Research Article

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The Importance of Vitamin D Deficiency as a Potential Marker Among Chronic Hepatitis B Patients

Kronik Hepatit B Hastalarında Potansiyel Belirteç Olarak D Vitamini Eksikliğinin Önemi

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ABSTRACT

Objectives: We aimed to identify the potential role of vitamin D_3 among patients with chronic hepatitis B (CHB) in Birjand, Iran.

Materials and Methods: In this case-control study, 292 patients were selected with CHB and 304 healthy subjects as control groups in the outpatient clinic of the infectious diseases department between January 2018 and December 2019. We quantified the levels of total vitamin D_3 in serum samples of them. Logistic statistical analysis was applied at the significance level of 5%.

Results: The mean age and serum vitamin D_3 level of the study and control groups were; 39.9±12.3 years, 43.0±9.3 years and 17.76±5.53 ng/mL, 22.07±2.41 ng/mL, respectively. So, a significant difference between means of vitamin D_3 serum in the two groups was observed (p>0.05). The prevalence of vitamin D_3 deficiency was higher among patients with hepatitis B virus (63.0%) than the healthy group (32.9%). Frequency distribution of serum vitamin D_3 levels showed a significant difference between the two groups (p=0.001). The risk of vitamin D_3 deficiency was significantly more than the healthy group (odds ratio: 3.17, p<0.001).

Conclusions According to the results; a high risk of vitamin D_3 deficiency related to CHB was found in this city. Future studies are warranted to consider the impact of vitamin D supplementation in CHB.

Keywords: Vitamin D_3 level, liver disease, chronic HBV infection

ÖZ

Amaç: İran, Birjand'daki kronik hepatit B (KHB) hastalarında vitamin D_3'ün potansiyel rolünü belirlemeyi amaçladık.

Gereç ve Yöntemler: Bu olgu-kontrol çalışması için, Ocak 2018 ile Aralık 2019 tarihleri arasında enfeksiyon hastalıkları bölümü polikliniğinden KHB'li 292 hasta ve kontrol grubu olarak 304 sağlıklı denek seçildi. Bunların serum örneklerindeki total vitamin D_3 düzeylerini belirledik. Lojistik istatistiksel analiz %5 anlamlılık düzeyinde uygulanmıştır.

Bulgular: Çalışma ve kontrol gruplarının yaş ortalamaları ve serum vitamin D_3 düzeyleri sırasıyla; 39,9±12,3 yıl, 43,0±9,3 yıl ve 17,76±5,53 ng/mL, 22,07±2,41 ng/mL idi. İki grup arasında serum vitamin D_3 ortalamaları arasında anlamlı bir fark gözlendi (p>0,05). Vitamin D_3 eksikliği prevalansı KHB'li hastalarda (%63,0) kontrol grubuna göre (%32,9) yüksekti. Vitamin D_3 seviyelerinin frekans dağılımı iki grup arasında anlamlı farklılık gösterdi (p=0,001). Vitamin D_3 eksikliği riski control grubuna göre anlamlı derecede fazlaydı (olasılık oranı: 3,17, p<0,001).

Sonuç: Sonuçlara göre; bu şehirde KHB'ye bağlı yüksek vitamin D_3 eksikliği riski bulundu. Her ne kadar gelecekteki çalışmaların KHB'de D vitamini takviyesinin etkisini dikkate alması garanti edilse de. Gelecekteki çalışmaların KHB'de D vitamini takviyesinin etkisi üzerine olması beklenmektedir.

Anahtar Kelimeler: Vitamin D_3 düzeyi, karaciğer hastalığı, kronik HBV enfeksiyonu

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Introduction

The liver is the main place for vitamin D_3 synthesis, where 25-hydroxylation occurs (1). Vitamin D_3 plays an appearing role in metabolic liver diseases. There is evidence about the interrelationship between vitamin D_3 and different chronic liver diseases owing to its immunomodulatory role (2,3). About 240 million individuals are infected with hepatitis B virus (HBV) chronically all over the world (4).

It has been shown that vitamin D_3 has very important biologic effects (5,6). Vitamin D_3 levels can affect the immune system and host response to HBV infection.

But, the association between vitamin D_3 metabolism and chronic hepatitis B (CHB) is less well characterized yet (7).

Different studies suggested low levels of vitamin D_3 are associated with high levels of HBV replication in CHB patients recently. Although, a study found a positive relationship between hepatitis B surface antigen (HBsAg) seroclearance and vitamin D_3 levels (8).

Also, another one showed a significant relationship between higher levels of HBV replication and low levels of vitamin D_3 in CHB infection (9). In addition, the role of vitamin D_3 may also affect disease progression in patients with HBV infection.

According to the mentioned contents, it was assumed that vitamin D_3 level may be one of the responsible agents for the very low serum levels of CHB patients. So, the purpose of this study was to specify the risk, associated factors, and symptoms related to vitamin D_3 deficiency among CHB patients compared to healthy individuals in Birjand.

Materials and Methods

This case-control study was carried out in Khorasan Jonoobi province of Iran in 2019 in the outpatient clinic of the infectious diseases department.

Sampling

In this study, 292 patients with CHB (HBsAg positive, anti-HBs negative), were randomly selected according to the calculated sample size by the following formula with a power of 90%. In addition, 304 natural immunized persons (HBsAg negative, anti-HBs has normal liver enzymes who have not received antiviral treatment were included. the healthy group was selected from collected samples of the master plan of the province (26).

$$n = \left[\frac{\frac{z_{1-\alpha}}{2} + z_{1-\beta}}{0.5 \ln\left(\frac{1+r}{1-r}\right)} \right] + 3$$

Vitamin D_3 Level Classification

Total vitamin D_3 levels were measured in the serum samples. Based on the World Health Organization, a level of 30 ng/mL or above is considered as vitamin D_3 sufficiency (10). Then, vitamin D_3 status was classified as normal (≥30 ng/mL), insufficient (20-29.9 ng/mL), and deficient (<20 ng/mL).

Laboratory Tests

For laboratory tests, 10 ccs of venous blood were taken from patients and healthy controls. The serum levels of vitamin D_3 were measured using a COBAS e411 analyzer, manufactured by Mannheim Roch diagnostic Gmbh in Germany, with the Elecsys kit (REF0589413). Other tests were performed on patients and healthy controls according to laboratory routines. Levels of alanine transaminase (ALT), aspartate transaminase (AST), (glycated hemoglobin) hemoglobin A1C (HbA1C) and bilirubin levels of liver enzymes were measured by the ARCHITECT I system biochemical auto-analyzer. Levels of total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), fasting blood sugar (FBS), and body mass index (BMI) were also measured.

The inclusion criteria for CHB patients were: patients who were admitted to the infectious diseases outpatient clinic with the diagnosis of CHB with the approval of the infectious specialist according to clinical and serological signs, willingness to participate in the study, didn't receive supplementation or injection of calcium and vitamin D_3 in the last six months and also with age ≥18 years. In addition, 304 healthy subjects without a history of hepatitis B disease were selected as healthy control group 26.

Patients' and healthy controls exclusion criteria include severe renal disease, history of cardiovascular disease, co-infection with cancer, pregnancy, diabetic disease, thyroid disorders, other viral hepatitis (hepatitis C virus, hepatitis D virus, human immunodeficiency virus), and other causes of liver disease such as alcohol consumption.

Variables of interest were: age, sex, BMI, and clinical symptoms such as FBS, glycated HbA1C, blood pressure, and HBsAg.

Ethics Approval

This study was approved by the Birjand University of Medical Sciences (BUMS) Ethics Board Committee (approval number: IR.BUMS.REC.1398.324).

Statistical Analysis

Descriptive statistics were used to describe the data, chi-square test was applied to determine the difference of symptoms related to vitamin D_3 deficiency between the study groups. Also, logistic regression was done to specify the relationship between considered variables and vitamin D_3 deficiency in two groups. All analysis was done by SPSS version 22.0. The significance in all of these tests was two-tailed with a 5% significance level.

Results

Out of the all subjects who participated in the study, 48.6% were male in the case group; with a mean age 29±5.3; and 52.2% female with mean age (31.5±7.8); also, of the 304 healthy subjects, 22.1% male; mean age 23.1±7.7, and 77.8% female with mean age 29.1±11.7. So; the distribution of gender was similar in the patients' group (Table 1). Healthy controls were younger than patients but no significant difference between them was observed ($p>0.05$). So that, the mean age of the CHB and control groups were, 32.9±12.3 years and 28.18±11.21 years, respectively. There was no significant difference in HbA1C level between genders, 5.71% vs 5.43% ($p=0.343$) (Table 1).

The mean of vitamin D_3 serum levels in the CHB and control groups were; 17.76±5.53 ng/mL, 22.07±2.41 ng/mL, respectively with significant differences (p=0.031). When categorized as deficient, insufficient, and sufficient. Then among the healthy subjects, vitamin D_3 levels were classified as 32.9%, 25.96%, and 41.15%, respectively.

Of 292 patients, 184 (63.1%), 56 (19.2%), and 52 (17.8%) had vitamin D_3 deficiency, insufficiency, and sufficient vitamin D_3 serum levels, respectively. The prevalence of vitamin D_3 deficiency was high among CHB patients (63.1%) as well as in healthy individuals (32.9%). Vitamin D_3 levels frequency distribution showed a significant difference in the two groups (p=0.001) (Table 2).

There is a negative correlation between vitamin D_3 levels and BMI and HbA1C in patients. Also, a positive correlation was noticed between age and vitamin D_3 levels, but none of these have significant values in the control group (p>0.05) (Table 3).

The results of the comparison of laboratory characteristics of CHB patients and healthy controls showed that the mean of ALT in patients was 32.82 IU/mL (8-117) and AST was 32.21 IU/ML (10-167). Of the all patients in total (21.04%) had ALT and (17.54%) had AST higher than 40 IU/ML while in the healthy group, only 15% had ALT and 5% had AST higher than 40 IU/mL. Also, there was a significant difference in ALT and AST between the two groups (p=0.001). Based on this result, between variables such as LDL, HDL, and BMI, age, sex, and vitamin D_3 levels; was observed no significant difference.

According to the logistic regression results, the risk of vitamin D_3 deficiency in men is 45% higher than in women which is not statistically significant [odds ratio (OR): 1.54, p=0.114). Among the patients, 75.3% were urban and 24.7% were rural residents. The distribution of vitamin D_3 deficiency in rural people is more than in urban population, which is significant in both groups (OR: 2.321, p=0.004). There was no significant difference in the BMI distribution between the two groups (p=0.13). In general, 47.3% of patients had a desirable weight, 35.5% had overweight and 8.2% had a BMI of more than 30 (Table 4).

Discussion

This study was conducted for the first time in this province (a region in the East of Iran) regarding vitamin D_3 pattern in patients with CHB and also to investigate factors associated with vitamin D_3 deficiency in CHB in comparison with the healthy group. In a period (1990-2010), the prevalence of vitamin D_3 deficiency was studied in Iranian society, and according to the results, in all regions; both sexes had moderate and significant vitamin D_3 deficiency (11).

Nghiem et al. showed that vitamin D_3 deficiency existed in many CHB patients and this deficiency had a relationship with the complications and outcome of the disease. Decreased liver function due to HBV-induced injuries to liver cells can be one of the causes of vitamin D_3 deficiency in CHB (12,13).

The results of this study showed that different degrees of the prevalence of vitamin D_3 deficiency existed among patients and healthy controls. The duration of exposure to sunlight exposure is an important factor in the changes in vitamin D_3 levels (14).

Table 1. The baseline characteristics of CHB group by sex

	Male	Female	p-value
HbA1C (mmol/mol)	5.71±1.24	5.43±1.11	0.343
BMI (kg/m²)	25.6±3.1	24.7±2.9	0.595
Age (year)	23.33±7.76	29.79±11.77	0.033
BP1[1] (mmHg)	120.38±1.7	110.96±2.0	0.243
BP2[2] (mmHg)	79.91±1.0	76.68±0.861	0.084
FBS[3] (mg/dL)	97.08±24.5	121.44±123.82	0.131

CHB: Chronic hepatitis B, HbA1C: Hemoglobin A1C, BMI: Body mass index, BP1[1]: Blood pressure (systolic), BP2[2]: Blood pressure (diastolic), FBS[3]: Fasting blood sugar

Table 2. Distribution frequency of serum vitamin D level in the study groups

Group	n	Serum vitamin D level		
		Deficiency (n, %)	Insufficiency (n, %)	Sufficient (n, %)
Patients	292	184 (63.1)	56 (19.2)	52 (17.8)
Control	304	100 (32.9)	79 (26.0)	125 (41.15)

Table 3. Correlation between serum vitamin D levels and assessed variables in the study groups

Variables	Serum vitamin D			
	Case		Control	
	r	p	r	p
Age (year)	0.371	0.07	0.159	0.189
BMI (kg/m²)	-0.039	0.69	0.106	0.382
HbA1C (mmol/mol)	-0.04	0.78	-	-

BMI: Body mass index, HbA1C: Hemoglobin A1C

Table 4. Results of logistic regression for risk of vitamin D deficiency against the variables of interest in the study groups

Variables	Vitamin D Deficiency		Odds ratio (95% CI)	p-value
	Yes	No		
Male	182 (62.7%)	150 (48.1%)	OR: 1.540	0.114
Female	110 (37.3%)	154 (51.9%)	*	-
Urban	197 (70.9%)	175 (62.1%)	*	-
Rural	95 (29.1%)	129 (37.9%)	2.321 (1.31-4.11)	0.004
Mean ± SD	24.39±4.60	25.26±3.79		-
Normal (18.5-24.9)	47.3%	44.4%	*	-
Overweight (25-29.9)	35.5%	40.04%	0.72 (0.568-1.07)	0.135
Obese (>30)	8.2%	11.1%	0.86 (0.38-1.93)	0.081
BP1	12.28±1.29	11.42±1.3	0.39 (0.16-1.78)	0.363
BP2	7.49±0.971	7.23±0.368	0.09 (0.031-0.41)	0.671
18-24	23 (8.6)	22 (9.3)	0.12 (0.58, 1.07)	0.133
25-34	76 (25.9)	64 (18.3)	0.997 (0.565-1.759)	0.091
35-44	84 (29.3)	91 (28.1)	1.21 (0.84, 1.98)	0.073
45-54	44 (15.5)	72 (21.7)	1.079 (0.851-1.367)	0.341
55-64	35 (12.1)	39 (11.6)	1.015 (0.691-1.492)	0.282
>65	21 (7.1)	18 (3.9)	*	-
CHB	184 (63.1)	45 (36.9)	3.17 (1.521-5.913)	-
Control	100 (32.9)	204 (67.1)	*	-

CI: Confidence interval, SD: Standard deviation, CHB: Chronic hepatitis B, BP1: Blood pressure (systolic), BP2: Blood Pressure (diastolic)

In some studies, vitamin D_3 levels were found to be inversely proportional to HBV-DNA viral load and a sufficient level of vitamin D_3 (15).

Previous studies showed the association between D_3 level and CHB (16,17,18), this study was in line with these studies too (19).

In this study, vitamin D_3 insufficiency/deficiency accounted for 82.1% of patients, which was similar to the reported prevalence from Japan and Germany (20,21). However, these results indicate that the relatively high prevalence of vitamin D_3 deficiency is similar to another study (22). It might be because sunshine hours differ among various latitudes as sunlight-related ultraviolet rays are the substantial factor for vitamin D_3 synthesis (22). However, this study showed that there was no association between the serum vitamin D_3 level and biological factors in both study groups. This failure could be due to variations in the subject's age, HBV genotype, and racial background.

BMI higher than normal is considered to be an effective factor in the level of vitamin D_3 stores (23). In this study, however, no significant relationship was found between serum levels of vitamin D_3 and BMI. This result was different from other studies (21,22).

The current study, showed no association between the biochemical parameters and the serum vitamin D_3 level by sex. It is obscurant whether vitamin D_3 deficiency is effective in CHB. We assume that sunlight exposure time might be short in the healthy subjects since they might go out less frequently than patients with CHB.

A high prevalence of vitamin D_3 insufficiency in healthy individuals, as well as CHB patients, can be associated with consuming poor foods in vitamin D_3 and lower sun exposure. Also, the results of Tabrizi et al. (21) as a systematic review study showed a high prevalence of vitamin D_3 deficiency among the Iranian population. The main reason for the higher vitamin D_3 deficiency prevalence in these people may be due to spending more time at home, and the clothing that may result in reduced vitamin D_3 synthesis. Also, the vitamin D_3 content is low in the Iranian diet (24).

In the published records on the prevalence of vitamin D_3 deficiency showed that vitamin D_3 deficiency prevalence was significantly different based on geographical regions in the Iranian population (10). In this study, however, vitamin D_3 deficiency was not correlated with liver function parameters significantly, probably due to that vitamin D_3 serum levels are affected by multiple factors. Roughly, one billion people worldwide apparently are vitamin D_3 deficient (11,25). In line with a previous study (3), our results confirm an inverse correlation between BMI and HbA1C loads and vitamin D_3 levels in the patients' group.

Study Limitations

Some limitations of this study were: influencing of several factors on serum vitamin D_3 levels; such as seasonal variation, diet, and geographical habitation. However, any information about these affecting factors for study subjects was not available. Another limitation is that vitamin D_3 may be an additional factor for the clinical outcomes of HBV infection and its interaction with vitamin D_3 receptor on the pathogenesis of HBV infection needs to be explored further. However, this study could not demonstrate the relevance between assessed variables and serum level vitamin D_3, partially due to having only a few patients with advanced liver fibrosis.

Conclusion

Our study findings reveal that probably this studied population suffers from an insufficiency of vitamin D_3. This indicates the need to consume foods rich in vitamin D_3, require higher sun exposure, or vitamin D_3 supplementation should be recommended in this area. It is noteworthy that although vitamin D_3 deficiency is apparent in patients, this deficiency is also a noticeable difference with healthy people. Therefore, supplementation of vitamin D_3 with the initial dose should be recommended and initiated.

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Ethics

Ethics Committee Approval: This study was approved by the Birjand University of Medical Sciences (BUMS) Ethics Board Committee (approval number: IR.BUMS.REC.1398.324).

Informed Consent: Written consent was obtained from the all of patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: F.O., M.Z., Concept: F.O., M.Z., Desing: F.O., M.Z., Data Collection or Processing: M.Z., Analysis or İnterpretation: F.O., M.Z., Literature Search: F.O., M.Z., Writing: F.O., M.Z.

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