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Meta-analysis: the impact of diabetes mellitus on the immunological response to hepatitis B virus vaccine in dialysis patients

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SUMMARY

Background
Patients on maintenance dialysis typically show a suboptimal immune response to hepatitis B virus vaccine compared with the non-uraemic population. A variety of inherited or acquired factors have been implicated in this diminished response. It is well known that patients with diabetes mellitus have a compromised immune system, and diabetic nephropathy is an important cause of chronic kidney disease. However, the impact of diabetes mellitus on the immune response to HBV vaccine in patients receiving long-term dialysis remains unclear.

Aim
To evaluate the influence of diabetes mellitus on the immune response to HBV vaccine in dialysis population by performing a systematic review of the literature with a meta-analysis of clinical studies.

Methods
We used the random effects model of DerSimonian and Laird with heterogeneity and sensitivity analyses. The end-point of interest was the rate of patients showing seroprotective antibody against hepatitis B surface antigen at completion of vaccine schedule in the diabetic vs. the nondiabetic dialysis individuals.

Results
We identified 12 studies involving 1002 unique patients on long-term dialysis. Aggregation of study results showed a significant decrease in response rates among the diabetic vs. the nondiabetic patients [pooled odds ratio = 0.52 (95% CI 0.38–0.71)]. The *P*-value was 0.29 for our test of study heterogeneity. Stratified analysis in various subgroups of interest did not meaningfully change our results.

Conclusions
Our meta-analysis showed a clear association between diabetes mellitus and impaired response to hepatitis B virus vaccine in individuals on long-term dialysis. Such a relationship is biologically plausible. Vaccination schedules with adapted vaccine doses and frequent serum testing for loss of immunity against hepatitis B virus should be considered in patients on maintenance dialysis with diabetes mellitus.

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INTRODUCTION

The frequency of hepatitis B virus (HBV) infection, as detected by persistent positivity for hepatitis B surface antigen in serum, is low but not negligible among patients with chronic kidney disease (CKD) on maintenance dialysis in the industrialised world.[1] In 2002, the Centers for Disease Control and Prevention (CDC, Atlanta, GA, USA) has reported that the prevalence of HBsAg seropositivity among dialysis patients was 1% in the US.[2] Also, outbreaks of HBV infection in haemodialysis (HD) units continue to occur.[3] Prevalence and incidence rates of HBV infection remain much higher within dialysis units in less-developed countries.[4] It is well known that patients undergoing long-term dialysis have a lower response to HBV vaccine compared with the non-uraemic population: the number of patients who develop protective antibody (anti-HBs) against HBV surface antigen (HBsAg) is lower, the antibody titres of those who mount an antibody response are reduced and decline faster over time.[5]

Diabetic patients have a compromised immune system and their immunological response to HBV vaccine is less optimal than nondiabetic individuals;[6] nevertheless, the influence of this metabolic disease on seroprotection rate after HBV vaccination is not well investigated in chronic dialysis patients. A few studies on HBV vaccination of patients with CKD and diabetes mellitus have been published and preliminary results have been given.[7]

The goal of this study was to investigate the available evidence on the relationship between diabetes mellitus and immune response to HBV vaccination in long-term dialysis population by performing a systematic review of the literature with a meta-analysis of clinical studies.

MATERIAL AND METHODS

Search strategy and data extraction

We performed electronic searches of the National Library of Medicine's MEDLINE database, Current Contents and manual searches of selected speciality journals to identify all pertinent literature. It has previously demonstrated that an electronic search alone may not sensitive enough. Four MEDLINE database engines (Ovid, PubMed, Embase and GratefulMed) were used. The key words 'hepatitis B', 'vaccine', 'diabetes mellitus', 'dialysis' and 'chronic kidney disease' were used. Reference lists from qualitative topic reviews and published clinical trials were also searched. Our search was limited to human studies that involved individuals aged >19 years published in the English literature. All articles were identified by a search from 1980 to November 2010. Data extraction was conducted independently by two investigators (F.F., V.D.) and consensus was achieved for all data. Studies were compared to eliminate duplicate reports for the same patients, which included contact with investigators when necessary. Eligibility and exclusion criteria were prespecified.

Criteria for inclusion

We included studies evaluating only patients undergoing maintenance hemodialysis (HD) and peritoneal dialysis (PD). Studies that restricted to students, military recruits or other cohorts that involved subjects <19 years of age were excluded. Many studies have identified an effect of diabetes mellitus on response rate to HBV vaccine. However, only studies that (i) specified either a relative risk and a measure of variance for vaccine response among dialysis patients with diabetes mellitus, compared with nondiabetic individuals, or (ii) presented data in a form that could be used to construct a 2×2 contingency table were considered for final inclusion. Both randomised controlled trials and observational studies were considered eligible for inclusion in the analysis. We included trials using plasma-derived or recombinant DNA hepatitis B vaccine. Patients who underwent primary vaccination schedule (naïve patients) or those who had failed to respond to prior vaccine schedule (nonresponder patients) against HBV vaccine were enrolled.

The decision as to inclusion or exclusion of clinical trials was not related to results. All dose schedules and routes of administration were included, as long as they involved primary vaccination regimens and not booster doses only.

Ineligible studies

Studies were excluded if they reported inadequate data on measures of response, or included individuals with positive serology for HBsAg, antibodies to HBsAg (HBsAb) or human immunodeficiency virus (HIV). Trials that were only published as abstracts or as interim reports were excluded; letters and review articles were not considered for this analysis. Trials that involved renal transplant recipients or patients with kidney failure at predialysis stage were excluded.

End-points of interest

We compared the seroprotection rate after completion of HBV vaccination schedule in patients with diabetes mellitus vs. nondiabetic patients. Patients vaccinated against

HBV are considered immune if protective titres of anti-HBs antibody can be demonstrated after completion of vaccination. The level of antibody production that defines seroprotection was 10 IU/mL across the studies. These definitions were consistent with standards published in the scientific literature.

Statistical methods

In all studies included in this analysis, data from patients who did not complete the vaccination schedule were excluded from the final analysis; thus, analysis was made by per-protocol (PP), not by intention-to-treat (ITT). A summary estimate of the odds ratio (OR) for seroresponse after vaccination among diabetic vs. nondiabetic patients was generated by use of a random-effects approach, as described by DerSimonian and Laird.[8] The Cochrane's Q test was used for quantifying the heterogeneity;[9] the I^2 index – the percentage of total variation across studies due to heterogeneity rather than chance,[10] was also used. The Galbraith plot was made to assess the heterogeneity and precision of single studies.[11] Pooled ORs were calculated in the subgroups of clinical trials as sensitivity analyses. The publication bias assessment (PBA), i.e. the number of void or negative trials necessary to render the meta-analysis meaningless, was made according to the Klein formula.[12] The publication bias was also measured by the test of funnel plot asymmetry. The 5% significance levels were used for alpha risk. Every estimate was given with its 95% confidence intervals (95% CI).

RESULTS

Literature review

Our electronic and manual searches identified 143 manuscripts, which were selected for full text review. One hundred and thirty-one (92%) studies were excluded because they did not fulfil the inclusion criteria. A list of the 143 bibliographic references is available from the authors on request. Twelve (8%) articles,[13–24] representing a total of 1002 unique patients, were included in our meta-analysis. There was a 100% concordance between reviewers with respect to final inclusion and exclusion of studies reviewed based on the predefined inclusion and exclusion criteria.

Patient characteristics

Some salient demographic characteristics of subjects enrolled in the included clinical trials are shown in Table 1. Many (six of 12, 50%) studies were from centres in developed world (western Europe and North America). There were two (17%) controlled randomised clinical trials (RCTs), and one clinical controlled trial (CCT). Nine were cohort studies, three (20%) having retrospective design.

Table 1 | Baseline characteristics of studies included in the analysis

Authors (reference number)	Country	Patients, *n*	Publication year
Waite *et al.*[13]	Canada	77	1995
Fabrizi *et al.*[14]	Italy	118	1996
Mettang *et al.*[15]	Germany	32	1996
Jha *et al.*[16]	India	50	2001
Eardley *et al.*[17]	UK	105	2002
Chin[18]	USA	66	2003
Elwell *et al.*[19]	USA	97	2003
Liu *et al.*[20]	Taiwan	69	2005
Chow *et al.*[21]	Hong Kong	64	2006
Ocak and Eskiocack[22]	Turkey	49	2008
Afsar *et al.*[23]	Turkey	188	2009
Chow *et al.*[24]	Hong Kong	87	2010

As listed in Table 2, recombinant HBV vaccine was used in all clinical studies. Intramuscular administration of HBV vaccine was used in the majority of patients (984, 98%). The mean age of subject cohorts ranged from 43 to 66 years (Table 3). The gender distribution ranged from 35% to 64% male. All clinical studies included patients on maintenance dialysis; 917 (92%) and 85 (8%) underwent regular HD and PD, respectively. All PD patients received continuous ambulatory peritoneal dialysis (CAPD).

Summary estimates of outcome

A significant decrease in response rates among patients with diabetes mellitus vs. nondiabetic patients was found; the pooled OR was = 0.52 (95% CI 0.38–0.71), $P = 0.001$ according to a random effects model. No significant heterogeneity occurred ($P = 0.295$). The publication bias assessment (PBA) was 41. The test of funnel plot asymmetry was not significant [alpha = 0.53; 95% CI, −2.98; 4.05 ($P = 0.77$)]. The comparison between patients with DM and nondiabetic patients has been shown in the Galbraith plot (Figure 1); it provides information on the heterogeneity between trials. It also reports the effect of treatment, the precision and the effect of each single trial included in the meta-analysis.

Table 2 | Vaccine schedules of studies included in the analysis

Authors	Vaccine route	Vaccine schedule, months	Vaccine dose, mcg
Waite *et al.*	Recombinant, IM	0, 1, 2, and 6	40
Fabrizi *et al.*	Recombinant, IM	0, 1, and 2	40
Mettang *et al.*	Recombinant, IM (n = 14)/ID (n = 18)	0, 1, 3, and 6	40 (IM) 10 (ID)
Jha *et al.*	Recombinant, IM	0, 1, and 2	40
Eardley *et al.*	Recombinant, IM	0, 1, and 2	40
Elwell *et al.*	Recombinant, IM	0, 1, and 6	40
Chin *et al.*	Recombinant, IM	0, 1, and 6	40
Liu *et al.*	Recombinant, IM	0, 1, 2, and 6	40
Chow *et al.*	Recombinant, IM	0, 1, and 6	20 (n = 14) 40 (n = 26) 80 (n = 24)
Ocak *et al.*	Recombinant, IM	0, 1, 2, and 6	40
Afsar *et al.*	Recombinant, IM	0, 1, 2, and 6	40
Chow *et al.*	Recombinant, IM	0, 1, and 6	40 (n = 42) 80 (n = 45)

ID, intradermal route; IM, intramuscular route.

Table 3 | Baseline characteristics of studies included in the analysis

Authors	Age (years)	Male, *n*	Time on dialysis (months)
Waite *et al.*	46 ± 14/59 ± 11	49 (64%)	13.9/19.8
Fabrizi *et al.*	63.4 ± 13.9	60 (51%)	37/31.1
Mettang *et al.*	60 ± 10/64 ± 11	17 (53%)	NA
Jha *et al.*	48 ± 1/46 ± 15	32 (64%)	NA
Eardley *et al.*	59/62	18 (51%)/40 (57%)	18
Elwell *et al.*	66 ± 14	38 (57%)	NA
Chin *et al.*	51 ± 2/59 ± 2	NA	NA
Liu *et al.*	56 ± 14/64 ± 8	28 (40%)	59/43
Chow *et al.*	43 ± 12	33 (51%)	9.3/1.2
Ocak *et al.*	61 ± 9/51 ± 17	31 (63%)	28/32
Afsar *et al.*	45 ± 14/49 ± 8	66 (35%)	99/81
Chow *et al.*	59 ± 9/60 ± 13	51 (59%)	5.5/3.8

Despite the test for heterogeneity was not significant, we explored some of the possible sources of study heterogeneity. As reported in Table 4, no heterogeneity was found in stratified analyses.

DISCUSSION

The impaired efficacy of HBV vaccine in dialysis population has been attributed to numerous factors notably immune compromise because of uraemia, older age,[25] male gender, nutritional status,[26] serological positivity for human immunodeficiency virus (HIV)[27] or hepatitis C (HCV) infection,[28] blood transfusion history and possession of the major histocompatibility complex aplotype HLA-B.[29] In addition, the failure to complete a full course of HBV vaccination may cause a poor active immunisation.[30] Diabetic nephropathy is the most common cause of chronic kidney disease and diabetic patients with normal renal function show a lower seroprotection rate than nondiabetic patients after HBV vaccination.[6] The link between diabetes mellitus and the

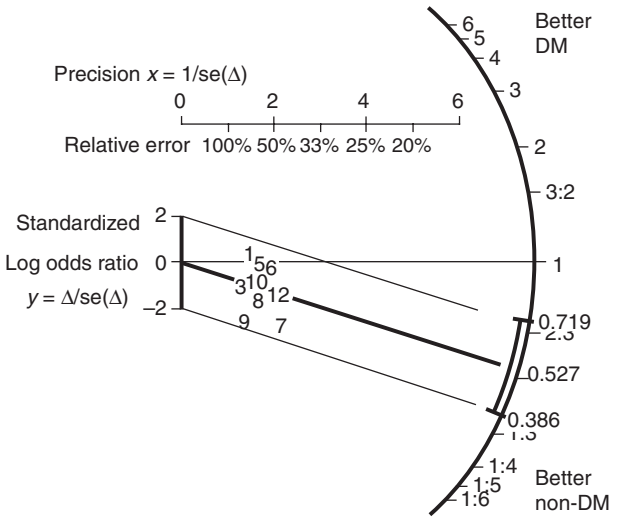

Figure 1 | Response rate to HB vaccine: diabetic vs. non-diabetic patients (Galbraith plot).

poor and nonpersistent immunological response to HBV vaccine in dialysis population remains controversial.

Our meta-analysis determined that patients with diabetes mellitus show a lower seroprotection rate to HBV vaccine than nondiabetic patients in dialysis population. These results were very robust as no heterogeneity occurred in primary analysis; also, the analysis in various subgroups yielded only minimal changes on the effect size. This phenomenon is biologically plausible as numerous changes in cellular and humoral immune responses have been described in non-uraemic patients with diabetes mellitus. As an example, the presence of DR3 and DR7 human leucocyte antigen (HLA) alleles in diabetic individuals has been implicated in this impaired immunological response.[31]

Our findings are consistent with data from other sources. The analysis of the FMCNA database (14546 patients with end-stage renal disease who received HBV recombinant DNA vaccine) revealed that the OR of seroprotection rate of HBV vaccine in DM vs. non-DM patients with CKD was 0.83 (95% CI, 0.77; 0.89), $P = 0.002$.[32] A lower response rate after HBV vaccination in diabetic vs. nondiabetic patients with CKD at predialysis stage has been found in at least two surveys.[33, 34]

This meta-analysis is potentially limited in a number of ways. First, as with all meta-analyses, this study has the potential limitation of publication bias. Negative trials are less likely to be published – we postulated that the authors who found a statistical association between diabetes mellitus and response rate to HBV vaccine would likely be to comment on such a finding in published manuscripts, whereas investigators who failed to find such an association would be less likely to give any comment. This is of particular concern, given that the evaluation of vaccine response according to diabetes mellitus was not a primary objective of most studies (11 of 12, 92%) included in our analysis. To limit the possible effect of publication bias, we used several strategies for identifying studies to include published and unpublished studies. Inclusion criteria, established *a priori*, were chosen to increase the likelihood that high-quality studies would be included. Secondly, there was in our studies incomplete information about nutritional status, HIV/HCV infection, serum haemoglobin concentration, erythropoietin use or adequacy of dialysis. However, the link between these parameters and seroresponse to HBV vaccine is still controversial in dialysis population. In their multiple logistic regression model, Chin[18] found that DM was a significant and independent predictor of failure to seroconvert after vaccination against HBV (OR, 3.4; 95% CI, 1.3–9.0; $P = 0.01$). Finally, we have made mostly a meta-analysis of observational studies and it is clear that a meta-analysis of randomised clinical trials is provided with better accuracy and reliability. The low heterogeneity found in primary and stratified analyses, the absence of publication bias and the good number ($n = 1002$) of patients available for our analysis strengthen our data.

Various approaches have been suggested in order to improve the response rate to hepatitis B vaccine in dialysis population including increased vaccine doses[14] or

Table 4 | Pooled odds ratio (OR) of failure to respond to vaccine (diabetic vs. nondiabetic patients) in various subgroups of interest

	Random-effects model OR (95% CI)	Q (P)	I^2
All studies ($n = 12$)	0.52 (0.38; 0.71)	12.97 (0.295)	22.9
I.M. patients ($n = 11$)	0.53 (0.38; 0.74)	12.9 (0.23)	30.2
Prospective studies ($n = 9$)	0.58 (0.41; 0.83)	5.9 (1.0)	0
HD patients ($n = 8$)	0.60 (0.41; 0.87)	8.09 (0.32)	25.9
Studies from western world ($n = 6$)	0.54 (0.33; 0.90)	6.9 (0.2)	42.2

shots; recent evidence has shown efficacy and safety of intradermal administration of recombinant vaccine towards HBV[35–37] in dialysis population. HBV vaccine has been given to uraemic patients not yet requiring regular dialysis.[33, 34] Numerous vaccine adjuvants have been recommended, such as interferon, interleukin and erythropoietin, among others. The Centers for Disease Control (CDC)[38] currently recommends that dialysis patients receive by intramuscular route double doses (20 mcg × 2) at 0, 1, 2 and 6 months with regular monitoring of antibody levels to ensure that antibody concentrations remain above the protective level of 10 mIU/mL. There is no evidence that the various approaches to improve HBV vaccination response rates have an effect in diabetics on dialysis. Studies on vaccination schedules with adapted vaccine doses or shots, intradermal administration of recombinant vaccine or use of vaccine adjuvants are under way among dialysis patients with diabetes mellitus.

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