Vitamin D and Parathyroid Hormone in Outpatients With Noncholestatic Chronic Liver Disease

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Background & Aims: **The liver plays a central role in vitamin D metabolism. Our aim was to determine the prevalence and type of vitamin D–parathyroid hormone (PTH) disturbance in ambulatory patients with noncholestatic chronic liver disease (CLD) and its relationship with disease severity and liver function.** ***Methods:*** **We studied 100 consecutive outpatients (63 men, 37 women; mean age, 49.0 ± 12.1 [SD] y) with noncholestatic CLD caused by alcohol (n = 40), hepatitis C (n = 38), hepatitis B (n = 12), autoimmune hepatitis (n = 4), hemochromatosis (n = 4), and nonalcoholic steatohepatitis (n = 2); 51 patients had cirrhosis. Serum concentrations of 25-hydroxyvitamin D (25[OH]D), PTH, calcium, phosphate, magnesium, creatinine, and liver function tests were determined.** ***Results:*** **Serum 25(OH)D levels were inadequate in 91 patients: vitamin D deficiency (<50 nmol/L) was found in 68 patients and vitamin D insufficiency (50–80 nmol/L) was found in 23 patients. Secondary hyperparathyroidism (serum PTH, >6.8 pmol/L) was present in 16 patients. The prevalence of vitamin D deficiency was significantly higher in cirrhotic vs noncirrhotic patients (86.3% vs 49.0%; *P* = .0001). In Child–Pugh class C patients, 25(OH)D levels were significantly lower than in class A patients (22.7 ± 10.0 nmol/L vs 45.8 ± 16.8 nmol/L; *P* < .001). Serum 25(OH)D independently correlated with international normalized ratio (negatively; *P* = .018) and serum albumin (positively; *P* = .007). Serum 25(OH)D levels of less than 25 nmol/L predicted coagulopathy, hyperbilirubinemia, hypoalbuminemia, increased alkaline phosphatase, and anemia and thrombocytopenia.** ***Conclusions:*** **Vitamin D inadequacy is common in noncholestatic CLD and correlates with disease severity, but secondary hyperparathyroidism is relatively infrequent. Management of CLD should include assessment of vitamin D status in all patients and replacement when necessary.**

The liver is a major organ in the vitamin D endocrine system. To function physiologically vitamin D must first be converted in the liver to 25-hydroxyvitamin D (25[OH]D), the main circulating form of vitamin D, and this in turn is converted in the kidney into 1, 25-dihydroxyvitamin D, the active metabolite.[1–3] Liver cells along with parathyroid glands and kidneys express a calcium-sensing receptor4 that plays a critical role in regulating systemic calcium homeostasis.

In recent years it has been recognized that the vitamin D endocrine system is not only the principal regulator of calcium and phosphate homeostasis and bone metabolism, but it also exerts potent noncalciotropic functions including antiproliferative, prodifferentiative, and immunomodulatory activities.[3] Vitamin D insufficiency has been linked, apart from osteoporosis, to a wide range of inflammatory, autoimmune, and metabolic disorders and malignancies.[5] On the other hand, the normal liver is a target organ for the vitamin D endocrine system[6] and parathyroid hormone (PTH).[7,8]

Although chronic liver disease (CLD), especially cholestatic, alcoholic, and in advanced stages from any causes, often (20%–60%) is complicated by bone disease,[9–11] the clinical relevance of vitamin D–PTH disturbances in hepatic osteodystrophy still is unclear.[9,12–22]

Vitamin D deficiency traditionally is considered to cause secondary hyperparathyroidism and this has been observed in up to 42% of patients with CLD in some studies,[16,22] whereas in other studies the PTH levels were normal[23] or even low.[24–26]

The few studies correlating 25(OH)D–PTH status and severity of the liver injury reported conflicting results. Some investigators[13,18,25–28] have suggested that 25(OH)D levels decrease with disease progression, but others did not find differences between cirrhotic and noncirrhotic patients[22] or between Child–Pugh groups.[24]

Despite accumulating evidence that vitamin D has a number of actions that may be relevant to liver function and CLD, including the regulation of secretion of metalloproteinases and their inhibitors, fibroblast proliferation, and collagen synthesis,[29,30] currently the evaluation and correction of vitamin D status is not part of the routine management of these patients.

It also should be noted that most work has been performed in patients with chronic cholestatic liver disease (particularly primary biliary cirrhosis) and studies often were limited by small numbers. In the present study we investigated vitamin D and PTH status in a diverse ambulant group of patients with noncholestatic CLD and a range of disease activity. Our aims were to determine the prevalence, extent, and type of disturbances in calcium–vitamin D–PTH status and its relationship with the severity of disease and liver function injury.

Materials and Methods

Patients

One hundred consecutive patients attending the outpatient clinic of the Gastroenterology Department at Canberra

Abbreviations used in this paper: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CLD, chronic liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus; GGT, γ-glutamyltransferase; INR, international normalized ratio; MMP, matrix metalloproteinase; 25(OH)D, 25-hydroxyvitamin D; PTH, parathyroid hormone.

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Hospital in whom there was a confirmed diagnosis of noncholestatic CLD were included in this study. The group consisted of 63 men and 37 women, with a mean age of 49.0 ± 12.1 (SD) years. The cause of CLD was alcohol use (n = 40), viral hepatitis C (n = 38), viral hepatitis B (n = 12), autoimmune hepatitis (n = 4), hemochromatosis (n = 4), and nonalcoholic steatohepatitis (n = 2). The diagnosis of CLD was based on consistent clinical findings, serologic markers (antibodies to hepatitis C virus [anti-HCV], hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody, hepatitis B e antigen, hepatitis B e antibody, hepatitis B virus DNA, and HCV RNA measurements by polymerase chain reaction, autoantibodies [antinuclear antibody, anti–smooth muscle antibody]), biochemical features (including iron studies and hemochromatosis gene test), endoscopic (n = 50) and imaging (including ultrasound, n = 100) evidence, and histologic examinations (liver biopsy examination, n = 37). Of 38 patients with CLD as a result of HCV, 8 subjects (including 4 with cirrhosis) had a history of alcohol overuse; the HCV cause was confirmed by liver biopsy examination in 2 of these patients. None of the patients had steatorrhea. The severity of cirrhosis was graded using the Child–Pugh score and patients were grouped into 3 categories: class A (scores 5–6; n = 15), class B (scores 7–9; n = 16), or class C (scores 10–15; n = 20). The Model for End-Stage Liver Disease score also was calculated according to the United Network for Organ Sharing formula.[31] None of the patients received vitamin D or calcium supplements, bisphosphonates, calcitonin, or hormone replacement therapy. Twenty-one patients were treated with spironolactone, 14 with furosemide, 6 with lamivudine (one of whom was also on adefovir), 5 with combination peginterferon alfa-2a or 2b and ribavirin, and 4 were on corticosteroids. Seven other patients had previously received either standard or pegylated interferon alone or in combination with ribavirin for hepatitis C treatment.

All patients were residents of the Canberra region (latitude, 33° 15′ S). All patients gave their informed consent to participate in the study, which was approved by the local ethics review committee.

Laboratory Analysis

Samples of venous blood were obtained in the morning after an overnight fast and were kept frozen at −70°C for the assay of 25(OH)D and intact PTH. The tests were performed using commercially available kits according to the manufacturers' instructions. 25(OH)D was measured with ^{125}I radioimmunoassay kit (DiaSorin, Stillwater, MN); the intra-assay and interassay coefficient of variation were 8.6% and 9.4%, respectively. The laboratory reference range was 31–107 nmol/L. Intact PTH was measured by 2-site chemiluminescent enzyme-labeled immunoassay for the 1–84 amino acid chain on the Immunolite 2000 auto-analyzer (Diagnostics Products Corporation, Los Angeles, CA); intra-assay and interassay coefficients of variation were 5.2% and 6.3%, respectively. The laboratory reference range was 1.3–6.8 pmol/L.

All subjects had serum total calcium, phosphate, magnesium, albumin, total bilirubin, aminotransferases, alkaline phosphatase, prothrombin time, creatinine, urea, sodium, potassium, glucose, hemoglobin, and full blood count determined by routine laboratory techniques. The serum calcium level was corrected for albumin concentration; the international normalized ratio (INR) for prothrombin time was calculated.

On the basis of data reported in the literature,[32,33] the serum 25(OH)D concentration was defined as deficient when it was less than 50 nmol/L (severe deficiency, <12.5 nmol/L; moderate deficiency, 12.5–25 nmol/L; mild deficiency, 25–49 nmol/L), insufficient when it was 50–80 nmol/L, and sufficient (adequate, desirable, normal) when it exceeded 80 nmol/L.

Statistical Analysis

Statistical analyses were performed with a statistical software package (Stata version 7; Stata Press, College Station, TX). Data are presented as mean values and SDs. For differences between groups, significance was assessed using an unpaired 2-tailed Student *t* test for continuous variables and the Pearson χ^2 test with the Fisher exact test for categoric variables. Correlations between 25(OH)D, PTH, biochemical markers of liver function, and demographic parameters were examined using linear regression analysis and the Pearson correlation coefficient. Multiple linear regression analysis was performed to identify independent variables associated with a low 25(OH)D level. The appropriateness of the regression model was assessed by Jack-knife residuals, Cook's d, and Mallow's C_p. A *P* value of less than .05 was considered statistically significant.

Results

Patient Characteristics

The patients were diverse in age, nature, and severity of their noncholestatic CLD. Table 1 summarizes the demographic, etiologic, and main biochemical and hematologic data on all subjects studied. The age of the patients ranged from 22 to 76 years. The cirrhotic patients were significantly older than the noncirrhotic patients, but there was no difference between the 2 groups regarding sex, with a male predominance in both groups. The main causative factor for cirrhosis was alcohol (72.5%), whereas in the noncirrhotic group it was viral hepatitis C (57.1%) and B (22.4%). As expected, the biochemical parameters of liver function and hematologic characteristics differed significantly between the cirrhotic and noncirrhotic patients. The former group had higher mean INR values, increased concentrations of serum bilirubin, alkaline phosphatase (ALP), γ-glutamyl transferase, and lower serum albumin, alanine aminotransferase, hemoglobin, and platelets. These differences were not related to sex and were more pronounced in advanced stages of cirrhosis. No differences were seen between the groups for creatinine and urea concentrations.

Vitamin D Status

In total, inadequate vitamin D status, defined as a serum 25(OH)D level lower than 80 nmol/L, was present in 91 patients, vitamin D deficiency (<50 nmol/L) was seen in 68 patients, and insufficiency (50–80 nmol/L) was seen in 23 patients. Only 9 noncirrhotic patients showed a normal (>80 nmol/L) serum 25(OH)D concentration (Table 2). There was no difference in serum 25(OH)D levels between the sexes (42.6 ± 28.0 nmol/L in men vs 43.3 ± 21.9 nmol/L in women).

The severity of CLD and the stage of cirrhosis according to Child–Pugh classification and Model for End-Stage Liver Disease score showed significant correlation with the serum 25(OH)D concentration (Table 2). The mean serum concentration of 25(OH)D was significantly lower in patients with cirrhosis compared with noncirrhotic patients. When patients