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Original Article

Serum 25-Hydroxy Vitamin D Levels in Patients with Acute Hepatitis (Ischemic, Toxic, and Viral): Association With Clinical Progression and Mortality

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Abstract

Objective: Vitamin D is a key regulator of calcium homeostasis and has anti-inflammatory and immunomodulatory effects. Active vitamin D has a direct effect on T cells and antigen-presenting cells. It also suppresses the differentiation of B cells to plasma cells and inhibits immunoglobulin production. Vitamin D supplementation is associated with a favorable outcome in chronic inflammatory diseases. In this study, we aimed to determine serum vitamin D levels in patients with acute toxic, ischemic, or viral hepatitis and whether the levels had an effect on clinical progression or mortality in patients with acute hepatitis.

Methods: Forty-eight patients (26 men and 22 women) and 35 controls (16 men and 19 women) aged >18 years who were diagnosed as having acute hepatitis and hospitalized in the Internal Medicine Department were enrolled. To determine serum 25-hydroxy (OH) vitamin D levels, two fasting blood samples, first in the initial 24–48 h following hospitalization and second on the day of discharge, were obtained from the participants. The SPSS Statistics v21.0 software was used for the quantitative evaluation of data.

Results: Serum vitamin D levels were significantly lower in the patient group (10.0±8.7) than in the control group (31.5±12.2), but no significant difference was detected in serum vitamin D levels among the patients. Serum vitamin D levels, except in patients with viral hepatitis, were low at discharge. Serum vitamin D levels were lower than the cutoff values in two patients with early mortality.

Conclusion: We demonstrated that serum vitamin D levels had no effect on clinical progression of acute hepatitis. Other prospective studies with large sample sizes are required to determine whether serum vitamin D levels can be used to predict clinical progression or mortality.

Keywords: Acute hepatitis, vitamin D, clinical progression, mortality

Introduction

Vitamin D is a hormone that affects various systems of the body. In addition to the known effect of vitamin D on the musculoskeletal system, recent epidemiologic studies associate low serum vitamin D levels with an increased risk for numerous diseases, including cancers (breast and colorectal cancers), autoimmune diseases (multiple sclerosis and type 1 DM), skin diseases (psoriasis, vitiligo, morphea, hyperkeratotic palmoplantar eczema, and acanthosis nigricans), infectious diseases (tuberculosis, otitis media, upper/lower respiratory tract infections, and influenza infection), type 2 DM, hypertension, cardiovascular diseases, and obesity. This is probably because of the anti-inflammatory and immunomodulatory characteristics of vitamin D, and its possible effects on cytokine levels. Presence of vitamin D receptors in the thymus and peripheral T cells shows vitamin D has important effects on T-cell development and activity. Active vitamin D has a direct effect on T cells and antigen-presenting cells, and it also suppresses the differentiation of B cells to plasma cells and inhibits immunoglobulin production (1, 2).

Although numerous studies have investigated the clinical role of vitamin D in chronic infectious diseases, there are few studies that reflect the importance of vitamin D, particularly for the prognosis of inflammatory diseases that acutely affect the liver such as acute toxic, ischemic, or viral hepatitis. It is not known how serum 25-hydroxy (OH) vitamin D levels are affected in acute liver injuries. In addition, it is unknown whether serum vitamin D levels change parallel to the recovery of clinical and biochemical test parameters in patients with acute hepatitis. This study aimed to detect serum vitamin D levels in patients with acute hepatitis and determine whether serum vitamin D levels are associated with acute toxic, ischemic, or viral hepatitis. We also investigated whether serum vitamin D levels contributed to prognosis and/or mortality of patients with acute hepatitis.

Methods

Forty-eight patients, aged >18 years (26 men and 22 women) with acute toxic, ischemic, or acute viral hepatitis and hospitalized in the Internal Medicine and Infectious Diseases Departments (November 2011–June 2013), and 35 controls (16 men and 19 women), who were age and sex

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matched to patients, with no systemic disease were prospectively included after their written approved consents were obtained. Approval was also obtained for the study from the ethical committee.

To determine serum 25-OH vitamin D levels, two fasting blood samples were obtained from the participants and stored in tubes, which had been externally plastered to protect against light. The first sample was obtained in the initial 24–48 h following the hospitalization of patients, the second sample was obtained on the day when clinical recovery was observed, symptoms disappeared, and the patient was ready for discharge. The blood samples were centrifuged at 6,000 rpm for 4 min and stored at -22°C until the day on which they would be sent to the laboratory for serum analysis. The samples obtained were measured using high-pressure liquid chromatography. After calibrating, the control sera were examined to ensure the safety of the study, and the results were assessed and given in ng/mL. The patients were monitored throughout their hospitalization until clinical recovery was observed and liver enzyme levels showed a tendency to recover.

When study findings were assessed, Statistical Package for Social Sciences Statistics v21.0 Chicago, USA (version 21.0 SPSS IBM, Armonk, US) was used for statistical analyses. In the descriptive statistics of data, the mean, standard deviation, ratio, and frequency were used. The distribution of data was examined using the Kolmogorov–Smirnov test. Qualitative data were analyzed using the chi-square test, and quantitative data were analyzed using an independent sample t-test. The impact level was examined with ROC curve and correlation.

Results

Of 48 patients included in the study, 26 were men (54.2%) and 22 were women (45.8%). Of 35 controls, 16 were men (45.7%) and 19 were women (54.3%). The mean age of patients with acute hepatitis (ischemic, toxic, and viral hepatitis) was 48.29±21.48 years, whereas that of controls was 48.13±21.48 years. In the patient group, 19 had acute ischemic hepatitis, 17 had acute toxic hepatitis, and 12 had acute viral hepatitis (Figure 1). Patients with acute viral hepatitis were diagnosed either with acute hepatitis A or acute hepatitis B. The average age of the patient groups was 63 years for patients with acute ischemic hepatitis, 41 years for those with acute toxic hepatitis, and 33 years for those with acute viral hepatitis.

In the patient group, the average serum 25-OH vitamin D levels, measured within the first 24–48 h following presentation to the clinic, were 12.1, 7.6, and 10.3 ng/mL in patients with acute ischemic, toxic, and viral hepatitis, respectively (Figure 2). In the entire patient group, the average serum 25-OH vitamin D level was 10 ng/mL. In the control group, the average serum 25-OH vitamin D level was 31.5 ng/mL, indicating that serum vitamin D levels were significantly lower in patients than in controls (p=0.05). Serum 25-OH vitamin D levels were compared among the three patient groups with acute ischemic, toxic, and viral hepatitis using the Kruskal–Wallis H test, and no significant difference was detected in serum vitamin D levels among the patients (p=0.366>0.05) (Table 1).

The average aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels on presentation to the hospital were the highest in patients with acute toxic hepatitis and the lowest in

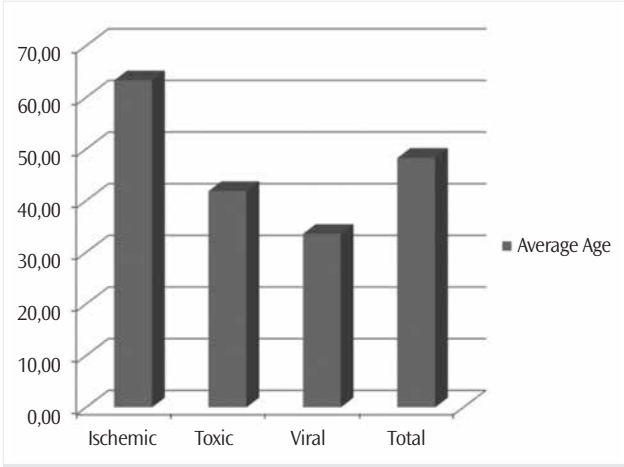

Figure 1. Average age chart of patients with respect to the type of hepatitis

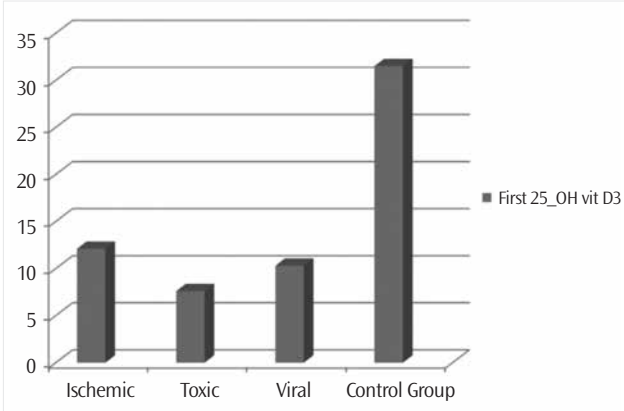

Figure 2. Serum 25-OH vitamin D3 levels measured at hospitalization in patients with acute ischemic, toxic, and viral hepatitis and in controls

those with ischemic hepatitis, with AST level of 672 U/L and ALT level of 632 U/L. Serum 25-OH vitamin D_3 levels were lower in all three patient groups than in the control group. AST and ALT levels were observed to decrease during the clinical course of the disease; with the exception of patients with viral hepatitis, no increase was observed in serum vitamin D levels when patients were discharged at the end of the follow-up period. Pearson's correlation test was used to determine whether there was a correlation between serum 25-OH vitamin D levels, measured on hospitalization, and levels of albumin, direct bilirubin, international normalized ratio (INR), ALP, and GGT, which were measured within the first 24 h during the follow-up of patients in the clinic. No correlation was detected between vitamin D levels and albumin level, INR, or other enzyme levels, which indicated cholestasis. Patients were subsequently grouped according to their albumin level (<3.5 ISI) and INR (>1.1 ISI) (group 1). Twenty-six patients met these criteria. The average serum vitamin D level was 10.22 ng/mL, indicating no statistically significant difference from the remaining patients (group 2) whose average serum vitamin D level was 9.22 ng/mL (Table 2).

The average serum vitamin D levels were 12.1±12.3 ng/mL in patients with ischemic hepatitis on presentation to the hospital and 8.8±4.6 ng/mL at discharge. The serum vitamin D levels were 7.6±3.7 ng/mL in patients with acute toxic hepatitis on presentation to the hospital and 6.9±3.6 ng/mL at discharge.

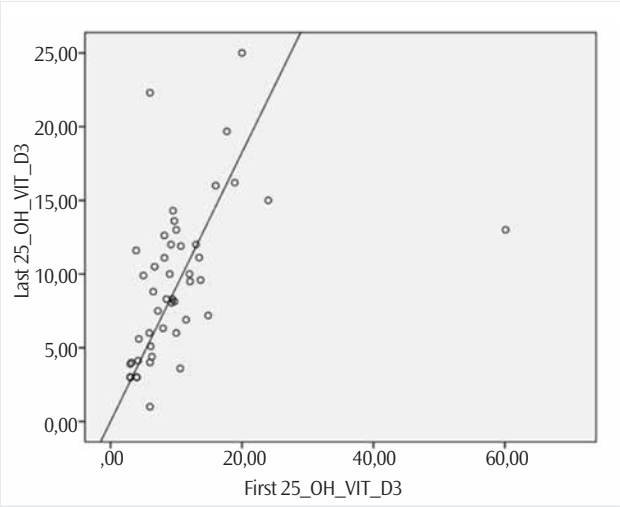

Figure 3. Correlation coefficients for the initial and final serum 25-OH vitamin D levels and scatter diagram

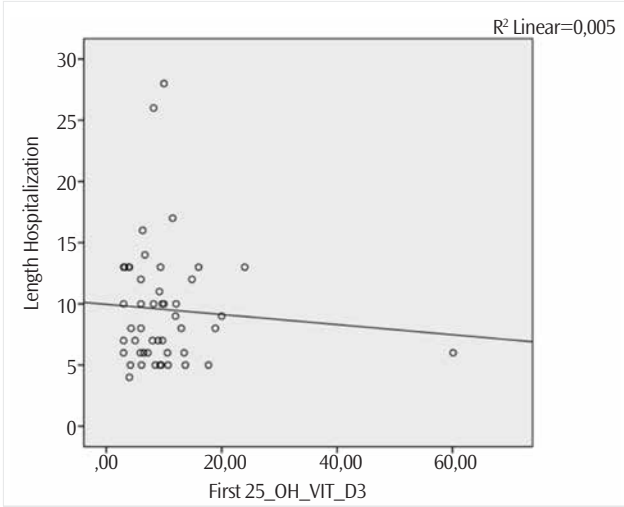

Figure 4. Spearman's correlation scatter diagram for initial serum 25-OH vitamin D levels and duration of hospitalization

Table 1. Comparison of patients with acute ischemic, toxic, and viral hepatitis with respect to their initial serum 25-OH vitamin D_3 levels

Initial 25-OH Vit D_3	n	Mean Rank	p
Ischemic hepatitis	19	27.13	
Toxic hepatitis	17	20.71	
Viral hepatitis	12	25.71	0.366
Total	48		

Table 2. Average serum vitamin D levels in groups 1 and 2 with respect to the clinical course

Clinical course	Average (Vitamin D)	n	Standard Deviation
Group 1 (alb<3.5; INR>1.1)	10.22	26	9.02
Group 2	9.95	22	7.6
Total	10.09	48	9.96

Table 3. Mortality status based on the cutoff value of serum 25-OH vitamin D3 level at 18.7

	Cutoff value of vitamin D<= 18.7		Cutoff value of vitamin D>18.7	
Mortality status	**%**	**n**	**%**	**n**
Yes	4.55	2	0	0
No	95.45	42	100	4

The average duration of hospitalization at the clinic was 9.5±4.9 days for patients. The average duration for each group was 7.2±3.0, 10.0±5.7, and 12.4±4.7 days for patients with acute ischemic, toxic, and acute viral hepatitis, respectively. This indicated that patients with acute viral hepatitis had the longest duration of hospitalization at the clinic. The follow-up (stay) durations of patient groups were compared using the Kruskal–Wallis H test, and p values of 0.001 was considered to be statistically significant (p=0.001). If a patient had a low serum 25-OH vitamin D level on presentation to the clinic, the level was generally low at discharge (r=0.449 and p=0.01) (Figure 3). Except for patients with viral hepatitis, serum vitamin D levels were even lower at discharge in patients with low serum vitamin D levels on presentation to the clinic. Initial serum 25-OH vitamin D levels and duration of hospitalization at the clinic were assessed using Spearman's correlation, and as r was -0.030 and p was 0.841, it was considered insignificant. There was no correlation between serum 25-OH vitamin D levels on presentation to the hospital and duration of hospitalization (Figure 4).

Early mortality was observed in two patients among 48 patients who were followed up in the study. Patient had ischemic hepatitis, and the other had toxic hepatitis. Serum vitamin D levels were lower in the two patients with early mortality (10.7 and 6.5 ng/mL) than the cutoff value for serum 25-OH vitamin D levels (18.7 ng/mL). According to the cutoff value of 18.7 ng/mL, the mortality rate was found to be 4.55% (Table 3).

Discussion

In this study, we significantly detected low serum 25-OH vitamin D levels in patients with acute toxic, ischemic, or viral hepatitis. Patients with acute toxic and ischemic hepatitis had low serum 25-OH vitamin D levels at discharge, whereas those with viral hepatitis had increased levels. In this study, patients with acute viral hepatitis had the longest duration of hospitalization at the clinic, and there was no correlation between serum 25-OH vitamin D levels and duration of hospitalization. We did not have any findings regarding the effect of low serum 25-OH vitamin D levels on prognosis.

Vitamin D is the key regulator of calcium metabolism. A study by Matsumura et al. (3), conducted at the Showa University School of Medicine in Tokyo, Japan, showed that replication was suppressed by decreasing HCV RNA and HCV core Ag levels when vitamin D and its metabolites were added to cell cultures with hepatitis C virus and HCV (3). Moreover, vitamin D_3 has supplementary benefits when administered along with IFN therapy to patients undergoing treatment for HCV (3-6). Furthermore, recent studies showed that it modified the immune reaction and affected the T-cell function,

which was critical in patients with chronic hepatitis C (HCV) infection (7, 8). Vitamin D supplements actually yield positive results in patients with chronic inflammatory diseases such as tuberculosis, multiple sclerosis, and psoriasis (9, 10).

We found that vitamin D was significantly lower in patients with acute ischemic, toxic, and viral hepatitis compared with the controls. Other than age and genetics, which may have a role in the predisposition to liver injury, factors that cause acute ischemic and toxic hepatitis, are partially known, and thus, are being investigated. Epidemiologic data demonstrated that the rate of diseases such as coronary heart disease, hypertension, and diabetes increase as we move away from the equatorial region, which is related to vitamin D or the lack of it. Low serum vitamin D levels were observed in patients with myocardial infarction, stroke, heart failure, diabetic cardiovascular disease, and peripheral arterial disease (11-13). Therefore, low vitamin D levels could affect as a reason or a result for acute liver injuries.

A cohort study by Frank Grünhage et al. (14), conducted at the University of Bonn Hospital (Germany), compared serum vitamin D levels and fibrosis in the liver of 712 subjects with chronic liver disease, regardless of the underlying etiology. The average serum 25-OH vitamin D level was 27.7±15.4 ng/mL, and vitamin D deficiency was observed in 63.1% of the patients (<30 ng/mL). A significant correlation was detected between serum 25-OH vitamin D levels and the fibrosis stage, indicating that the rise of the histologic stage fibrosis in the liver was correlated to decreased serum vitamin D levels (14). Because our study included patients with acute hepatitis, we did not obtain biopsy samples from them.

Patients with acute viral hepatitis had the longest duration of hospitalization and a later decrease in AST and ALT levels compared with those with acute ischemic or toxic hepatitis; this corresponds with the well-known literature data that in acute hepatitis, enzyme levels may take 3–6 weeks to decrease (15). Serum 25-OH vitamin D levels were only increased at discharge in patients with acute viral hepatitis, possibly resulting from the later vitamin D examinations in patients with acute viral hepatitis compared with the other patients because their duration of hospitalization was an average of 12 days. On the basis of this information, serum vitamin D levels may normalize later in patients with acute hepatitis in parallel with enzyme level decreases. The recovery of clinical and laboratory test parameters are more rapid in patients with acute toxic or ischemic hepatitis, and their serum vitamin D levels at discharge are as low as that at presentation to the hospital. It is possible to comment that what affects the liver has a greater effect on vitamin D synthesis, or it is not parallel to the rapid recovery in enzymes. However, these results show that patients require a longer follow-up period beyond discharge and that serum 25-OH vitamin D levels must be measured at a later date. Through examinations over a long period, it will be possible to demonstrate that as time passes following the acute incident, serum vitamin D levels will increase because 25-OH vitamin D levels may have been measured at an earlier date for the second time.

Patients were subsequently grouped separately according to their albumin level of <3.5 and INR level of >1.1 (group 1), and 26 patients were identified to meet these criteria. The average serum vitamin D level was 10.22 ng/mL in these patients, indicating no statistically significant difference from the remaining patients (group 2) whose average serum vitamin D level was 9.22 ng/mL. Consequently, no correlation was detected between serum vitamin D levels and clinical severity.

It is striking that in this study, among patients with acute hepatitis, two with a fulminant course that resulted in mortality had lower serum 25-OH vitamin D levels (10.7 ng/mL and 6.5 ng/mL) than the cutoff value (18.7 ng/mL). This indicates that low serum 25-OH vitamin D levels may be a risk factor for mortality in patients with acute hepatitis. However on the basis of these data, it is not possible to claim that vitamin D deficiency causes mortality. In large observational studies, vitamin D deficiency had an impact on mortality in the overall population (16-20). Another restrictive factor is the limited number of cases in our study. The literature also does not have sufficient data regarding the same.

Conclusion

Serum 25-OH vitamin D levels were low in patients with acute hepatitis, indicating that serum 25-OH vitamin D levels might be a biochemical marker that can be used for diagnosing acute hepatitis. Low serum 25-OH vitamin D levels were not proven to have an effect on the clinical course. As the recovery of clinical and laboratory test parameters occurs later in patients with viral hepatitis, serum vitamin D levels were detected to increase compared with that at the baseline. Prospective studies with more numbers of patients are required to determine whether low serum vitamin D levels have an effect on the clinical course and/or mortality.

Ethics Committee Approval: Ethics committee approval was received for this study from.

Informed Consent: Verbal informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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Conflict of Interest: No conflict of interest was declared by the authors.

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