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Original Article

Mineral-related hormones are closely associated with the titers of antibody against hepatitis B surface antigen in prevalent dialysis patients

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Abstract: Objectives: Hepatitis B virus infection confers a significant burden on patients with end-stage renal disease, but determinants of host reactivity against hepatitis B virus are still unclear. More importantly, the association between hepatitis B virus serologic reactivity and mineral-bone parameters has rarely been addressed. Methods: Chronic hemodialyzed patients with reactive anti-hepatitis B surface antigen antibody (anti-HBs antibody >10 mIU/ml) were prospectively enrolled and analyzed. We performed correlation analysis between their anti-HBs antibody titers and mineral-related hormones as well as nutritional parameters. Significant associations were further investigated with regression analysis to validate the relationship after adjusting for potential confounding factors. Results: Among the chronic dialysis patients recruited, we found that anti-HBs antibody levels correlated significantly with intact parathormone (r=0.29; *P*=0.04), fibroblast growth factor-23 levels (r=0.27; *P*=0.049), and ferritin (r=-0.27; *P*=0.047) after adjustment for calcium, phosphate, and vitamin D levels. Linear regression analysis further showed that ferritin (*P*=0.03), intact parathormone (*P*<0.01), and fibroblast growth factor-23 (*P*=0.04) demonstrated significantly negative, positive, and positive associations with anti-HBs antibody titers in chronic dialysis patients, respectively. Conclusions: This pilot study suggests that mineral-regulating hormones including intact parathormone and fibroblast growth factor-23 might play a role in influencing the reactivity against hepatitis B virus in chronic dialysis patients.

Keywords: End-stage renal disease, ferritin, fibroblast growth factor-23, hepatitis B, parathyroid hormone

Introduction

Renal insufficiency compromises the immune system of end-stage renal disease (ESRD) patients. Uremia leads to dysregulation of both cellular and humoral immunity through the action of uremic toxins, hyperparathyroidism, as well as a high prevalence of vitamin D deficiency [1-3]. Phagocytic defects, lymphopenia, and inertness in antigen-presentation are among the reported consequences of uremia, contributing to the susceptibility of ESRD patients to bacterial and viral infections, particularly blood borne pathogens.

Hepatitis B virus (HBV) infection constitutes a major burden in chronic kidney disease (CKD) and ESRD patients under chronic dialysis. Multiple reports have elucidated the natural history, histological progress, and clinical outcomes of HBV infection in chronic dialysis patients. Abnormal liver function and biopsy-proven chronic active hepatitis occur in 30%-50% of ESRD patients with chronic HBV infection, and the clinical picture is dominated by asymptomatic progressive fibrosis, despite the lack of prominent hepatocellular necrosis or inflammation [4]. HBV surface antigen (HBsAg) positivity in chronic dialysis patients is associated with higher risk of cirrhosis with liver failure, hepatocellular carcinoma, and variably increased mortality compared with HBsAg negativity [5].

Although many studies focus on the complications resulting from HBV infection in these patients, few address the effect of the metabolic consequences of ESRD on the immune

reactivity against HBV. Findings from past reports raise the possibility that iron profiles might affect virus-specific antibody titers in chronic hemodialysis patients [6]. In addition, hyperphosphatemia, hyperparathyroidism, and vitamin D deficiency, common metabolic sequels of chronic dialysis patients, are potential modifiers of adaptive immunity [7, 8]. We hypothesize that the immune reactivity against HBV in chronic dialysis patients might be modified by complications arising from ESRD, particularly nutritional imbalance and chronic kidney disease-mineral bone disorder (CKD-MBD)-related parameters. Using anti-HBsAg antibody (anti-HBs Ab) as a surrogate, we evaluated the relationship between anti-HBs Ab titers and nutritional/mineral-related parameters in a cohort of chronic dialysis patients without recent HBV vaccination or acute HBV infections.

Materials and methods

Study design

ESRD patients undergoing chronic hemodialysis for more than 3 months in National Taiwan University Hospital (NTUH) between 2012 and 2013 were enrolled if their anti-HBs Ab titers were reactive by definition (see below). Known hepatitis B carriers were excluded. All the patients were questioned about their HBV vaccination experiences, and we searched throughout their electronic medical records to identify any episodes of acute hepatitis in the recent 5 years before enrollment. Data regarding demographic profile (age, gender), duration of dialysis, and patient comorbidities were collected upon recruitment. Diabetes mellitus (DM) and hypertension were diagnosed if patients were past or current hypoglycemic agent users and anti-hypertensive medication users, respectively. Cirrhosis and heart failure were documented with imaging studies if patients had compatible symptoms. Autoimmune disorders and malignancy history were recorded based on certified rheumatologist diagnoses and findings of pathologic examinations, respectively. Etiologies of ESRD were also documented according to chart review and the catastrophic illness registration record.

The NTUH ethics committee (NO. 201208069 RIC) approved the current study, and all participants provided written informed consent. The study was conducted with adherence to the Declaration of Helsinki.

Serologic assays

At the beginning of the hemodialysis session, blood samples were obtained immediately and sent to the central laboratory for hemograms (leukocyte counts, hemoglobin, and platelet counts) and serum biochemistry analyses (azotemia severity, electrolyte panels, iron profiles, albumin, glucose, cholesterol, and triglycerides). Part of the samples was cryopreserved for analysis of mineral-related hormones, including 25-hydroxyvitamin D, 1, 25-dihydroxyvitamin D, intact parathyroid hormones (iPTH, PTH 1-84), and fibroblast growth factor 23 (FGF-23). Vitamin D levels were measured through radioimmunoassay (DiaSorin, Stillwater, MN, USA), while iPTH was tested with enzyme-linked immunosorbent assay (ELISA) (DiaSorin LIAISON, Stillwater, MN, USA), according to our previous protocol [7, 9]. FGF-23 levels were tested with a commercial ELISA kit (Immutopics, San Clemente, CA, USA).

Titers of anti-HBs Ab were determined using a commercial chemiluminescence immunoassay (ARCHITECT Anti-HBs Reagent kit; Abbott Diagnostics). Reactivity of anti-HBs Ab was defined by an anti-HBs antibody concentration higher than or equal to 10 mIU/ml.

Statistical analysis

Statistical analyses were performed using SPSS 18.0 software (SPSS Inc., Chicago, IL, USA). We described continuous variables as means ± standard deviations, comparing them with the results of an independent samples *t*-test or a Mann-Whitney *U*-test, if the variable did not satisfy a normal distribution. We described categorical variables as event numbers with percentages, comparing them with Chi-square test results. We analyzed the correlation between anti-HBs Ab and the mineral-related parameters (serum calcium, phosphate, calcium-phosphate products, parathorhome, 25-hydroxy-and 1, 25-dihydroxy-vitamin D, FGF-23) and nutritional parameters (albumin, lipid profile, glucose, iron profile, hemoglobin) using Pearson's correlation coefficients, after adjusting for demographic variables and comorbidities. Finally, variables with a statistically significant correlation were entered into linear regres-

Table 1. Baseline clinical features of enrollees

Clinical characteristics	Population
Demographic profiles	
Age (years)	68 ± 13
Gender (male %)	35 (63)
Duration on dialysis (years)	5.6 ± 4
Comorbidities	
Diabetes mellitus (%)	24 (43)
Hypertension (%)	50 (89)
Cirrhosis (%)	0 (0)
Heart failure (%)	1 (2)
Autoimmune disorder (%)	3 (5)
Any cancer (%)	4 (7)
Primary renal diseases	
Chronic glomerulonephritis (%)	16 (29)
Diabetic nephropathy (%)	18 (32)
Lupus (%)	2 (4)
Polycystic kidney disease (%)	2 (4)
Others (%)	18 (32)

Data are expressed as mean ± standard deviation for continuous variables, and number (percentage) for categorical variables.

sion analyses, with anti-HBs Ab titers as the dependent variable. In all analyses, a two-sided *p*-value less than 0.05 was considered statistically significant.

Results

Clinical characteristics of participants

A total of 56 chronic dialysis patients were enrolled in the current study, with an average age of 68 ± 13 years, a higher percentage of males (63%), and average dialysis duration of 5.6 ± 4 years (**Table 1**). Nearly 90% of patients had concurrent hypertension; about 45% had DM; and less than 10% had malignancy, rheumatologic disorders, and heart failure. None of the participants had liver cirrhosis. In addition, none of them reported receiving HBV vaccination within the recent 5 years before recruitment, nor did they have acute hepatitis episodes during this period.

Among these patients, one-third of ESRD cases originated from diabetic nephropathy (32%), followed by chronic glomerulonephritis (29%), lupus (4%), and polycystic kidney disease (4%).

The participants' laboratory data are provided in **Table 2**. Most of these patients were adequately dialyzed (urea reduction ratio, 74.5 ± 5.5; single pool Kt/V, 1.69 ± 0.32). The hemoglobin and albumin levels of these chronic dialysis patients were 10.0 ± 1.4 g/dL and 4.0 ± 0.3 g/dL, respectively. Mineral-bone metabolism related hormones were also measured, and the mean 25-hydroxyvitamin D and 1, 25-dihydroxyvitamin D levels were 19.5 ng/ml and 24.3 ng/ml, respectively. The distribution of iPTH and FGF-23 did not conform to normal distribution, and thus these two variables were analyzed after natural logarithmic transformation. Anti-HBs Ab titers were determined in all participants (**Figure 1**), and were also natural logarithmically transformed for analysis.

Correlation between anti-HBs Ab titers and CKD-MBD-related parameters

We next evaluated the correlation between anti-HBs Ab titers and the CKD-MBD profiles and nutritional parameters (**Table 3**). We found that after adjusting for calcium, phosphate, 25-hydroxy-and 1, 25-dihydroxy-vitamin D levels, anti-HBs Ab titers (natural log-transformed) correlated significantly with iPTH (r=0.29; *P*=0.04), FGF-23 levels (r=0.27; *P*=0.049), and ferritin (r=-0.27; *P*=0.047).

Regression analyses for the effect of selected variables on hepatitis B surface antigen reactivity

We subsequently performed multivariate linear regression analyses targeting anti-HBs Ab titers (natural log-transformed) in chronic dialysis patients, incorporating demographic data (*i.e.*, age, gender, and dialysis vintage), comorbidities (DM, autoimmune disorders), and selected laboratory parameters (**Table 3**). With only iPTH included in the model, higher iPTH levels were significantly associated with higher anti-HBs Ab titers (*P*=0.04). We further added FGF-23 in another model, and found that ferritin (*P*=0.03), iPTH (*P*<0.01), and FGF-23 (*P*=0.04) demonstrated significantly negative, positive, and positive associations with anti-HBs Ab titers in chronic dialysis patients, respectively. Sensitivity analysis including concurrent use or non-use of iron therapy or phosphate binders did not alter the study results significantly.

Discussion

In this study, we found that the reactivity against HBV in chronic dialysis patients without

Table 2. Laboratory profiles

Laboratory data	Population
Azotemia	
Pre-dialysis urea nitrogen (mg/dL)	87.2 ± 21.1
Pre-dialysis creatinine (mg/dL)	11.1 ± 2.3
Urea reduction ratio (%)	74.5 ± 5.5
Single pool Kt/V	1.69 ± 0.32
Electrolyte panels	
Sodium (meq/L)	134.8 ± 2.8
Potassium (meq/L)	4.9 ± 0.7
Chloride (meq/L)	99.1 ± 2.8
Magnesium (mmol/L)	1.1 ± 0.2
Nutritional parameters	
Hemoglobin (mg/dL)	10.0 ± 1.4
Ferritin (ng/ml)	707 ± 340
Iron saturation (%)	28 ± 11
Albumin (g/dL)	4.0 ± 0.3
Glucose (mg/dL)	95 ± 20
Total cholesterol (mg/dL)	148 ± 37
Triglyceride (mg/dL)	104 ± 59
HDL (mg/dL)	48 ± 16
LDL (mg/dL)	79 ± 28
Mineral-bone metabolism profile	
Calcium (mg/dL)*	9.3 ± 0.7
Phosphate (mg/dL)	4.7 ± 1.2
Calcium-phosphate product	44.4 ± 11.9
Intact parathyroid hormone (pg/mL)	540 ± 408
25-hydroxy-vitamin D (ng/ml)	19.5 ± 8
1, 25-dihydroxy-vitamin D (ng/ml)	24.3 ± 18.7
FGF-23 (pg/ml)	8505 ± 16069

Data are expressed as mean ± standard deviation for continuous variables. *Albumin-corrected levels. Abbreviations: FGF-23, fibroblast growth factor-23; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

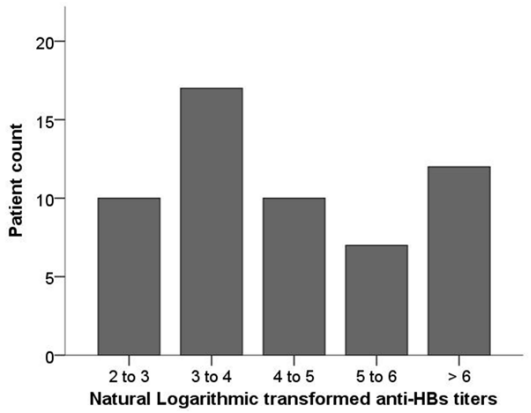

Figure 1. Distribution of anti-hepatitis B surface antigen antibody titers in the current cohort.

recent HBV vaccination or hepatitis episode, is positively associated with mineral-related hormones, including iPTH and FGF-23, independent of clinical variables. Our study specifically addresses CKD-MBD parameters and their influences on the reactivity against HBV in this unique population, and our findings might contain potential implications for managing HBV infection and even HBV vaccination efficacy.

Effective immunity against HBV is influenced by multiple factors, including host genetics, environmental, and viral features. Among host factors, age is particularly important; past studies suggest that the response to HBV vaccination diminishes in the elderly, with lower seroconversion rates after immunization [10], possibly related to immune senescence. A recent study identifies that older adults exhibit an age-sensitive B- and T-cell response to the HBV vaccine, with a disproportionately high rate of older participants being vaccine non-responders and exhibiting a compromised T-cell proliferative response [11]. Other potential immunogenicity modifiers related to hosts are genetic, including HLA class I and II alleles, as well as non-HLA genes [12, 13]. However, for patients under chronic dialysis, studies focusing on host-factors influencing serologic responses against HBV are rare. A small-scale study in elderly patients with ESRD suggests that the immunologic response to HBV is similarly reduced with ageing [14]. However, younger patients with renal failure still manifest poor HBV immunogenicity after vaccination, and the mechanism underlying this phenomenon is largely unexplored. Our study serves as an attempt to identify emerging clinical and biochemical markers for determining immunity against HBV among this ever-increasing pool of ESRD population. The reactivity against HBV in this study is not expected to result from recent vaccination or hepatitis episodes, but might reflect an evolution of their HBV-specific immunity over time.

We also found that higher ferritin levels are associated with lower anti-HBs Ab titers in chronic dialysis patients (**Table 3**). Ferritin is an iron homeostasis parameter describing body iron storage status, and iron turnover is tightly regulated physiologically. Excessive iron accumulation, demonstrated by elevated ferri-

Table 3. Multivariate linear regression analyses results, with natural log-transformed anti-HBs Ab as the dependent variable

Results	*T* value	B coefficient	*P* value
Model 1-with intact PTH			
Calcium	-1.91	-0.25	0.06
Intact PTH	2.09	0.28	0.04
Model 2-with intact PTH and FGF-23			
Ferritin	-2.27	-0.28	0.03
Intact PTH	2.72	0.35	<0.01
FGF-23	2.12	0.26	0.04

Model components included age, gender, dialysis vintage, diabetes, autoimmune disorders, laboratory data (albumin, ferritin, Ca/P, and dialysis adequacy), and vitamin D forms. Abbreviations: Anti-HBs Ab, anti-hepatitis B surface antigen antibody; FGF-23, fibroblast growth factor-23; PTH, parathyroid hormone.

tin levels, is frequently observed in patients under chronic dialysis, since utilization of intravenous iron is a common practice for boosting the erythropoietin response. Intense concern has been raised over the consequences of iron overload in ESRD patients, including oxidative stress induction and cardiovascular events. On the other hand, ferritin is also a positive acute phase reactant, with its levels increasing alongside subclinical inflammation [15]. Based on these phenomena, there might be several reasons for the observed negative association between serum ferritin levels and host reactivity against HBV. First, excessive iron, manifesting as high serum ferritin levels, could be linked to impairment of adaptive immunity. Experimental iron overload in animals affects lymphocyte proliferation and response, despite normal lymphocyte numbers [16]. Second, iron therapy in chronic dialysis patients affects redox balance, which plays an important role in immunoregulation, by potentially increasing plasma levels of oxidative stress markers (*e.g.* malonyldialdehyde and thiobarbituric acid-reactive substances) [17, 18]. Finally, hyperferritinemia might be a sign of amplified inflammatory status in ESRD patients, and chronic inflammation potentially hampers effective mounting of immune responses [19]. Indirect evidence also suggests that the genetic heterogeneity of several cytokines contributes to HBsAg seroconversion, lending support to the role of inflammation in modifying HBV immunity [20].

Serum iPTH and FGF-23 levels, on the other hand, were positively correlated with anti-HBs Ab titers in chronic dialysis patients (**Table 3**). Several putative reasons might explain this interesting finding. Anecdotal reports have addressed the complex relationship between hyperparathyroidism, inflammation, and immunity. The conventional view favors an immunosuppressive role for hyperparathyroidism, especially in ESRD patients, but more recent studies show a more heterogeneous effect of PTH in influencing immunity [21]. Patients with primary hyperparathyroidism exhibit increased adipose tissue expression of genes involved in immune activation, compared with those without hyperparathyroidism [22]. However, direct incubation of human lymphocytes with PTH or 1-34 PTH fragments did not alter lymphocytic proliferation or the capacity for interleukin-6 (IL-6)/IL-8 production [23]. On the contrary, the effect of FGF-23 on immunity is still an uncharted field. Preliminary reports suggest that FGF-23 could indirectly modulate innate immune responses through regulation of CYP27B1, the activating enzyme of 25-hydroxyvitamin D within monocytes [24]. Another study also provides histopathologic evidence of FGF-23 expression in macrophages from atherosclerotic plaques [25]. Despite these insightful findings, the effect of FGF-23 on adaptive immunity, which is vital for combating HBV, has not been studied before. Our pilot results might shed light on the potential immunoregulatory roles of PTH and FGF-23, both of which are frequently elevated in chronic dialysis patients. PTH and FGF-23 are stimulated by persistent hyperphosphatemia, a potential marker of increased protein intake and nutritional competence, in chronic dialysis patients [26]. Meta-analysis has found that nutritional adequacy is significantly associated with improved serologic responses to HBV vaccination in CKD patients [27]. However, we tried to take into account the influence of serum phosphate and albumin levels in our regression analysis (**Table 3**), and the associations between anti-HBs Ab and iPTH/FGF-23 remained significant. It is likely that a single measure of serum phosphate could not be representative of time-averaged phosphate levels, to which PTH and FGF-23 would be more sensitive. Further study might be needed to confirm our findings.

Some limitations do exist in the present study. The sample size is modest, and this cohort mainly consisted of chronic hemodialysis pati-

ents. Since the phenotypes of mineral-bone disorders differ between hemodialysis and peritoneal dialysis patients, these results might not be applicable to patients undergoing peritoneal dialysis. Furthermore, there may be other unidentified factors that influence anti-HBs Ab and mineral-related hormones.

Conclusion

In the current pilot study, we investigated the relationship between mineral-related parameters of chronic dialysis patients and the reactivity against HBV, manifesting as anti-HBs Ab titers. Serum ferritin levels were negatively associated with anti-HBs Ab levels, while iPTH and FGF-23 levels were positively associated with anti-HBs Ab levels. Larger studies incorporating more variables are required to confirm and expand our findings.

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Disclosure of conflict of interest

None.

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