

## Original Research

# Seroconversion after Hepatitis B vaccination in chronic kidney disease patients on maintenance hemodialysis: Does diabetes affect seroconversion response?

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### Abstract

**Background and aims:** Patients with chronic kidney disease (CKD) on maintenance hemodialysis (MHD) have a higher prevalence of Hepatitis B. Hepatitis B is preventable by vaccination, however, the seroconversion response is less effective in patients of CKD. Since diabetes is an important cause of CKD, this study aimed to compare seroconversion rates after Hepatitis B vaccination in normal individuals, patients with non-diabetic CKD (NDCKD) on MHD and patients with diabetic chronic kidney disease (DCKD) on MHD. We also aimed to determine whether an association existed between seroconversion rates and the duration of diabetes. **Materials and methods:** This was a case-control study conducted on the following subjects who had completed the Hepatitis B immunization schedule – normal subjects, patients with NDCKD stage 5, and patients with DCKD stage 5 on MHD. Anti-HBs levels were measured in the three groups and seroconversion rates were measured and compared. **Result:** Of 132 subjects, 44 each were normal controls, NDCKD, and DCKD on MHD. 100% of normal individuals seroconverted. Among the subjects on MHD, more NDCKD (72.7%) seroconverted when compared to DCKD (52.3%, p-value 0.048). Non-responders had diabetes for more than 10 years. **Conclusion:** Among patients on MHD, those with DCKD have lower rates of seroconversion compared to those with NDCKD. Older age, less dialysis, and longer duration of diabetes adversely influenced seroconversion.

**Keywords:** diabetes, CKD, dialysis, Hepatitis B, vaccination, titers, seroconversion.

### Introduction

Non-communicable diseases (NCDs) including diabetes mellitus (DM), hypertension, and chronic kidney disease (CKD) are increasing in prevalence in India and contribute to morbidity, mortality, and health care costs [1]. Chronic kidney disease is now a global health problem [2]. The prevalence of CKD in India is estimated to be 800 per million population, and that of ESRD is 232 per million population [3]. India is the diabetes

capital of the world and the most common cause of ESRD in India is not surprisingly diabetic nephropathy, with around 31% of cases of CKD being due to diabetic nephropathy [3]. Hemodialysis (HD) is the main method of renal replacement therapy (RRT) in those with CKD and there are about 130,000 patients receiving hemodialysis at present [4]. Blood-borne infections including Hepatitis B and C are of concern during dialysis, and 0.7% of individuals who undergo HD become Hepatitis B positive [5]. Outbreaks of Hepatitis B have



been reported in dialysis units and are ascribed to not screening for HBsAg at the initiation of dialysis and periodically, sharing blood-contact equipment, or ineffective vaccination [6]. HBV DNA does not traverse the dialyzer membrane, however, the degree of infectivity of dialysate and ultra filtrate remains unclear [7]. Hepatitis B can be prevented by vaccination; however, patients of CKD mount an immune response that is less effective [8]. The response rate to the HBV vaccine in hemodialysis patients ranges from 50% to 80% [9]. Comorbidities, age, degree of uremia, vitamin D levels, and immunological factors affect seroconversion [10]. Additionally, it is conceivable that patients who have diabetes and are therefore immunocompromised, may have an even poorer response to Hepatitis B vaccination. Hence, our study aimed to compare the rates of seroconversion in otherwise normal subjects who received Hepatitis B vaccination, patients with non-diabetic CKD undergoing MHD and diabetics with CKD undergoing MHD. We also aimed to find whether the seroconversion in patients with diabetes was influenced by the duration of diabetes.

## Objectives

1. To compare seroconversion rates after Hepatitis B vaccination in normal subjects, non-DCKD stage 5D and DCKD stage 5D patients
2. To find if an association exists between seroconversion rate and the duration of diabetes.

## Materials

This was a case-control study conducted on 132 subjects in a medical college hospital on the west coast of south India. Institutional Ethical Committee approval was obtained and written informed consent was obtained from all subjects recruited for the study.

## Inclusion criteria

Cases – adult patients at least 18 years of age with stage 5 CKD as defined by  $GFR < 15$  ml/

min/1.73 m<sup>2</sup> on maintenance hemodialysis who had completed Hepatitis B vaccination schedule (extended schedule for patients on dialysis at 0, 1, 2, and 6 months) [11] at least 3 months prior to sampling.

Controls – were health care professionals (HCPs) adult patients at least 18 years of age – healthy individuals with no known diabetes, hypertension, renal disease who had completed Hepatitis B vaccination schedule at least 3 months prior to sampling.

## Exclusion criteria

Known cases of Hepatitis B positivity.

## Methods

Hepatitis B vaccination, as per hospital policy, is given to all patients on maintenance hemodialysis as per the following protocol. Injection Shanvac B 40 µg (2 ml) – 1 ml intramuscular injection is given into each deltoid at 0, 1, 2, and 6 months. Shanvac-B is a recombinant vaccine produced by a culture of genetically engineered cells of *Pichia pastoris* which carry the gene that codes for the major surface antigen of the Hepatitis B virus.

Anti HBS antibody titer was analyzed after 3 months of completion of vaccination schedule using HEPALISA microwell ELISA test kit by J. Mitra & Co. Pvt Ltd. Patients were classified based on antibody titers levels as adequate responders (titer >10 mIU/ml), excellent responders (titer >100 mIU/ml) and non-responders (titer <10 mIU/ml).

Seroconversion rates of the 3 groups were compared and analyzed by Chi-Square test using SPSS software version 20.

For controls, Hepatitis B immunization was given as per the national schedule i.e., 20 µg intramuscularly into the deltoid at 0, 1 and 6 months. Controls were health care professionals from the institute who had been immunized as per institute policy, and whose titers were measured at least 3 months after completion of the schedule. Controls had no known

comorbidities like diabetes, hypertension, liver disease, or chronic kidney disease.

## Results

We studied a total of 132 subjects of which 44 were normal controls, 44 were non-DCKD stage 5D and 44 were DCKD stage 5D patients. The mean age of patients with DCKD was higher (DCKD: 62.8 years, NDCKD: 53.11 years,  $p$ -value $<0.001$ ). Of the 88 patients undergoing MHD, there were 64 (72.72%) males and 24 females (27.27%). The cause of CKD was diabetes in 44 of the patients, hypertension in 34 cases, and CKDU (chronic kidney disease of unknown etiology) in 10 cases (Table 1).

About 70% of all vaccinated males achieved seroconversion when compared to 82.7% of all vaccinated females. This difference did not reach statistical significance. 90% of CKD 5D aged less than 50 years seroconverted, when compared to 54.4% of those aged  $>50$  ( $p<0.004$ ) (Table 2).

Patients on more than 5 years of MHD did not differ in seroconversion rates from those with  $<5$  years of MHD (57.1% vs. 63.5%,  $p=0.652$ ). Those who underwent MHD for 12 hours/week had a better titer response (78.6%) when compared to those who were dialyzed for 8 hours (59.5%), but this difference was not statistically significant. ( $p=0.176$ ) (Table 3).

About 100% of normal individuals were seroconverted, compared to 52.3% of those with

Table 1: Characteristics of the study population.

Parameters	NDCKD	DCKD	p-Value
Mean age	53.11	62.8	$<0.001$
Gender	Female:13; male:31	Female:11; male:33	
Mean number of years since initiation of HD	3.36	2.61	
Mean hours of HD/week	8.27	9	

Table 2: Age and seroconversion.

Age (Years)	Hepatitis B titers response		Total
	Non-responders	Responders	
$<50$	2 (10%)	18 (90%)	20 (100%)
$>50$	31 (45.6%)	37 (54.4%)	68 (100%)
Total	33 (37.5%)	55 (62.5%)	88 (100%)

Table 3: Hours of hemodialysis and seroconversion.

Hours of MHD/week	Seroconversion response		Total
	Non-responders	Responders	
8	30 (40.5%)	44 (59.5%)	74 (100%)
12	3 (21.4%)	11 (78.6%)	14 (100%)
Total	33 (37.5%)	55 (62.5%)	88 (100%)

DCKD ( $p < 0.0005$ ) (Figure 1). Among the subjects on MHD, more NDCKD (72.7%) seroconverted when compared to DCKD (52.3%,  $p = 0.048$ ).

Of the 44 NDCKD cases, 32 (72.7%) seroconverted after vaccination, of which 21 (47.7%) with an antibody titer considered excellent, and 11 (25.5%) with adequate antibody response. Of the 44 DCKD cases, however, only 23 (52.3%) were seroconverted. Of these, 13 (29.55%) had an excellent response and 10 (22.7%) had an adequate response (Table 4).

Non-responders tended to have diabetes for more than 10 years though this difference was not statistically significant (Figure 2).

### Discussion

Worldwide, diabetes is the cause of CKD in most patients undergoing hemodialysis [12].

Patients with MHD are at increased risk of Hepatitis B infection due to frequent blood and blood product transfer and possibly contaminated dialysate [13]. Thus, as a standard of care, in almost all dialysis centers, patients complete the extended schedule of Hepatitis B vaccination. Patients with CKD not only have lower antibody titers on vaccination with Hepatitis B [14], they maintain these titers for a shorter duration when compared with individuals with normal renal function [15]. Seroconversion rates after vaccination in these patients vary from 10% to 50% [16].

The determinants of seroconversion after the Hepatitis B immunization schedule in patients on MHD are dialysis adequacy, vaccination early in the course of CKD, nutrition, and gender [16]. It is found that the rate of seroconversion varies by the stage of CKD, with patients early in the course of the disease faring better [17]. The decreased immune response seen to

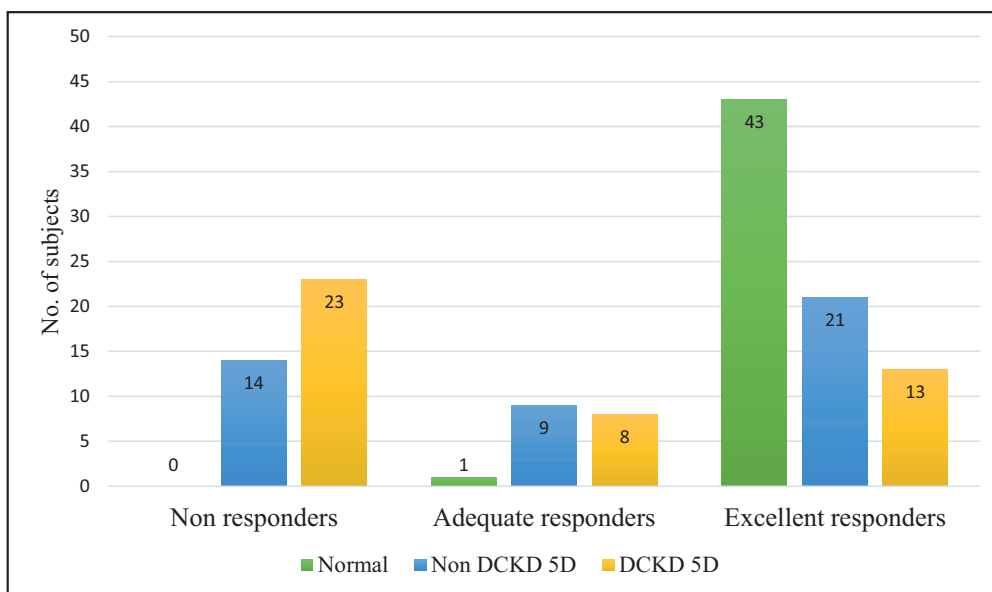


Figure 1: Comparative bar graph showing seroconversion responses of control and study groups.

Table 4: Seroconversion among the 3 groups.

Categories	Hepatitis B titers response		Total
	Non-responders	Responders	
Normal	0 (0%)	44 (100%)	44 (100%)
NDCKD 5D	12 (27.3%)	32 (72.7%)	44 (100%)
DCKD 5D	21 (47.7%)	23 (52.3%)	44 (100%)
Total	33 (25%)	99 (75%)	132 (100%)

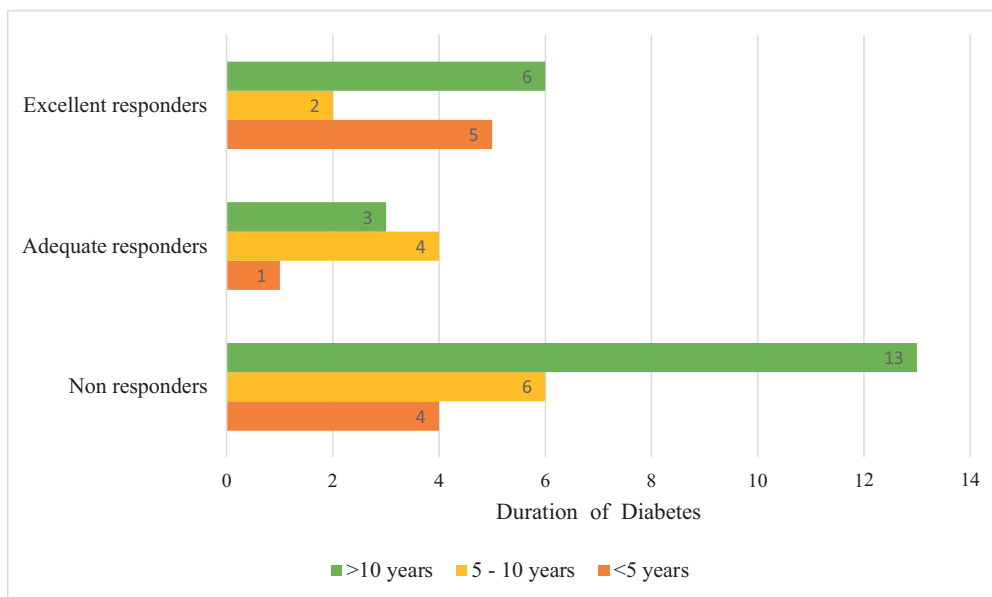


Figure 2: Bar graph showing seroconversion among DCKD patients and duration of diabetes.

the vaccine in patients with MHD is multifactorial and includes poor nutrition, the decreased immune response due to the uremia itself, as well as to the dialyzer membrane [18]. Diabetes may further influence the picture.

In this study, we measured the antibody titers after completion of the Hepatitis B immunization schedule in normal controls, patients with DCKD 5D and patients with NDCKD 5D. Not surprisingly, we found that most of the normal controls had an excellent antibody response when compared to patients on MHD. However, the DCKD patients had an even poorer rate of response when compared to the cases with NDCKD. The effect of diabetes on seroconversion has been studied. The biological basis for impaired immune response to the vaccine may be due to impaired cell-mediated immunity [19], the presence of DR3, DR7, DQ2 HLA alleles [20]. The immune response to vaccination was not affected by glycemic control [21] or insulin requirement [22]. The effect of diabetes on seroconversion rates in patients with MHD remains unclear with some studies showing no association between diabetes and poor seroconversion [22] and some studies showing that diabetics had lower immune response [23].

The significantly higher age group of our DCKD patients appears counterintuitive. However, our NDCKD group included patients with

CKDU. CKDU occurs in a younger population [3] and this may explain the lower mean age of the NDCKD patients.

We found that the number of males was higher in the group of non-responders. A study on Italian HCWs who received Hepatitis B vaccination showed that increased immune reactivity was seen in females [24]. This gender-based immune privilege may be related to the fact that several genes which play a key role in immunocompetence are located on the X chromosome [25]. Though not statistically significant, we found that patients with longer duration of diabetes tended to have poorer seroconversion rates. This result was corroborated by a study done in Egypt, which also showed a slightly lower rate of seroconversion in patients with a longer history of diabetes [26]. Though some studies show no correlation between the duration of diabetes and decreased immune response [23]. Interestingly, though the average weekly duration of hemodialysis in our patients was 8–9 hours, which is lower than the international average of 9–15 hours, the seroconversion rate in our MHD population was about 62.5% as opposed to the published rates of 10–50% [16]. Whether patients of Indian ethnicity have a better immune response remains to be studied, however, ethnicity does play a role in seroconversion after vaccination as shown by a study conducted in Taiwan [27].

Limitations and confounding factors in this study were limited by the small sample size, and by the fact that it was conducted at a single center. Also, the advanced age of the DCKD patients may have influenced the seroconversion rates.

## Conclusion

Even with the limitations, a significant result emerges, namely older patients and those with DCKD mount a less effective immune response to Hepatitis B immunization. Therefore, vaccination at the time of diagnosis of DM or during the early stages of CKD/DKD may achieve better seroconversion. This has implications for clinicians as well as policy makers.

Future direction: Further multi-centric studies regarding the role of ethnicity in the immune response are required. Additionally, considering the significantly lower immune response of males, the efficacy of adding booster doses to the vaccination schedule or using adjuvants to enhance the immune response in male CKD patients may be an avenue for research.

## Conflict of Interest

The authors declare no conflict of interest.

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