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Original Article **Open Access**

Evaluation of α-fetoprotein and selected inflammatory enzyme markers in chronic hepatitis B patients seropositive and seronegative for hepatitis B envelope antibody in UITH, Ilorin, Nigeria

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Abstract:

Background: Hepatitis B virus (HBV) can cause both acute and chronic hepatitis and is a leading contributor to hepatic cirrhosis and hepatocellular carcinoma (HCC), imposing a substantial burden on healthcare systems due to its high morbidity, mortality, and treatment costs. HBV infection remains a major public health concern, particularly in sub-Saharan Africa. Investigating the serum levels of alpha-fetoprotein (AFP) and selected inflammatory markers in individuals seropositive for hepatitis B envelope antibody (HBeAb) provides valuable insights into disease progression, early detection of HCC, and monitoring treatment efficacy. This study assessed serum levels of AFP and selected inflammatory markers such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), total protein, albumin, and globulin among chronic HBV patients seropositive and seronegative for HBeAb at the University of Ilorin Teaching Hospital (UITH), Ilorin, Nigeria.
Methodology: A comparative cross-sectional study was conducted among 70 chronic HBV patients at UITH, Ilorin, Nigeria, including 30 patients seropositive and 40 patients seronegative for HBeAb. Sociodemographic information of the patients was collected using a designed form. Serum levels of AFP, ALT, AST, total protein, albumin, and globulin were determined using ELISA and spectrophotometry. Data were analyzed using the Mann-Whitney U test and Spearman's correlation, with $p \leq 0.05$ considered statistically significant.
Results: Serum AST and ALT levels were significantly lower in patients seropositive for HBeAb (17.43±33.90 IU/L and 11.13±10.95 IU/L) than patients seronegative for HBeAb (34.90±22.95 IU/L and 23.00±8.68 IU/L; $p=0.040$ and $p=0.000$ respectively). AFP level was also significantly lower in patients seropositive (17.59± 44.32 ng/mL) compared to patients seronegative (44.31±14.80ng/mL) for HBeAb ($p=0.003$). Serum total protein and globulin were significantly higher in patients seropositive for HBeAb (75.97±11.89g/L and 29.70 ±4.17g/L; $p=0.001$ and $p=0.000$ respectively). Serum albumin was higher in patients seropositive for HBeAb (46.33±9.54 g/L), but this was not statistically significant from patients seronegative (41.95 ±7.80g/L) for HBeAb ($p=0.081$).
Conclusion: HBeAb seroconversion is associated with improved liver function, reduced hepatic inflammation, and decreased HCC risk. Monitoring AFP and liver enzyme markers can aid the management of chronic HBV infected patients in resource-limited settings.

Keywords: HBV, HBeAb, HBsAg, AFP, liver enzymes, hepatocellular carcinoma

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Évaluation de l'α-fœtoprotéine et de certains marqueurs enzymatiques inflammatoires chez des patients atteints d'hépatite B chronique, séropositifs et séronégatifs pour l'anticorps anti-HBs, à l'UITH d'Ilorin, au Nigéria.

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Résumé:

Contexte: Le virus de l'hépatite B (VHB) peut provoquer des hépatites aiguës et chroniques et contribue fortement à la cirrhose hépatique et au carcinome hépatocellulaire (CHC), imposant un fardeau considérable aux

systèmes de santé en raison de sa morbidité et de sa mortalité élevée, ainsi que du coût important des traitements. L'infection par le VHB demeure un problème majeur de santé publique, notamment en Afrique subsaharienne. L'analyse des taux sériques d'alpha-fœtoprotéine (AFP) et de certains marqueurs inflammatoires chez les personnes séropositives pour l'anticorps anti-HBe (HBeAb) apporte des informations précieuses sur la progression de la maladie, le dépistage précoce du carcinome hépatocellulaire (CHC) et le suivi de l'efficacité du traitement. Cette étude a évalué les taux sériques d'AFP et de certains marqueurs inflammatoires, tels que l'aspartate aminotransférase (AST), l'alanine aminotransférase (ALT), les protéines totales, l'albumine et les globulines, chez des patients atteints d'hépatite B chronique, séropositifs et séronégatifs pour l'HBeAb, au Centre hospitalier universitaire d'Ilorin (UITH), à Ilorin, au Nigéria.

Méthodologie: Une étude transversale comparative a été menée auprès de 70 patients atteints d'hépatite B chronique à l'UITH, à Ilorin, au Nigéria, dont 30 patients séropositifs et 40 patients séronégatifs pour l'HBeAb. Les données sociodémographiques des patients ont été recueillies à l'aide d'un formulaire spécifique. Les concentrations sériques d'AFP, d'ALT, d'AST, de protéines totales, d'albumine et de globulines ont été déterminées par ELISA et spectrophotométrie. Les données ont été analysées par le test U de Mann-Whitney et la corrélation de Spearman, un seuil de signification statistique étant fixé à $p \leq 0,05$.

Résultats: Les concentrations sériques d'AST et d'ALT étaient significativement plus faibles chez les patients séropositifs pour les anticorps anti-HBe (17,43±33,90 UI/L et 11,13±10,95 UI/L) que chez les patients séronégatifs (34,90±22,95 UI/L et 23,00±8,68 UI/L; $p=0,040$ et $p=0,000$ respectivement). Le taux d'AFP était significativement plus faible chez les patients séropositifs (17,59±44,32 ng/mL) que chez les patients séronégatifs (44,31±14,80 ng/mL) pour les anticorps anti-HBe ($p=0,003$). Les taux de protéines totales et de globulines sériques étaient significativement plus élevés chez les patients séropositifs pour les anticorps anti-HBe (75,97±11,89 g/L et 29,70±4,17 g/L; $p=0,001$ et $p=0,000$ respectivement). L'albuminémie était plus élevée chez les patients séropositifs pour les anticorps anti-HBe (46,33±9,54 g/L), mais cette différence n'était pas statistiquement significative par rapport aux patients séronégatifs (41,95±7,80 g/L) pour ces mêmes anticorps ($p=0,081$).

Conclusion: La séroconversion des anticorps anti-HBe est associée à une amélioration de la fonction hépatique, une réduction de l'inflammation hépatique et une diminution du risque de carcinome hépatocellulaire. Le suivi de l'AFP et des marqueurs enzymatiques hépatiques peut faciliter la prise en charge des patients atteints d'une infection chronique par le VHB dans les contextes aux ressources limitées.

Mots-clés: VHB, anticorps anti-HBe, AgHBs, AFP, enzymes hépatiques, carcinome hépatocellulaire

Introduction:

Hepatitis B virus (HBV) infection remains one of the most prevalent and serious infectious diseases globally, particularly in sub-Saharan Africa and the Western Pacific, where it is highly endemic. According to the World Health Organization (WHO), over 296 million people were chronically infected with HBV in 2019, with more than 800,000 annual deaths resulting from complications such as cirrhosis and hepatocellular carcinoma (1,2). Despite the availability of effective vaccines and antiviral therapies, HBV diagnosis rates in low- and middle-income countries (LMICs) remain disproportionately low compared to high-income countries, estimated at only 0.8% versus 18% respectively (3). As a result, large portion of HBV-infected individuals remain undiagnosed and untreated, facilitating continued transmission and disease progression (4).

HBV is a partially double-stranded DNA virus with a strong tropism for hepatocytes (5). It is transmitted through perinatal routes, sexual contact, blood transfusions, and other exposures to infected body fluids (1,6). The course of HBV infection is marked by dynamic phases characterized by changes in viral replication and host immune response. Serological markers such as hepatitis B envelope antigen (HBeAg) and its corresponding antibody, hepatitis B envelope antibody (HBeAb), are central to monitoring disease progression.

HBeAg is typically associated with active viral replication and high infectivity, while the appearance of HBeAb marks a transition to a less replicative state, often indicating immune control over the virus and improved clinical prognosis (7,8). HBeAb is not only valuable diagnostically but also prognostically. It is often used to guide treatment decisions and evaluate the likelihood of favorable treatment outcomes (9). Patients who seroconvert to HBeAb tend to exhibit lower viral loads, reduced liver inflammation, and improved liver enzyme profiles (10). Moreover, seroconversion has been associated with decreased risk of progression to cirrhosis and hepatocellular carcinoma (11,12). As such, evaluating the biochemical changes associated with HBeAb status is clinically relevant in assessing disease activity and therapeutic response.

Liver enzymes, particularly alanine aminotransferase (ALT) and aspartate aminotransferase (AST), are widely used indicators of hepatocellular injury. Elevated levels of ALT and AST are commonly seen in patients with active HBV infection and correlate with the degree of hepatic inflammation and necrosis (13,14). ALT is considered a more specific marker of liver damage than AST due to its predominance in hepatocytes (15,16). Therefore, declining enzyme levels in HBeAb-positive individuals often reflect disease remission or therapeutic success.

Other important indicators of liver function include serum albumin, globulin, and total protein. Albumin, synthesized in the liver, plays a key role in maintaining oncotic pressure and transporting hormones and drugs

(17). Decreased albumin levels are associated with chronic liver diseases, especially cirrhosis (18). Globulins, which include immunoglobulins, are elevated in response to viral infections and immune activation (19). Elevated total protein and globulin levels in HBeAb-positive patients may thus reflect an enhanced immune response and restoration of liver synthetic function (20).

Alpha-fetoprotein (AFP) is another clinically significant biomarker, particularly for hepatocellular carcinoma (HCC). In healthy adults, AFP levels are typically undetectable; however, they can rise markedly in the context of chronic HBV infection and liver cancer (21, 22). The clinical utility of AFP in monitoring HBV patients lies in its role as a non-invasive screening tool for early detection of HCC, especially when interpreted alongside imaging studies and liver function tests (23,24). Studies have shown that AFP levels are often significantly higher in HBeAg-positive individuals compared to those who have seroconverted to HBeAb (25,26).

In Nigeria, HBV is considered hyperendemic, with prevalence estimated among the highest in sub-Saharan Africa (15,27). The combination of high disease burden, low vaccination coverage, and inadequate access to early diagnostic services makes HBV a critical public health threat in the country. Given these challenges, the use of readily available biochemical markers such as ALT, AST, AFP, albumin, and globulin can be instrumental in guiding early diagnosis, staging, and treatment decisions.

This study, therefore aimed to evaluate the serum levels of alpha-fetoprotein and selected liver-related biochemical parameters among chronic HBV patients seropositive and seronegative for HBeAb at the University of Ilorin Teaching Hospital (UITH), Ilorin, Kwara State, Nigeria. By examining these markers across these two groups, the study aims to provide insight into the clinical significance of HBeAb seroconversion and its association with improved liver function and reduced HCC risk. These have potential implications for enhancing HBV monitoring and management protocols in Nigeria and other resource-limited settings.

Materials and method:

Study site:

This study was carried out in the General-Out-Patient clinic of the University of Ilorin Teaching Hospital (UITH), a major tertiary healthcare facility located in Ilorin, the capital city of Kwara State in Nigeria. The hospital is affiliated to the University of Ilorin and provides a wide range of healthcare services to patients from Ilorin and its surrounding areas.

Study design and population:

This was a comparative cross-sectional study of patients with diagnosis of chronic HBV infections attending the outpatient clinic of UITH, Ilorin, which formed the study population. Diagnosis of HBV infection was made based on the detection of hepatitis B surface antigen (HBsAg) in the serum of patients using standard serological testing methods.

Ethical approval:

Ethical approval was obtained from the Ethical Review Committee of UITH Ilorin, and from Al-Hikmah University, Kwara State, Nigeria. Informed consent was obtained from all participants before collection of data.

Study participants, inclusion and exclusion criteria:

The study participants included 70 chronic HBV patients that were seropositive (n=30) and seronegative (n=40) for hepatitis B envelope antibody (HBeAb). Participants who have received HBV vaccination, those with other liver diseases such as hepatitis C, autoimmune liver disease, liver cirrhosis, pregnant women, patients with unstable medical conditions such as uncontrolled hypertension or diabetes and those with history of liver transplantation, were excluded from the study.

Data and sample collection/handling:

Participants were consecutively recruited at the clinic. Sociodemographic data were collected using a designed form. Approximately 5ml of blood was collected aseptically by venipuncture from each selected participant into sterile plain test tube and transported immediately from the clinic to the laboratory for analysis.

Laboratory analyses

All laboratory analyses were carried out at the Chemical Pathology laboratory, UITH, Ilorin. The blood was allowed to clot in the test tube, and the serum was separated by centrifugation at 3000 rpm for 5 minutes. The serum specimen was transferred separately to different vials and preserved at -2^{0}C until analysis.

Alpha-fetoprotein (AFP) assay:

Serum level of alpha-fetoprotein was determined using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (ACCUlite®). The method is based on a sandwich ELISA principle, wherein serum AFP binds to immobilized anti-AFP antibodies on microtiter wells, followed by the addition of an enzyme-conjugated secondary antibody. The bound complex was visualized with a tetramethyl benzidine (TMB) substrate, and absorbance was measured at 450 nm using a microplate reader. Concentrations were extrapolated from a standard curve generated with known AFP standards.

Alanine aminotransferase (ALT) assay:

ALT activity was measured using the kinetic UV method with the Randox® ALT reagent kit. The assay monitors the rate of decrease in NADH absorbance at 340 nm as ALT catalyzes the conversion of alanine and α-ketoglutarate to pyruvate and glutamate. Pyruvate is subsequently reduced to lactate, by lactate dehydrogenase, resulting in oxidation of NADH to NAD+. The change in absorbance per minute was used to calculate enzyme activity in IU/L.

Aspartate aminotransferase (AST) assay:

AST activity was assessed using the Randox® AST reagent kit and kinetic UV method. The assay measures the conversion of aspartate and α-ketoglutarate to oxaloacetate and glutamate, with oxaloacetate being reduced to malate, by malate dehydragenase, accompanied by the oxidation of NADH. The rate of NADH consumption was measured at 340 nm, and AST activity was calculated in IU/L.

Total protein determination:

Total serum protein was quantified using the Biuret method (Agappe® total protein kit). Proteins in the serum react with copper ions in an alkaline medium to form a violet-colored complex. The intensity of the color, which is directly proportional to protein concentration, was measured spectrophotometrically at 540 nm. Protein concentration was calculated using a known protein standard.

Albumin assay:

Serum albumin was estimated using the bromocresol green (BCG) method (Agappe® albumin kit). At acidic pH, albumin binds to BCG to form a blue-green complex, which was measured spectrophotometrically at 630 nm. Albumin concentration was determined by comparing absorbance to that of a standard solution.

Globulin calculation:

Serum globulin levels were derived by subtracting the measured albumin concentration from the total protein concentration for each sample: Globulin (g/L) = Total Protein – Albumin

Data analysis:

All data were carefully entered into Microsoft Excel spreadsheet and assessed for accuracy and completion before statistical analysis using the Statistical Package for the Social Sciences (SPSS) version 27.0. Before analysis, the data were assessed for Gaussian distribution and thereafter, appropriate statistical analysis tests was applied.

The Student's *t*-test was used to determine differences in means of the variables with Gaussian distribution. Mann-Whitney U test was used to determine differences in medians of the variables without Gaussian distribution. Correlation between variables was determined using Spearman's Rho correlation. *P*-values less than 0.05 (2-tailed) were considered as statistically significant.

Results:

Socio-demographic characteristics of study participants:

As shown in Table 1, the age of participants ranged from 15 to 42 years. Of the 70 participants, 13% were between the age of 15-24 years, 53% were between 25-34 years while 34% were between 34-44 years of age. The frequency of male participants (68.5%) was higher than the female participants (31.5%), and 63% were single while 37% were married.

Table 1: Socio-demographic characteristics of patients

Characteristics	Number	%
Age group (years)		
15-24	9	13
25-34	37	53
34-44	24	34
Total	70	100
Marital status		
Married	26	37
Single	44	63
Total	70	100
Sex		
Male	48	68.5
Female	22	31.5
Total	70	100
Education level		
Primary	5	7
Secondary	26	37
Tertiary	39	56
Total	70	100
HBeAb		
HBeAb seronegative	40	57.1
HBeAb seropositive	30	42.9
Total	70	100

Table 2: Comparative levels of alpha-feto protein and liver enzymes in chronic HBV patients seropositive and seronegative for hepatitis B envelope antibody

Parameters	HBeAb positive (n=30)	HBeAb negative (n=40)	*t*-value	*p*-value
AST (IU/L)	17.43±33.90	34.90±22.95	2.106	0.040**
ALT (IU/L)	11.13±10.95	23.00±8.68	4.246	0.000**
AFP (ng/mL)	17.59±44.32	44.31±14.80	3.174	0.003**

(**) means statistically significance at $p<0.05$

Table 3: Comparative levels of serum total protein, albumin and globulin in chronic HBV patients seropositive and seronegative for hepatitis B envelope antibody

Parameters	HBeAb positive (n=30)	HBeAb negative (n=40)	*t*-value	*p*-value
Total protein (g/L)	75.97±11.89	67.20±9.39	2.892	0.001**
Albumin (g/L)	46.33±9.54	41.95±7.80	1.781	0.081
Globulin (g/L)	29.70±4.17	25.25±2.00	4.642	0.000**

(**) means statistically significance at $p<0.05$

Results of AFP and liver enzymes in the study participants:

As shown in Table 2, AST levels were significantly lower in patients seropositive for HBeAb compared to patients seronegative for HBeAb (p=0.040). ALT levels were also significantly lower in patients seropositive for HBeAb compared to patients seronegative for HBeAb (p=0.000). Serum alpha-fetoprotein level was significantly lower in patients seropositive for HBeAb compared to patients seronegative for HBeAb (p=0.003).

Results of serum total protein, albumin and globulin in the study participants:

As shown in Table 3, serum total protein level was significantly higher in patients seropositive for HBeAb compared to patients seronegative for HBeAb (p=0.001). Serum albumin level was not significantly different in patients seropositive for HBeAb compared to patients seronegative for HBeAb (p=0.081) but serum globulin level was significantly higher in patients seropositive for HBeAb compared to patients seronegative for HBeAb (p=0.000).

Discussion:

The study indicates that chronic HBV patients seropositive for HBeAb have significantly lower serum AST and ALT levels compared to patients seronegative for HBeAb. This reduction in liver enzyme levels suggests reduced liver damage in HBeAb-positive individuals. This finding aligns with previous research. Patients with resolved HBV infection, often associated with the presence of HBeAb, have been reported to exhibit significantly lower ALT levels, indicating improved liver health (28). Similarly, individuals seropositive for HBeAb have been shown to have lower viral loads, consistent with a reduced risk of liver damage (29). The observed differences in liver enzyme levels between patients seropositive and seronegative for HBeAb may also reflect the impact of therapeutic interventions. Antiviral therapy plays a pivotal role in the clinical management of chronic HBV infection (12).

Our study revealed a significant increase in serum total protein in patients seropositive for HBeAb, indicating an overall elevation in protein content in their blood. This finding aligns with the study by Chan et al., (29), which reported that HBeAb seroconversion was associated with improved liver function, including increased total protein levels, reflecting the restoration of liver synthetic capacity. Although our study reports an insignificant increase in albumin levels in patients seropositive for HBeAb. It is important to note that albumin is a major protein synthesized by the liver. In hepatitis, liver inflammation can lead to reduced albumin production. A study by Hu et al., (30) had highlighted the correlation between HBeAb positivity and stabilized albumin levels, suggesting better liver function.

The significant increase in serum globulin levels in patients seropositive for HBeAb aligns with the idea that globulins consist of various antibodies and enzymes, reflecting an enhanced immune response. This agrees with the study by Wang et al., (24), which reported that patients seropositive for HBeAb had higher levels of certain immunoglobulins, contributing to improved viral control. The presence of HBeAb suggests an immune response against HBV, which could lead to reduced liver inflammation and improved liver function. This finding also agrees with the study by Yuen et al., (31) which highlighted the importance of HBeAb seroconversion in predicting favorable outcomes in chronic hepatitis B.

The observation in our study of an enhanced immunological response, as reflected in high serum total protein and globulin levels, is consistent with the attempt by the liver to combat HBV infection. The results indicate that patients seropositive for HBeAb have a more favorable protein profile, suggesting better liver function and potentially less severe liver disease. This is supported by a systematic review by Martinot-Peignoux et al., (32), which emphasized the importance of monitoring serum protein parameters in assessing liver health and the effectiveness of antiviral treatment in hepatitis B.

The significant decrease in AFP levels in patients seropositive for HBeAb is a notable finding in our study. Elevated AFP is widely recognized as a potential marker for hepatocellular carcinoma (HCC) in patients with chronic liver diseases, including hepatitis B. This observation agrees with the study by Zhang et al., (33), which emphasized that higher AFP levels were associated with an increased risk of HCC, particularly in hepatitis B patients. The decreased AFP levels in patients seropositive for HBeAb may indeed reflect improved liver health (34). The results underscore the importance of monitoring AFP levels in hepatitis B patients, especially those with different serological markers such as HBeAb. This aligns with guidelines proposed by the American Association for the Study of Liver Diseases (AASLD), which recommend regular surveillance for HCC in hepatitis B patients, including AFP measurements. Monitoring AFP can assist healthcare professionals in identifying patients at higher risk of liver cancer.

The reduced AFP levels in patients seropositive for HBeAb can be attributed to the ability of the immune system to suppress viral replication and limit liver cell damage. This aligns with a study by Chen et al., (26) which highlighted the immunological control of hepatitis B as a significant factor in liver health and cancer risk reduction.

Conclusion:

The comprehensive analysis of various biochemical parameters in patients with chronic HBV patients seropositive for HBeAb compared to their seronegative counterparts, provides valuable insights into the complex dynamics of HBV infection and its impact on liver health. The results showed that patients seropositive for HBeAb exhibit significantly improved liver health, as evidenced by lower AST and ALT levels, indicative of reduced liver cell damage and inflammation. This improvement can be attributed to the successful resolution or control of the HBV infection, as reflected in their HBeAb-positive status. Additionally, the elevation in serum total protein and globulin levels in patients seropositive for HBeAb suggests a strengthened immune response and better liver function, further highlighting the positive influence of HBeAb seroconversion on overall health. Furthermore, the notable decrease in alpha-fetoprotein levels in patients seropositive for HBeAb indicates a decreased risk of hepatocellular carcinoma, underscoring the clinical significance of these findings in cancer prevention and liver care.

These results collectively emphasize the importance of regularly monitoring these serum markers in hepatitis B patients to tailor appropriate treatment strategies and cancer screening protocols, ultimately contributing to improved patient outcomes. Healthcare providers are encouraged to implement routine monitoring of key serum biomarkers such as AST and ALT in hepatitis B patients. Furthermore, AFP should be acknowledged as a vital marker in the early detection and monitoring of hepatocellular carcinoma risk.

Contributions of authors:

MAN and SAY conceived and designed the study; MAN and OJO conducted participant recruitment, sample collection, and laboratory assays; SAY and OJO performed statistical analyses and data interpretation; MAN drafted the initial manuscript; SAY and OJO critically revised the manuscript for important intellectual content; and SAY supervised the overall research activity. All authors reviewed and approved the final manuscript.

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Conflict of interest

Authors declare no conflict of interest.

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