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Review

The effect of diabetes mellitus on immunological response to hepatitis B virus vaccine in individuals with chronic kidney disease: A meta-analysis of current literature

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ABSTRACT

Background: Patients with chronic kidney disease (CKD) often fail to produce protective antibodies to hepatitis B virus (HBV) surface antigen after vaccination. Diabetes mellitus (DM) is the most common cause of CKD; however it is not clear whether it affects immunological response to HBV vaccine in these patients.
Aims: We aimed to evaluate the immunological response to HBV vaccine in diabetic patients with CKD by conducting a meta-analysis of the current literature.
Methods: Only studies that evaluated the seroprotection rate for diabetic against non-diabetic CKD patients or the immunological response of these groups to HBV vaccine were included. We applied the random effects model of DerSimonian and Laird, with heterogeneity (Q statistic), publication bias (Egger and Begg test) and sensitivity analyses. The rate of patients showing seroprotective anti-HBsAg titers (>10 IU/mL) at completion of HBV vaccination schedule in the diabetic versus the non-diabetic CKD patients was set as our end-point of interest.
Results: We identified seven studies that fulfilled our inclusion criteria involving 15,073 unique patients with CKD. Aggregation of study results showed a significant decrease in response rates among the diabetic versus the non-diabetic patients [pooled odds ratio = 0.58 (95% CI 0.37–0.89), $Q(6) = 11.3$, $I^2 = 50\%$]. The P-value was 0.07 for our test of heterogeneity.
Conclusions: Our meta-analysis determined that HBV vaccination's seroprotection rate in diabetic CKD patients is significantly lower than that in non-diabetic CKD patients. Therefore, using vaccine adjuvants such as oral levamisole, granulocyte macrophage-colony stimulating factor or intradermal injection might be advisable in these patients.

Contents

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1. Introduction

Chronic kidney disease (CKD) patients, including end stage renal disease patients and those who are on maintenance dialysis, are highly vulnerable to be infected with blood born viruses such as hepatitis B virus (HBV). To avert HBV infection in these patients, vaccination is the most effective primary preventive strategy [1–3]. Nonetheless, we well know that the compromised immune system in these patients results in poor and non-persistent immunological responses to HBV vaccination in comparison with individuals with intact renal function [4–6]. Today, diabetic nephropathy is the most common cause of CKD in both developing and industrialized world [7]. It is well known that diabetic patients have a compromised immune system, and their immunological response to HBV vaccine is less optimal than non-diabetic individuals; nevertheless, the influence of this metabolic disease on seroconversion after HBV vaccination is not well investigated in CKD patients and only a few studies on HBV vaccination of the renal disease patients with diabetes mellitus (DM) has been reported [8]. Therefore, in this review, we aimed to investigate whether the suboptimal response to HBV vaccination in CKD patients was further exacerbated by DM.

2. Search strategy and data extraction

We conducted searches of MEDLINE, Scopus, ISI and Cochran Central Register of Clinical Trials from 1995 to 2009 and confined these to English language studies to identify the relevant literature. The keywords we used were different combinations of "Hepatitis B vaccine" or "HBV vaccine" with the following terms: "ESRD"; "renal failure"; "dialysis" or "hemodialysis"; "chronic kidney disease" or "CKD". Data were extracted by a single investigator; rechecked twice; and entered in to Excel spreadsheets. The decision to include or exclude a study and predefined assumptions were made and agreed by two authors before the meta-analysis (Fig. 1).

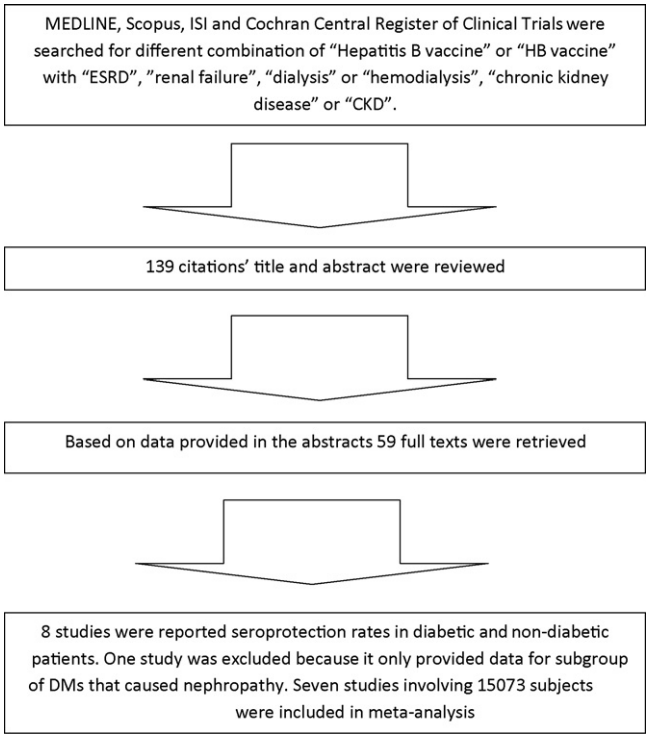

Fig. 1. Search strategy and study selection.

3. Criteria for inclusion

We included both prospective and retrospective peer reviewed published studies comparing the response rate in diabetic CKD patients (study group) vs. non-diabetic CKD patients (control group). We also included studies that had reported response rates in both diabetic and non-diabetic subjects separately. Studies that recruited dialysis patients were considered still eligible. Trials of the plasma-derived and recombinant DNA HBV vaccine were included. All dose schedules and routes of vaccine administration were accepted as qualifying.

4. Ineligible studies

Studies that reported inadequate data on measures of response, or included the individuals with positive serology for hepatitis B virus surface antigen (HBsAg), antibodies to HBsAg (HBsAb) and antibodies to hepatitis B virus core antigen (HBcAb) or HIV and patients with concurrent administration of immunosuppressive medicines were excluded.

5. End-points of interest

We evaluated the serological response to HBV vaccine in study and control groups and compared the rate of patients with protective anti-HBs titers after completion of HBV vaccination schedule in diabetic vs. non-diabetic patients. The level of antibody production that defines seroprotection was 10 IU/mL across the studies.

6. Statistical methods

We omitted the data from patients who did not complete the vaccination program thus; analysis was made per protocol, not by intention to treat. The pooled odds ratios (OR) and their 95% confidence interval (CI) for seroprotection rate after the completion of vaccine schedule in diabetic vs. non-diabetic patients were computed by using the random effects model according to DerSimonian and Laird method. The Q statistic was used for quantifying the heterogeneity; I^2 was used to provide a measure of the degree of inconsistency in the studies' results. Sensitivity analysis using a random effects model was also conducted to assess the robustness of final results. The publication bias assessment was performed by both Egger regression asymmetry test and Begger adjusted rank correlation test for publication bias. Probability of 0.1 was considered significant for test of heterogeneity and publication bias assessment tests. Every estimate in the figures is given with its 95% confidence interval.

7. Results

We reviewed 139 citations and based on their titles and abstracts, we obtained full texts of 59 potentially relevant study reports. Only 8 studies had reported the seroprotection rate after HBV vaccination in diabetic and non-diabetic patients with CKD separately. One study was excluded because it only provided data for subgroup of DMs that caused nephropathy [9]. Only one study had compared diabetic and non-diabetic patients in two different arms. A total of 15,073 individual patients were included in our meta-analysis (Fig. 2). There were 8822 (58%) and 6251 individuals enrolled in study (diabetic) and control (non-diabetic) groups, respectively. There were two reports of retrospective studies with one and two arms [10,11]. Two studies were prospective cohorts of two groups of patients [8,12]. Three studies had single arm prospective cohort designs [13–15]. Except in two studies that we could not assure, in all other trials both study (diabetic) and control (non-

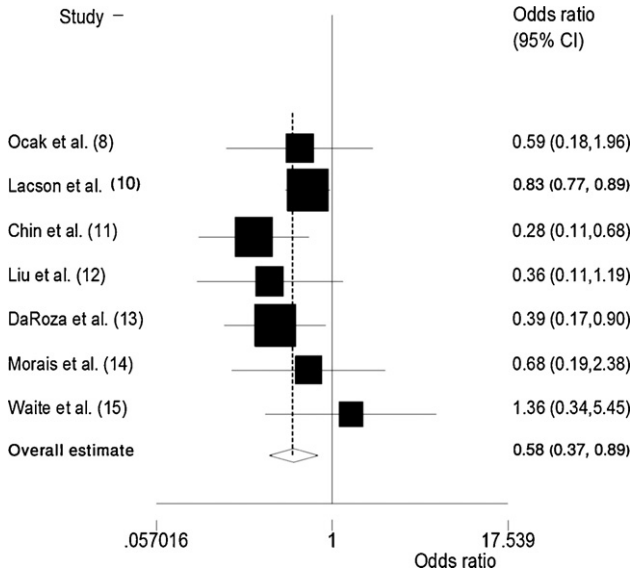

Fig. 2. Summary estimate of ORs of seroprotection rate of HBV vaccine in DM vs. non-DM patients with CKD. Square areas do not correspond to study weights in meta-analysis.

diabetic) groups, received the same vaccine dosage and schedule. There was a 100% agreement between authors regarding final inclusion and exclusion of studies according to the predefined inclusion and exclusion criteria.

8. Patients' characteristics

Some demographic and clinical characteristics of the subjects enrolled are presented in Tables 1–3. All trials were published in English language from 1995 to 2008. Three studies were from the USA and two from Canada [10,11,13–15], one each from Turkey and Taiwan [8,12]. All patients had CKD. 92% (13,939/15,073) of subjects underwent standard hemodialysis and 8% (1134/15,073) of subjects were receiving medical treatment. Mean age of subject cohort ranged from 50 to 60 years of age; mean time requiring dialysis ranged from <12 to 54 months; and gender distribution ranged from 40% to 64% male (Table 3). As presented in Table 2, four studies did not enroll subjects with a prior history of vaccination and who had failed to respond to prior vaccination. Data of vaccine schedules of the included studies are also shown in Table 2. Only, in one study the vaccine was used intradermally with a reinforced schedule.

Table 1
Characteristics of studies included in the analysis.

Ref. no.	Authors	Publication year	Study design	Patients (*n*)
[8]	Ocak and Eskiocak	2008	Prospective	49
[10]	Lacson et al.	2005	Retrospective	14,546
[11]	Chin et al.	2003	Retrospective	97
[12]	Liu et al.	2005	Prospective	69
[13]	DaRoza et al.	2003	Prospective	166
[14]	Moralis et al.	2007	Prospective	70
[15]	Waite et al.	1995	Prospective	77

9. Summary estimates of outcome

Table 4 represents seroprotection rates in both study and control groups. Fig. 2 lists individual ORs with 95% confidence intervals for seroprotection rates after HBV vaccination (diabetic vs. non-diabetic subjects). The pooled OR was 0.58 (95% CI 0.37–0.89) according to a random effects model. The test for heterogeneity was significant [$Q = 11.3$ (df = 6), $p = 0.07$, $I^2 = 50\%$]; the publication bias assessment according to Begg's and Egger's formulas was not significant ($P_{Begg} = 0.2$, $P_{Egger} = 0.16$). The pooled OR was 0.81 (95% CI 0.75–0.88) according to the fixed effect model (inverse variance method). In sensitivity analysis, final estimation did not depend on any single study result. Fig. 2 shows estimated pooled ORs (with 95% CI) after the completion of the vaccination schedules.

10. Discussion

It is previously determined that in individuals with normal renal function, diabetic patients show a lower seroprotection rate than non-diabetic patients after HBV vaccination [16]. The presence of DR3 and DR7 human leukocyte antigen (HLA) alleles in diabetic patients, and increased tolerance to stimulation

Table 2
Characteristics and vaccine schedules of studies included in the analysis.

Ref. no.	Authors	Vaccine type	Vaccine used	Schedule (months)	Vaccine dose (μg)	Route of injection	Prior vaccine use
[8]	Ocak and Eskiocak	Recombinant	Euvax	0,1, 2 and 6	40	IM	NR
[10]	Lacson et al.	Recombinant	Engerix and Recombivax	0, 1, 6 and 0, 1, 2, 6	40	IM	0%
[11]	Chin et al.	Recombinant	Recombivax	0, 1, and 6	40	IM	NR
[12]	Liu et al.	Recombinant	Engerix	0,1, 2 and 6	40	IM	0%
[13]	DaRoza et al.	Recombinant plasma-derived	NR	0, 1, and 6 0,1, 2 and 6	40	IM	0%
[14]	Moralis et al.	Recombinant	NR	2 × 1 week	16 × 5	ID	61.4%
[15]	Waite et al.	Recombinant	Engerix	0,1, 2 and 6	40	IM	0%

IM, intramuscular; ID, intradermal; NR, not-reported.

Table 3
Baseline characteristics of patients included in the analysis.

Ref. no.	Authors	Age (years)	Male (%)	Anti-HCV$^+$ (%)	Time on dialysis (m)	Treatment
[8]	Ocak and Eskiocak	55.1	63.2	NR	30.6	HD
[10]	Lacson et al.	60.5	54	6.3%	11.4	93% HD
[11]	Chin et al.	53.7	53.4	0%	<12	HD
[12]	Liu et al.	58	40.5	21.7%	54.5	68.1% HD 31.9% CAPD
[13]	DaRoza et al.	59.8	64	NR		CRF
[14]	Moralis et al.	54.5	57	0%	26.4	HD 66% CAPD 1% CRF 30%
[15]	Waite et al.	50.1	63.6	NR	NR	HD

HD, hemodialysis; CAPD, continuous ambulatory peritoneal dialysis; CRF, chronic renal failure.

Table 4
Summary of seroprotection rate after HBV vaccination in each study.

Ref. no.	Authors	Seroprotection (HBsAg-Ab > 10 IU/mL)	
		Study (diabetic) group % (*n*/*N*)	Control (non-diabetic) group % (*n*/*N*)
[8]	Ocak and Eskiocak	57.8 (11/19)	70 (21/30)
[10]	Lacson et al.[a]	NR	NR
[11]	Chin et al.	52 (25/48)	79 (39/49)
[12]	Liu et al.	65 (13/20)	83.6 (41/49)
[13]	DaRoza et al.	71.7 (33/46)	86.5 (103/119)
[14]	Moralis et al.	77 (17/22)	83 (40/48)
[15]	Waite et al.	78.5 (11/14)	73 (46/63)

[a] Raw data were not provided by the authors.

and reduced cytokine secretions of peripheral blood mononuclear cells (PBMCs) are proposed as mechanisms that underlie this impaired immunological response [17,18]. Diabetic nephropathy is the most common cause of CKD. In these patients, as well as aforementioned immunological mechanisms, uremia impairs antigen presentation, T-cell activation and subsequent antibody production [19]. Therefore, theoretically seroconversion after HBV vaccination should be reduced in diabetic CKD patients in comparison with non-diabetic CKD subjects. However, this difference has not been adequately investigated and quantified. By conducting a meta-analysis of studies that reported frequency of DM in responders and non-responders, we determined that the pooled OR for seroprotection rates was significantly lower in diabetic vs. non-diabetic CKD patients. Our primary analysis also showed that study results were slightly heterogeneous. Discrepancies between the type of vaccines used, vaccine schedules, patients' characteristics, history of subjects' previous non-response to HBV vaccine in some studies, degree of renal dysfunction and status of serum glucose control in diabetic subjects can underlie this heterogeneity. Sensitivity analysis also demonstrated that our final result was not dependent on result of any single study. Our meta-analysis had both advantages and limitations. This meta-analysis aggregated data of observational studies; therefore, the accuracy of the results might not be as robust as a meta-analysis of controlled clinical trials or prospective cohort studies with matched control groups. The analysis did not find a significant publication bias and this was a positive outcome of this study. This implies that the studies' findings and final summary estimate were not dependent on the sample size of the studies included in analysis and that the chance of missing relevant literature data was small. Robustness in sensitivity analysis and non-significant publication bias underscore the validity of our summary estimate of the DM effect on immunological responses to the HBV vaccine in CKD patients. The analyses were strengthened by vast number of patients available for analysis ($n = 15{,}073$).

Fabrizi et al. in two meta-analyses have shown that granulocyte macrophage-colony stimulating factor (GM-CSF) and intradermal HBV vaccine injection significantly enhance immunological responses to HBV vaccine in patients with CKD [20,21]. Recently, we have demonstrated in a meta-analysis that oral levamisole is another immune modulator that can be successfully administered to these patients to boost their seroprotection rate after HBV vaccination [22]. Based on the findings of this meta-analysis and the body of other evidences, we strongly advise that diabetic CKD patients receive a vaccine adjuvant. Furthermore, intradermal HBV vaccination is recommended to be applied in these patients instead of intramuscular vaccine injection.

11. Conclusion

Diabetes mellitus significantly decreases the seroprotection rate of HBV vaccine in chronic kidney disease patients. Using vaccine adjuvants such as oral levamisole, granulocyte macrophage-colony stimulating factor or intradermal injection might be advisable in these patients.

Conflict of interest statement: The authors declare that they have no conflicts of interest relevant to the manuscript.

References

[1] Fabrizi F, Lunghi G, Poordad FF, Martin P. Novel perspectives on hepatitis B vaccine in dialysis population. Int J Artif Organs 2002;25(March (3)):174–81.
[2] Sali S. HBV vaccination in chronic renal failure patients. Hepatitis Monthly 2006;6(1):25–9.
[3] Miller ER, Alter MJ, Tokars JI. Protective effect of hepatitis B vaccine in chronic hemodialysis patients. Am J Kidney Dis 1999;33(February (2)):356–60.
[4] Casciato DA, McAdam LP, Kopple JD, Bluestone R, Goldberg LS, Clements PJ, et al. Immunologic abnormalities in hemodialysis patients: improvement after pyridoxine therapy. Nephron 1984;38(1):9–16.
[5] Kurz P, Kohler H, Meuer S, Hutteroth T, Meyer zum Buschenfelde KH. Impaired cellular immune responses in chronic renal failure: evidence for a T cell defect. Kidney Int 1986;29(June (6)):1209–14.
[6] Vanholder R, Van Loo A, Dhondt AM, De Smet R, Ringoir S. Influence of uraemia and haemodialysis on host defence and infection. Nephrol Dial Transplant 1996;11(April (4)):593–8.
[7] Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. Nature 2001;414(December (6865)):782–7.
[8] Ocak S, Eskiocak AF. The evaluation of immune responses to hepatitis B vaccination in diabetic and non-diabetic haemodialysis patients and the use of tetanus toxoid. Nephrology (Carlton) 2008;13(March (6)):487–91.
[9] Taheri S, Shahidi S, Moghtaderi J, Seirafian S, Emami A, Eftekhari SM. Response rate to hepatitis B vaccination in patients with chronic renal failure and end-stage-renal-disease: influence of diabetes mellitus. J Res Med Sci 2005;10(6):384–90.
[10] Lacson E, Teng M, Ong J, Vienneau L, Ofsthun N, Lazarus JM. Antibody response to Engerix-B and Recombivax-HB hepatitis B vaccination in end-stage renal disease. Hemodial Int 2005;9(October (4)):367–75.
[11] Chin AI. Hepatitis B virus vaccine response in hemodialysis: baseline patient characteristics. Hemodial Int 2003;7:296–303.
[12] Liu YL, Kao MT, Huang CC. A comparison of responsiveness to hepatitis B vaccination in patients on hemodialysis and peritoneal dialysis. Vaccine 2005;23(June (30)):3957–60.
[13] DaRoza G, Loewen A, Djurdjev O, Love J, Kempston C, Burnett S, et al. Stage of chronic kidney disease predicts seroconversion after hepatitis B immunization: earlier is better. Am J Kidney Dis 2003;42(December (6)):1184–92.
[14] Morais EO, Resende MR, Oliveira AM, Sinkoc VM, Garcia MT, Angerami RN, et al. Intradermal hepatitis B vaccination in patients with advanced chronic renal failure: immunogenicity and follow-up. Aliment Pharmacol Ther 2007;25(April (7)):849–55.
[15] Waite NM, Thomson LG, Goldstein MB. Successful vaccination with intradermal hepatitis B vaccine in hemodialysis patients previously nonresponsive to intramuscular hepatitis B vaccine. J Am Soc Nephrol 1995;5(May (11)):1930–4.
[16] Pozzilli P, Arduini P, Visalli N, Sutherland J, Pezzella M, Galli C, et al. Reduced protection against hepatitis B virus following vaccination in patients with type 1 (insulin-dependent) diabetes. Diabetologia 1987;30(October (10)):817–9.
[17] Alper CA, Kruskall MS, Marcus-Bagley D, Craven DE, Katz AJ, Brink SJ, et al. Genetic prediction of nonresponse to hepatitis B vaccine. N Engl J Med 1989;321(September (11)):708–12.
[18] Geerlings SE, Hoepelman AI. Immune dysfunction in patients with diabetes mellitus (DM). FEMS Immunol Med Microbiol 1999;26(December (3–4)):259–65.
[19] Girndt M, Sester M, Sester U, Kaul H, Kohler H. Defective expression of B7-2 (CD86) on monocytes of dialysis patients correlates to the uremia-associated immune defect. Kidney Int 2001;59(April (4)):1382–9.

[20] Fabrizi F, Dixit V, Magnini M, Elli A, Martin P. Meta-analysis: intradermal vs. intramuscular vaccination against hepatitis B virus in patients with chronic kidney disease. Aliment Pharmacol Ther 2006;24(August (3)):497–506.
[21] Fabrizi F, Ganeshan SV, Dixit V, Martin P. Meta-analysis: the adjuvant role of granulocyte macrophage-colony stimulating factor on immunological response to hepatitis B virus vaccine in end-stage renal disease. Aliment Pharmacol Ther 2006;24(September (5)):789–96.
[22] Alavian SM, Tabatabaei SV. Effects of oral levamisole as an adjuvant to hepatitis B vaccine in adults with end-stage renal disease: a meta-analysis of controlled clinical trials. Clin Ther 2010;32(January (1)):1–10.