Status of Vitamin “D” in Patients of Liver Cirrhosis A Nepalese Study

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ABSTRACT:

INTRODUCTION: Many studies in recent years demonstrated a very high prevalence of vitamin D deficiency and insufficiency in patients of liver cirrhosis. There is no such study in liver cirrhosis patients from Nepal. We evaluated serum 25-hydoxy vitamin D (25 OHD) level in patients with liver cirrhosis of varying severity attending liver Unit of Bir Hospital and center for liver disease, Kathmandu, Nepal.

METHOD: Prospective study of serum level of 25 OHD was done in consecutive liver cirrhosis patients attending outpatient department. A normal 25 OHD level was defined as a concentration greater than 30 ng/ml, while insufficiency and deficiency were defined as 20-30 and less than 20 ng/ml. Patients who were taking vitamin D supplement were excluded from the study.

RESULT: 90 patients were available for study after exclusion. The etiology of liver cirrhosis was alcohol (70%), viral (20%), autoimune (2%) and cryptogenic (8%). Their CTP class was A (15%), B (35%) and C (50%). The mean 25 OHD level was 18 ng/ml. Four patients (5%) had normal 25 OHD while 4 patients (5%) have vitamin D insufficiency. Most patients (90%) had vitamin D insufficiency. 25 OHD levels were significantly lower in CTP C than CTP A and B.

INTRODUCTION

One of the fat soluble vitamins, vitamin D is mostly known as a regulator of calcium and bone metabolism. The term vitamin D refers to a group of secosteroid compounds namely; vitamin D3 and vitamin D2. Vitamin D (both forms D3 or D2) is a hormone which requires two processes of hydroxylation to finally attain its biologically active form 1,25(OH)2D. The first process of hydroxylation takes place in liver, at position C25 to form 25-hydroxyvitamin D, also known as 25(OH) D or calcidiol. The 25(OH) D of vitamin is the major circulating form of vitamin D. The second hydroxylation occurs at position C1a to form 1,25 (OH)2D, also known as calcitriol. The calcitriol (1,25(OH)2D) is produced primarily but not exclusively in the kidneys. Calcitriol (1,25(OH)2D) is released in blood, where it binds to vitamin D binding protein (DBP) and reaches its target tissues to exert its endocrine functions through the vitamin D receptor (VDR). Apart from kidney, 1,25(OH)2D is also produced in several extrarenal tissues for its paracrine and autocrine functions. Most cells in the body have VDR. Many cell types can also produce 1,25(OH)2D. 1,25(OH)2D is capable of regulating a wide variety of genes that have important functions in regulating cell growth and differentiation. An important role of Vitamin D has been observed in various chronic diseases, infectious and cardiovascular diseases, diabetes mellitus and some types of cancer.

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In addition to these diseases, vitamin D has been also associated with chronic liver diseases 4.

There is an emerging interest to explore the relationship between vitamin D deficiency and prevalence and severity of chronic liver disease. Recent studies have shown that the prevalence of vitamin D insufficiency and deficiency is higher in patients with chronic liver disease than in general population ranging between 64 and 92% 5,6. Several studies around the globe have suggested the low vitamin D status is a common feature in liver cirrhosis. A number of studies have reported that the incidence of vitamin D deficiency increases as the liver disease progresses4. In these lights of all these studies, the aim of this study was to assess vitamin D deficiency in patients with liver cirrhosis in Nepal.

METHOD

This is a prospective observational study. A Serum level of 25 (OH) vitamin D of consecutive liver cirrhosis patients attending outpatient department of the Center for Liver Diseases and liver unit of Bir hospital from January 1, 2015 to December 30, 2016, were measured. Patients who had used calcium and/or vitamin D supplements in the past three months were excluded. A venous blood sample was collected after overnight fast. After 30 minutes, samples were centrifuged for 30 minutes and refrigerated until analysis. The 25(OH)D was measured by chemiluminescent micro-particle in immunoassay in Architect Analyzer. Diagnosis of liver cirrhosis was based upon clinical examination, laboratory tests, imaging diagnosis and liver biopsy whenever applicable. Severity of disease was assessed as per Child Pugh classification.

DEFINING OPTIMAL VITAMIN D STATUS

Serum 25 (OH) D concentrations reflects a objectively verifiable vitamin D restoration in human body; but there is no exact definition of its normal range in real clinical setting. Thus, much controversy surrounds the definition of ‘adequate’ vitamin D status. The abnormal calcium, phosphate and bone metabolism may develop, on a biochemical level, rendering patients at greater risk of osteopenia, osteoporosis and fractures 7. Optimal vitamin D status has often hinged on the inverse relationship between PTH and 25(OH)D. However, specific levels have not been defined for patients with liver disease. Despite all these, historically, vitamin D insufficiency was defined as serum 25(OH)D levels < 20 ng/ml (i.e. 50 nmol/L) for the general population 8. The Institute of Medicine (IOM) of the National Academies in the United States suggests a serum 25(OH)D concentration of 20 ng/ml as adequate. Contrary to the stipulation of IOM, the Endocrine Society of Maryland, USA recommends 25(OH)D levels of 30 ng/ml (i.e. 75 nmol/L) and even suggests that concentrations between 40 and 60 ng/ml (i.e. between 100 and 150 nmol/L) may be advantageous as a precautionary measure because of the variability of assays in 25(OH)D determination. For the purpose of this study Vitamin D deficiency has been defined as serum 25(OH)D levels lower than 20ng/ml (i.e.50 nmol/L) and vitamin D insufficiency has been defined as serum levels between 20 and 30 ng/ml (i.e.50-75nmol/L).

RESULT

During study period a total of 112 patients were enrolled. After exclusions, 90 patients were available for the study. The reasons for exclusions were patient taking vitamin D prior to the study and unconfirmed liver cirrhosis. Among these 90 patients, the median age was 55 years with the range starting from 20 to 76 years. The etiology of liver cirrhosis was alcohol in 70%, viral infection in 20%, autoimmune in 2%, and; cryptogenic in 8% of the patients (Figure 1). When assessed by Child Pugh classification, 15% were in Child-Pugh class A, 35% in Child-Pugh class B and 50% in Child-Pugh class C (Figure 2)
The mean 25 OHD level was 18 ng/ml in the range between 8 ng/ml and 34 ng/ml. Only 4 patients (5%) had normal 25 OHD while another 4 patients (5%) had vitamin D insufficiency. Most patients 82 patients, (90%) had vitamin D deficiency. It was also found that the 25 OHD levels were significantly lower in Child-Pugh class C compared to Child-Pugh class A and B (P<0.05).

Vitamin D level in different CTP score groups

<table>
<thead>
<tr>
<th>CTP Score</th>
<th>Mean Vitamin D level (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-6</td>
<td>28.2</td>
</tr>
<tr>
<td>7-9</td>
<td>21.6</td>
</tr>
<tr>
<td>10-15</td>
<td>12.6</td>
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</tbody>
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**DISCUSSION**

Vitamin D is now widely recognized to have multiple extra-skeletal health functions. The liver is one of the major organs involved in the metabolism. Recent studies have demonstrated a very high prevalence of Vitamin D deficiency and insufficiency in patients with liver diseases. The prevalence of vitamin D deficiency in CLD has been reported to range from 64 to 92% and is commonly inversely related to disease progression 9, 10.

A number of studies have observed an inverse association between vitamin D status (assessed by 25 (OH)D levels) and disease severity (assessed by the Child-Pugh score) 11. But our study showed the level of vitamin D deficiency is directly proportional with disease progression. This could be due to average low level of vitamin D in general population and dietary restrictions in nepalese cirrhotic patients as they follow strict dietary restriction once the disease progresses. This discrepancy needs to be further evaluated in large study. Many studies have reported the low serums level of 25 OHD in patients with liver cirrhosis 12. The study of Putz- Bankuti in 2012 showed that 71% of the research subjects have deficiency of vitamin D. The same study showed no significant difference in 25(OH)D between patients with alcoholic cirrhosis and cirrhosis of non-alcoholic origin 13.

The study conducted by Rode et al, noted that patients with cirrhosis were more likely to be deficient in 25(OH)D (75%,P=0.028). Several clinical applications of 25(OH)D levels have been suggested, as a prognostic predictive factor for mortality and infections in patients with liver cirrhosis by Anty et al. 14. Furthermore in this context, Malham et al clearly emphasized the importance of monitoring vitamin D in all cirrhotic populations, especially those with alcoholic liver cirrhosis. New sets of evidence have suggested the therapeutic strategy of oral Vitamin D supplementation in CLD.

Lim et al 15 suggested periodic monitoring of 25(OH)D in patients with chronic liver disease and cirrhosis, and substitution therapy in those with levels <30 ng/mL, which includes administration of 5000 IU of vitamin D3 daily or 5000IU of vitamin D2 or D3 weekly for 3 months, followed by 1000IU/day indefinitely. Stokes et al affirmed that the risk of bone disease in CLD patients, particularly those with cirrhosis, warrants the routine use of vitamin D therapy, and the importance of adequate vitamin D concentrations remains from a preventative perspective. The Guidelines of Endocrine Society recommend that all adults who are vitamin D deficient to be treated with 50000IU of vitamin D2 or vitamin D3 once a week for 8 weeks or its equivalent of 6000IU of vitamin D2 or vitamin D3 daily to achieve a serum level of 25(OH)D above 30ng/mL, followed by maintenance therapy of 1500–2000IU/day. Furthermore, they have set minimal daily dietary recommendations of vitamin D intake for patients at high risk for vitamin D deficiency, depending on their age group. The extent of the recommended screening indications is limited to hepatic failure and does not cover the full spectrum of liver diseases.

**CONCLUSION**

Our study corroborates the fact that Vitamin D deficiency and insufficiency is highly prevalent in patients with liver cirrhosis of Nepal and it further decreases with increase in disease severity. We recommend the importance of monitoring vitamin D in all cirrhotic populations.

**REFERENCES**
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