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*Original Article*

# Prospective Analysis of Factors Influencing the Antibody Response to Hepatitis B Vaccine in Hemodialysis Patients

Alexandra Ouzouni, Elena Papadopoulou, Fotini Miari, Theodoros Pliakogiannis, Sofia Mademtzoglou, Kiriaki Traianou, Chrisovalantou Giannioti, Fani Papoulidou, Maria Kalientzidou and Kalaitzidis Kleonikos

Department of Nephrology, General Hospital of Kavala, Greece

**Abstract**

**Background.** Patients on maintenance hemodialysis typically show a suboptimal immune response to hepatitis B (HB) virus vaccination compared to the non-uremic population. The aim or our study was the identification of factors implicated in the vaccine response of our hemodialysis patients.

**Methods.** We studied prospectively 63 hemodialysis patients who were seronegative for HB (37 males, 26 females). Their mean age was 62.2±11.28 years (range 35-80) and hemodialysis. Duration 55.96±50.1 months (range 6-225) fourteen of them (22.2%) were diabetics. Our patients followed a four-dose vaccination schedule (0, 1, 2 and 6 months) with 40 μg of a recombinant DNA HB vaccine. The antibody response was determined 1 month after the fourth dose of vaccination by assessing the titre of antiHBs antibodies (ab). Immune response was defined as sufficient when the antiHBs ab level was ≥ 12 mIU/ml. During the 6-month vaccination period we also monitored monthly and time-averaged Kt/V, residual renal function (RRF), BMI, serum creatinine, albumin, transferrin, ferritin, CRP, iPTH and the dose of erythropoietin and Vitamin D that they received.

**Results.** An optimal immune response was achieved in 34 patients (54%, responders) (antiHBs: 295.95±341.67 mIU/ml), whereas 29 patients (46%, non-responders) showed a suboptimal response (antiHBs: 1.98±2.92 mIU/ml) ($p=1.75x10^{-5}$). There was a statistically significant negative correlation between the antiHBs ab titre and BMI ($r=-0.28$, $p=0.024$). A significant difference was also found between the BMI of responders and non-responders as groups (24.8±5.5 vs. 27.2±4.5, $p=0.02$). Grouping our patients according to the existence of diabetes, age (cut off 60 years), and hemodialysis efficiency ($Kt/V\geq1.2$) we found a statistically significant difference in the antiHBs ab titre between diabetics and non-diabetics (8.43±12.3 vs. 200.2±317.7 mIU/ml, $p=0.03$), younger and older patients (262±365.09 vs. 84.36±189.1 mIU/ml, $p=0.0145$) and patients with efficient and inefficient hemodialysis (234.71±337.1 vs. 79.14±200.99 mIU/ml, $p=0.032$). Treatment with vitamin D analogues, RRF and hypoalbuminemia were not found to be implicated in the immune response of our patients.

**Conclusions.** It seems that increased BMI; diabetes; advanced age and inefficient hemodialysis impaired the immune response to HBV vaccination of our hemodialysis population. Future studies should be conducted to investigate the need for tailored vaccination schedules for this hemodialysis subpopulations.

**Keywords:** antibody response, hemodialysis patients, hepatitis B, vaccination.

## Introduction

Patients on maintenance hemodialysis are at high risk of infection with hepatitis B virus (HBV) despite segregation, universal precautions, vigorous vaccination protocols and the widespread use of erythropoetin leading to the reduced need for blood transfusions. At the same time hemodialysis patients typically show a suboptimal immune response to HB virus vaccination compared to the non-uremic population [1]. Protective antibody levels develop only in 60% of the hemodialysis population [2,3]. Many factors may be implicated in this suboptimal immune response such as uremia per se, altered renal metabolism of immunological active protein, the specific effect of renal replacement therapy, malnutrition, chronic inflammation, inefficient dialysis, age, race, diabetes mellitus and many more [4-15]. Moreover factors like insufficient vaccine dosing or omitting a dose may lead to suboptimal antibody production in hemodialysis patients [2-16]. In this context the aim or our study was the identification of factors implicated in the vaccine response of our hemodialysis population.

## Patients and methods

From a cohort of 112 hemodialysis patients from our unit we studied prospectively 63 who were seronegative for HB (37 males, 26 females). An unsuccessful attempt for vaccination for HB was performed in 21 of the 63 patients included in the study. Positive patients for hepatitis B (HBeAg and anti-HBc) and those with a sufficient anti-HBs titer from former anti-HB vaccination, acute inflammatory status, malignancy and decompensated chronic liver disease were excluded. In addition, patients with autoimmune disease and patients which received immuno-suppressants

*Correspondence to:* Ouzouni Alexandra, Nephrology Department, General Hospital of Kavala, Amerikanikou Erythrou Staurou 113, 65001 Kavala, Greece; Tel.: 00302510292034; Fax: 00302510292034; E-mail: alouzouni@mail.gr

in the last three months were also excluded. The prevalence of hepatitis B and hepatitis C infection in unit is 2.67% (3 patients) and 7,15% (8 patients) respectively. The demographic and laboratory characteristics of our study population are shown in Table 1.

The laboratory values are the mean value of the six months observation period. The Mean age of our patients was 62.2±11.28 years (range 35-80) and hemodialysis duration 5.96±50.1 months (range 6-225). Fourteen (22.2%) of our patients were diabetics. Our patients followed a four-dose vaccination schedule with 40 μg of a recombinant DNA HB vaccine administered by deltoid intramuscular injection at time 0, 1, 2 and 6 months. We chose to use this vaccination schedule recommended by the U.S. Food and Drug Administration for Preventing Transmission of Infections Among Chronic Hemodialysis Patients because of the higher protective antibody response obtained (86%) in correlation with the three dose schedule (64%) recommended by the European best practice Guidelines [17,18].

**Table 1.** Demographic and laboratory characteristics of our hemodialysis patients

| Parameters | Values |
|---|---|
| Patients Number | 63 |
| Males | 37 |
| Females | 26 |
| Male/Female ration | 1.42 |
| Age (years) | 62.2±11.28 |
| Time on HD* (months) | 55.96±50.1 |
| Diabetics | n=14 (22.2%) |
| Time-averaged Kt/V | 1.56±1.08 |
| RRF* (ml/min) | 5.41±5.36 |
| BMI* (kg/m2) | 26.03±4.13 |
| Serum creatinine (mg/dl) | 9.53±2.48 |
| Serum albumin (g/L) | 3.47±0.44 |
| Serum transferrin (g/L) | 1.81±0.53 |
| Serum ferritin (mg/dl) | 675.92±511.84 |
| CRP* (mg/dl) | 1.05±1.41 |
| iPTH* (pg/ml) | 187.21±171.31 |
| Erythropoietin dose (IU/week) | 4790±3450 |

* HD: hemodialysis, RRF: residual renal function, BMI: body mass index, CRP: C reactive protein, iPTH: intact parathormon

The antibody response was determined 1 month after the fourth dose of vaccination by assessing the titre of antiHBs antibodies (ab). AntiHBs titers were measured in plasma samples by enzyme immuneassay (Abbott Laboratories USA). The immune response was defined as sufficient when the antiHBs ab level was ≥12 mIU/ml. Those with levels 12-100 mIU/ml were termed "poor responders", whereas those with levels >100 mIU/ml were termed "good responders". During the 6-month vaccination period we also monitored monthly time-averaged Kt/V, residual renal function (RRF), BMI, serum creatinine, albumin, transferrin, ferritin, CRP, iPTH and the dose of erythropoietin and Vitamin D that they received.

*Statistical analysis*

Results are reported as mean ± SD. Statistical significance was calculated for differences between means by use of an unpaired t-test. Correlation between variables was performed by the Pearson correlation test. A P value of less than 0.05 was considered significant.

**Results**

An optimal immune response was achieved in 34 patients (54%, responders) (antiHBs: 295.95±341.67 mIU/ml), whereas 29 patients (46%, non-responders) showed a suboptimal response (antiHBs: 1.98±2.92 mIU/ml) (p=1.75x10-5). In the responder group 20 patients (59%) had an antibody titre of antiHBs > 100mIU/ml (good responders) and 14 patients (41%) had an antibody titre of antiHBs 12-100mIU/ml (poor response). There was a statistically significant negative correlation between the antiHBs ab titre and BMI (r=-0.28, p=0.024). A significant difference was also found between the BMI of responders and non-responders as groups (24.8±5.5 vs. 27.2±4.5, p=0.02). (Figure 1).

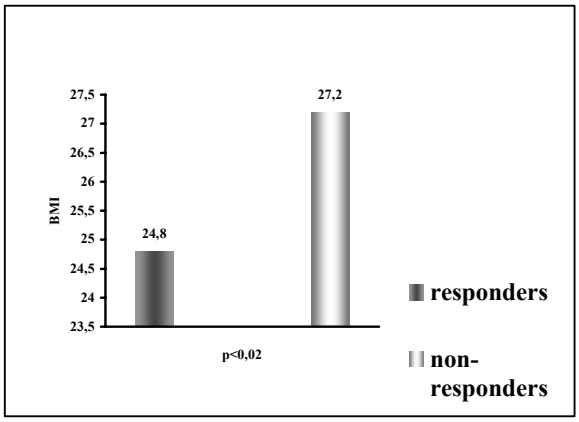


**Fig. 1.** Difference of BMI between responders and non-responders

Grouping our patients according to the existence of diabetes, age (cut off 60 years), and hemodialysis efficiency (Kt/V≥1.2) we found a statistically significant difference in the antiHBs ab titre between diabetics and non-diabetics (8.43±12.3 vs. 200.2±317.7 mIU/ml, p=0.03) younger and older patients (262±365.09 vs. 84.36±189.1 mIU/ml, p=0.0145) and patients with efficient and inefficient hemodialysis (234.71±337.1 vs. 79.14±200.99 mIU/ml, p=0.032) (Table 2). Treatment with vitamin D analogues, RRF and serum levels of creatinine, albumin, transferrin, ferritin, CRP and iPTH were not found to be implicated in the immune response of our patients.

**Table 2.** Differences in the antibody response according to the existence of diabetes mellitus, age and hemodialysis efficiency in our hemodialysis patients

| Parameters | HBsAb (mIU/ml) | P |
|---|---|---|
| Diabetics | 8.43 | 0.03 |
| Non-diabetics | 200.2 | |
| Age < 60 years | 262 | 0.0135 |
| Age > 60 years | 84.36 | |
| Kt/V < 1.2 | 79.14 | 0.032 |
| Kt/V > 1.2 | 234.71 | |

## Discussion

In our series, the percentage of patients responding to the HB vaccine was 54% which is similar to the results obtained in other groups [2,3]. This percentage is lower than in the general population despite using a double vaccination dose, reflecting the immune deficiency of patients with chronic renal failure. Many factors impinge on the effectiveness of a vaccine. Not only the potency of the vaccine is important, but also patient characteristics. Along with uremia, malnutrition, obesity, diabetes mellitus, increased age, seropositivity for antibody against hepatitis C, impaired T-cell receptor expression and HLA DR3, DR7, DQ2 have been associated with poor response of hemodialysis patients to HBV vaccine [2-12,14,15]. Conversely, there is evidence that Epo therapy improves response rates [13]. But it is worth mentioning that there is great controversy in the literature about the factors which are implicated in the antibody response of the hemodialysis population.

In our study we found a better antibody response in the group with lower BMI. In one study Chow KM *et al* found an inadequate anti HBs response in obese hemodialysis patients, which could in part be attributed to a low vaccine dose, so it could be assumed that obese patients are in need of an even higher vaccine dose or maybe the dose should be calculated according to body weight [2].

We also found a better antibody response in the non-diabetic group, consistent with the findings of the previous study [2]. However another study of Eardley *et al* did not confirm this finding in this paper the existence of diabetes mellitus did not affect response rates to the HB vaccine in hemodialysis patients [8]. We also found that patients in the younger age-group had a better respond rate to the vaccination schedule than our older patients, the same finding was also previously reported by other studies [2,5,9,12]. However other studies did not confirm an association between age and antibody response to the HB vaccine in HDpts [8,11]. Our study showed also a better immune response to vaccination in patients with higher Kt/V consistent with the findings of Kovacic V *et al* and Ibrahim S *et al* [10,11], a finding not confirmed by other studies [8,9,12].

Despite the limitations of the present study, that is the limited number of patients and the heterogeneous study population, as there was an attempt for vaccination against HBV in some of our patients in the past, our findings are of clinical relevance as some of the factors influencing the antibody response could be modifiable. So maybe there is need for a dose adjustment of the vaccine dose according to body weight in patients with a high BMI and diabetes mellitus. Another option is to vaccinate our patients at an early stage of chronic kidney disease before dialysis is started in an attempt to achieve a better antibody response at a younger age. Moreover optimizing the hemodialysis dose could also lead to a better immune response to the HB vaccination.

## Conclusions

In conclusion, it seems that increased BMI; diabetes mellitus; advanced age and inefficient hemodialysis impaired the immune response to HBV vaccination of our haemodialysis population. However since there is great controversy in the literature about the factors which are implicated in the antibody response of hemodialysis patients it seems that there is need of a systemic review of the literature and meta-analysis of clinical trials, moreover future studies should be conducted to investigate the need for tailored vaccination schedules for specific hemodialysis subpopulations.

*Conflict of interest statement.* None declared

## References


1. Schreiber GB, Busch MP, Kleinman SH, Korelitz JJ. The risk of transfusion transmitted viral infection. *N Engl J Med* 1996; 334: 1685-90.
2. Chow KM, Law MC, Leung CB, Szeto CC, Li PK. Antibody response to hepatitis B vaccine in end stage renal disease patients. *Nephron Clin Pract* 2006; 103(3): c89-93.
3. Stevens CE, Alter HJ, Taylor PE, *et al*. Dialysis vaccine trial study group. Hepatitis B vaccine in dialysis receiving hemodialysis. Immunogenicity and efficacy. *N Engl J Med* 1984; 311: 496-501.
4. Dumann H, Meuer S, Koehler H. Hepatitis B vaccination and interleukin 2 receptor expression in chronic renal failure. *Kidney Int* 1990; 38: 1164-68.
5. Fabrizi F, Martin P, Dixit V, Bunnapradist S, Dulai G. The effect of age on immunological response to hepatitis B vaccine in end-stage renal disease. Meta analysis. Alim Pharm & Therap 2004; 20(10): 1053-1062.
6. Fabrizi F, Dixit V, Dunnapradist S, Martin P. The dialysis mode and immunological response to hepatitis B virus vaccine in dialysis population. Meta-analysis. *Alim Pharm & Therap* 2006; 23(8): 1105-1112.
7. Stachowski J, Pollok M, Barth C, Maciejewski J, Baldamus CA. Non-responsiveness to hepatitis B vaccination in hemodialysis patients: association with impaired TCR/CD3 antigen receptor expression regulating co-stimulatory processes in antigen presentation and recognition. Nephrol Dial Transplant 1994; 9: 144-152.
8. Eardley KS, Jones H, Osman H, Smith S. Efficacy of the accelerated hepatitis B vaccination schedule used in hemodialysis patients post-exposure to virus: a single-center experience. *Nephrol. Dial Transplant* 2002; 17(11): 1982-1987.
9. Peces R, de la Torre M, Alkazar R, Urra JM. Prospective analysis of the factors influencing antibody response to hepatitis B vaccine in hemodialysis patients. *Am J Kidney Dis* 1997; 29(2): 239-45.
10. Kovacic V, Sain M, Vukman V. Efficient hemodialysis improves the response to hepatitis B virus vaccination. *Intervirology* 2002; 45(3): 172-6.
11. Ibrahim S, el Din S, Bazzal I. Antibody level after hepatitis B vaccination in hemodialysis patients: impact of dialysis adequacy, chronic inflammation, local endemicity and nutritional status. *J Nati Med Assoc* 2006; 98(12): 1953-7.
12. Fernandez E, Betrin MA, Gomez R, Montolin J. Response to the hepatitis B virus vaccine in hemodialysis patients: influence of malnutrition and its importance as a risk factor for morbidity and mortality. *Nephrol Dial Transplant* 1996; 11: 1559-1563.

13. Hassan K, Shternberg L, Alhaj M *et al*. The effect of erythropoietin therapy and hemoglobin levels on the immune response to Engerix B vaccination in chronic kidney disease. *Ren Fail* 2003; 25(3): 471-8.
14. Girndt M, Sester U, Sester M, Kaul H, Koehler H. Impaired cellular immune function in patients with end-stage renal failure. *Nephrol Dial Transpland* 1999; 14: 2807-2810.
15. Kara IH, Yilmaz ME, Suner A, Kodiroglu AK, Isikoglu B. The evaluation of immune responses that occur after HBV infection and HBV vaccination in hemodialysis patients. *Vaccine* 2004; 22(29-30): 3963-7.
16. Peces R, Laures AS. Persistence of immunologic memory in long-term hemodialysis patients and healthcare workers given hepatitis B vaccine: role of booster dose on antibody response. *Nephron* 2001; 89(2): 172-6.
17. U. S. Food and Drug Administration. Recommendations for Preventing Transmission of infections Among Chronic Hemodialysis Patients. 2001; 50 (RR05): 1-43.
18. European best practice Guidelines. Section VI. Hemodialysis-associated infection. VI.6 Prevention and management of HBV, HCV and HIV in HD patients. *Nephrol Dial Transplant* 2002; 17: 78-81.