



ORIGINAL RESEARCH ARTICLE

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# Investigating the effect of serum level of uric acid on the immunogenicity of hepatitis B vaccination in dialysis patients

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## Abstract

**Introduction** HBV infection is a significant concern in dialysis patients, influenced by various factors. This study aims to investigate the impact of serum uric acid levels on the immunogenicity of hepatitis B vaccination in dialysis patients.

**Method** A cross-sectional study was conducted, involving 125 hemodialysis patients. Prior to dialysis, assessments were made for uric acid, vitamin D, HBsAg, and HBsAb. Patients were divided into two groups based on uric acid levels: high level ( $\geq 6.5$  mg/dl) and low level ( $< 6.5$  mg/dl). Each group received three doses of a high-dose hepatitis B vaccine (40 mcg) at 0, 1, and 6 months. After 8 weeks of the 3rd dose of the vaccine, the anti-hepatitis B antibody titer (HBsAb) was measured and recorded. Data were analyzed using SPSS version 22.

**Results** Among patients with high uric acid, 30 (26.8%) had low HBsAb and 82 (73.2%) had high HBsAb ( $> 10$ ). In patients with low uric acid, 1 (7.7%) had low HBsAb and 12 (92.3%) had high HBsAb ( $> 10$ ). There was no statistically significant difference in HBsAb between the two groups. The immune response of HBsAb and uric acid did not show significance based on demographic variables and laboratory results.

**Conclusion** This study found no correlation between uric acid levels and the immunogenicity of hepatitis B vaccination in hemodialysis patients. However, it is important to note that the group with low serum uric acid was very small compared to the other group and this may have influenced these results. Further studies with larger patient populations are needed to provide more conclusive evidence in this area.

**Keywords** Uric acid, Hemodialysis, Immunogenicity, Hepatitis B, Vaccination

## Introduction

End Stage Renal Disease (ESRD) is a progressive disease in the world [1]. Global epidemiological studies have reported an increase in the prevalence of ESRD in newly developed countries such as China, India, Brazil, and Iran. [1–3]. Among renal replacement therapies (RRT) in patients with ESRD, hemodialysis is a common method [4]. The possibility of HBV transmission through environmental contact between patients and workers of dialysis units has been seen in various studies [5]. One of the possible factors for the continuation of hepatitis B

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infection in hemodialysis is the presence of latent hepatitis B [6, 7].

Uric acid is the end product of purine breakdown in humans, while other mammals metabolize it to allantoin through uricase [8]. Humans have higher levels of uric acid compared to other mammals due to the absence of uricase [9]. This loss of the uricase gene in human evolution is likely attributed to the strong antioxidant effect of uric acid, which plays a significant role in the body's antioxidant capacity [10]. Uric acid has been found to have a protective effect in neurodegenerative diseases like Parkinson's and Alzheimer's [11]. Hyperuricemia is defined as a serum uric acid level exceeding 6.8 mg/dL [12]. However, while uric acid acts as an antioxidant, its antioxidant property can be reversed at higher than normal levels. Studies have shown that the metabolism of micronutrients such as iron, selenium, magnesium, and uric acid affects immune system function, and imbalances in these elements can disrupt defense reactions against diseases or immunization after vaccination [13, 14].

Manuti et al. [15] evaluated the immunological response to hepatitis B vaccine in ESRD patients. They found that the seroconversion rate in this population was 63%. Proper control of hemoglobin, calcium, and albumin increased the immunological response, while factors such as old age, gender, and diabetes mellitus had no effect on the rate of seroconversion. Dede Sit et al. [16] also found that adequate dialysis and early vaccination before starting dialysis treatment play a crucial role in increasing the rate of seroconversion. Factors such as old age, male sex, duration of dialysis, and nutritional status were identified as influencing the rate of seroconversion. Mahzouni et al. [17] investigated the status of hepatitis B antibody titer in 133 Hemodialysis Patients and found no significant difference in HBsAb titer based on sex, age, or diabetes status. However, a significant difference was observed between HBsAb titer and history of hepatitis vaccination. Given the importance of HBV infection in ESRD and hemodialysis patients, the variable immune response to hepatitis B vaccination, and the lack of research on the effect of uric acid level on vaccine response in this population, this study aims to investigate the impact of uric acid level on the immunogenicity of hepatitis B vaccination in hemodialysis patients.

## Methods

In this descriptive-cross-sectional study, all patients with RRT hemodialysis treatment without a history of hepatitis B vaccination (referred to Shafa, Jayalalita and Saman dialysis centers in Kerman, Iran) from April 2018 to March 2019 were included in the study. Exclusion criteria included a history of liver disease-cirrhosis, a history of viral or medicinal hepatitis, and the use of allopurinol

or other drugs that lower uric acid levels. Confounding variables (demographic information, history of diabetes, autoimmune diseases and smoking, history of vaccination, and the duration of dialysis) were recorded. Before dialysis, uric acid, vitamin D, HBsAg and HBsAb check were evaluated. Then, patients were divided into 2 groups based on the level of uric acid: high level  $\geq 6.5$  mg/dl and low level  $< 6.5$  mg/dl. All patients were vaccinated with a high dose of hepatitis B vaccine (recombinant vaccine, GenHepvax produced by Encyto Pasteur Iran) (40 mcg) three times for 0, 1 and 6 months. After 8 weeks of the 3rd dose of the vaccine, the anti-hepatitis B antibody titer (HBsAb) was checked. Data analysis was done by SPSS (version 22, SPSS Inc., Chicago, IL). The results were reported descriptively by mean (standard deviation) and frequency (percentage). Independent T test was used to compare the average level of hepatitis B antibody in the two groups (high and low uric acid), and Kaplan–Meier test was used to describe the data related to HBsAb level in the patients. The significance level was considered less than 0.05.

## Ethical considerations

This study was approved by the ethics committee of Kerman University of Medical Sciences (ethic number:IR.KMU.AH.REC.1398.149). The informed consent was also obtained from all participants in the study. Ethical indices were considered in all stages of the research.

## Results

One hundred twenty-five patients without a history of hepatitis B vaccination were enrolled in the study. Among these patients, 60 (48%) were males and 56 (52%) were females. The average age of the patients was  $58.52 \pm 14.36$  years and the patient's weight was  $64.59 \pm 12.96$  kg. In most patients (111 (88%)), high blood pressure was the cause of kidney failure. Five patients (4%) had a history of smoking. In terms of laboratory indices before hepatitis B vaccination, all patients were negative for HBsAg, HBsAb, and HCV Ab (Table 1). Among the examined patients, serum uric acid was more than 6.5 mg/dl in 112 (89.6%), and was less than 6.5 mg/dl in the remaining 13 (10.4%) patients. Results showed that 94 patients (75.2%) had HBsAb more than 10 and 31 patients (24.8%) had HBsAb less than 10. The comparison of laboratory findings between the two groups (those with uric acid above 6.5 mg/dl and those with less than 6.5 mg/dl) was shown in Table 2. According to this table, the mean values of ferritin, vitamin D, Hb, creatinine, cholesterol, and PTH were not significantly different between the two studied groups. However serum albumin, calcium and triglycerides were significantly lower in the group with high serum uric acid. The mean values of dialysis adequacy in

**Table 1** Demographic variables in the evaluated patients

Variable		
Gender	Male	60
	Female	65
Age (Mean)	58.52	
Weight (Kg)	64.59	
Center	Javad Alaima Clinic	90
	Saman Clinic	35
Cause of renal failure	diabetes	84
	high blood pressure	110
	Autoimmune disease	9
	ACS	1
	Heart failure	8
	Polycystic kidney	9
	IHD	1
	idiopathic	1
	CABG	1
	CVA	2
	HF	1
	HLP	1
Smoking	Nephrotic syndrome	5
	Yes	5
Uric acid	No	121
	≥6.5	112
HBsAb	<6.5	13
	>10	31
	≤10	94

Data presented as Number or Mean

ACS Acute coronary syndrome, IHD Ischemic heart disease, CABG Coronary artery bypass graft surgery, CVA Cerebrovascular accident, HF Heart failure, HLP Hyperlipidemia

**Table 2** Comparison of average laboratory findings in the two groups, uric acid ≥ 6.5 and uric acid < 6.5 mg /dl

	Uric acid ≥ 6.5 mg /dl		Uric acid < 6.5 mg /dl		P value
	Mean	SE	Mean	SE	
Ferritin	241.14	23.95	247.38	82.79	0.934
Vitamin D	43.46	2.28	45	10.56	0.839
Hemoglobin	10.56	0.16	10.65	0.32	0.865
Serum albumin	3.79	0.04	4.10	0.16	0.045
Serum calcium	8.39	0.088	9.23	0.59	0.001
Adequacy of dialysis	1.15	0.03	0.95	0.13	0.08
Creatinine	6.95	2.21	8.14	1.92	0.067
Tri glyceride	111.74	5.83	149.38	17.12	0.04
Cholesterol	121.37	3.43	137.53	8.24	0.125
PTH	344.77	35.09	463.82	96.86	0.273

Data are presented as Mean. p-value < 0.05

PTH parathyroid hormone

the group with high level of uric acid is higher than the group with low level of uric acid. However, this difference was not significant. Comparison of the characteristics of patients (age, sex, place of registration, cause of renal failure, smoking, and weight) between the two groups was summarized in Table 3. The frequency of men was more than women in both groups. The most common cause of renal failure in both groups was related to high blood pressure. There was no statistically significant difference between the two groups in terms of all mentioned variables. Table 4 indicated the frequency of HBsAb status in the two groups. Based on this table, in patients with high uric acid, 30 (26.8%) had low HBsAb and 82 (73.2%) had high HBsAb. In patients with low uric acid, 1 (7.7%) had low HBsAb and 12 (92.3%) had high HBsAb. There was no statistically significant difference between the two groups in terms of HBsAb ( $P=0.131$ ). The average uric acid ( $4.46 \pm 1$ ) in patients with low HBsAb was less than its level in patients with high HBsAb ( $4.79 \pm 1.35$ ). This difference was not statistically significant ( $p.v=0.213$ ). The comparison of laboratory findings based on HBsAb level (less than 10 and more than 10) was shown in Table 5. This table showed that the mean values of all the studied parameters were not significantly different in patients with low compared to those with high HBsAb levels. The mean values of Hb and TG in the group with low HBsAb were insignificantly higher compared to the group with high HBsAb. The characteristics of patients (age, sex, place of registration, cause of renal failure, smoking, and weight) were also compared between patients with low and high HBsAb levels (Table 6). According to this table, there were no statistically significant differences of gender, average age, or weight, cause of renal failure, or smoking between patients with high compared to those with low HBsAb levels ( $P > 0.05$ ). Uric acid was < 3.5 mg/dl in 38 (30.4%), was between 3.5–6.5 mg/dl in 74 (59.2%), and was more than 6.5 mg/dl in 13 (10.4%). Using Pearson’s test, it was found that there is no relationship between uric acid and HBsAb ( $P=0.857$ ) (Table 7).

### Discussion

The effectiveness of hepatitis B vaccine in patients undergoing hemodialysis is less than in healthy individuals. The main reason for this issue is the decrease in the immunity level of these patients and the gradual decrease of HBsAb. This effectiveness is variable in a wide range between 50 and 80% of the normal rate and this variable rate of response to the vaccine depends on factors related to immunization and factors related to the host seroconversion and adequate response are defined as Anti-HBs > 10 IU/L, and > 100 IU/L, respectively. also the antibody titer < 10 IU/L is defined as hyporesponsive [16]. Our study showed that 24.8% of

**Table 3** Comparison of the characteristics of patients (age, sex, place of registration, cause of renal failure, smoking, and weight) in the two groups, uric acid  $\geq 6.5$  mg/dl and uric acid  $< 6.5$  mg/dl

Variable		Uric acid $\geq 6.5$ mg/dl	Uric acid $< 6.5$ mg/dl	P value
Gender	Male	57	8	0.467
	Female	55	5	
Age (Mean)		58.67	57/15	0.719
Weight (Kg)		64.84	62.46	0.532
Cause of renal failure	diabetes	76	8	0.64
	high blood pressure	98	12	
	Autoimmune disease	9	0	
	ACS	1	0	
	Heart failure	8	0	
	Polycystic kidney	8	1	
	IHD	1	0	
	idiopathic	1	0	
	CABG	1	0	
	CVA	2	0	
	HF	1	0	
	HLP	1	0	
Smoking	Yes	5	0	0.437
	No	107	13	

Data are presented as Number or Mean.  $p$ -value  $< 0.05$

ACS Acute coronary syndrome, IHD Ischemic heart disease, CABG Coronary artery bypass graft surgery, CVA Cerebrovascular accident, HF Heart failure, HLP Hyperlipidemia

**Table 4** Comparison of the rate of seroconversion after HBV vaccine in the two groups of patients with uric acid  $> 6.5$  and those with uric acid  $< 6.5$  mg/dl

HBsAb level	Uric acid (Mean $\pm$ SD)	Uric acid $\geq 6.55$ mg/dl	Uric acid $< 6.55$ mg/dl	P value
$> 10$	4.46 $\pm$ 1	30	1	0.131
$\leq 10$	4.79 $\pm$ 135	82	12	

Data are Number or Mean  $\pm$  Standard deviation.  $p$ -value  $< 0.05$

hemodialysis patients were hyporesponsive against hepatitis B virus vaccine and their antibody titer is less than 10 IU/L. These data seem relatively high and are comparable with other studies as, Mahzouni et al., who found that 29.32% of evaluated patients were hyporesponsive against hepatitis B virus vaccine [17]. However, Ebrahim et al., in Egypt assessed the antibody level after hepatitis B vaccination in dialysis patients. This group showed that 6.9% of patients had a titer of less than 10 [18]. The difference between Ebrahim et al. and our study can be related to the sample size, the number of examined patients and also to the timing of the assessment. Ebrahim et al., evaluated the patients response after the 4th dose of the vaccine, however we

**Table 5** Comparison of laboratory findings based on HBsAb level ( $> 10$  and  $\leq 10$ )

	HBsAb level $> 10$		HBsAb level $\leq 10$		P value
	Mean	SE	Mean	SE	
Ferritin	183.38	46.95	261.05	26.23	0.146
Vitamin D	42.38	4.85	44.02	2.63	0.762
Hemoglobin	10.70	0.27	10.53	0.18	0.619
Serum albumin	3.79	0.08	3.84	0.05	0.643
Serum calcium	8.47	0.2	8.47	0.08	0.976
Adequacy of dialysis	1.16	0.06	1.11	0.04	0.524
Creatinine	6.51	0.38	7.26	0.23	0.104
Tri glyceride	133.61	12.91	109.73	6.02	0.065
Cholesterol	120.61	7.85	123.86	3.42	0.664
PTH	338.64	55.41	363.26	40.12	0.749

Data are presented as Mean.  $p$ -value  $< 0.05$

PTH parathyroid hormone

only gave the patients 3 doses of the vaccine. Most of the similar studies also showed that gender was not an effective factor in the amount of antibody titer, which are comparable with our results, where there were no differences between males and females or between patients according to their ages and their HBsAb titer.

**Table 6** Comparison of the characteristics of patients (age, sex, place of registration, cause of renal failure, smoking, and weight) based on HBsAb level (> 10 and ≤ 10)

Variable		HBsAb level > 10	HBsAb level ≤ 10	P value
<b>Gender</b>	Male	15	50	0.642
	Female	16	44	
<b>Age (Mean)</b>		60.25	57.94	0.44
<b>Weight (Kg)</b>		65.81	64.2	0.551
<b>Cause of renal failure</b>	diabetes	24	60	0.118
	high blood pressure	25	85	
	Autoimmune disease	3	6	
	ACS	0	1	
	Heart failure	2	6	
	Polycystic kidney	4	5	
	IHD	1	0	
	idiopathic	0	1	
	CABG	0	1	
	CVA	0	2	
	HF	0	1	
	HLP	0	1	
<b>Smoking</b>	Yes	2	3	0.422
	No	29	91	

Data are presented as Number or Mean. *p*-value < 0.05

ACS Acute coronary syndrome, IHD Ischemic heart disease, CABG Coronary artery bypass graft surgery, CVA Cerebrovascular accident, HF Heart failure, HLP Hyperlipidemia

**Table 7** Correlation coefficient of uric acid and HBsAb

Uric acid		
Pavle	Pearson coefficient	HBsAb
0.857	-0.016	

Asghari et al. showed that gender has no significant relationship with antibody titer status and immunity level of individuals [19]. However, some studies showed difference in HBsAb between men and women. Kazemini et al., reported a higher titer among women compared to men. [20]. In another study, a better response to hepatitis B vaccination was reported in young and male individuals [16]. Meanwhile, some studies showed that age was an effective factor in antibody titer. Yang et al. concluded that the rate of response to the vaccine decreases with increasing age (more than 40 years) [21]. Baba Mahmoudi et al. also showed that old age and the frequency of vaccine injections have a significant effect on the rate of response to it, and Hbs antibody titers decrease over time [22]. Asghari et al. also concluded that age was effective in the immunogenicity of hepatitis B vaccine, and the immunogenicity decreases with increasing age [19]. Alavian et al. investigated the effect of diabetes on the immunity of the hepatitis B vaccine

and concluded that diabetics had a significant decrease in response compared to non-diabetics [23]. These different results can be explained by differences in the studied groups,, residential area, health level, diet of different communities and people's level of awareness. Diabetic people are always exposed to infectious diseases and should have regular vaccinations. The immunity level of diabetic patients is at the level of healthy people, and if diabetes is controlled, diuresis is normal, and they do not suffer from ketonuria, they show a suitable response to many vaccines [24],our results also showed no differences of HBsAb titer between patients with various etiologies ( diabetes or others).In patients with high level of uric acid, 30 (26.8%) had low HBsAb level and 82 (73.2%) had high HBsAb level. In patients with low level of uric acid, 1 (7.7%) had low HBsAb and 12 (92.3%) had high HBsAb level. There was no statistically significant difference between the two groups in terms of HBsAb. A study showed that uric acid can strongly enhance T-cell immune responses induced by HBsAg-pulsed-DCs vaccine. Uric acid may act as an effective adjuvant of dendrocyte-containing vaccine against HBV infection [25]. In our study, laboratory findings (ferritin, vitamin D, hemoglobin, serum albumin, serum calcium, dialysis adequacy, creatinine, triglyceride, cholesterol, PTH) were not related to HBsAb.

In Magellan et al.'s study, it was found that a higher serum zinc level reduces the risk of non-response to hepatitis B vaccination, and male gender was associated with an increased risk of not producing antibodies against hepatitis B [26]. In some studies, malnutrition, uremia, and generalized immunosuppression in dialysis patients have been reported among the possible contributing factors to the lack of proper response to hepatitis B vaccination [27]. However, in our study, the low level of serum albumin, as a sign of malnutrition in dialysis patients, was not related to the response to hepatitis B vaccination. Manuti et al. showed the seroconversion rate with percentage of 63%. This group indicated that the proper control of hemoglobin, calcium and albumin and the passage of longer time from hemodialysis can significantly increase the immunological response to this vaccine. Old age, gender and diabetes mellitus had no effect on the rate of seroconversion [15]. The advantage of our study was to investigate the level of uric acid, which has not been investigated in response to hepatitis B vaccine in hemodialysis patients. One of the limitations of our study was the small sample size of the group of patients with low serum uric acid. Therefore, studies including sufficient number of patients with chronic kidney failure before and during dialysis may be more informative.

## Conclusion

In our study, there was no correlation between uric acid level and immunogenicity of hepatitis B vaccination in hemodialysis patients. More studies on a larger number of patients are necessary in this field.

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## Authors' contributions

Conception and design of the study; Najmeh Shamspour, Nasibe Golestani. Generation, collection, assembly, analysis and/or interpretation of data; Najmeh Shamspour, Nasibe Golestani, Jalal Azmandian, Habibeh Ahmadi-pour. Drafting and/or revision of the manuscript; Najmeh Shamspour, Nasibe Golestani. Approval of the final version of the manuscript. Najmeh Shamspour, Jalal Azmandian.

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## Availability of data and materials

The data supporting this study's findings are available from the corresponding author upon reasonable request.

## Declarations

### Ethics approval and consent to participate

Data collection forms were anonymous and fiduciary, confidential, and non-disclosure of participants' secrets. Ethical consents were obtained from all patients. This study was approved by the ethics committee of Kerman University of Medical Sciences (ethic number:IR.KMU.AH.REC.1398.149).

### Consent for publication

Not applicable.

### Competing interests

There was no conflict of interest.

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