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**Is hemodialysis a reason for unresponsiveness to hepatitis B vaccine? Hepatitis B virus and dialysis therapy**

Sit D *et al.*Hepatitis B virus and dialysis therapy

Dede Sit, Bennur Esen, Ahmet Engin Atay, Hasan Kayabaşı

Dede Sit, Bennur Esen, Ahmet Engin Atay, Hasan Kayabaşı, Department of Internal Medicine and Nephrology, Bagcilar Education and Research Hospital, Istanbul 34200, Turkey

**Author contributions:** Sit D, Esen B, Atay AE and Kayabaşı H planned and wrote the manuscript; Sit D and Atay AE edited and responsed to critics of reviewer.

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**Correspondence to: Dede Sit, Associated Professor,** Department of Internal Medicine and Nephrology, Bagcilar Education and Research Hospital, Mimar Sinan Avenue, 6. Street, Bagcilar, Istanbul 34200, Turkey. drdede75@hotmail.com

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**Abstract**

Impaired renal function is associated with high risk of chronicity of hepatitis B virus (HBV) infection. Patients on hemodialysis (HD) or peritoneal dialysis are at increased risk viral transmission due to frequent necessity of blood product transfer as well as use of contaminated dialysate or dialysis materials. Additionally health professionals may cause to viral spread via contaminated hands and carelessness against hygiene rules. The frequency of chronic HBV infection may be as high as 80% in patients on renal replacement therapies. This is because HBV vaccination is essential to eliminate chronic HBV infection. However response rates of HD patients to HBV vaccination varies between 10%-50%. Dialysis adequacy and early vaccination before the onset of dialysis therapy seem to be major determinants of high seroconversion rates. Older age, male gender, duration of dialysis therapy and nutritional status are other well known factors associated with seroconversion rate. There are controversial reports regarding to the role of the presence of diabetes mellitus, HCV positivity, erythropoietin resistance, hyperparathyroidism, vitamin D inadequacy. The role of genetic alteration in the functions or production of cytokines is still need to be elucidated.

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Key words: Hepatitis B virus; Vaccine; Hemodialysis; Response; End stage renal disease

**Core tip:** Due to immunesuppresive effect of uremia and dialyser membranes chronicity of hepatitis B virus (HBV) infection is frequently observed. Seroconversion rates of HBV vaccine is diminished in chronic kidney disease patients when compared to general population which gradually decreases as renal functions deteriorates. Efficient dialysis is major determinant of response to HBV vaccination. In contrast to 3 doses of 20 uq HBV vaccine for general population, patients on hemodialysis or peritoneal dialysis usually require 4 doses of 40 uq HBV vaccine

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INTRODUCTION

Hepatitis B virus (HBV) infection is an important public health problem affecting approximately 500 million people worldwide[1-3]. According to 2010 data, 360 million people have chronic HBV infection that leads to more than 1 million death/year due to acute hepatitis, cirrhosis or hepatocelular carcinoma[4,5].

Patients with chronic kidney disease (CKD) exhibit impaired immune response against host agents including HBV via bone marrow supression due to uremia and loss of CD4 T cells by use of bioimcompatibility of dialysate and membranes[6,7]. Patients on HD or PD have increased risk of HBV related complications. On the other hand, the seroconversion rates of HBV vaccination in patients with CKD is significantly lower than general population[8,9].

THE EPIDEMIOLOGY OF HEPATITIS B VIRUS INFECTION

Chronic HBV infection is associated with high morbidity and mortality by leading to carrier state or chronic infection[10-14]. Pediatric population; especially newborn, as well as individuals at advanced age are at increased chronicity risk of HBV infection[15]. Clinical course of chronic HBV infection may vary from asymptomatic carrier state to cirrhosis or even hepatocellular carcinoma[16].

Recently, the rates of HbsAg positivity is 0.1% in western countries[17]. However it is significantly higher in some areas like Southeastern Asia and Middle east region. Majority of southeast and Middle east Asian countries have an intermediate or high endemicity of HBV infection[18]. Based on the data in 2009, the rate of HBsAg positivity was 4.4% in Turkish population (ranging from 2.5% to 9.1%)[19]. Figure 1 shows the geographic distribution of chronic HBV infection.

THE RISK OF CHRONICITY IN THE GENERAL POPULATION AND DIALYSIS PATIENTS

The chronicity rate of HBV infection is 5%-10% in general population whereas it may be as high as 60%-80% in patients receiving renal replacement therapy (RRT)[20]. Nucleoside analogues and interferon are choices of treatment however sustained viral response is achieved in only 30%-40% of patients on dialysis[21]. Owing to the fact that chronicity rate of HBV is high and success rate of antiviral therapy is low in dialysis population, preventive measures against HBV is of vital importance.

Since the first recommendation of HBV vaccination by the Center for Disease Control and Prevention, United States in 1982, administration of recombinant HBV vaccine which is composed of HBV surface antigen (HBsAg) is routinely used[22].

ADMINISTRATIONS OF HEPATITIS B VACCINE

Former vaccines were derived from human plasma however as a consequence of innovations in vaccine technology, vaccines produced by recombinant DNA technology were introduced[23]. Recombinant HBV vaccine composed of HBV surface antigen (HBsAg) are associated with high seroconversion rates[24]. Recombinant HBV vaccine contains 20 ug HBsAg solution with 0.5 mg Aluminium salt[25]. A number of adjuvants including levamisole, zinc, interferon, interleukin-2 and thymopoietin were added to increase the effectiveness[26-32].

Neutralizing antibodies against HBsAg indicates prior infection with HBV or triggered immune response against HBsAg in HBV vaccine[33-37]. Exposure to HBV is defined as appearance of HBsAg with or without antibody to HBeAg and HBcAg[38]. A group of patients may be in the window period which is associated with sole appearance of IgM class antibody against HBcAg[39]. Seroconversion of HBV is defined as appearance of antiHBs in the absence of HBsAg, HBeAg, HBcAg and undetectable HBV DNA[40]. Table 1 summarizes the interpretation of serologic results.

HBV vaccination should be started before the initiation of RRT[41]. Currently intramuscular administration HBV vaccine given at 0, 1, 2 and 6th months in the dose of 40 ug is recommended. Instead of gluteal region which contains muscle and fat, deltoid muscle is a preferable area to increase response rates[42].

There is a variable response rates to HBV vaccination among HD patients. Inadequate seroconversion rate in general population and patients on RRT are 5%-10% and 40%-50%; respectively[43]. According to another report, still 20% of vaccinated patients on HD does not achieve antibody formation against HBsAg[44].

Lack of consensus exist regarding to determine optimal vaccination schedule for patients with CKD at predialysis stage. For patients on RRT, the recommended vaccination schedule contains twice the dose of general population (40 µg) in 4 cycles at intervals of 0, 1, 2 and 6 mo administered by intramuscular route at one sites[45]. Additional three cycles of HBV vaccine should be administered to patients who do not response to primary schedule[46,47] (Figure 2).

THE RATES OF RESPONDERS AND NONRESPONDERS TO HBV VACCINATION ON DIALYSIS PATIENTS

Because patients on RRT have blunted immune response, they exhibited unsatisfactory response to HBV vaccination when compared to healthy individuals[48]. Dacko *et al*[49] concluded that efficient hemodialysis as well as age, nutritional status and systemic inflammation are determinants of adequate response to HBV vaccination[49]. Similarly Hashemi *et al*[50] stated that duration of dialysis, hemoglobin and parathyroid hormone level and accompanying HCV infection do not affect immune response to HBV vaccination[50].

Seroconversion and adequate response are defined as anti-HBs > 10 IU/mL and > 100 IU/mL; respectively. Buti *et al*[51] stated that seroconversion was achieved in 76.7% of HD patients whereas adequate response was observed only in 53.5% at the 3rd month of vaccination[51]. In a report from Saudia Arabia, adequate response rates reach to 89.5% in HD patients[52]. Similarly, some reports determined a satisfactory seroconversion rates among HD patients. Jadoul *et al*[53] showed that seroconversion rates among HD patients is 89.65%[53]. Suboptimal response to HBV vaccine in HD patients is probably related to immunologic factors and poor nutritional status. Patients on RRT have impaired humoral and cellular immune response leading to underproduction of antibody.

Seroconversion rates may vary in different stages of CKD. Agarwal *et al*[47] performed a study to determine response rates to HBV vaccine in mild (creatinine 1.5 mg/dL to 3.0 mg/dL), moderate (creatinine 3.0 mg/dL to 6.0 mg/dL) and severe (creatinine > 6.0 mg/dL) CKD[47]. They pointed that seroconversion rates by 3 doses of 20 ug HBV vaccine in mild, moderate and severe CKD were 87.5%, 66.6% and 35.7%; respectively that were significantly lower than 4 doses of 40 ug with a seroconversion rate of 100%, 77% and 36.4%; respectively.

There are some reports with regard to the role of administration route on the rate of serconversion in HD patients. In a metaanalysis including 14 study and 718 adult patients on HD, Fabrizi *et al*[54] concluded that seroconversion rate of intramuscular administration of HBV vaccine is significantly lower that that of intradermal administration [odds ratio (OR) 0.454, 95%CI : 0.3; 0.67), *P* = 0.001)[54].

There are controversial report regarding to success rate of HBV vaccination in patients at predialysis stage and patients on dialysis therapy. Taheri *et al*[55] indicated that response rate of HBV vaccination in predialysis patients is similar to dialysis patients. In contrast, Seaworth *et al*[56] observed that patients at predialysis stage have more favorable outcome than patients at dialysis stage suggesting to early vaccination as soon as possible.

In conclusion, several factors including advanced age, DR3, DR7 and DQ2 positivity and the absence of A2 alleles may influence response to hepatitis B vaccine in HD patients. Natural HBV infection achieves higher seroconversion rates than HBV vaccination however current HBV vaccination schedule provides a remarkable seroconversion rates.

THE PATHOGENESIS OF UNRESPONSIVENESS TO HBV VACCINATION

HBV vaccination stimulates specific antibody production by the activation of B cells which is mediated by CD8 cytotoxic T cells and CD4 helper T cells[57]. As previously known, uremia is associated ith impaired immune response via several ways including cellular and humoral immune mechanisms. Patients on dialysis have lymphocytopenia, shortened life duration of lymphocytes and/or dysfunctional lymphocytes. Adequate CD4 lymphocyte count is essential to provide antibody production subsequent to vaccination[58,59].

Sengar *et al*[60] showed that impaired immune response to HBV transmission linked to a group of human leukocyte antigen (HLA). Alper *et al*[61] determined an association between inadequate response to HBV vaccine and HLA-DR3 and HLA-B8 in Caucasian population. By time, some HLA groups were identified as predictors of low response to HBV vaccine. Pol *et al*[62] and Hohler *et al*[63] showed that low responders to HBV vaccine have enhanced expression of DRB 1 × 3, DRB 1 × 7 and DRB 1 × 14[62,63].

Walker *et al*[64] pointed out that nonresponders to HBV vaccine exhibit excess of HLA-DR7 and absence of HLA-DR1. In accordance with this study, patients with HLA-DR1, -DR5, -DR2, -DQ5 and-DP4 usually well respond to HBV vaccine and usually seroconvert[63].

Albumin level as a nutritional marker has been shown to directly affect antibody response to HBV vaccination. Brown *et al*[65] showed that patients with hypoalbuminemia are unable to produce adequate titers of antiHBs. Creatinine level is an indicator of protein intake and nutrition in general population however due to lower excretion rate in patients with CKD, it is not suitable marker for the assessment of nutritional status.

Age is another factor that may affect antibody response to vaccination[66]. Owing to fact that bone marrow depression by aging, humoral and cellular responses are impaired in elderly patients. Patients at advanced age have lymphocytopenia, monocytopenia and neutropenia as well as functional deterioration of these cells. Lymphocyte mediates humoral response against viral antigens in different steps. Only 15% of responders were older than 60 years however 55% of nonresponders were above 60 years of age[47]. Decline of anti-HBs level is quicker in older ages suggesting defective function of T lymphocytes and inadequate production of interleukins. In a study from Egypt, seroconversion rate of HBV vaccination may be as high as 89% while it was only 51% above 60 years[67]. Seroconversion rates significantly decline in older ages. The mean age of responders was 40.6 years while that of nonresponders was 59.6 years in the same study.

Also male patients on dialysis have significantly diminished antibody response to HBV vaccine when compared to female patients. Male gender is associated with impaired response to vaccine. Seroconversion rates of female and male dialysis patients were 85.6% and 68.3%; respectively and only 29% of seroconversion were male[21].

Body weight, diabetes mellitus, hyperparathyroidism, erythropoietin resistance, vitamine D deficiency, use of low bioimcompatible dialysis material, iron overload, high number of blood product transfer, vitamin deficiency and hepatitis C positivity are well-known factors that are associated with poor response to vaccination[68-71]. On the otherhand, Roozbeh *et al*[72] stated that age, gender, BMI and serum albumin level do not significantly affect seroconversion rates.

Dialysis adequacy is probably a globally validated determinant of seroconversion rates. Seroconversion rates significantly correlated with renal function. Ghadhiani *et al*[73] reported that seroconversion rate of patients with GFR < 15 mL/min, 15 to 60 mL/min and > 90 mL/min are 44%, 90% and 96%; respectively.

Controversion exist about the role of diabetes mellitus on response to HBV vaccine. Al Saran *et al*[52] concluded that the presence of DM has nonsignificant effect on seroconversion rates. However Chin *et al*[74] stated that dialysis patients with DM have poor response to HBV vaccine.

Afsar *et al*[69] carried out a study in dialysis patients to evaluate the relation of EPO resistance and response to HBV vaccine, and observed that erythropoietin resistance inversely influence the response to HBV vaccine.

Vast majority of reports determined that HCV positiviy is related with poor response to HBV vaccination[75]. However some recent reports failed to demonsrate a negative impact of HCV positivity on response to HBV vaccination[76]. Table 2 summarized the factors involved in the pathogenesis of unresponsiveness to HBV vaccination.

THE ROLE OF DIALYSIS THERAPY ON RESPONSE TO HBV VACCINATION

Patients on dialysis therapy have functionally and/or numerically defective regulatory T cells leading to immunodeficiency and dysintegration between antigen presenting cells and CD4 T cells[77]. Accordingly, patients on HD deteriorated neutrophile and macrophage functions resulted with inhibited chemotaxis and opsonization; both play reactive role against host antigens. Selective T cell depletion is frequently observed immunologic defect in dialysis patients that causes diminished production of IL-1, IL-2, IL-6 and TNF-α[78]. In addition, interferon-gamma is produced by T cells and induces endocellular lysis of microorganims and antigens.

Immunodeficiency is less frequently detected in patients receiving PD. They generally have depressed bactericidal activities of macrophages like opsonization, phagocytosis and lymphocytopenia which reflects diminished peritoneal host defense[79]. Dialysis membranes and use of reaginic dialysis material are associated with excessive but non-effective immune response[80].

Regulation of immune response and interaction of mediators involved in immune response are complex processes and some unknown factors may influence their functions[81]. Roy *et al*[82] stated that decreased level of cytokines that mediate the function of T helper cells may be associated with low response to HBV vaccine. Deficiency of Th-1 like cells and defective or inadequate production of some cytokines by Th-1 cells are associated with immunosupression and low response to viral agents[83]. IL-1, IL-2, IL-6, IL-12 and IFN gamma are major cytokines involved in response to viral agents. Genetic polymorphisms and polymorphic variant of spesific cytokines are associated with unresponsiveness to HBV vaccine[84].

FOLLOW-UP OF SEROCONVERSION OF HBV INFECTION

The recommended antibody titer to HBsAg should be > 100 IU/mL[85]. An importatnt proportion of dialysis patients that achieve adequate response (> 100 IU/mL) require booster dose in every 5 years to maintain anti-HBs titer[86]. Patients that failed to produce adequate antibody response should undergo to booster vaccination at 1 year and at 5 year of primary vaccination schedule[73].

The antibody titer < 10 IU/mL is defined as hyporesponse and > 10 IU/mL is accepted as positive seroconversion[87]. However anti-HBs titer below 100 IU/mL is evidence of low response.

Positive seroconversion (AntiHBs > 10 IU/mL) does not always warrant protection against HBV infection in dialysis patients. Lombardi *et al*[88] suggested that antiHBs titer of at least 50 IU/mL should be target level in HD patients.

Because the exact reason of lower serconversion rates to HBV vaccine is not known, the best strategy to overcome the unresponsiveness is to adminstrate additional HBV vaccine. Wismans *et al*[89] showed that seroconversion rate after 1 and 3 additional 20 µg dose of HBV vaccine achieve a response rate of 38% and 75%; respectively. Similarly, another study demonstrated 61% seroconversion rate after additional vaccination[90].

DECREASE OF ANTI-HBS TITERS

On the other hand, a group of dialysis patients that well respond to HBV vaccination and produce neutralizing antibody against HBsAg do not maintain antibody level within time. Although decline in antiHBs titer by time is globally known in general population as well as dialysis patients. it is significantly frequent and quicker in patients on RRT.

At the first year of vaccination, anti-HBs > 10 IU/mL is protected in 82,5% of general population by 3 doses of 20 µg however it was only 53% in dialysis patients by 4 doses of 40 µg[91]. At the 3rd year of vaccination, vast majority of HD patients have undetectable antiHbs level. American Association for the Study of Liver Diseases recommend annual screening of antiHBs titers and booster vaccination as antiHBs titer is around 10 IU/mL[40].

NEW INSIGHTS TO IMPROVE SEROCONVERSION RATES

Innovations in recombinant DNA vaccine technology may be hopeful to increase seroconversion rates and sustain response. IL-12-based vaccination therapies may restore HBV-specific CD4(+) T cell responses and augment seroconversion[92]. In agreement with Zheng *et al*[92], Lau *et al*[93] showed that combination HBV vaccine with interferon-gamma or interleukin-12 may enhance therapeutic efficacy[93]. Accordingly, Sorni *et al*[94] mentioned that IFN-adjuvanted HBV vaccination may be beneficial for hyporesponsive patients. In addition, nano-adjuvants seem to be frequently used to overcome unresponsiveness[95].

CONCLUSION

Despite increased awareness against HBV and improvement in hygiene preservations, patients receiving RRT are still at increased risk of HBV transmission. Addtionally due to immunosuppresive effect of uremia and dialyser membranes, chronicity of HBV infection is frequently observed. Seroconversion rates of HBV vaccine is diminished in CKD patients when compared to general population which gradually decreases as renal functions deteriorate. Efficient dialysis is major determinant of response to HBV vaccination. That is why early vaccination against HBV as soon as possible is essential to overcome unresponsiveness to HBV vaccine. In contrast to 3 doses of 20 µg HBV vaccine for general population, patients on HD or PD usually require 4 doses of 40 µg HBV vaccine. Patients with CKD should be screened annually to detect decline of AntiHBs titer and administer additional doses of HBV vaccine.

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**Figure 1 Distribution of chronic hepatitis B virus infection (From Weinbaum *et al*[96]).**



**Figure 2 Schedule of hepatitis B vaccine (Schillie *et al*[97]).** HBsAg: HBV surface antigen.

**Table 1 Interpretation of serologic markers of hepatitis B virus**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| HBsAg | Total anti HBC | IgM anti HBc | AntiHBs | Interpretation |
| - | - | - | - | Noninfected |
| + | - | - | - | Acute infection (early phase) |
| + | + | + | - | Acute infection |
| - | + | + | - | Recovering acure infection |
| - | + | - | + | İmmunized patient, past infection |
| + | + | - | - | Chronic infection |
| - | + | - | - | Chronic infection with low level viremia or false positive |
| - | - | - | + | Immıunized |

HBsAg: HBV surface antigen.

**Table 2 Factors related to unresponsiveness to hepatitis B virus vaccination in the general population and patients with chronic kidney disease**

|  |  |
| --- | --- |
| General population | Patients with chronic kidney disease |
| Obesity | Dialysis |
| Smoking |  Inflammation |
|  |  Administration route of vaccine |
| Diabetes Mellitus |  |
|  | Hyperparathyroidism |
| Lymphomas |  |
| Newborns and advanced ageInflammationCeliac disease | Co-existing HCV Advanced age Vitamin D deficiencyMale genderHypoalbuminemiaErythropoietin resistanceIL-18 and IFN-y gene polymorphisms |