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Effect of Dialysis Prescription Dose on Hepatitis B Vaccination Immunological Response in Hemodialysis Patients

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Abstract

Background: End stage renal disease (ESRD) patients are at increasing risk for hepatitis B virus (HBV) infection, also they are considered immunocompromised and their response to vaccination is low compared to normal persons.

Aim of Study: The aim of our study is to determine the immunological response after HBV vaccination, and its relation to dialysis prescription dose in hemodialysis (HD) patients.

Patients and Methods: This cross sectional study included 100 ESRD patients on maintenance HD, selected from dialysis units of Shebin Elkom Teaching Hospital, Menoufia Governorate and Ain Shams University Hospital, from November 2019 to November 2020. All patients were ESRD on thrice weekly HD sessions, 3-4 hours for each session using bicarbonate dialysate and polysulfone dialyzers. The blood flow rate ranged from 220-350ml/min, the dialysate flow rate was 500ml/min. All patients were negative for serological markers of HBV infection, including HBsAg and anti-HBc antibodies. The study included 59 males and 41 females. Their ages ranged between (23-76 years). 14 Patients received 4 doses of hepatitis B vaccine with dose 2.0 mL, administered at 0, 1, 2 and 6 months by intramuscular (deltoid) injection (according to infection control program in dialysis units in Egypt), 86 patients previously completed their course of vaccination so received a booster dose then HBV antibody titer was measured a month after for both groups.

Results: Eighty-eight patients (88%) mounted a response with HBsAb >10 mIU/ml, and thus were considered as adequate responders. 54 patients out of responders (61.4%), mounted a high response with HBsAb >1000mIU/ml. Twelve patients (12%) were non-responders. Age, gender, anthropometric measures, hemoglobin level, serum albumin, ferritin, parathyroid hormone (PTH) level and hepatitis C virus infection had no effect on the response to the vaccine. Similarly, there was no difference in diabetic state between the two groups. There were highly significant differences between responders and non-responders regarding dialysis adequacy [urea reduction ratio (URR) and KT/V] and CRP.

Conclusion: There was a high response to HBV vaccine in ESRD patients and there were significant relations between dialysis adequacy in the form of URR and KT/V and CRP and HBV antibody titer.

Key Words: *Hemodialysis – Hepatitis B virus vaccine antibody – Dialysis adequacy.*

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Introduction

HBV infection is an important public health problem affecting approximately 500 million people worldwide **[1]**. According to 2010 data, 360 million people have chronic HBV infection that leads to more than 1 million deaths/year due to acute hepatitis, cirrhosis or hepatocellular carcinoma **[2]**. Clinical course of chronic HBV infection may vary from asymptomatic carrier state to cirrhosis or even hepatocellular carcinoma **[3]**.

Hepatitis B prevalence remains a challenge in dialysis. The United States Renal Data System (USRDS) indicates that 1% of dialysis patients tested positive for hepatitis B surface antigen (HBsAg) while in a registry study of Asian-Pacific countries, the prevalence of HBsAg in HD populations ranged from 1.3% to 14.6% **[4]**. In general, the incidence of HBsAg positivity among dialysis patients ranges from 0%-7% in low-prevalence countries to 10%-20% in endemic areas.

However, it is significantly higher in some areas like southeastern Asia and Middle East. The majority of Southeast Asia and Middle East countries have an intermediate or high endemicity of HBV infection. Based on the data in 2009, the rate of HBsAg positivity was 4.4% in the turkish population (ranging from 2.5% to 9.1%) **[5]**.

The chronicity rate of HBV infection is 5%-10% in the general population, whereas it may be as high as 60%-80% in patients receiving renal replacement therapy (RRT) **[6]**. In a study done in Egypt, the prevalence of HBV infection in hemodialysis is 3% (1.7% is hepatitis B alone and 1.3%

dual infection of hepatitis C and B [7]. Owing to the fact that the chronicity rate of HBV infection is high and success rate of antiviral therapy is low in dialysis population, preventive measures against HBV infection is of vital importance. Since the first recommendation of HBV vaccination by the Center for Disease Control and Prevention, the United States in 1982, administration of recombinant HBV vaccine which is composed of HBsAg is routinely used [8].

HBV vaccination should be started before the initiation of RRT. Currently, intramuscular administration of HBV vaccine at 0, 1, 2 and 6 months at a dose of 40 µg is recommended. Instead of gluteal region which contains muscle and fat, deltoid muscle is a preferable area to increase response rates [9]. There are variable response rates to HBV vaccination among HD patients. Inadequate seroconversion rates in the general population and patients on RRT are 5%-10% and 40%-50%, respectively [10]. According to another report, 20% of vaccinated patients on HD still do not achieve antibody formation against HBsAg [11].

Patients with chronic kidney disease (CKD) exhibit an impaired immune response against host agents including HBV due to bone marrow suppression caused by uremia and loss of CD4 T cells by use of bio-incompatible dialysate and membranes [12]. Patients on HD or peritoneal dialysis (PD) have an increased risk of HBV related complications. On the other hand, the rates of seroconversion induced by HBV vaccination in patients with CKD is significantly lower than those in the general population [13].

This study aimed to determine the immunological response after HBV vaccination, and its relation to dialysis prescription dose in hemodialysis (HD) patients.

Patients and Methods

Technique: The study got approval from ethics and research committee (ERC), Faculty of Medicine, Ain Shams University. Also, patients participating in the study were informed and consents were taken.

A cross sectional study was done on 100 ESRD patients on maintenance HD, selected from attendants to dialysis units of Shebin Elkom Teaching Hospital, Menoufia Governorate and Ain Shams University Hospital, Cairo, during the period from November 2019 to November 2020. It included 59 males and 41 females. Their ages ranged between (23-76 years) with mean age 56.1 ± 12.7 years.

Inclusion criteria:

- All patients were ESRD on regular HD sessions thrice weekly, 3-4 hours for each session using bicarbonate dialysate. The blood flow rate ranged from 220-350ml/min, the dialysate flow rate was 500ml/min, and polysulfone dialyzers.
- All of the patients were negative for all serological markers of HBV infection, including HBsAg and anti-HBc antibodies.
- 14 Patients received 4 doses of hepatitis B vaccine (the second generation recombinant DNA-HB vaccine (Energix HB) with dose 2.0mL (40 µg HBVsAg), administered at 0, 1, 2 and 6 months period by intramuscular (deltoid) injection (according to infection control program in dialysis units in Egypt), 86 patients previously completed their course of vaccination so received a booster dose then HBV antibody titer was measured a month after, for both groups.

Exclusion criteria:

- Age <18 years.
- Pregnancy.
- The presence of active neoplasm.
- Patients receiving immunosuppressive drugs for any reason.

All Patients were subjected to the following:

1- History and clinical examination:

All included patients were subjected to:

- Full history taking including age, gender, medical comorbidities, etiology of ESRD, regimen of HD, duration on HD, type of dialysis access (fistula, graft or a catheter), drug history & diseases that may affect immune response to HB vaccine as well as symptoms & signs of any infection.
- Complete clinical examination.
- Calculation of BMI - was calculated as:

Body weight in kilograms divided by the square of body height in meters expressed by kg/m^2.

2- Laboratory investigations:

Complete blood count (CBC), serum albumin, random blood sugar (RBS), serum calcium(Ca) and serum phosphorus (Po4), serum iron, total iron binding capacity (TIBC), serum ferritin, parathyroid hormone level (PTH), C reactive protein (CRP) and glycated hemoglobin (HbA1c).

3- Adequacy of dialysis measures:

Serum urea (pre-dialysis and post-dialysis) and calculation of dialysis adequacy through urea reduction ratio (URR) & KT/V.

We assessed dialysis adequacy using the Kt/V formula and the URR for all patients:

Single-pool Kt/V (spKt/V) was assessed using the Daugirdas second-generation formula; (Kt/V Daugirdas = -ln [(BUNPost / BUNPre) - (0.008 * Hours)] + [(4 - (3.5 * BUNPost / BUN Pre)] * UF Vol / Weight Post) **[14]**.

The postdialysis blood urea nitrogen (BUN) sample was obtained at the end of the dialysis session by slowing the blood pump to 50-100ml/min for 10-20sec, after which the blood pump was stopped and a blood sample was obtained either from the arterial bloodline sampling port or from the tubing attached to the arterial needle **[14]**.

URR was calculated and expressed as a percentage *URR = Pre BUN-Post BUN/Pre BUN.

4- *Serological study:*

1- Hepatitis B surface antigen (HBsAg) using ELISA using precheck diagnostic ELISA kit from USA **[15]**: All patients were negative.

2- Hepatitis B surface antibody (HBsAb) titer in serum:

The blood samples were taken under complete aseptic condition and before any drug medications. Blood was collected by vein puncture, allowed coagulation at room temperature 10-20mins, then was centrifuged for 20min at speed of 2000-3000 r.p.m then supernatant was removed. Hemolytic, lipemic or contaminated serum was not used. The specimens were stored frozen at –20 °C until testing. Specimens were capped and were frozen at –20 °C prior to assay.

Full test Name: Hepatitis B surface antibodies (HBsAb) (ELISA) Kit.

Intended use: Immunoassay for the in-vitro quantitative determination of human antibodies to the HBsAg in human serum and plasma.

The electrochemiluminescence immunoassay "ECLIA" is intended for use on Elecsys and cobase immunoassay analyzers.

Summary of test:

Anti-HBs is a specific (generally IgG) antibody that is directed against HBsAg. Anti-HBs can be formed following a hepatitis B infection or after hepatitis B vaccination. Antibodies are formed against the HBsAg determinant (a), which is common to all subtypes, and against subtype-specific determinants. The Elecsys Anti-HBs assay uses a mixture of purified antigens of the HBsAg subtypes ad and ay from human serum.

3- Detection of HCV-Ab by (ELISA):

The HCV-Ab ELISA test is for clinical lab diagnosis of patients who are suspected of having a hepatitis C virus infection. This HCV Ab ELISA test is an enzyme-linked immunosorbent assay for in-vitro qualitative identification of IgG antibodies to hepatitis C virus in human serum/plasma.

Statistical analysis:

The results were summarized as mean ± standard deviation (SD). Student's *t*-test was used for testing the significance of differences of values measured between responders and non-responders and p-value <0.05 was taken as statistically significant. Also, Chi-square test was used. All analyses were performed using SPSS version 16.

Results

Patients were divided according to vaccination response into 2 groups:

1- Non responders to vaccine (12 patients out of 100) (12%) (HBV antibody titer less than 10 IU).

2- Immune responders (88 patients out of 100) (88%): (HBV antibody titer above 10IU); those were further subdivided into 3 subgroups:

- Low immune responders (19 patients/88) (21.59%): (HBV antibody titer between 10-99 IU).
- Good immune responders (15 patients/88) (17.05%): (HBV antibody titer between 100-999IU).
- High immune responders (54 patients/88) (61.36%): Those with HBV antibody titer above 1000IU.

Demographic data:

A total of 100 chronic HD patients were enrolled in our study (59 males and 41 females). The mean age was 56.1 ± 10.1 years (range 23-76); there was no statistical difference between the responders compared with the non-responders group (56.1 ± 10.1 vs 56.1 ± 12.7 years, respectively, p=0.595).

The etiology of ESRD was hypertension in 42 cases (42%), diabetes mellitus (DM) in 25 cases (25%), obstructive uropathy in 8 cases (8%), autosomal dominant polycystic kidney disease (ADPKD) in 6 cases (6%), eclampsia in 6 cases (6%), interstitial nephritis in 2 cases (2%), chronic glomerulonephritis in 2 cases (2%), congenital atrophy and unknown causes in 9 cases (9%). There was no significant difference between good responders and low and non-responders regarding the original renal disease (p=0.922) (Tables 1A,2A).

Table (1): Comparison between responders and non-responders with vaccination against hepatitis B virus infection.

Table (1-A): Demographic data and Anthropometric measures of both groups.

Parameter	Responders	Non-responders	*p*-value
Age (years)	56.1±10.1	56.1±12.7	*p*=0.595
Gender	51/37	8/4	*p*=0.757
Weight (kg)	80.3±15.2	87.4±22.2	*p*=0.442
Height (meters)	1.65±0.064	1.63±0.05	*p*=0.355
BMI%	29.4±5.2	32.6±7.5	*p*=0.176
Dry weight (kg)	77.6±14.8	85±21.6	*p*=0.390
IDWG (kg)	2.4±1.2	2.7±0.86	*p*=0.312

BMI: Body mass index. IDWG: Interdialytic weight gain.

Table (1-B): Lab investigations of responders and non-responders.

Parameter	Responders	Non-responders	*p*-value
Hb (g/dl)	10.2±1.5	9.8±1.7	*p*=0.277
WBCs/mm^3	5.8±1.5	6.2±2.5	*p*=0.655
Platelets/mm^3	247.8±76.6	246.2±77.8	*p*=0.879
Serum calcium (mg/dl)	8.7±0.98	8.8±1.3	*p*=0.914
Po4 (mg/dl)	5.27±1.44	5.25±1.28	*p*=0.952
PTH(pg/ml)	508.2±441.2	638.3±536.2	*p*=0.344
Serum albumin (g/dl)	4.05±0.59	3.9±0.59	*p*=0.280
CRP	6.12±4.9	17.7±14.9	*p*=0.00
Serum iron (ug/dl)	73.1±33.9	82.3±39.7	*p*=0.288
Ferritin (ng/ml)	446.7±353.4	502.6±394.5	*p*=0.525
TIBC	289.4±105.1	272.7±103.4	*p*=0.146
TSAT %	27.3±13.6	33.01±14.7	*p*=0.070
HbA1c %	5.57±0.94	5.42±0.74	*p*=0.796
Random blood sugar	132.4±60.01	125.6±41.3	*p*=0.674

Hb : Hemoglobin. CRP : C reactive protein.
WBCs : White blood cells. TIBC : Total iron binding capacity.
Po4 : Phosphorus. TSAT% : Transferrin saturation.
PTH : Parathyroid hormone. HbA1c : Glycated hemoglobin.

The hemodialysis prescription:

The duration on HD therapy among the studied patients ranged from (9-242) months, and there was no significant difference between good and high responders vs low and non-responders (54.2± 39.12 vs 53.2±43.04 months respectively; *p*=0.403) (Table 2A).

All patients received 3-4 hours of HD. 72 patients (72%) were using high-flux polysulfone membrane and 28 patients (28%) were using low-flux membrane with significant differernce between responders and non-responders (676.9±442.8 vs 446.2±448.9) respectively (*p*=0.016) with different surface areas (1.4, 1.7 and 2.2m^2). The dialysate flow rate was 500mL/min and the blood flow rate ranged from 220 to 350mL/min.

According to dialysis access: Arterio-venous fistulas in 96 patients (96%), internal jugular vein catheter in 2 patients (2%), 1 patient using femoral permicath (1%), 1 patient had arterio-venous graft as his dialysis access (1%); with no difference between good and high responders vs low and non-responders (*p*=0.774).

The mean and standard deviation of URR of responders and non-responders were (63.4±4.3) and (56.9±3.3) respectively; *p*=0.00 (≤0.001), with highly significant difference between the 2 groups.

The mean and standard deviation of KT/V of responders and non-responders were (1.19±0.13) and (1.003±0.095) respectively; *p*=0.00 (≤0.001), with highly significant difference between the 2 groups (Table 2B).

Table (2-A): Hemodialysis details in good and high responders VS low and non-responders.

Items	Good and high Responders	Low and Non-responders	*p*-value
HD duration (months)	54.2±39.12	53.2±43.04	*p*=0.403
Session duration (hours)	3.92±0.25	3.97±0.18	*p*=0.251
Vascular access:			
- Arteriovenous fistula	66	30	*p*=0.774
- Arteriovenous Graft	1	0	
- Femoral permicath	1	0	
- Int. jugular vein catheter	1	1	
Etiology of ESRD:			
- ADPKD	5	1	*p*=0.922
- Congenital atrophy	1	0	
- DM	18	7	
- Eclampsia	3	3	
- Chronic Glomerulonephritis	1	1	
- HTN	28	14	
- Chronic Interstitial nephritis	1	1	
- Obstuctive nephropathy	6	2	
- Unknown	6	2	

Table (2-B): Comparison between Responders and Non responders regarding adequacy of dialysis.

Items	Responders (88)	Non-responders (12)	*p*-value
Urea pre (mg/dl)	162.8±36.4	161.2±40.5	*p*=0.852
Urea post (mg/dl)	60.3±18.2	69.7±18.9	*p*=0.021 (≤0.05)
URR %	63.4±4.3	56.9±3.3	*p*=0.00 (≤0.001)
KT/V	1.19±0.13	1.003±0.095	*p*=0.00 (≤0.001)

URR: Urea reduction ratio.

Table (3): KT/V in all subgroups.

	Non responders (Ab titer <10IU) (No=12)	Low responders (Ab titer 10-100 IU) (No=19)	Good responders (Ab titer 100-100IU) (No=15)	High responders (Ab titer >1000IU) (No=54)	Kruskal-Wallis	*p*-value
KT/V:						<0.001
						p_1=0.339
Mean ± SD	0.98±0.072	1.01±0.107	1.15±0.17	1.21±0.12	55.9	p_2=0.002
						p_3=<0.001
						p_4=0.011
						p_5=<0.001
						p_6=0.057

*p*1 Is the relation between non responders and low responders (10-100).
*p*2 Is the relation between non responders and intermediate responders (100-1000).
*p*3 Is the relation between non responders and high responders (>1000).
*p*4 Is the relation between low responders and intermediate responders.
*p*5 Is the relation between low responders and high responders.
*p*6 Is the relation between intermediate responders and high responders.

Effect of nutritional status on HBV antibody response:

There was no significant differences in serum albumin levels and the BMI between responders and non-responders (Table 1A,B).

Effect of DM and hepatitis C virus status on HBV antibody response:

Regarding DM; 25 patients were diabetics (25%); 18 patients were good and high responders (26.1% of these 2 subgroups) and 7 patients were low and non-responders (22.6% of these 2 sub-groups), with a non-significant difference (p=0.708) (Table 2A). We used HbA1C as an indicator of glycemic control for diabetic patients included in the study. There was no significant differences between the responders and the non-responders groups regarding HbA1C Levels with mean and standard deviation of (5.57±0.94) and (5.42±0.74) respectively; (p=0.796) (Table 1B).

In our study group, 50 patients (50%) had HCV as shown by anti-HCV positive antibodies; 32/50 patients were good and high responders, while 18 patients were low and non-responders, with a non-significant difference (p=0.280).

Effect of CRP on HBV antibody response:

There was a highly significant difference between responders and non-responders regarding CRP levels with mean and standard deviation of (6.12±4.9) and (17.7±14.9) respectively; p=0.00 (≤0.001) (Table 1B).

Our results revealed highly significant positive correlations between levels of HBV antibody titer and dialysis adequacy parameters in the form of urea reduction ratio (p=0.00 ≤0.001), KT/V (p=0.00 ≤0.001).

Table (4): Correlation between HBV antibody titer of all patients (100) and different parameters.

Table (4-A)

Items	Antibody titer	Antibody titer (min-max)	Test of significance & *p*-value
Gender:			
- Male	585.9±496.4	2-1000	Mann Whitney
- Female	650.2±434.7		U=0.527
			p=0.598 (>0.05)
Vaccination way:			
- Booster vaccine dose	646.8±446.6	2-1000	Mann Whitney U=2.27
- Recently vaccinated	400.3±459.8		p=0.023(≤0.05)

Table (4-B)

Item	Correlation	Test of significance & *p*-value
Age (years)	r=–0.028	p=0.779 (>0.05)
Weight (Kg)	0.028	p=0.784 (>0.05)
Height (meter)	0.114	p=0.259 (>0.05)
BMI%	–0.014	p=0.893 (>0.05)
Dry Weight (Kg)	0.018	p=0.861 (>0.05)
IDWG (Kg)	0.113	p=0.262 (>0.05)
Urea pre (mg/dl)	–0.025	p=0.806 (>0.05)
Urea post (mg/dl)	–0.275	p=0.006 (≤0.05)
URR%	0.626	p=0.00 (≤0.001)
KT/V	0.632	p=0.00 (≤0.001)
HD Session duration (hours)	–0.093	p=0.356 (>0.05)
Total HD duration (months)	0.057	p=0.571 (>0.05)
Hb	0.186	p=0.065 (>0.05)
WBCs	–0.115	p=0.255 (>0.05)
Platelets	–0.009	p=0.928 (>0.05)
Serum calcium	0.021	p=0.834 (>0.05)
PO4	–0.005	p=0.962 (>0.05)
PTH	–0.070	p=0.489 (>0.05)
Serum albumin	0.059	p=0.560 (>0.05)
CRP	–0.695	p=0.00 (≤0.001)
Serum iron	–0.035	p=0.730 (>0.05)
Ferritin	0.018	p=0.858 (>0.05)
TIBC	0.083	p=0.410 (>0.05)
TSAT	–0.076	p=0.453 (>0.05)
Blood glucose	–0.089	p=0.376 (>0.05)
HbA1c	–0.077	p=0.449 (>0.05)

Also, we found negative correlations between levels of antibody titer and level of post dialysis urea level (p=0.006 ≤0.05), CRP (p=0.00 ≤0.001).

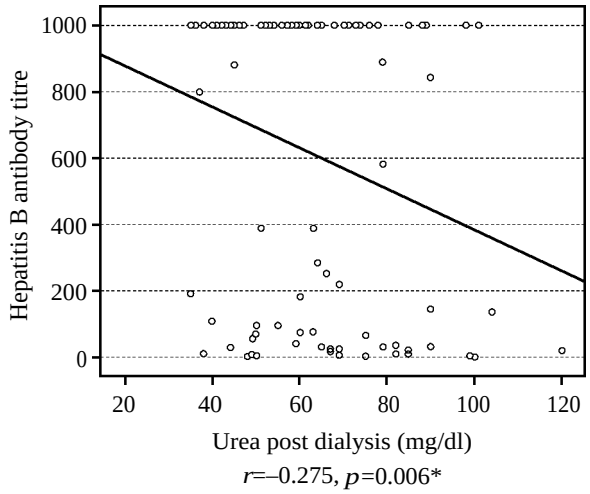

Fig. (1): Correlation between urea post dialysis and Hepatitis B antibody titre

Regression analysis for all significant results:

Predictors	*t*	B	95 CI%	*p*-value
CRP	5.8	–0.444	25.4-12.6	<0.001
Urea post	1.9	0.173	0.24-8.6	0.063
KT/V	1.03	0.337	(–920)-2920	0.304
URR	0.611	0.198	(–40.2)-8.6	0.542

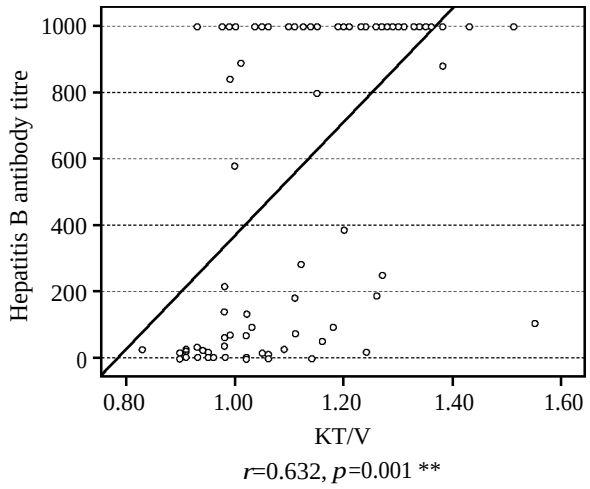

Fig. (2): Correlation between KT/V and Hepatitis B antibody titre

Discussion

Our study was done on 100 ESRD patients on maintenance HD. It was conducted to determine the immunological response after HBV vaccination, its relation to dialysis prescription dose in HD patients, and to show the effect of dialysis adequacy on seroconversion.

Our results showed a high response to hepatitis B vaccination among HD patients, the incidence of response was 88% (HBVantibody titer >10 IU) and there were 61.3% high responders (N 54/88pts) (HBV antibody titer > 1000IU. This was similar to (Abdel-Moniem et al., 2019) who reported 54/70 patients were responders (80%) **[16]** and to (Almueilo, 2017) who reported HB vaccine seroconversion rate of 70.3% in 101 HD patients **[17]**. Also, Al Saran et al., in their study reported that 129 out of 144 (89.64%) patients were responders (anti-HBs ≥10), whereas non-responders (anti-HBs <10IU/l) were 15 out of 144 (10.4%) patients **[18]**.

Ayub et al., followed-up 83 HD patients and collected quantitative serologic measurements every 2 months over a 1-year period to determine HB vaccine immune response in these patients. The authors reported that 1 month after the vaccination period 41 % of the patients were non-responders (anti-HBs <10IU/l), 21.7% poor responders (anti-HBs between 10 and 100IU/l), and 37.3% good responders (anti-HBs >100IU/l), respectively, and all patients displayed decreasing antibody titers during the observation period. Moreover, anti-HBs titer in good responders dropped to unprotected level in 8 and 32% after 1 and 2 years in these patients, respectively **[19]**. In contrast, reduced response was reported by Buti et al., who followed-up 60 HD patients up to 3 years after primary hepatitis B vaccination series (4 doses of Engerix B, 20mg/dose) to evaluate the level of anti-HBs titer and its persistence. The authors reported that HD patients not only had lower response rates to HB vaccination (73% of patients were responders with anti-HBs levels ≥10IU/l versus 27% non-responders even with further booster dose, anti-HBs persistently <10IU/l), but also it was a transient response in many patients (41 % of responders had no detectable anti-HBs levels after 3 years of follow-up **[20]**.

In the current study, the mean URR in the responders was 63.4±4.3% that was significantly higher as compared with the non-responders (56.9±3.3%), (p=0.00 ≤0.001). This came in accordance with Abdel-Moniem et al., 2019 **[16]** who showed that the responders to HBV vaccination had significantly higher URR% in comparison with non-responders (63.64±9.11 vs 52.73±63.64; p<0.05). The positive effect of efficient HD on the response to HB vaccination was also reported by Dede et al., 2010 **[21]**. In our study, the mean Kt/V in the responders was 1.19±0.13 that was significantly higher as compared with the non-responders (1.003±0.095), (p=0.00 ≤0.001). This came in agreement with Abdel-Moniem et al., 2019 **[16]**

who showed that the responders to HBV vaccination had significantly higher Kt/V in comparison with non-responders (1.17 ±0.19 vs. 0.94± 1.17, $p<0.05$).

Our study showed no significant differences between the responders and non-responders regarding the duration of dialysis session and total duration of dialysis/month. This came in accordance with (Almueilo, 2017) [17] but against a study conducted by Erdog˘du et al., [22] and Hatami et al., [23].

In our study, there was no significant difference in the mean age between the responders and non-responders (56.1 ± 10.1 and 56.1 ± 12.7 years) respectively. This came in agreement with other study [19], who showed that there was no significant difference in the mean age between the responders and non-responders of HD patients who received HBV vaccination. In contrast, it had been reported that age negatively influenced the response to the HBV vaccine in HD patients in a meta-analysis of 31 clinical trials and was attributed to the age-associated changes in immune status [24].

Our results showed no significant differences regarding gender distribution between the responders and non-responders. There was higher male prevalence in the two groups. This agreed with Asan et al., [25] who showed that gender did not affect the response to HBV vaccine. Some studies have indicated that males develop a weaker response to HBV vaccination than females; Navarro et al., 1996 [26]; Dog˘ukan et al., [27]; Morse and High, 2015 [28].

Although some studies reported that BMI is a determinant of the response to the HB vaccine Gasim et al., [29], our study showed no relationship between these variables. These results came in accordance with Hatami et al., [23].

In our study, the mean hemoglobin level in the responders was 10.2 ± 1.5gm/dl and in the non-responders, the mean level was 9.8 ± 1.7gm/dl with no significant difference between the two groups. In another study carried out on HD and peritoneal dialysis patients, higher hemoglobin levels were found to be associated with greater odds of vaccination response in univariate regression Lacson et al., [30].

In our study, the mean CRP in the non-responders was 17.7 ± 14.9 that was significantly higher as compared with the responders (6.12 ±4.9), ($p\leq 0.001$). This goes with Amira and Lesi, 2017 [31] who reported that the low responsiveness in HD patients may be related to uremic toxins accumulation, increased systemic and vascular inflammatory biomarkers concentration, advanced glycation end products. This disagreed with Almueilo, [17] who showed that there was no difference between responders and non-responders regarding CRP levels.

We showed that HCV does not interfere with the development of a protective antibody response after vaccination, although lower titers of HBs-Ab have been reported after vaccination of HCV-positive patients in comparison with HCV-negative patients [32]. Our results showed no significant difference in the prevalence of positive HCV antibodies between the responders (46.4%) as compared with the low and non-responders (58.1%). This came in accordance with the study of Almueilo, [17] who showed that the response to the vaccine in 12 patients with HCV infection was not significantly different from patients negative for HCV antibodies. A meta-analysis of 8 studies on 520 HD patients also noted that there were no significant decreases in immune response among HCV-positive versus HCV-negative HD patients [33]. In contrast, Navarro et al., noted that HCV infection might reduce the effectiveness of the hepatitis B vaccine in HD patients [26].

In our study, there was no significant difference in the prevalence of DM between the responders (26.1%) as compared with the low and non-responders (22.6%). This agreed with another study [34] who included 64 ESRD patients on maintenance HD who received HBV vaccination. Similar results were reported by (Sezer et al., 2000) [35]. Saran et al. in their study aimed to determine factors affecting the response to HB vaccine among HD patients and used HbA1c as an indicator for glycemic control in diabetic patients. The authors reported no significant differences between responders and non-responders in relation to HbA 1 c levels [18].

This contradicts previous findings which state that higher prevalence of DM is associated with lower chance of vaccination response [36]. Several hypotheses about the biological basis for potentially impaired cellular immune response to vaccination among persons with diabetes were suggested, including a reduction in the number of circulating helper T cells, the CD4-to-CD8 lymphocyte ratio, and lymphocyte blastogenesis [37] and defects with antigen presentation [38]. Impaired vaccine response also has been linked to the presence of DR3, DR7, and DQ2 human leukocyte antigen alleles among persons with diabetes [39].

In our study, the prevalence of HTN between the responders (88.4%) was significantly higher as compared with the low and non-responders (71%) (p=0.032 ≤0.05). This disagreed with (Ayub et al., 2014 **[19]** who showed that the incidence of HTN was significantly higher in the non-responders as compared with the responders. However, Hatami et al., 2019 **[23]** showed that there was no association between the response to the HB vaccine and HTN (p=0.2).

It is well known that low levels of albumin show poor prognosis whatever the etiology of ESRD **[40]**. Dialysis patients are at an increased risk for malnutrition, especially in the setting of inadequate dialysis, which might lead to insufficient protective immunity after vaccination **[41,42]**. Our results showed a non-significant positive correlation between HBV antibody titer and serum albumin level. Other studies showed similar results results **[17,18,43]**, while one revealed a significant positive correlation between anti-HBs titer and serum albumin levels in the HD subgroup (p=0.02) **[44]**.

In our study, the mean PTH level in the responders was 508.2±441.2 and in the non-responders, the mean level was 638.3±536.2 with no significant differences between both groups. However, in a meta-analysis by Udomkarnjananun et al., 2020 **[45]**, it was found that HBV vaccine responders had higher PTH levels. However, previous studies have demonstrated a negative impact of PTH on the immune system **[46]**.

It is to be noted also that we found better immune response shown by higher level of antibodies among those receiving the booster dose of HBV vaccine 646.8±446.6 vs 400.3±459.8 in recently vaccinated patients, p=0.023, indicating the necessity to follow-up the hemodialysis patients with giving them the booster dose.

Conclusion:

We report a high response rate to hepatitis-B vaccination among our patients. Adequacy of dialysis as expressed by (URR and Sp KT/V) had a positive association with response to HBV vaccine in HD patients. Systemic inflammation and high CRP had a negative correlation with vaccine response.

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تأثير جرعة الغسيل الكلوى على الاستجابة المناعية للتطعيم ضد الإلتهاب الكبدى بى فى مرضى الاستصفاء الد موى المنتظم

الهدف من دراستنا هو تحديد درجة الاستجابة المناعية بعد التطعيم بلقاح مصل فيروس الإلتهاب الكبدى ب، وتحليل العوامل التى تؤثر على الاستجابة غير الكافية للتطعيم فى مرضى الاستصفاء الدموى المنتظم وإظهار تأثير جرعة الغسيل الكلوى على هذه الاستجابة.

وشملت هذه الدراسة المقطعية على ١٠٠مريض من مرضى الغسيل الكلوى الدموى الذى يترددون على مستشفى شبين الكوم التعليمى ومستشفيات جامعة عين شمس وحدات الغسيل الكلوى، فى الفترة نوفمبر ٢٠١٩ إلى ٢٠٢٠. وتراوحت أعمارهم بين ٢٣ و ٧٦ سنة.

خضع جميع المرضى لأخذ التاريخ الكامل بما فى ذلك العمر والجنس والأمراض المصاحبة الطبية ومسببات الفشل الكلوى ونظام HD والمدة على HD ونوع الوصول إلى غسيل الكلى (الوصلة الشريانية أو وريد صناعى أو القسطرة) والتاريخ الدوائى والأمراض التى قد تؤثر على المناعة الاستجابة للقاح HB وكذلك أعراض وعلامات أى عدوى، الفحص السريرى الكامل، حساب مؤشر كتلة الجسم، الفحوصات المخبرية تعداد الدم الكامل (CBC)، نسبة الألبومين، سكر الدم العشوائى (RBS)، الكالسيوم والفسفور S.Ca و Po4، الحديد، القدرة الكلية على الارتباط بالحديد (TIBC، S.ferritin) هرمون الغدة الجار درقية (PTH)، الروتين التفاعلى (CRP)، نسبة السكر التراكمى (HbA1c). وحساب كفاية غسيل الكلى من خلال نسبة خفض اليوريا (URR) و KT/V دراسة مصلية مستضد التهاب الكبد السطحى (HBsAg)، عيار الجسم المضاد السطحى لإلتهاب الكبد B، الكشف عن HCV-Ab.

تم أخذ النتائج وإجراء المقارنات وخلصنا إلى معدل استجابة مرتفع للتطعيم ضد إلتهاب الكبد B، بين مرضانا. كان لفعالية غسيل الكلى (URR، KT/V) ارتباط إيجابى مع الاستجابة للقاح HBV فى مرضى HD، كان استخدام أغشية التدفق العالى مع استجابة أفضل للقاح من استخدام أغشية التدفق المنخفض، وكان للإلتهاب الجهازى (مستويات عالية من CRP) ارتباط سلبى مع استجابة لقاح.