ORIGINAL ARTICLE

Oral vitamin D replacement is effective in chronic liver disease

Fréquence du déficit en vitamine D et effet de la supplémentation orale au cours des maladies chroniques du foie

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Summary

Background & aims. — End-stage chronic liver disease is associated with vitamin D deficiency but the prevalence across a broad-spectrum of liver disease is unknown. This study prospectively examines prevalence of vitamin D deficiency and response to replacement in chronic liver disease.

Methods. — One hundred and fifty-eight outpatients with chronic liver disease were enrolled. Serum 25-hydroxyvitamin D (25[OH]D) levels were classified as: severely deficient less than 25 nmol/l, deficient 25—54 nmol/l or replete greater than 54 nmol/l. Sixty-five of 158 (41%) had cirrhosis.

Results. — 25[OH]D was suboptimal in 101/158 (64%), including severe deficiency in 24 patients (15%). Vitamin D deficiency occurred in liver disease of all aetiologies, including patients with only mild liver disease. 25[OH]D increased by 60.0% (19.11 ± 13.20 nmol/l) in patients with deficiency after vitamin D replacement and decreased by 25.2% (-18.33 ± 12.02 nmol/l) in non-treated initially replete patients over a median of 4 months.

Conclusions. — Vitamin D deficiency improves with oral vitamin D supplementation and levels fall without supplementation. Chronic liver disease patients are at very high risk of vitamin D deficiency regardless of etiology or severity.

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Vitamin D deficiency is common in chronic disease, but the prevalence across the broad spectrum of chronic liver disease (CLD) is not well documented. The importance of vitamin D deficiency is highlighted by the increasingly recognized role vitamin D has in immunoregulation [1], cellular growth and differentiation, antioxidation, and regulation of fibroblast proliferation and collagen synthesis [2].

Previous studies have focussed on vitamin D deficiency in cholestatic liver disease, especially primary biliary cirrhosis [3], and in patients with advanced cirrhosis [4]. Although
Oral vitamin D replacement is effective in chronic liver disease. Vitamin D deficiency is well accepted as a consequence of CLD, no prospective studies have determined the response to standard vitamin D replacement therapy. We sought to examine prospectively the prevalence of vitamin D deficiency in chronic liver disease of different etiologies and stages, evaluate if serum 25-hydroxyvitamin D (25(OH)D) levels correlate with severity of liver disease and determine the response to standard oral replacement therapy.

**Patients and methods**

Patients attending the outpatient liver clinic between November 2006 and July 2007, during a period of the year when cumulative sunlight exposure is higher, were enrolled prospectively (n = 158) with etiologies detailed in Table 1. Sixty-five of 158 (41%) had cirrhosis and 82 (52%) were men. The majority of the patients were of Anglo-Saxon, European or Asian descent. The Melbourne Health Human Research Ethics Committee approved the study.

**Laboratory analysis, treatment and statistical analysis**

25(OH)D were measured by radioimmunoassay (Diasorin, Stillwater, MN, USA). Consistent with our laboratory’s ranges and the literature, 25(OH)D was classified as: severely deficient (< 25 nmol/l), mildly deficient (25—54 nmol/l) or replete (> 54 nmol/l) [5]. All subjects had measurements of serum albumin, bilirubin, aminotransferases, alkaline phosphatase and gamma-glutamyl transferase. Cirrhosis was diagnosed on liver biopsy or a combination of appropriate radiological findings and clinical diagnosis.

Patients with suboptimal 25(OH)D were treated with standard oral replacement doses of ergocalciferol (vitamin D2 1000IU) or cholecalciferol (vitamin D3 50 mcg) supplements daily.

One-way analysis of variance and regression analyses were performed, and scatter plots were generated using Minitab 15 (Minitab Inc. [2007] Pennsylvania). Validity checks of statistical assumptions were satisfactory.

**Results**

Suboptimal 25(OH)D levels were present in 101 patients (64%) and 24 (15%) had severe vitamin D deficiency (Table 1). There was no significant difference in 25(OH)D between males and females. Patients with cirrhosis were more likely to be deficient (75%) (P = 0.028) and were over-represented in the severely deficient category (63%). Vitamin D deficiency was seen in liver disease across all etiologies including in subgroups with a low incidence of cirrhosis. Surprisingly, no patients with cholestatic liver disease were severely deficient of 25(OH)D, with 40% recording replete levels.

Patients with initially replete 25(OH)D without supplementation demonstrated an average 25.2% decrease (−18.33 ± 12.02 nmol/l, 72.72 vs. 54.39 nmol/l) over a median period of 4 months. Oral vitamin D supplementation resulted in a 41.0% increase in mean 25(OH)D in patients with mild deficiency (16.38 ± 12.74 nmol/l, 39.92 vs. 56.30 nmol/l) and a 141.1% increase in patients with severe deficiency (22.23 ± 14.12 nmol/l, 15.75 vs. 37.98 nmol/l). Overall, for patients with vitamin D deficiency there was a 60% increase in mean 25(OH)D (19.11 ± 13.20 nmol/l, 31.86 vs. 50.97 nmol/l) over a median period of 4 months.

25(OH)D levels correlated with serum albumin (r = 0.230, P = 0.006) and inversely with bilirubin (r = −0.240, P = 0.004) as surrogate markers of liver disease severity and with the presence of cirrhosis (r = −0.175, P = 0.028).

**Discussion**

Although previous investigators have noted vitamin D deficiency as a complication of CLD, this is the first study to

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Serum 25(OH)D in Liver clinic population.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category</td>
<td>Severe deficiency (&lt; 25 nmol/l)</td>
</tr>
<tr>
<td>Total (n = 158) (%)</td>
<td>24 (15)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male (n = 82) (%)</td>
<td>10 (12)</td>
</tr>
<tr>
<td>Female (n = 76) (%)</td>
<td>14 (18)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>52.2 ± 18.4</td>
</tr>
<tr>
<td>Non-cirrhotic (n = 93) (%)</td>
<td>9 (10)</td>
</tr>
<tr>
<td>Cirrhotic (n = 65) (%)</td>
<td>15 (23)</td>
</tr>
<tr>
<td>Etiology of liver disease</td>
<td></td>
</tr>
<tr>
<td>Viral (n = 60) (%)</td>
<td>9 (15)</td>
</tr>
<tr>
<td>NASH (n = 23) (%)</td>
<td>4 (17)</td>
</tr>
<tr>
<td>Alcoholic (n = 22) (%)</td>
<td>5 (23)</td>
</tr>
<tr>
<td>Autoimmune (n = 12) (%)</td>
<td>3 (25)</td>
</tr>
<tr>
<td>Hemochromatosis (n = 9) (%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Cholestatic (n = 5) (%)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Wilson’s (n = 2) (%)</td>
<td>1 (50)</td>
</tr>
<tr>
<td>Other (n = 25) (%)</td>
<td>2 (8)</td>
</tr>
</tbody>
</table>
demonstrate its broad based prevalence and show a correlation with liver disease severity. Our results are similar to a previous study in patients with advanced cirrhosis, despite including patients with varying degrees of liver disease [4]. Vitamin D deficiency is a common problem in our community (latitude 38°S) with one third of young women having mild to moderate deficiency [6], but our results in CLD illustrate that vitamin D deficiency is considerably more common and severe.

This is the first study to demonstrate that oral supplementation is effective for vitamin D deficiency in CLD, with a 60% increase in median levels in deficient patients with short term oral supplementation, further challenging traditional teaching that malabsorption is the major factor leading to deficiency. Larger and more consistent increases in 25(OH)D may be possible with improved patient compliance, higher replacement doses and longer treatment. The 25.2% fall in patients with initially replete 25(OH)D levels highlights the possible need for long-term supplementation, not only for 25(OH)D deficient patients, but for all patients with CLD. Endocrinologists have proposed an optimal 25(OH)D level is greater than 75 nmol/L, as relative hyperparathyroidism occurs below this level [7], however routine measurement of parathyroid hormone levels was beyond the scope of this study. If this classification were applied, 90% of our patients (142 of 158) would be classified as vitamin D deficient.

This high incidence of vitamin D deficiency highlights the need for further studies into the effects of vitamin D deficiency on liver disease. Bachar-Dahan et al. have recently demonstrated that serum 25(OH)D levels in vivo inversely correlate with hepatic stellate cell proliferation and production of collagen, by directly inhibiting other mediators [8]. 25(OH)D levels are inversely related to the severity of NASH steatosis, necroinflammation and fibrosis on histology [2]. 25(OH)D levels and vitamin D receptor polymorphisms may influence susceptibility, response and treatment of viral hepatitis B [1], autoimmune hepatitis, primary biliary cirrhosis [9] and hepatocellular carcinoma [10,11].

Limitations of our study include that all the patients were derived from a single clinic and the use of surrogate markers for liver disease severity rather than a liver biopsy. Nevertheless, the variety and severity of patients included is reflective of many other liver clinics in the Western world. We would also recommend higher doses of oral vitamin D replacement and longer treatment, as vitamin D did not reach desirable levels in all patients.

In conclusion, vitamin D deficiency occurs in the majority of chronic liver disease patients regardless of severity, however, the degree of deficiency correlates with liver disease severity. This predisposes patients to hepatic osteodystrophy and may have a negative impact on the natural history. Vitamin D levels can be improved by low dose oral supplementation and serum vitamin D levels continue to fall in patients without supplementation. Further research to determine optimal replacement doses in chronic liver disease patients is required.

Conflict of interest statement

No potential conflict of interest relevant to this article was reported.

Acknowledgement

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References

[8] Bachar-Dahan L, Weisman Y, Reif S. 1,25-Dihydroxyvitamin D suppressed hepatic stellate cells proliferation, and collagen type I expression, and increased matrix metalloprotease expression. Hepatology 2008;48(Suppl.):317A.