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Full Length Research Paper

Vitamin D levels in patients with chronic hepatitis B virus infection and natural immunized persons

[1]Canan Demir* and [2]Mehmet Demir

[1]Bursa Şevket Yılmaz Education and Research Hospital, Infectious Disease Department , Bursa/TURKEY, [2]Bursa Yüksek İhtisas Education and Research Hospital, Cardiology Department , Bursa/TURKEY.

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Vitamin D deficiency is associated with several adverse health outcomes and vitamin D appears to have systemic antimicrobial effects that may be crucial in a variety of both acute and chronic illness. In our study we compared 25- hydroxy vitamin D levels, between chronic hepatitis B Virus infection, natural immunized persons and control groups. Thirty five chronic hepatitis B virus infection patients (Group I) and thirty natural immunized persons (Group II) and thirty healthy adult were included in this study. Hepatitis markers were determined by commercial kit based on chemilumminesans assay. Routine biochemical parameters, hepatitis B virus serology, hepatitis B virus-DNA, 25-hydroxy vitamin D and parathormone levels were performed. Baseline characteristics of the study groups were comparable. Group I patients had a lower vitamin D level than group II and the control group (7.65±4.19; 12.1±7.13 and 14.17±9.18ng/ml, p<0.001, respectively). Additionaly group I patients had a higher parathormone level than group II and the control group (88.21±34.2; 75.14±23.4 and 74.16±20.15ng/ml, p=0.001, respectively). Also vitamin D levels were correlated hepatitis B virüs-DNA levels. In the hepatitis B virus infected patients, diminished vitamin D levels may be an indicator of the presence of replication and poor prognosis.

Keywords: Vitamin D, hepatitis B, immune system.

INTRODUCTION

The Hepatitis B virus (HBV) infection is a major public health problem worldwide. Hepatitis B is an infectious disease, associated with an estimated 350 million chronically infected patients (1,2).

HBV is a 42-nm DNA virus in the family Hepadnaviridae. The virus has a partially double-stranded DNA with core antigen surrounded by a shell containing surface antigen (HBsAg). The immune response to HBsAg provides the immunity against HBV. Antibodies to HBcAg indicate infection, IgM anti-HBc indicates recent infection and usually disappears within six months, while IgG anti-HBc persists for life and indicates past infection. Antibody to HBsAg (anti-HBs) appears after clearance of HBsAg or after immunization. The presence of HBsAg for more than six months is defined as chronic HBV infection (3).

The clinical course of hepatitis B is determined by the interaction of viral replication status and host immune response. HBV infection is generally asymptomatic but HBV is the most common and important cause of cirrhosis and hepatocellular carcinoma worldwide (2,4).

Vitamin D deficiency is associated with several adverse health outcomes. A plethora of health benefits, including a boost in longevity with vitamin D replacement, is evident. Vitamin D has an emerging role in regulating inflammation as well as an important role in immunomodulation. Vitamin D may also improve survival in acute illness by boosting innate immunity. Vitamin D appears to have systemic antimicrobial effects that may be crucial in a variety of both acute and chronic illness (5-8).

*Corresponding author E-mail: drcananmd@gmail.com
Tel: +90 2242573328

Given this information, we thought that vitamin D deficiency could be related to HBV infection and prognosis.
As far as we know, there is no study performed until today about the association of vitamin D deficiency in the patients with HBV infection and immune response. The aim of this study is to define the pattern of vitamin D levels in patients with chronic HBV infection and natural immunized persons.

MATERIALS AND METHOD

Selection of the patients

35 patients, who has been followed in the outpatient clinic of infection diseases department because of the chronic hepatitis B (HbsAg positive, anti-HBs negative for at least 6 months), has normal liver enzymes and has not received antiviral treatment (22 male; average age 32.5 ± 9.8; Group I), and 30 natural immunized person (HBsAg negative, anti HBs and antiHBcIgG positive) (18 male; mean age 31.1±5.5; Group II) were included in our study. 30 age-matched healthy adult subjects as a control group (17male; mean age 32.4 ± 8.4).
Since the level of vitamin D 25(OHD) differs due to seasonal changes (effect of the sunlight), the study was started in the winter season and continued up to the end of March.
Patients with chronic renal failure, chronic liver disease, cardiac failure (EF below 50%), bone disorders, troide disorder, previus gastrectomy or having intestinal malabsorption and taking calcium, vitamin D or anti-depressant drugs, hepatitis C, hepatitis D, Human immunodeficiency virus infections and systemic bacterial or fungal infection and other causes of liverdisease such as alcohol consumption and autoimmune hepatitis were exluded from the study.

Laboratory tests

Serum PTH measurements were done using an electrochemiluminescence method on an E 170 Modular Analytic System (Roche, USA) device. 25-hydroxy vitamin D levels were measured using a BioSource 25OH-Vit.D3-Ria-CT Kit (Biosource Europe S.A. Rue de L'Industrie, 8, B-1400 Nivelles, Belgium). Reference ranges of 25-OHD3 were accepted as 10-50 ng/ml for winter season and 20-120 ng/ml for summer season (8). Hepatitis markers were determined by commercial kit based on chemilumminesans assay. HBV DNA was quantified by PCR Cobas Taqman 48 (Roche) system.

Statıstıcal Analysıs

Statistical analyses were done using SPSS (Statistical Package for the Social Sciences ver. 13, SPSS Inc, Chicago, Illinois, USA) software and Epi info pack program. Numeric variables were presented as median ± standard deviation, categorical variables were presented as percentage values. The equality of the data to the normal distribution was assessed with the Shapiro-Wilk test. Since the data was not normally distributed, the Mann-Whitney U test, a non-parametric statistical test was used to compare the average values between the groups. Categorical variables were compared using the chi-square test or Fisher's exact chi-square test. For all statistical studies, a p value <0.05 was set to be significant.

RESULTS

Evaluating basic characteristics, there was no statistically significant difference between the three groups in terms of age, gender distribution, body mass index, smoking, creatinin, AST, ALT and TSH levels (Table I).
Given the main biochemical parameters, group I patients had a lower vitamin D level than group II and the control group (7.65±4.19; 12.1±7.13 and 14.17±9.18ng/ml, $p<0.001$, respectively) and group I patients had a higher parathormone level than group II and the control group (88.21 ± 34.2 and 75.14 ± 23.4 and 74.16 ± 20.15 pg/ml,p:0.001, respectively) (Table I).
Also when HBV-DNA levels were categorized, vitamin D levels were corelated HBV-DNA levels (Table II).

DISCUSSION

Recent studies have revealed the functions of vitamin D other than those in bone metabolism. It was reported that it is involved in autoimmune disorders, such as inflammatory bowel disease, rheumatoid arthritis, multiple sclerosis, psoriasis, diabetes, certain cancer types, hypertension, heart failure, atherosclerosis, peripheral artery disease, and in several infectious diseases (10).
Vitamin D directly leads to vitamin D receptors (VDR) and CYP27B1 expressions in the vascular smooth muscle cells and in endothelial cells (11).
Recently, it has been recognized that there are functions of vitamin D other than those in the bone metabolism. It has been demonstrated in the studies conducted that vitamin D deficiency may play a role in the development of autoimmune diseases, inflammatory bowel disease, rheumatoid arthritis, psoriasis, multiple sclerosis, diabetes, certain cancer types, cardiac failure, stroke and infectious diseases such as tuberculosis and pneumonia and that vitamin D treatment is efficacious in these patients (12-16).
Evidence exists that vitamin D may have a protective role in influenza and other viral diseases, such as the risk of developing acquired immunodeficiency syndrome in HIV, hepatitis, and other viral infections (17-20).

Table I. Comparison of clinical and biochemical features of HBV patients and controls.

	Group I (n=35)	Group II (n=30)	Control (n=30)	P value
age (years) sex	32.5 ± 9.8	31.1 ± 5.5	32.4 ± 8.4	NS
(males) (n,%)	22 (55%)	18 (60%)	17 (56.6%)	NS
(body mass index (kg/m2)	22.96 ± 3.35	22.51 ± 2.85	23.49 ± 4.39	NS
creatinin (mg/dl)	0.89 ± 0.9	0.78 ± 0.8	0.75 ± 0.8	NS
hemoglobin(g/dl)	14.1 ± 1.4	13.1 ± 1.3	13.9 ± 1.3	NS
AST(mg/dl)	29.17 ± 3.18	26.7 ± 2.15	27.8 ± 3.4	NS
ALT (mg/dl)	31.25 ± 3.9	33.16 ± 2.3	31.9 ± 3.14	NS
TSH(mcIU/ml)	1.35 ± 1.1	1.22 ± 1.09	1.52 ± 1.45	NS
parathormone(pg/ml)	88.21 ± 34.2	74.16 ± 20.15	75.14 ± 23.4	0.001
25OHvitaminD(ng/ml)	7.65 ± 4.19	14.17 ± 9.18	12.1 ± 7.13	<0.001

Table II: Comparison of vitamin D levels according to HBV DNA in chronic HBV group controls.

HBVDNA(IU/ml)	n	vitamin D (mg/dl)
< 6 IU/ml	2	9.32± 4.26
6-1000 IU/ml	12	8.96 ± 4.15
1000-1000000 IU/ml	15	6.62 ± 3.21
>1000000 IU/ml	6	5.13 ± 2.7

Sabetta et al. demonstrated that maintenance of a vitamin D serum concentration of 38 ng/mL or higher should significantly reduce the incidence of acute viral respiratory tract infections, including influenza, at least during the fall and winter in temperate zones (21).

In Indian children younger than 5 years, subclinical vitamin D deficiency was a significant risk factor for severe acute lower respiratory tract infections (22).

Chronicity of hepatitis B infection is also influenced by mutations in the VDR gene, with polymorphisms being associated with higher viral load, disease progression and severity.Of note, the t allele is associated with enhanced Th1 cellular immunity and promotes more efficient clearance of several viral infections, including hepatitis B and dengue virus (23,24). One study in patients with HCV demonstrated that vitamin D inhibits viral RNA replication, supposedly by inducing oxidative stress in a manner similar to the action of cyclosporine (25). Petta et al. demonstrated that low 25 (OH)D serum levels, are associated risk of severe fibrosis and low sustained viral response to IFN in patients with genotype 1 chronic HCV. Another study also showed that Vitamin D supplementation improves response to antiviral treatment for recurrent hepatitis C(26,27). Vitamin D is linked not only to liver fibrosis but also to liver cirrhosis. A significant correlation exists between VDR genetic polymorphisms and the occurrence of hepatocellular carcinoma in patients with liver cirrhosis; this association is even more prominent in alcoholic patients (28,29). In the present study vitamin D levels were examined chronic HBV infection and natural immunized persons. Vitamin D levels were found to be lower in the chronic HBV patients than natural immunized persons and controls ($p<0.001$).

When three groups were compared in our study, 25 OH vitamin D levels of the patients chronic HBV were significantly lowerthan other group and control groups ($p<0.001$). Additionally were found a relationship vitamin D levels and viral load (HBV-DNA). Our present data shows that vitamin D deficiency may be related to viral replication in patients with HBV infection.

Kaleli et al showed that neopterin levels as a marker forthe immune activation were higher in the replicative HBV carriers(30).

It is known that vitamin D suppresses pro-inflammatory cytokines and causes an increase in IL-10 levels (11). Because of that effect, it is thought that vitamin D deficiency might be related to development of viral replication. In our study, when three groups were compared, PTH levels of replicative HBV patients were significantly higher than PTH levels of the nonreplicative patients and controls ($p=0.001$).

As a result our study revealed a relationship between vitamin D deficiency and viral replication in patients with chronic HBV infection. But the vitamin D levels were found to be similar in previus HBV infection (natural immunized) group and the control group. This situation suggests that vitamin D deficiency may increases of viral replication and vitamin D supplementation may be useful in those patients.

The most important restriction of our study is the limited number of patients. There is a need for large-scale research into this issue.

Disclosure

Conflict of interest none declared

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