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Original article

The predictive roles of obesity and serum vitamin D levels in body response to hepatitis B vaccine

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Summary. *Background:* Hepatitis B vaccination is the most successful way to prevent the virus infection. Serum concentration of vitamin D has recently been proposed as a novel predictor of response to antiviral treatment in chronic hepatitis infection. *Objectives:* This study aimed to verify whether the relationship between obesity, serum levels of vitamin D and TNF- α, after immunization with hepatitis B vaccine, plays a role in predicting the rates of antibody titer. *Methods:* The present study included 45 men and women aged 20 to 50 years old who were assigned in following two groups based on BMI: (A) normal weight and (B) overweight or obese subjects. Both groups received Hepatitis B vaccine in three dozes at; 0, 1, 2 month intervals. Then, Linear Regression analysis was used to evaluate the relationship between serum vitamin D levels and antibody titers. *Results:* A total number of 45 patients (30 males and 15 females) with a mean age of 35.765±6.63 years were studied. There was a significant difference shown in the mean of vitamin D (P= 0.013) and TNF-α (P= 0.469) between the two groups. Linear regression analysis revealed a significantly lower HBSAg among only female participants with overweight or obesity (P= 0.015). Serum vitamin D level was a main predictor of body response to hepatitis B vaccine and 1 ng/ml increase in serum vitamin D level was associated with a rise of 8.77 IU/mL in HBSAg levels**.** *Conclusions:* In our study, after adjusting of other factors, serum vitamin D level was a main predictor of body response to hepatitis B vaccine. Moreover, our study revealed an association between vitamin D deficiency and poor body response to vaccination in obese patients.

Keywords: Hepatitis B; Hepatitis B vaccine; Obesity; Vitamin D; TNF-α

Background

Hepatitis B is a contagious liver disease produced by hepatitis B virus (HBV)(1). Worldwide, more than 240 million people have persistent liver infections and more than 780 thousand people died of acute or chronic HBV infection every year(2). In Iran, about 1.5 million people are living with HBV infection that estimated to be in 2.14% and 2.55% of men and women(3).

Hepatitis B immunization is the most successful and economical way to prevent the virus infection(4). A great deal of proof has showed that more than 90% of populations, especially children and infants, can be preserved from the virus infection by hepatitis B vaccination(5, 6). Nevertheless, some vaccines cannot get protective antibodies to hepatitis B surface antigen (anti-HBs) (higher than 10 IU/L) because of many risk factors such as older age, renal diseases and unsuitable administration of the vaccination(7, 8).

Formerly, obesity has been described as a risk factor for the defective vaccine efficacy(9, 10).The initial study on the association between obesity and hepatitis B vaccination response was showed by Weber et al. in 1985. The authors announced that a higher body mass index (BMI) would evolve a poor antibody response

in health care workers(11). In 2008, Dinelli et al. outlined that a case could get seroprotection of hepatitis B vaccine after a dropped BMI(12). Regarding both obesity/overweight and chronic HBV infection are 2 important public health issues globally, more studies should be conducted to carried out the effects of obesity/overweight on the hepatitis B vaccines responses.

Effects of obesity on immunologic response to hepatitis B vaccine might be complicated with a chains of complex mechanisms(13). First, reduced immune system has been seen in both obese animals and humans(14). Young et al. announced that obesity was significantly related with the diminished naïve T-cells from thymus., diminished numbers and reduced activities of CD8+ T-cells and NK cells were observed in obesity subjects vs. compared to the lean controls (15).

Autocrine, intracrine and endocrine roles of vitamin D (1, 25(OH) D3), is an important mediator of immune function, influencing both innate and adaptive immunity(16). T cells are richly supplied with vitamin D receptor (VDR) and have a critical role in the pathogenesis of viruses(17). HBV attack activates the toll like receptors (TLR-2), and enhances CYP27B1 (1α-hydroxylase) enzyme within macrophages to change vitamin $25(OH)D_2$ to $1,25(OH)D_3$ which increases regulatory T cells and the secretion of IL-10, and decreases the IL-2 release from dendritic cells(18). Furthermore the synthesis of antimicrobial proteins by this transcription of mRNAs cytokine can help in the phagocytosis of the HBV pathogens (17).

It was shown that patients with persistent hepatitis B (CHB) often hurt from serious vitamin D deficiency(19, 20). The study of Farnik H indicated a significant relationship between higher levels of HBV replication and low 25(OH) D_3 serum levels in CHB patients (20).

Objectives

Overall, the relationship between vitamin D metabolism and CHB is less well identified. Therefore, we conducted a study to assess the relationship between obesity; serum levels of vitamin D and TNF-α after immunization with hepatitis B vaccine.

Materials and methods

Participants

This study was carried out in 2014–2015 in a group of healthy volunteers living in Tabriz, Iran. The sample size was 45 including men and women aged 20 to 50 years old with BMI of more than 18 5 Kg/m2 (normal or overweight). The subjects assigned in following two groups (A) normal weight and (B) overweight or obese subjects (Fig 1).

To minimize any known confounding effects, the subjects with the following conditions have been excluded from the study: (a) subjects who had been diagnosed with chronic hepatitis C virus infection, alcoholic liver diseases, drug-related hepatitis, cirrhosis; (b) subjects who had received cancer therapy; (c) who consumed alcohol (d) women who were pregnant; and (e) those who received hepatitis B vaccine.

Treatment

Both groups received Hepatitis B vaccine including three intramuscular injections in the deltoid muscle. The vaccination was in three dozes at; 0, 1, 2 month intervals.

Anthropometric and laboratory measurements

Weight was measured using digital scales (Soehne, Germany) with patients minimally clothed. Height was measured using a fixed to wall, non-stretch tape meter in a standing position. The BMI was then calculated in kilograms per meter square. Baseline characteristics of the study participants were collected via face-to-face interviewed by a trained professional nutritionist.

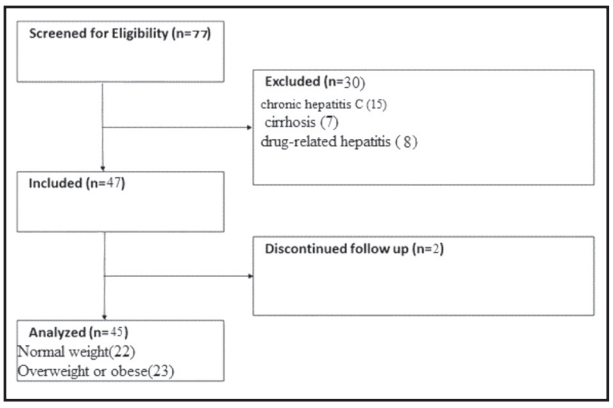

Figure 1. Patient flow diagram

Waist circumference obtained at the end of exhalation in the horizontal- line at middle point of the lowest rib and the iliac crest and hip circumference measured at the widest point of hips using a flexible tape at nearest 0.5 cm.

Five milliliters of fasting blood sample were obtained from each participant after 8–12 h overnight fast at the study entry and at the end of research to evaluate biochemical parameters. Serum hepatitis B antibody titer was calculated using an ELISA kit (Biomerieux, USA). The antibody titers of ≥10 and < 10 MIU/ML was considered as responders and non – responders, respectively.

Additionally serum 25(OH) D_3 levels measured using a 25 OH-vitamin D-Ria-CT Kit (Biosurce Europe, Belgium) and serum levels of tumor necrosis factor α (TNF α) were measured using enzyme-linked immunosorbent assay (ELISA) (DIAsource Co, Belgium).

It should be declared that the study protocol was accepted by ethics committee of Tabriz University of medical sciences (ethics committee number: IR. TBZMED.REC.1393. 209) and all participants were asked to sign informed consent.

Statistical analysis

Distribution of data related to normality was assessed by Kolmogorov–Smirnov test. Data with normal are reported as mean ± standard deviation. Comparisons of changes (endpoint minus baseline) between groups were done by independent t test. Paired t test was used for within-group comparisons (pre-and post-study values in each group).

In the univariate analyses, each socio- demographic related factor entered separately as a dichotomous variable. Then all variables including those with significant and non-significant relationship in univarate analysis were entered in the multivariate analyses by Backward: LR method and the variables of final step are presented. The results of regression analysis are presented as un-adjusted and adjusted Odds Ratio (ORs) as well as their 95% confidence intervals. Analysis was conducted using SPSS version 17 statistical software (SPSS Inc., Chicago, Ill). P values<0.05 were considered statistically significant.

Results

Baseline characteristics of these patients are summarized in Table 1. A total number of 45 patients (30 males and 15 females) with a mean age of 35.765±6.63 years were included in the study. Of those, 22 were in the control group and 23 patients in the case group.

Individuals in the control group were older than the cases. (36.08±6.73 vs. 35.45±6.68years, p=0.753). Two groups were assigned based on BMI, therefore these factors (BMI, weight, waist and hip circumference) were higher in case group. Other information is existence in table 1.

With regard to the biochemical parameters, patients in case group had higher vitamin D concentra-

Table 1. Table 1.Baseline characteristics of the study participants

Variables	Case group (n=22)	Control group (n=23)	P-value
Sex (n (%))			
Male	15 (68.2%)	15 (65.2%)	-
Female	7 (31.8%)	8 (34.8%)	
	Mean± SD		
Age (year)	35.45 ± 6.68	36.08 ± 6.73	†0.753
Weight (kg)	86.36 ± 10.00	64.17 ± 11.02	††0.001
Height (cm)	170.81 ± 7.55	168.60 ± 12.96	††0.491
BMI (kg/m²)	29.61 ± 3.15	22.42 ± 1.41	††0.001
Waist circumference (cm)	103.77 ± 10.14	81.69 ± 9.90	††0.001
Hip(cm)	114.13 ± 9.92	91.78 ± 10.90	††0.001

Data are presented as mean ± SD or n (%).

† Independent-samples t-test.; p<0.05 considered significant

tion and TNF-α levels compared with control group (P= 0.013), (P= 0.469) respectively.

The Comparison of biochemical characteristics at the beginning and the end of the study among two groups have been showed in Table 2. When comparing the beginning and end of the study, HBSAg increased significantly in both groups (P = 0.00). As, vitamin levels significantly decreased in the end of the study, when compared to the beginning of study in both groups (P<0.05). Comparison of serum antibody titer, vitamin D and TNF-a concentrations between the gender, showed a significantly change in HBSAg in both gender (P <0.001). (Table 3)

In linear regression analysis among female participants; waist, HBSAg A, BMI status and vitamin D levels were main predictors in the end of the study. Women with overweight or obesity had less of HBSAg compared to normal women (Table 4).

Discussion

We found that there was a significant association between serum vitamin D and HBSAg levels in subjects after immunization. In the other words, after adjusting of other factors, serum vitamin D level was a main predictor of body response to hepatitis B vaccine and 1 ng/ml increase in serum vitamin D level was associated with a rise of 8.77 IU/mL in HBSAg levels.

In our study $25OHD_3$ level was associated with a higher increase in body response to hepatitis B vaccine. In many studies Vitamin D deficiency had been noticed with poor response to vaccination (40). In agreement with the finding, Emanuel Zitt et al showed that in patients with chronic kidney disease vitamin D deficiency was related with poor antibody formation upon hepatitis B vaccination(41). Also, Lee x et al; reported that Vitamin D levels were related with poor response to the immunization(42). On the contrary, Rajesh Jhorawat et al. in hemodialysis patients did not find evidence for direct effect of vitamin D levels on the hepatitis B seroconversion. They recruited 60 patients of end-stage renal disease on maintenance hemodialysis and administrated 20 μg of intramuscular recombinant hepatitis B vaccine at 0, 1, 2, and 6 months and measured Anti-HBs antibody titers were at 4 and 7 months of vaccination and the titer ≥10 IU/mL was considered as positive(43).

Obesity Effects on immunology response might be had several mechanisms. Obese animals and hu-

Table 2. Comparison of biochemical characteristics before and after the study among the groups

Variable	Case (n=22)	Control (n=23)	††P-value
	Median (25th percentile, 75th percentile)		
HBSAg (IU/mL)			
Baseline	0(0 -0.72)	1.06(0-6.30)	0.054
End	14.65(9.13 - 22.40)	23.45(16.52- 32.52)	0.002
†P-value	<0.001	<0.001	
Vitamin D (ng/mL)			
Baseline	34.08(31.50-37.87)	28.62(22.53 – 34.17)	0.820
End	24.46(20.43-28.38)	17.74(7.10-29.03)	0.964
†P-value	0.001	0.012	
TNF-α (pg/mL)			
Baseline	243.13(230.27-267.14)	246.04(229.75 – 267.7)	0.011
End	541.78(256.48 – 628.85)	522.08(310.61 – 622.19)	0.207
†P-value	0.002	0.001	

HBSAg; hepatitis B surface antigen
†Wilcoxon signed-ranks test; ††Mann-Whitney-U test
p<0.05 considered significant

Table 3. Comparison of serum antibody Titer, vitamin D and TNF-α before and after the study between genders

Variable	Females (n=15)	Males (n=30)	††P-value
	Median (25th percentile, 75th percentile)		
HBSAg (IU/mL)			
Baseline	0(0 -2.89)	1.06(0-5.49)	0.456
End	20.96(11.02 - 29.26)	20.78(14.21- 23.65)	0.865
†P-value	0.001	<0.001	
Vitamin D (ng/mL)			
Baseline	31.13(16.16-34.20)	32.65(28.21 – 37.61)	0.075
End	25.99(18.72-28.33)	21.11(14.92 – 28.66)	0.263
†P-value	0.256	<0.001	
TNF-α (pg/mL)			
Baseline	235.38(208.73-267.70)	245.45(232.05 – 267.59)	0.360
End	569.47(311.20 – 671.95)	518.38(205.76 – 602.79)	0.048
†P-value	0.001	0.001	

HBSAg; hepatitis B surface antigen
†Wilcoxon signed-ranks test; ††Mann-Whitney-U test
p<0.05 considered significant

Table 4. Multivariate regression analysis of serum levels HBSAg in the end of the study in female participants. (n=15)

variable	unadjusted			adjusted		
	B(SE)	Beta	P-value	B(SE)	Beta	P-value
Waist (cm)	-4.99(.14)	-0.70	0.005	-	-	
HBSAg (IU/mL)	2.53(0.89)	0.63	0.015	-	-	
BMI (kg/m2)	-16.49(3.35)	-0.81	<0.001	-13.20(3.25)	-0 .65	0.002
Vitamin D (ng/ml)	15.9(5.29)	0.65	0.011	8.77(3.93)	0.361	0.047

Data are presented as beta (SE) for linear regression analyses or OR (95% CI) for logistic regression analyses.
BMI; body mass index; HBSAg; hepatitis B surface antigen
p<0.05 considered significant

mans had Impaired immune system (31). Young et al. reported that obesity was significantly associated with the decreased naïve T-cells from thymus. Compared to the lean controls, diminished numbers and decreased activities of CD8+ T-cells and NK cells were observed in obesity subjects(32). Moreover, Nieman et al. announced that the proliferations of T and B-cell diminished in obese with mitogen stimulation(33).

In our study BMI status were main predictors in prognosis of HBSAg levels. Previous investigations have described an association between obesity and weak antibody response to hepatitis B vaccine (23-25). Several assessments have shown that lymphocytes from individuals with overweight or obese have altered number and also a diminished lymph proliferative response to "in vitro" stimuli(26, 27). TANAKA et al. reported that obese patients had decreased number of CD3+, CD4+ and CD8+ T cells and a reduced blastogenic T cell response to mitogens. Also, weight reduction caused an increase in T cell responses and in the number of CD4+ and NK cells(28). Different studies have described a relation between obesity and a reduced response to hepatitis B vaccine in adults (11,29,30).

Results of this study showed that, patients with overweight had higher vitamin D and TNF-α levels compared with control group that had normal weight. When comparing the beginning and end of the study, HBSAg increased significantly in both groups. But this increase in control group higher than case group. In addition, Women with overweight or obesity had less of HBSAg compared to normal women. Also, since obese subjects had a thicker skin than those in non-obese, needle length used for vaccination might be as a potential risk assigned to the poor response in obese patients(34). A needle length that is not suitable to penetrate the deltoid fat pad and reach the muscle mass may report for the reduced immune response among persons with overweight or obese. The less plentiful blood supply in adipose tissue may retard antigen presentation to the B and T cells responsible for the immune response. However, the needle should not be so long that it involves the underlying bone. Also, older age, comorbid conditions, and medication use have been related with diminished vaccine response and may amazed the relationship between obesity and immune response(24).

Vitamin D may have a protective role in influenza and other viral diseases and may reduce the risk of evolving AIDS in HIV-positive patients, hepatitis and other viral infections(38). Preservation of a vitamin D serum concentration of 38 ng/mL or higher could significantly decrease the occurrence of acute viral respiratory tract infections, including influenza, at least during the fall and winter in temperate zones(39).

It is well known that obese patients often suffer from a persistent low-grade chronic inflammatory state, which might be also intricate in the lower responses to HBV vaccines(35). It is described that most cells of the immune system such as monocytes and macrophages express vitamin D receptors and can convert 25(OH) D to calcitriol via their own 1α-hydroxylase(44). In macrophages calcitriol convinced the synthesis of bactericidal peptides such as cathelicitin(45). This effect of vitamin D on antibody development might be regulated via direct effects on B cells(46). Alternatively, vitamin D might impede with plasma cell generation(47). It is showed that vitamin D may directly mediate the immoderate production of antibodies by inhibiting the generation of plasma cells(48). Macrophages are cells with a large volume for cytokine production, in particular TNF-α, which is one of the most main products delivered from these cells(50). Transcriptional activation of the TNF-α gene in macrophages is dependent on the NF-κB-dependent transcriptional activation, which is a main mediator of immune, inflammatory and stress responses. It inhibits monocyte yield of inflammatory cytokines such as IL-1, IL-6, IL-8, IL-12 and TNFα(51). Some investigation showed that hypovitaminosis D is related with higher serum levels of inflammatory biomarkers, such as IL-6, TNF-α, and C-reactive protein (CRP) (52).

Vitamin D is described to conquer proinflammatory cytokines (53). Because of these effects, it is thought that deficiency of vitamin D may be associated to the development of poor body response to hepatitis B vaccine (54, 55).

In our study, after adjusting of other factors, serum vitamin D level was a main predictor of body response to hepatitis B vaccine. As a result, our study revealed a relationship between vitamin D deficiency and poor body response in obesity patients. This suggests that vitamin D supplementation may be useful in patients with overweight health problem.

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