ORIGINAL ARTICLE

Prevalence of hepatitis B and vaccination response in patients with end-stage kidney disease on dialysis at a tertiary centre in the Eastern Cape province of South Africa

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ABSTRACT

Introduction: Hepatitis B virus (HBV) infection remains a concern in dialysis populations where vaccination has been less successful than in the general population. Possible reasons for poor response to vaccination in this population include malnutrition, age, uraemia, dialysis vintage, human immunodeficiency virus (HIV) infection and the generalized immunosuppressive state of patients with chronic kidney disease (CKD).

Methods: This retrospective point prevalent cohort study evaluated the prevalence of HBV infection in a dialysis population at a tertiary centre in South Africa where there is a high prevalence of HIV. In addition, antibody responses following natural HBV infection versus vaccination were examined in the same population as well as factors that may affect the HBV vaccination antibody response.

Results: There were 107 study participants. The prevalence rate of chronic HBV was high at 6.5% (n = 7), whereas 48 (45%) patients demonstrated evidence of HBV exposure. Patients with naturally acquired immunity demonstrated a more robust and sustained antibody response over the study period, whereas booster dose(s) were required to achieve similar levels of protection in the vaccinated group. Only one (2.1%) of those requiring vaccination never achieved an adequate seroprotection response to vaccination at any time point during the study period. Older age was the only factor shown to reduce seroconversion after primary vaccination. Despite high HIV prevalence (23%), HIV status did not affect antibody response to vaccination.

Conclusion: We therefore conclude that in a cohort of dialysis patients with high HBV prevalence, natural immunity provides sustained and adequate protection. HBV vaccination in this dialysis cohort was successful, but additional booster doses were frequently required to achieve adequate seroprotection, regardless of HIV status.

Keywords: Hepatitis B, Dialysis, Prevalence, Vaccination, Immunity, Antibody.

INTRODUCTION

Hepatitis B is a global health problem, with an estimated 257 million people chronically positive for hepatitis B surface antigen (HBsAg). The burden of chronic hepatitis B is increasing despite its being a vaccine-preventable disease, with effective vaccines having been available since 1982 [1]. Hepatitis B virus (HBV) is an important cause of serious liver disease, including acute and chronic hepatitis, cirrhosis, and primary hepatocellular carcinoma [2]. In addition to its effects in the liver, extra-hepatic manifestations may be observed in up to 20% of patients infected with HBV and include mixed cryoglobulinaemic vasculitis, polyarteritis nodosa, and kidney disease [3].

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Liver disease is also a significant cause of morbidity and mortality in patients on maintenance dialysis, with HBV infection among the important aetiologies [4].

South Africa is an endemic HBV country, with serological evidence of past exposure ranging from 5% to 76% in the population where most infections are acquired perinatally or in early childhood [5]. The prevalence of chronic hepatitis B ranges between 4% and 9% with rates of up to 16% reported in some communities in the Eastern Cape province of South Africa [1,6,7]. The prevalence of HBV is generally greater among dialyzed patients than in the general population [8,9]. Compared to high-income countries, lower-income nations report higher HBV infection rates within dialysis units, a major reason being the higher background prevalence of HBV in the general population [8].

Over the past few decades, there has been a substantial decrease in the incidence of HBV infection in haemodialysis patients, particularly in high-income countries. This is attributable to safer blood donations, a decline in blood transfusion requirements with increased erythropoietin use, and improved guidelines on infection control and vaccination. Despite this progress, dialysis patients remain at greater risk of acquiring HBV because of their increased exposure to blood products, shared haemodialysis equipment, frequent breaching of skin, immunodeficiency, and continuing high prevalence rates, especially in low-income countries. The primary means of protection for dialysis patients is a targeted vaccination strategy against HBV [10-12].

The hepatitis B vaccine currently used in the South African extended programme for immunisation (EPI) is the Heberbiovac HB vaccine (Biovac, South Africa), which is a preparation of yeast (*Pichia pastoris*)-derived recombinant small hepatitis B surface antigen (HBsAg). This vaccine appears to be more immunogenic and produces a heightened and sustained immunological response compared to other hepatitis B vaccines [13,14].

Antibody responses from HBV vaccination in patients with chronic kidney disease (CKD) are suboptimal, often with higher vaccine doses required to achieve desirable antibody levels [11,15]. Numerous clinical, demographic and biochemical parameters have been postulated to explain the poor immunogenicity of HBV vaccines in advanced CKD. These include age, sex, body mass index, positive serological status for hepatitis C (HCV) or human immunodeficiency virus (HIV), blood transfusion history, interleukin genotypes, possession of the major histocompatibility complex haplotypes HLA-B8, SCOI, DR3,18 and inappropriate nutritional status, which may hamper the differentiation of monocyte-derived dendritic cells of the immune system [16]. The albumin concentration is frequently used as a surrogate, albeit imperfect, marker of nutritional status in dialysis patients in whom a low concentration is a strong predictor of mortality and poor outcomes [17].

There is a paucity of data regarding the prevalence of HBV infections and the response to HBV vaccination among patients on maintenance dialysis in South Africa. Accordingly, the aim of this study was to evaluate the prevalence of HBV infection and immunity in a high-HIV prevalence dialysis cohort in the Eastern Cape province of South Africa. Furthermore, we sought to examine the influence of age, serum albumin levels, dialysis modality, dialysis vintage, and cause of end-stage kidney disease on the immune response after vaccination.

METHODS

In this single-centre retrospective point prevalent cohort study, we analysed the records of all patients currently on haemodialysis and peritoneal dialysis at the Division of Nephrology, Livingstone Tertiary Hospital, Gqeberha (previously known as Port Elizabeth) in January 2021. The treatment period reviewed was from January 2012 to January 2021. All patients included were either already receiving dialysis therapy in January 2012 or were initiated on dialysis therapy after January 2012 and before January 2021. Patients who had died during the study period were excluded owing to inability to access records. Baseline was defined as the date of starting dialysis therapy. Baseline demographic data including age, sex, clinical information, albumin level, mode of dialysis and dialysis vintage were recorded. Hepatitis B immunity was classified according to Table 1.

In our unit, non-immune, unvaccinated patients are given a dose of 40 µg Heberbiovac intramuscularly at month 0,

Table 1. Characterisation of hepatitis B immunity status according to HBV serology.

Immune status	HBsAg	HBcAb	HBsAb
Past infection with immunity	–	+	+
Vaccine-acquired immunity	–	–	+
Chronic hepatitis B	+ [a]	+	–
Past infection with waning immunity; or occult infection	–	+	–

Abbreviations: HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; HBcAb, hepatitis B core antibody; HBsAB, hepatitis B surface antibody.
[a] Must persist for 6 months or more.

1 and 2, with a booster in month 6. Antibody levels are monitored at 6-month intervals to assess response. A booster dose is given if the antibody levels are less than 100 IU/mL. Booster vaccination consisted of a single intramuscular injection of 40 µg Heberbiovac vaccine. This protocol remained unchanged during the entire study period. We defined response to HBV vaccination according to antibody titre levels with a titre of less than 10 IU/mL as non-response; between 10 IU/mL and 100 IU/mL as seroconversion and more than 100 IU/mL as seroprotection [18]. In those who received primary vaccination at study entry, we also set out to determine the proportion who developed an adequate seroprotection response after 6 months. Antibody titres were measured using the ARCHITECT Anti-HBs assay (Abbott Diagnostics, Ireland).

Statistical analysis was carried out using Stata statistical software version 15.1 (Stata Corp. L.P., College Station, Texas). Prevalence of HBV infection was calculated as the percentage of patients who were HBcAb positive at baseline. Continuous variables were summarised as median with interquartile range (IQR) and compared with seroprotection status using the Wilcoxon rank-sum test. Categorical variables were presented as frequencies and percentages and compared using the chi-squared test or Fisher's exact test, as appropriate. A P value < 0.05 was considered statistically significant.

Ethics considerations

Ethical clearance for conducting the study was obtained from Walter Sisulu University Human Research and Ethics Committee (Protocol Number 028/2021).

RESULTS

There were 107 study participants with a median age of 42 (IQR 35–49) years and a median time on dialysis of 43 months (IQR 18–79). In the cohort, 55 (51%) were males. Of the 107, 63 (59%) and 44 (41%) patients were on haemodialysis and peritoneal dialysis, respectively. Of the 106 with available HIV serology at baseline, 82 (77%) were HIV negative whereas 24 (23%) were HIV positive. Causes for CKD included hypertension (36%, n = 38), glomerular disease (34%, n = 36), unknown cause (15%, n = 16), autosomal dominant polycystic kidney disease (7%, n = 7) and other (9%, n = 10).

Baseline hepatitis B serology is presented in Table 2. Forty (37%) patients had a negative HBsAb titre and were eligible for vaccination. Six of these patients were HBcAb positive, indicating prior HBV exposure, of whom 2 were subsequently found to have detectable HBV viral loads. Seven patients were positive for HBsAg that persisted beyond 6 months, indicating chronic infection. Sixty patients (56%) were HBsAb positive, indicating existing immunity. Forty-eight (45%) patients had serological evidence of past or current HBV infection (HBcAb positive). Of these, 35 (73%) had natural immunity, 7 (15%) had chronic hepatitis B and 6 (13%) had cleared the HBsAg but did not have measurable HBsAb. At baseline, only 25 (23%) patients had vaccine-acquired immunity.

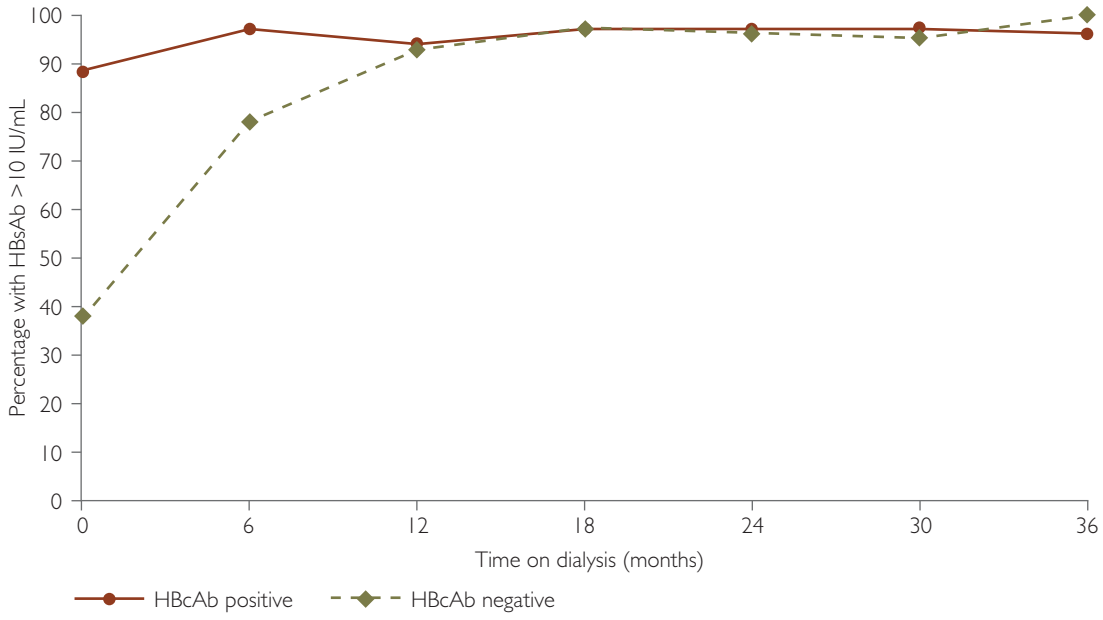
Figures 1a and 1b illustrate the maintenance rates over the study period of surface antibody titre >10 IU/mL and >100 IU/mL, respectively, in those who were HBcAb negative and positive at baseline. In patients with no evidence of prior HBV exposure, seroconversion status rose from 38% to 100% in the remaining cohort (n = 23) over the study period due to vaccination, while those who were HBcAb positive and HBsAg negative sustained HBsAb positivity over time varying between 88% and 96%. A total of 32 patients (30%) required a booster dose in the course of their dialysis treatment and, of these, 11 (34%) required a second booster dose.

Comparison of baseline demographics by seroprotection status is presented in Table 3. Only older age was associated with lower seroprotection (P = 0.016). During the study period, 23 patients (28%) developed a seroprotective response following their primary vaccination course, whereas in those with data extending beyond six months of follow-up, 46 of 47 (98%) developed a seroprotective response at some time point during the study period with only 2 patients achieving this beyond 36 months.

Table 2. Baseline hepatitis B serology (n = 107).

HBsAb titre	<10 IU/mL	10–100 IU/mL	>100 IU/mL	HBsAg positive
n (%)	40 (37)	14 (13)	46 (43)	7 (7)
Of these, number HBcAb positive, n/n (%)	6/40 (15)	6/14 (43)	29/46 (63)	7/7 (100)

Abbreviations: HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBcAb, hepatitis B core antibody.



	Baseline	6 months	12 months	18 months	24 months	30 months	36 months
HBcAb positive n/n (%)	37/42 (88)	34/35 (97)	32/34 (94)	31/32 (97)	30/31 (97)	29/30 (97)	24/25 (96)
HBcAb negative n/n (%)	19/50 (38)	36/46 (78)	40/43 (93)	33/34 (97)	26/27 (96)	21/22 (96)	23/23 (100)

Figure 1a. Hepatitis B seroconversion status (HBsAb titres >10 IU/mL) over time, according to baseline HBV exposure*.
Abbreviations: HBsAb, hepatitis B surface antibody; HBcAb, hepatitis B core antibody; HBV, hepatitis B virus.
*7 patients who were hepatitis B surface antigen positive at baseline were removed from this analysis.
Note: Seroconversion was defined as HBsAb positivity (titres >10 IU/mL).

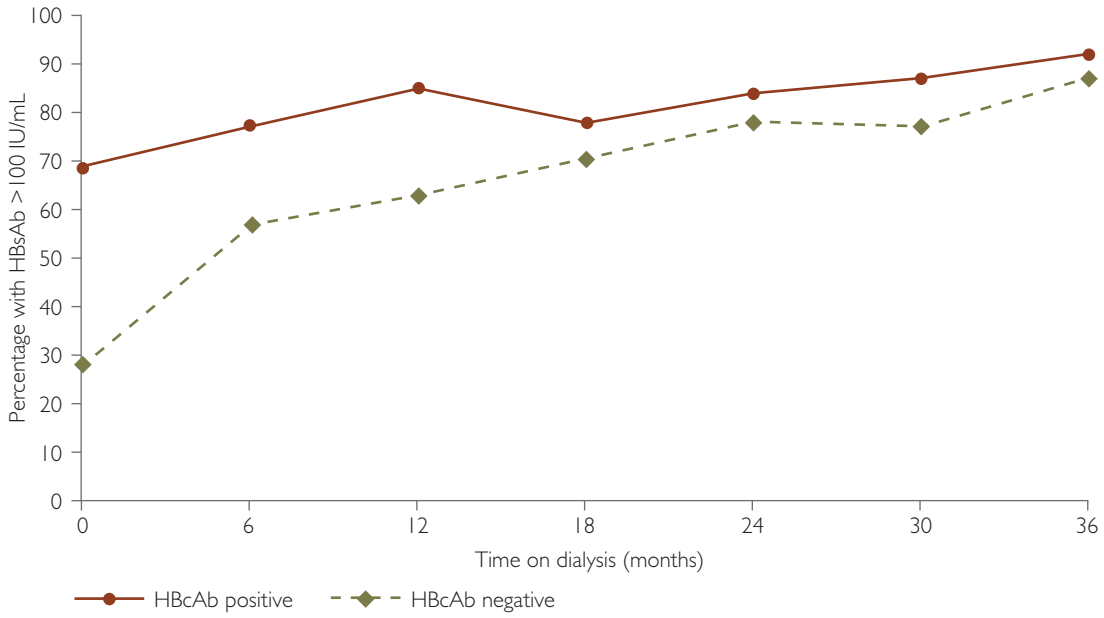
DISCUSSION

This study of dialysis patients in the Eastern Cape province demonstrated a high prevalence of HBV infection at 45%, which reflects the high background endemicity of HBV in South Africa [5]. Chronic HBV infection was found in 6.5% of patients and is similar to other studies in South Africa [1,6,7]. Six patients were only HBcAb positive, of whom two fulfilled the diagnostic criteria for occult HBV infection [19]. Improvements in the detection of HBV–DNA now enables better identification of occult HBV infection [20]. This is important as these patients still pose a transmission risk in the dialysis unit and are at risk of a flare following immunosuppression following kidney transplantation [21]. The remaining four patients represented waning immunity, most likely due to HBV infection acquired in early childhood [22].

At the start of the study, relatively few (37%) patients presented no evidence of immunity and therefore required primary vaccination, whereas 88% of those with natural immunity had HBsAb titres more than 10 IU/mL. Given the widespread availability of vaccination, this represents a missed opportunity in CKD care and may reflect the frequent late presentation of advanced CKD in South Africa. Over the course of the study, 30% of patients required a booster dose, with 34% of these needing a second booster dose. This is consistent with previous data showing a waning of antibody titres over time [15,16,23].

Interestingly, about 90% of the patients with naturally acquired immunity demonstrated a sustained antibody response compared to vaccine-acquired immunity that required booster doses to achieve similar levels over the first 12 months. This suggests the immune response to natural HBV infection is more robust and sustained and may therefore allow for less frequent antibody titre monitoring to save costs for these patients. To improve vaccination response, double dosing of the hepatitis B vaccine has been advocated. This has been shown to improve and prolong adequate vaccination response and was the strategy used in this study [15,24-27].

In the general population, seroconversion is considered an appropriate protective response to HBV vaccination. However, in vulnerable populations such as dialysis patients, a



	Baseline	6 months	12 months	18 months	24 months	30 months	36 months
HBcAb positive n/n (%)	29/42 (69)	27/35 (77)	29/34 (85)	25/32 (78)	26/31 (84)	26/30 (87)	23/25 (92)
HBcAb negative n/n (%)	29/42 (69)	27/35 (77)	29/34 (85)	25/32 (78)	26/31 (84)	26/30 (87)	23/25 (92)

Figure 1b. Hepatitis B seroprotection status (HBsAb titres >100 IU/mL) over time according to baseline HBV exposure*.
Abbreviations: HBsAb, hepatitis B surface antibody; HBcAb, hepatitis B core antibody; HBV, hepatitis B virus.
*7 patients who were hepatitis B surface antigen positive at baseline were removed from this analysis.
Note: Seroprotection was defined as HBsAb positivity (titres >100 IU/mL).

Table 3. Baseline patient demographics by seroprotection (HBsAb >100 IU/mL) status six months after primary vaccination.

	Total, N = 82*	No seroprotection n = 59 (72%)	Seroprotection n = 23 (28%)	P value
Age (years), median (IQR)	42 (33–48)	44 (36–50)	37 (29–46)	0.016
Male, n (%)	42 (51)	32 (54)	10 (44)	0.380
Dialysis modality (HD), n (%)	46 (56)	36 (61)	10 (44)	0.150
Time on dialysis (months) median (IQR)	44 (18–73)	44 (17–72)	46 (19–81)	0.760
Albumin (g/L), median (IQR)	33 (31–37)	34 (29–37)	33 (32–37)	0.830
HIV-positive status, n (%)	21 (26)	14 (24)	7 (30)	0.560

Abbreviations: HBsAb, hepatitis B surface antibody; IQR, interquartile range; HD, haemodialysis; HIV, human immunodeficiency virus.
*Only 82 patients had complete records for all variables included.

seroprotective response is considered important since low HBsAb titres have the potential to be overwhelmed in significant exposures [12,27,28]. Overall, a seroprotective HBsAb titre at baseline was seen in 43% of patients. This was attributed to previous vaccination or natural immunity from earlier HBV infection. While almost all patients without past HBV exposure developed surface antibody positivity through vaccination, only 28% manifested sero-protection following the initial primary vaccination course. However, most patients (87%) did eventually achieve an adequate seroprotection response (HBsAb titre >100 IU/mL) by 36 months, reflecting the utility of six-monthly HBsAb titre surveillance with booster dosing for waning or low levels. At extended follow-up beyond 36 months, there was only one vaccine non-responder. This patient was HIV negative but had diabetic nephropathy, which may

be a factor in affecting the immune response. Consideration can be given to even higher dose (80 µg) vaccination in true non-responders [15]. Inadequate seroprotection after primary vaccination was associated with older age at the time of vaccination (P = 0.016) but not with gender and concurs with other studies [29]. In contrast to other studies though, albumin levels and dialysis vintage were not associated with seroprotective response [9,11,30]. There was a large difference in seroprotection between dialysis modalities. However, the small sample size limited meaningful statistical comparison; prior studies have not confirmed a difference between modalities [31].

Our study cohort demonstrated a high prevalence of HIV. HIV/AIDS and chronic HBV co-infection were also common at 14%, in keeping with previous studies [32,33]. Individuals co-infected with HIV and HBV experience a more rapid and severe progression of chronic HBV sequelae, leading to further morbidity and mortality [32,34]. This vulnerability is further exacerbated in the dialysis population, underscoring the importance of HBV vaccination in these patients [35]. The antibody response in the HIV-infected individuals in our cohort was comparable to that recorded in previous publications [35]. Although some authors have reported lower seroprotection rates in the HIV-infected end-stage kidney disease population [34], seroprotection response did not differ with HIV status in our study. All of the patients with HIV in our cohort are receiving antiretroviral therapy and this may account for their equivalent response rates. HIV viral loads were not recorded, although it is the unit's policy to maintain fully suppressed HIV viral loads in all dialysis patients.

Strengths and limitations

The main strength of our study is the longitudinal examination of HBV immunity and vaccine response in a dialysis population in an endemic HBV area with a high HIV prevalence. To our knowledge, it represents the first such study in dialysis patients in southern Africa. Limitations include the relatively small sample size, precluding meaningful multivariate analysis. Some longitudinal data were also missing, thus limiting our ability to accurately analyse antibody trends over time. Furthermore, the previous vaccination status of participants prior to dialysis initiation was not available.

CONCLUSIONS

HBV infection is highly prevalent in the dialysis population in South Africa and, despite vaccine availability, relatively few patients demonstrated evidence of vaccine-induced immunity at the start of dialysis. Natural immunity appears to provide a more robust and sustained immune response. While a low percentage of our patients achieved full seroprotection after the initial vaccination course, most developed an adequate seroprotective response over time, demonstrating the effectiveness of six-monthly antibody surveillance with booster dosing according to the HBV vaccination policy. The waning of antibody response in those with vaccine-induced immunity necessitates regular monitoring of the HBsAb titres in this sub-population, so as to evaluate the need for booster vaccination. Finally, 2% of our patients demonstrated occult hepatitis B infection and clinicians should be aware of this phenomenon, which may explain non-response to vaccination, represents an ongoing infection risk and may pose a risk of severe reactivation of HBV with immunosuppression following kidney transplantation.

Conflict of interest statement

All authors declare that they have no conflict of interest.

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