



# Hepatitis B Surface Antigen and DNA Quantification among e Negative Chronic HBV Infected Patients in Two Nigerian Hospitals

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## Abstract

**Introduction & aim:** Hepatitis B is a public health problem, responsible for about 6000 deaths annually. HBV DNA and HBsAg quantification have implication for chronicity, response to treatment, frequency of long-term complications and chances of cure. This study aimed to describe the pattern of quantitative hepatitis B surface antigen and DNA quantification among patients with e negative chronic hepatitis B infection.

**Materials & method:** One Hundred and Twenty-One asymptomatic, treatment naïve, e negative chronic hepatitis B infection patients were recruited. HBsAg and HBV DNA quantification and anti HBe were done on their sera.

**Results:** Of the 121 Subjects recruited, 75 (62%) were males while 46 (38%) were females with ages ranging from 18 to 68 years. Twelve (10%) patients were negative for anti HBe while 109 (90%) were positive for it. The HBsAg quantification ranged from 0.25 to 52,000 IU/ml with a median of 5289IU/ML and mean  $3.33 \pm 1.32 \log_{10}$  UI/ml. Ninety-Three (77%) patients had their HBsAg quantification  $\geq 1000$  IU/ml. HBV DNA quantification ranged from 15 to 26,000 UI/ml with a median of 560 UI/ml and mean  $2.67 \pm 1.24 \log_{10}$  UI/ml. Ninety-Two (76%) patients had HBV DNA  $< 2000$  UI/ml. There was no correlation between HBsAg and HBVDNA quantification ( $\rho = 0.13$ ,  $p = 0.13$ ).

**Conclusion:** Quantitative HBsAg level are high among Nigerian patients with e negative chronic HBV infection despite low HBV DNA count. There was no correlation between HBsAg and HBV DNA quantification.

**Keywords:** Chronic Hepatitis B; Hepatitis B surface antigen quantification; HBV DNA quantification; Correlation; Nigeria

## Introduction

Chronic hepatitis B infection is a public health problem with about 240 million people affected worldwide [1]. The infection is most common in Africa with a prevalence of 8.83% [1]. The pool prevalence of HBV infection in Nigeria is 13.6% [2], and is the most common cause of chronic liver disease in the country [3,4].

Chronic Hepatitis B infection is responsible for about 600,000 deaths annually [5]. Majority of this mortality is attributable to liver cirrhosis and or hepatocellular carcinoma, which are the most important long-term complications of HBV infection [6]. However, not all patients with chronic hepatitis B infected patients will develop these complications. The main challenge for Clinicians is to identify those patients that are likely to develop these long-term complications and recommend the appropriate treatment. Major international and local guidelines suggested the use of serum HBV DNA quantification and serum

alanine transferase (ALT) as markers to select patients with active chronic hepatitis B infection [7-10]. European Association for the Study of the Liver (EASL) and Asian Pacific Association for the study of the liver (APASL) guidelines recommended HBVDNA quantification greater than or equal to 2000IU/ml and raised serum alanine transaminase as criteria for active chronic hepatitis B infection which should be treated. However, serum level of both HBVDNA and alanine transaminase fluctuate [10]. Apart from this, long term complications have been observed even in patients with either HBV DNA level less than 2000 UI/ml and or normal serum alanine transaminase [11]. Therefore, HBsAg quantification (qHBsAg), HB core related antigen (HBcrAg) and HBV RNA among others, have been suggested as additional markers that could predict more precisely, patients with active infection who are likely to have long term complications [12].

There is a renewed interest in the quantitative HBsAg (qHBsAg) assay as a marker of hepatitis B viral activities in the last ten years [13]. It is said to correlate well with covalently closed circular (ccc) DNA and intra hepatic DNA which are responsible for the perpetuation of the virus in the body [14,15]. In addition, it is said to separate inactive carriers from active disease, predicts the possibility of spontaneous sero conversion and response of patients to Pegylated interferon [13]. The three commercially available automated assays for quantification of HBsAg level detect all forms of HBsAg and are comparable [16,17].

There is however paucity of data on the pattern of quantitative hepatitis B surface antigenaemia and its correlation with the viral load in sub-Saharan Africa.

The aim of this study was to describe the pattern of Hepatitis

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B surface antigen and DNA quantification among patients with e negative chronic hepatitis B virus infection attending two hospitals in south west Nigeria and determine if any, correlation between the two.

## Materials & Methods

This was a cross sectional study done among patients attending Sacred Heart Hospital Abeokuta, Ogun State and University College Hospital, Ibadan, Oyo state. Sacred Heart Hospital is a 300-bedded mission owned hospital that has been in existence for more than 120 years. It provides primary and secondary levels of care to people of Ogun state and its neighbouring states of Lagos, Oyo and Ondo. The University College Hospital is a 900-bedded premier teaching hospital in Nigeria founded about 60 years ago. It provides specialist care in various medical fields to the western region and the whole country in general. The study was carried out between January 2016 and August, 2017. Chronic hepatitis B was defined as being hepatitis B positive for at least six months and/ or Positive HBsAg with negative IgM antibody to the core antigen (anti HBe). Only patients who were at least 18 years old, treatment naïve and asymptomatic as evidenced from history, examination and abdominal ultrasound were recruited for the study. All the patients that met the inclusion criteria and consented to the study during the study period were recruited. Ethical approvals were obtained from the ethics committees of both hospitals. Informed consent was taken from all the patients and the study was done according to Helsinki declaration amended by the 64<sup>th</sup> World Medical Association general assembly, Fortaleza, Brazil, 2013 [18]. Five milliliters of blood were taken from each patient and the serum were stored in -80°C until analysis. HBsAg quantification was done using COBAS E 411 from Roche diagnostics and uses chemiluminescence method with lowest detectable level of 0.25 IU/ml and maximum of 13,000 IU/ml. Serial dilutions were done on the samples of patients with values greater than 13,000 IU/ml until the final value was arrived at. HBV DNA quantification was done with using CAPCTM ETAQMAN 48 from Roche diagnostics that uses real time PCR method with lowest detectable limit of 15 IU/ml. Anti HBe was done using LumiQuick<sup>®</sup> Diagnostics (California, USA) immunochromatography test kits with accuracy of 99.6%.

The analysis was done using Statistical Package for Social Sciences version 20. HBsAg quantification and HBV DNA quantification were divided in to two categories with cut offs of 999 IU/ml and 1999 IU respectively [19]. Chi square, students' T test and spearman's correlation were used to test for associations as appropriate. P value less than 0.05 was considered significant.

## Results

One hundred and twenty-one patients were recruited for this study which comprised of 75 (62%) males and 46 (38%) females. Their ages ranged from 18 to 68 with a mean of 36.6 ± 9.7 years. Twelve (10%) patients were negative for antibodies to hepatitis e antigen while 109 (90%) were positive. HBsAg quantification ranged from 0.25 to 52,000 IU/ml with a median of 5289 IU/ml. The log 10 of the HBsAg quantification ranged from -0.60 to 4.72 IU/ml mean 3.33 ± 1.32 IU/ml, median 3.72 log 10 IU/ml.

The HBsAg quantification was more than or equal to 1000 IU/ml (high) in 93 (77%) while it was less than 1000 IU/ml (low) in 28 (23%) patients. There was no significant relationship between sex (p=0.46), anti HBe (0.11) and the value of quantitative hepatitis B surface antigen. There was a negative correlation between the age of the patients and the value of HBsAg quantification and this was significant (rho= -0.2, p=0.01).

HBV DNA quantification ranged from 15 to 26,000,000 with a median of 560 IU/ml. The log 10 of the HBV DNA ranged from 1.18 to 7.41 with a mean of 2.67 ± 1.24, median 2.74 log 10 IU/ml) Ninety-Two (76%) of the patients had HBV DNA quantification that were less than 2000 IU/ml (low) while 29 (24%) had HBV DNA quantification levels that were equal or more than 2000 IU/ml (high).

There was no significant relationship between sex and the value of the HBV DNA quantification (p= 0.512). However, there was a significant inverse relationship between anti HBe and the HBV DNA level (rho= - .14, p= 0.02). There was also a significant inverse correlation between the age of the patients and the HBV DNA quantification (rho=-0.223 p=0.014).

Only 20 (16%) patients had HbsAg quantification that was less than 1000 IU/ml and HBV DNA quantification that was less than 2000 IU/ml. Seventy-Two patients (60%) patients had HbsAg quantification that was equal to or more than 1000 IU/ml though their HBV DNA quantification were more less 2000 IU/ml (Table 1). There was no statistically significant correlation between HbsAg quantification and HBV DNA quantification among the patients) (rho=0.136, P= 0.136).

## Discussion

Hepatitis B surface antigen is a vital viral protein that is secreted into the patient blood and its quantification is an important marker both for the evaluation for possible treatment and prediction of response to treatment [20]. The median of 5,289 IU/ml of the surface antigen quantification in this study is slightly higher than 4,672 IU/ml reported among the Senegalese with chronic hepatitis B [21]. The difference may be because the Senegalese study included only patients with normal ALT while our subjects were recruited irrespective of their serum ALT. The mean of 3.33 log 10 IU/ml for surface antigen quantification in this study was lower than 3.82 log 10 IU/ml among Ivorian patients with chronic hepatitis B and HIV infections [22]. The HIV infection in that cohort could explain the difference. Hepatitis B tends to be more severe in HIV co- infected patients compare to HBV mono infected cohort [23]. Twenty two percent (28 patients) had HBsAg quantification that was less than 1000 IU/ml, which

**Table 1:** Cross tabulation of HBsAg quantification and HBV DNA levels using cut off points of 1000 IU/ml and 2000 IU/ml respectively.

		HBV DNA quantification (UI/ml)		Total
		< 2000	≥ 2000	
HBsAg quantification (UI/ml)	< 1000	20	8	28
	≥ 1000	72	21	93
	Total	92	29	121



is lower than 14.9% reported in a study among the Chinese [24]. However, in another study among asymptomatic, treatment naïve Chinese patients with chronic hepatitis B, only 12.7 % of their patients had quantitative surface antigenemia that was more than or equal to 1000 IU/ml [25]. These variations in the levels of the surface antigens may be due to the different phases of the chronic hepatitis B in the patients, the genotypes of the virus and the presence of amino acids substitution in the hepatitis B viral proteins, promoter basal core or pre-core mutations [20,26,27]. Hepatitis B surface antigen quantification of less than 1000 IU/ml is used to identify inactive patients especially when the HBV DNA is less than 2000 IU/ml [28]. Titer of HBsAg quantification less than 100 IU/ml among those with HBV DNA less than 2000 IU/ml was found to accurately identify inactive carriers better and predict subsequent loss of HBsAg [29]. The suggestion of 100 IU/ml may be more reliable because the study involved repeated measurement of the surface antigen quantification rather than a single measurement as it was the case of the study that suggested 1000 IU/ml. Ninety four percent of our patients with HBV DNA quantification less than 2000 IU/ml had HBsAg quantification that was more than 100 IU/ml. This may mean that majority of our patients with chronic hepatitis B in Nigerian have active diseases and that functional cure may not be achievable. A study however suggested that different sub- proteins of the hepatitis B surface antigen rather than the total q HBsAg is more important in this prediction [30].

The negative correlation between age and the level of the HBsAg is similar to the findings by Kim et al. [26], and Jang et., among the Koreans [31]. This is not surprising as HBsAg quantification tends to be higher in immune tolerance phase which is typically found among relatively younger people than immune reactive and reactivation phases whose subjects tend to be older [31].

HBV DNA quantification has been designated the most important marker that determines the risk of a patient having chronic complications of hepatitis B later in life (32). The range of the log DNA value from 1.18 to 7.41 in this study is similar to 2.5 to 5.4 among the Senegalese patients [33]. That same study reported high prevalence of pre-core mutation among their Senegalese patients and this might be the reason for the low viremia in them. No study to the best of our knowledge, has investigated the presence and prevalence of pre-core mutations in our population of patients. The mean of 2.7 log<sub>10</sub> IU/ml in this study is similar to the mean of 2.7 log<sub>10</sub> IU/ml and 2.6 log<sub>10</sub> IU/ml found among the Senegalese patients with chronic hepatitis B [21]. It is also similar to that reported by a French study with multi-national patients with chronic hepatitis B [34]. Ninety-Two (76%) of the patients in this study had HBV DNA less than 2000 IU/ml and this is similar to 74% reported among patients in Burundi [35]. Akere et al, in a study in Ibadan reported 46% of their patients having HBV DNA quantification that was less than 2000 IU/ml [36]. About 18% of the patients studied by Akere et al., were HBeAg positive while this present study was among HBeAg negative patients only. HBV DNA quantification tend to be higher among patients who are HBeAg positive than those who are HBeAg negative [37]. A Taiwanese study reported that 50.5% of their

patients had HBV DNA quantification that was more than 2000 IU/ml [38]. Apart from the likely different genotypes of the HBV in the two populations studied, the Taiwanese study comprised of relatively older people with non-hepatic malignancies which are known cause of immunosuppression. The predominate genotype of hepatitis B in Nigeria and indeed west Africa is E [37,39]. The fact that the hepatitis B viral load is low does not necessarily mean that the infection is inactive. In an Egyptian study, 26% of the patients with HBV DNA quantification level less than 2000 IU/ml were found to have significant fibrosis on liver biopsy [40]. Interestingly, 78% of the patients in our study with hepatitis B viral load less than 2000 IU/ml had quantitative surface antigen quantification that was more than 1000 IU/ml. Jen chen et al., in a review of the REAVEL-HBV study submitted that long term maximal and consistent suppression of the HBV DNA level is desirable rather than an arbitrary level of HBV DNA level [41]. One cannot agree with him less knowing fully well that serum HBV DNA levels fluctuate [21].

This study found no correlation between HBV DNA level and HBsAg quantification among the patients. This shows that transcriptional activity might be different from viral replication in patients with HBeAg negative chronic hepatitis B. A UK study done among patients of West African extraction did not find any correlation between HBV DNA and HBsAg quantification among HBeAg negative patients [42]. There was however a correlation between HBV DNA quantification and HBsAg quantification reported in Taiwanese [15,43], and French studies [34], although their subjects were mixture of both HBeAg positive and HBeAg negative patients. Some studies have found a good correlation between HBsAg quantification and HBV DNA viral quantification among HBeAg positive patients [44].

This study showed a weak negative correlation between HBV DNA quantification and age though it didn't attain statistical significance. This is reasonable as the viral load tend to decrease from the immunetolerance to immune reactive to reactivation phase. Alams et al., reported less HBV DNA levels among patients that were older than 40 years compared to those that were less than 40 years.

Although hepatitis B is said to be commoner and run a more aggressive course in males, there was no relationship between sex and HBV level in this study. Perhaps other factors other than HBV DNA levels are responsible for the more aggressive course of HBV infection in males.

## Conclusion

A larger percentage of patients with chronic hepatic B infection and e negative antigenemia in south west Nigeria have low viremia and high qHBsAg quantification. There is no correlation between HBV DNA quantification and quantitative surface antigenemia. This might mean higher tendency to having long term complications despite relatively low viremia. It may be beneficial to reduce the threshold of treatment in e negative HBV patients when the surface antigen quantification is high despite low viremia.

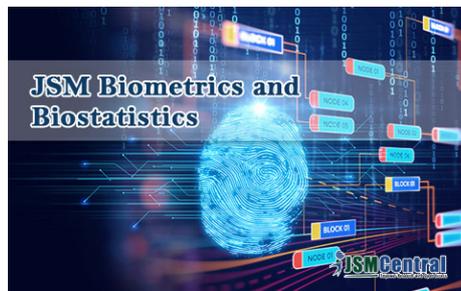
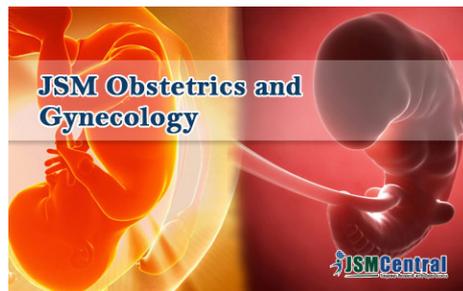
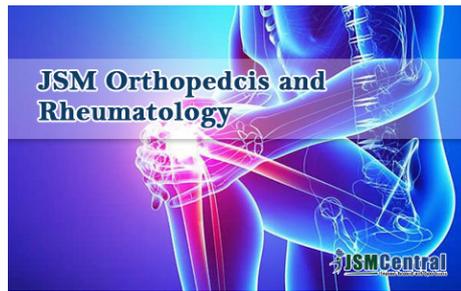


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