Sharma *et al* and Shao *et al*, who reported that HBV infection usually occurs at birth or during early childhood. The longer the HBV infection is, the more spontaneous immune clearance due to HBeAg sero conversion and HBV replication inhibition[29,30].

Our results showed that HBV DNA viral load is varied widely in patients with chronic hepatitis, the lowest value was of 4.63 IU/ml only, but the highest value up to 2.2×10^8 IU/ml. This finding possibly explained that HBV isolates have different genetic subtypes, viral mutation and different immune ability to HBV. Also, the distribution of HBV DNA viral load was found not significantly related in age groups which was agree with Yap *et al*. Study and differ with study by Sha *et al*[31,32]. Also, the distribution of HBV DNA viral load levels were found to be not significantly related in gender group which were agreement with another studies by Demir *et al* and Kirisci *et al*[14,13] and disagreement with Sha *et al*[32].

Data of this study, found statistical significance of correlation between HBeAg value and HBV DNA levels and this correlation appeared to be tighter at the highest HBeAg levels. Our results suggested that a high HBeAg level effectively indicates the relative HBV DNA level. These results agreement with others previous study Kirisci *et al* and disagreement from other study by Kaya *et al* and a clinical utility of these findings is that we can use high HBeAg levels to estimate corresponding HBVDNA levels without qPCR detection of HBV DNA. This is particularly useful in the setting of rural hospitals where quantitative analysis of HBV DNA levels cannot be performed[13,16].

Our results showed that the HBV DNA viral load in HBeAg positive serum was significantly higher than that in HBeAg negative serum ($P < 0.01$) and the HBeAg value was significantly higher in serum of high HBV DNA viral load than in serum of low

HBV DNA viral load. Our finding was agree with different studies by Inci *et al*, Sha *et al* and Chen *et al*[32-34]. But disagree with other studies by Kaya *et al* and Ali. Who reported that HBeAg value were not related to HBV DNA viral load[7,16]. These results suggested the reliability of HBV DNA and HBeAg in indicating virus replication levels. In our study, high HBV DNA viral load showed in 19(20.9%) HBeAg negative patients, indicating that there is still active HBV replication in HBeAg negative patients. Our finding was agree with several study by Chu *et al*. Who demonstrated that these may be due to the mutation of the Pre C and C gene that prohibits the synthesis and secretion of HBeAg or decrease HBeAg production and quick HBV replication[35]. Additionally, there were no significant differences in age group, gender, but there were significant differences in ALT and AST levels between HBeAg positive and negative patients. Our finding was agree with Shao *et al*. Who found that there were a significant correlation with ages, but there were no significant correlation in gender, ALT and AST levels between positive and negative HBeAg patients[30].

Our results showed that the HBV DNA viral load in HBeAg positive serum was significantly higher than that in HBeAg negative serum (P< 0.01) and the HBeAg value was significantly higher in serum of high HBV DNA viral load than in serum of low HBV DNA viral load. Our finding was agree with different studies by Sha *et al* and Chen *et al*[32,34]. But disagree with other studies by Ali and Chun *et al*. Who reported that HBeAg value were not related to HBV DNA viral load[7,36]. These results suggested the reliability of HBV DNA and HBeAg in indicating virus replication levels. In our study, high HBV DNA viral load showed in 19(20.9%) HBeAg negative patients, indicating that there is still active HBV replication in HBeAg negative patients. Our finding was agree with several studies by Chu *et al* and Gemer *et al*. Who demonstrated that these may be due to the mutation of the Pre C and C gene that prohibits the synthesis and secretion of HBeAg or decrease HBeAg production and quick HBV replication[35,37]. Additionally, there were no significant differences in age group, gender, but there were significant differences in ALT and AST levels between HBeAg positive and negative patients. Our finding was agree with Shao *et al*. Who found that there were a significant correlation with ages, but there were no significant correlation in gender, ALT and AST levels between positive and negative HBeAg patients[30].

In our study, HBeAg negative and HBeAg positive patients, HBV DNA viral load in the elevated ALT patients was significantly lower than that of patients with normal ALT, the correlation of HBV DNA viral load to ALT levels were significant. Although the HBV DNA viral loads of HBeAg positive patients were significantly higher than those of HBeAg negative patients, their ALT values were not different. These discrepancy may be attributable to the mutation of the pre C or C gene that may lower HBeAg production but produce C antigen. With a high HBV DNA viral load, the production of C protein is enhanced. The loss of HBeAg is possibly associated with lower immune tolerance to HBV antigens, thus causing a stronger immune response or inflammatory activities of the liver[38].

The distribution of HBVDNA viral load was found significantly related in ALT and AST ($p < 0.05$) and HBeAg group ($p < 0.05$). These study agreement with Ali, Kirisci *et al* and Sha *et al*[7,13,30]. And disagreement with Tulin *et al* and Eren *et al*. That showed there were not any correlation between ALT and serum HBV DNA levels, reinforcing the fact that viral load doesn't have any impact on disease severity[19,39]. Also, our study was agree with Chen *et al* and Babamahmoodi *et al* for no correlation between HBV DNA level and AST enzyme while there was a significant relationship between HBV DNA level and ALT enzyme[28,40].

In our study, there were 91 patients with HBeAg negative chronic hepatitis B. Of these patients, 19 patients had serum HBV DNA levels > 2000 IU/mL, elevated serum ALT levels and 72 patients had serum HBV DNA levels ≤ 2000 IU/mL, normal serum ALT levels. In the current study, the results showed that serum ALT level was not correlated with the HBV DNA level in HBeAg negative inactive carriers patients. These findings were agreement with Kim *et al*. But disagreement with

study by Lin *et al*[41,42]. These disagreement might be due to the use of different determinant for inactive carriers which was in our study defined the ULN of the HBV DNA levels range <2000 IU/ml for an inactive carrier while the previous study enrolled patients with HBeAg negative and persistent normal ALT levels regardless of their HBVDNA levels.

Table No.1: Patients characteristics, serological and biochemical data for chronic hepatitis B patients

S.No		HBV DNA ≥ 2000IU/mL	HBV DNA < 2000IU/mL	χ2	p-value
1	Age ± SD	37.53 ±16.8	38.56±12.76	3.52	0.317
2	Gender, no (%)				
3	Male	30 (36.6)	52 (63.4)	1.62	0.203
4	Female	6 (23.1)	20 (76.9)		
5	ALT, ±SD, IU/L	59.06±68.72	33.15±27.24		
6	≤40	18 (24.3%)	56 (75.7%)	8.58	0.003
7	>41	18 (52.9%)	16 (47.1%)		
8	AST±SD, IU/L	54.19±70.12	25.53±12.34		
9	≤35	22 (25.6%)	64 (74.4%)	11.41	0.001
10	>36	14 (63.6%)	8 (36.4%)		
11	HBeAg				
12	Positive	17 (100%)	0 (0.0%)	40.35	0.001
13	Negative	19 (20.9%)	72 (79.1%)		

Table No.2: HBeAg serostatus patients distribution with demographic, biochemical test and virological data

S.No		HBeAg Positive	HBeAg Negative	χ2	P- value
1	Age ± SD	30.53±15.24	39.65 ± 13.57	6.54	0.077
2	Gender				
3	Male	14(17.1)	68(82.9)	0.456	0.500
4	Female	3(11.5)	23(88.5)		
5	ALT ± SD, U/L	57.52 ± 36.89	38.84 ± 47.99	6.7	0.008
6	AST ± SD, U/L	53.94 ± 58.65	31.5 ± 39.50	8.85	0.003
7	HBV DNA U/mL	65063637.7 ± 59327525.0	3318581.17±24001805.41	40.35	0.001

CONCLUSION

To conclude, our study showed that low levels of HBeAg and HBV DNA viral load were more than high levels which indicated low viral infectivity. The low levels of HBeAg and HBV DNA viral load were more than high levels which indicated low viral infectivity. There was high correlation between HBV DNA level and HBeAg positive patients, also high relationship between HBV DNA level and HBeAg with serum biochemical levels (ALT, AST). HBeAg, HBV DNA and ALT could jointly contribute to the comprehensive evaluation of viral replication and host reaction. Finally, HBV DNA PCR- based tests can serve as an important supplementary tool in a number of clinical settings, especially in detecting low levels of viraemia in non- replicative HBV disease and also in patients with past HBV infection.

ACKNOWLEDGEMENT

The authors wish to express their sincere gratitude to Biology -Microbiology Department, Faculty of Science, Sana'a University, Yemen for providing necessary facilities to carry out this research work.

CONFLICT OF INTEREST

There is no conflict of interests regarding the publication of this paper.

FUNDING

This study was fully self-funded, no fund was received by any donor agent.

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Please cite this article in press as: Al-Huthaifi A M *et al.* Serum HBEAG and HBV DNA marker levels in patients with chronic Hepatitis B infection in Sana'a City - Yemen, *International Journal of Arts and Science Research,* 7(1), 2020, 20-28.