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VITAMIN D SERUM LEVELS IN PATIENTS WITH LIVER CIRRHOSIS IN SOUTHERN IRAN

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ABSTRACT

Introduction: Serum concentration of vitamin D is associated with the severity of liver disease, and, as the liver disease progresses, its level is reduced. Many studies have investigated serum levels of vitamin D in cholestatic liver diseases such as primary biliary cirrhosis and alcohol-related liver diseases. Data on the vitamin D level in patients with liver cirrhosis are inadequate. The general objective of this study was to determine serum vitamin D levels in patients with liver cirrhosis.

Methods: In this cross-sectional study, cirrhosis diagnosis was conducted based on stable clinical and paraclinical symptoms, serological markers of hepatitis and liver enzymes, and liver biopsy on patient referred to Shahid Mohammadi Hospital in Bandar Abbas in 2015. The severity of cirrhosis in these patients was determined according to Child-Pugh (CHILD) classification and model for end-stage liver disease (MELD) score. Vitamin D lower than 50 nmol / L equal to 20ng / ml was considered as vitamin D deficiency; data were analyzed using the IBM SPSS 21.0 statistical software and using descriptive statistics, independent student t-test, chi-square, and Pearson test.

Results: Seventy-eight patients (43.3%) were in the case group, and 102 cases (56.7%) were in the control group. The mean age of the patients participating in the study was 48.45 years. Among them, 124 patients (68.9%) were male and 56 (31.1%) were female. Hepatitis B and hepatitis C, each with 22 patients (28.9%), were the most common cause of cirrhosis in our patients. The mean duration of disease in patients participating in the study was 48.42 ± 12.31 months. The frequency of CHILD classes was, respectively, 32 patients (41%) in class A, 33 patients (42.3%) in class B, and 13 patients (16.7%) in class C. Vitamin D levels were significantly higher in the control group (P <0.001). There was an adverse relationship between the score on the Child-Pugh, MELD, and levels of vitamin D (P <0.001).

Conclusion: Vitamin D levels were significantly lower in cirrhotic patients; further, if the severity of cirrhosis is higher, vitamin D levels are lower. According to our results, it is recommended to check the vitamin D levels in cirrhotic patients and treatment in vitamin D deficiency cases.

KEYWORDS: Cirrhosis, Vitamin D, Treatment, Liver, Iran

1. INTRODUCTION

The liver plays an important role in the metabolism of vitamin D. Therefore, liver diseases interfere with the production of vitamin D metabolism. Thus, it can lead to abnormal metabolism of calcium and bone (1). Vitamin D deficiency in adults can lead to osteopenia or osteoporosis, make it worse, or lead to osteomalacia and muscle weakness (2, 3). Cirrhosis has been determined by histological changing the liver to regenerative nodules surrounded by fibrous bands. This event occurs in response to chronic liver injury. The exact prevalence of cirrhosis in the world's population is not clear. Alcoholic liver disease and hepatitis C are the most common causes of cirrhosis in Western countries and in Asian countries; the most common cause of cirrhosis is hepatitis B (4, 5).

The role of vitamin D in chronic liver disease has recently gained greater attention. Some researchers believe that level of 25 (OH) D decreases with the progression of liver disease (6-10), but some others did not find any

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difference between cirrhotic and non-cirrhotic patients (11) or between the Child-Pugh groups (12). Despite the evidence gathered about the role of vitamin D in a number of activities related to liver function, including regulation of secretion of metalloproteinases and their inhibitors, fibroblast proliferation and collagen synthesis (13, 14), now evaluation and correction of vitamin D status are not part of the routine treatment of these patients. In addition, vitamin D has immunomodulatory effects in a way that reduces the proinflammatory cytokines levels and enhances the innate immune response (15-17). Various studies have reported conflicting results regarding serum concentrations of vitamin D and severity of liver disease, as some studies have shown that serum levels of 25-hydroxyvitamin D is reduced with progression of liver disease, and some researchers have not reported a difference between cirrhosis and non-cirrhotic diseases. However, many more studies have investigated serum levels of vitamin D in cholestatic liver diseases such as primary biliary cirrhosis and alcoholic liver disease (18, 19). In this study, we decided to evaluate the levels of vitamin D in patients with non-alcoholic cirrhosis compared with healthy subjects admitted to Shahid Mohammadi hospital in Bandar Abbas in 2014.

The general objective of this study was to determine serum level of vitamin D in the liver cirrhotic patients admitted to Shahid Mohammadi hospital in Bandar Abbas in 2014. The specific objectives were to determine serum level of vitamin D in patients with non-alcoholic cirrhosis and in the control group and according to gender. Also, we have determined the prevalence of vitamin D deficiency based on Child-Pugh (CHILD) and model for end-stage liver disease (MELD) scores.

2. MATERIALS AND METHODS

2.1. Research Design and Setting

This study is a cross-sectional study conducted in 2015. The population of the study consisted of all patients with liver cirrhosis due to various reasons referred to Shahid Mohammadi Hospital of Bandar Abbas in 2014. In this study, 78 patients in the case group and 102 healthy relatives of patients who had been admitted to clinics and hospitals across the province took no drugs and were in the control group in terms of age and gender of the patients. This study was conducted in Shahid Mohammadi Hospital of Bandar Abbas and the level of vitamin D in patients with cirrhosis and also liver-related parameters (enzyme levels, criteria CHILD, MELD, etc.), communications, and their changes were discussed.

2.2. Inclusion and Exclusion Criteria

All cirrhotic patients referred to Shahid Mohammadi Hospital clinics that liver cirrhosis in them was not due to alcohol were included into the study. Patients who received vitamin D and calcium or their supplement, the bisphosphonate, calcitonin, or had received hormone-replacement therapy, patients with alcoholic cirrhosis, malabsorption patients, and patients with chronic renal failure were excluded.

2.3. Data Collection

Sampling method in this study was continuously available; to gather information, a checklist containing demographic information and test results was used. Cirrhosis diagnosis was conducted based on stable clinical and para-clinical symptoms, serological markers of hepatitis (anti-HCV Ab, HbS Ag, anti-HBC Ab, HBe Ag, anti HBe Ag), autoantibodies ([antinuclear antibody, anti-smooth muscle antibody]) and investigation of liver enzymes, and also liver biopsy. Severity of cirrhosis in these patients was determined based on the degree of with ascites, albumin, prothrombin time, and bilirubin encephalopathy degree using the Child-Pugh classification and MELD ratings. Based on this classification, patients can be divided into three groups: Group A that the disease has been well compensated (Score: 5, 6), Group B with significant impairment of performance (score 7 to 9), and group C with un-compensated disease and complete failure of performance (points 10 to 15). The serum levels of vitamin 25 (OH) D, calcium, phosphorus, bilirubin, creatinine, and INR and PT were measured. Vitamin D less than nmol / L 50 (20ng / ml) will be considered as vitamin D deficiency. Values lower than 12.5 nmol / L (5ng / ml) were considered as a severe deficiency, 12.5–25 nmol / L (5–10 ng / ml) as moderate deficiency, 25–49 nmol / L (10–20ng / ml) as mild deficiency and the amount 50–80 nmol / L (20-30ng / ml) was regarded as insufficient. Serum concentrations higher than 80 was considered normal.

2.4. Research Ethics

The information for patients was kept confidential. Data were collected in checklist using codes instead of patients' name. The research proposal is approved by research committee of Hormozgan University of Medical Sciences (Thesis code: 90-92/164)

2.5. Statistical Analysis

Data were analyzed using IBM SPSS Statistics for Windows (Version 21.0. Armonk, NY: IBM Corp.) statistical software and statistical indicators of mean, standard deviation, percentage frequency, and statistical tests of independant-samples t-tes and chi-square to compare the variables between different classes of cirrhosis and gender groups.

3. RESULTS

3.1. Baseline Characteristics

In this study, 78 patients (43.3%) were in the intervention group and 102 (56.7%) in the control group with a mean age of 47.45 years (mean age of the intervention group was 49.44 years and in the control group was 47.69 years).
Among the study participants, 124 patients were (68.9%) men and 56 (31.1%) were women, the gender distribution of patients in the two groups was that, in the intervention group, 51 patients (65.4%) were men and 27 cases (34.6%) were female, and 73 patients in the control group were (71.6%) men and 29 cases (28.4%) are women.
Considering the difference in the percentage of gender and mean age of both groups, this difference with was investigated using t-test in terms of significance that there was no significant difference ($P = 0.14$ in terms of gender and $P = 0.28$ in terms of age). The mean duration of disease in patients participating in the study was 48.42 ± 12.31 months.

3.2. Main Results

The frequency of the diseases leading to cirrhosis was noted that the highest frequency was hepatitis B and C (Table 1). According to CHILD classification, class A was the most prevalent type (Table 1).

Table 1. Frequency of the diseases leading to cirrhosis and patient classification frequency in terms of Child-Pugh scores (Class A-C)

Diseases	n (%)
Hepatitis B	22 (28.9)
Hepatitis C	22 (28.9)
Autoimmune hepatitis	9 (11.8)
Nonalcoholic steatohepatitis (NASH)	7 (9.2)
Primary sclerosing cholangitis (PSC)	7 (9.2)
Hemochromatosis	2 (2.6)
Primary biliary cholangitis (PBC)	1 (1.3)
Cardiovascular	1 (1.3)
Child-Pugh Score Classification	
Class A	32 (41)
Class B	33 (42.3)
Class C	13 (16.7)

The results suggest that there was a significant difference in terms of vitamin D levels between the two groups, so this amount was significantly higher in the control group ($p < 0.001$) (Table 2). Among those participating in the study significant difference was observed in terms of gender in the levels of vitamin D ($P < 0.001$), so that this amount was significantly higher among males than females. Statistical analysis of the data showed that there is a significant difference among three classes according to the level of vitamin D ($p = 0.001$), and this amount in the Class A was higher than Class B and in Class B was more than class C. Analysis of the data also showed that the level of vitamin D in patients with scores of CHILD was indirectly correlation ($p < 0.001$) so that, the points are negatively correlated with the level of vitamin D (Pearson correlation = - 0.413).

Vitamin D levels in patients with a MELD score has indirect correlation ($p < 0.001$), so that the MELD score was negatively correlated with the level of vitamin D (Pearson correlation = - 0.432). Among the patients participating in the study, there was a significant relationship between the MELD score and the score related to CHILD ($p < 0.001$) so that the MELD score was positively associated with CHILD score (Pearson correlation = 0 .814).

Table 2. Vitamin D level in the case and control groups based on gender and Child-Pugh classification

Variable			Vit. D level (ng/ml)	p-value
Groups	Case		10.64	<0.001
	Control		24.4	
	Total		18.48	
Sex	Male		20.74	<0.001
	Female		13.49	
Sex in both group	Case	Male	12.28	
		Female	9.98	
	Control	Male	27.12	
		Female	17.55	
Child-Pugh Classification	Class A		13.46	0.001
	Class B		9.89	
	Class C		5.58	

4. DISCUSSION

In our study, most of the leading causes of cirrhosis were hepatitis B and C (28.9%) in that the frequency between CHILD classes was, respectively, reported at 41% in class A, 42.3% in class B, and 16.7% in class C; this indicates that less than half of the patients in our study had compensated cirrhosis status. In this study, vitamin D levels in the control group were higher than the case groups. The level of vitamin D in Class A was higher than Class B and C. In our study, the most common causes of cirrhosis were hepatitis B and hepatitis C, which is similar to results in other parts of the world (4) as Michitaka et al. in Japan and Hajiabbasi et al. in Iran have mentioned hepatitis B and C as the most important cause of cirrhosis (20, 21). In our study, less than half of the patients have been in the compensated cirrhosis state, which was similar to the results obtained by Lee et al. and Hajiabbasi (20, 22). The level of vitamin D in our study in cirrhotic patients was lower than the levels in the control group. These results were consistent with findings obtained by Arteh et al. (18), Savic et al. (23), Schwartz et al. (24), and Miroliae et al. (25).

Statistical analysis of the data showed that levels of vitamin D in the Class A were more than Class B and Class C. This finding was similar to the results obtained by Malham et al. (5), Savic et al. (23), Chen et al. (26), Finkelmeier et al. (27). and Stokes et al. (28). The level of vitamin D in patients had indirect correlation with MELD score ($p<0.001$). This relationship was that with increasing MELD score, levels of vitamin D decreased (Pearson correlation = - 0.317). Trépo et al. (29) and Putz-Bankuti et al. (30) also had similar results with the findings of our study. Given that, the vitamin D deficiency increases risk of heart disease, malignancies, autoimmune diseases and infections, and osteoporosis, it can be concluded that its deficiency can have a role in the prognosis of cirrhotic patients (31).

This study had some limmitations. However, we included all eligible patients in one-year period but higher sample sizes are needed to assess the relationship between cirrhosis and its severity and vitamin D level. Also, the prevalence of vitamin D deficiency is high in Hormozgan province which should be considered for illustration of the results.

5. CONCLUSIONS

Vitamin D levels were significantly lower in cirrhotic patients; further, the higher severity of cirrhosis causes lower vitamin D levels. Considering this issue, the prescription of vitamin D supplementation in cirrhotic patients may be reasonable.

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CONFLICT OF INTEREST:

The authors declare that they have no conflict of interests.

AUTHORS' CONTRIBUTIONS:
Both authors contributed to this project and article equally. Both authors read and approved the final manuscript.

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