Management of osteoporosis, fat-soluble vitamin deficiencies, and hyperlipidemia in primary biliary cirrhosis

Cynthia Levy, Keith D Lindor

Primary biliary cirrhosis (PBC) is a chronic cholestatic liver disease, likely of autoimmune cause, which affects approximately 1:5000 people in the United States. Because of its ultimate progression to end stage liver disease, PBC was the leading cause for orthotopic liver transplantation (OLT) in this country until ursodeoxycholic acid (UDCA) became available as an effective therapy in delaying or preventing OLT. Regardless of advances in the understanding and management of this complex malady, the overall survival of a cirrhotic patient continues to be less than in the general population, but it may approach that of the general population if UDCA is started earlier in the disease.

Most patients are diagnosed either during the asymptomatic phase of PBC or after presenting with non-specific symptoms. When symptoms start, extrahepatic complications may predominate over symptoms related to portal hypertension or hepatic insufficiency. Pruritus and fatigue have been consistently reported as the most common symptoms of PBC at the time of diagnosis and at follow-up [1]. Osteoporosis and fat-soluble vitamin deficiencies are considered late complications of cholestasis and may have an enormous impact on a patient's quality of life.

Given the impact of these extrahepatic manifestations on the quality of life of patients with PBC, this article focuses on reviewing the treatment of osteoporosis, fat-soluble vitamin deficiencies, and hyperlipidemia in the setting of PBC. The management of pruritus and fatigue is discussed in another article.

Osteoporosis

In a recent study involving 176 patients with PBC in the authors’ institution, the prevalence of osteoporosis was 20%, which represents a 30-fold increase in the relative risk of developing severe bone disease compared with age- and weight- matched population [2]. The independent predictors of a t score up to $\leq -2.5$ were, age greater than 57 years, body mass index (BMI) up to $\leq 24$ Kg/m$^2$, advanced histologic stage, and previous history of bone fractures. Of note, after 3 years of follow-up, the rate of bone loss in patients with early stages of disease equalized that of patients with advanced stages. Springer et al [3] observed a 35% prevalence of osteoporosis among 72 PBC patients in Canada.

Osteoporosis is also a problem immediately after OLT. The prevalence of skeletal fractures after OLT ranges from 17% to 65% [4,5]. Bone mass is lowest during the first 3 months post-transplantation for PBC when compared with the pre-OLT levels. From 3 to 12
months post-OLT, bone mass tends to equal that of the pre-transplant period, and after 12 months the bone mass tends to be higher than before OLT [4]. These findings are in agreement with the idea that some toxic substance that was previously increasing the risk of osteoporosis is in lower concentration after liver transplantation.

Several mechanisms have been postulated to explain this increased prevalence of bone disease, including (1) vitamin K deficiency, (2) decreased osteoblastic function, (3) increased rate of bone loss, (4) hypogonadism, and (5) genetic polymorphisms. The severity of liver disease correlated with a decreased BMD in the lumbar spine in a few [5,6] but not all studies [7–10]. The pathogenesis of osteoporosis is further explored in Dr. Floreani’s article in this issue.

**Treatment**

A combined analysis of previous trials assessing treatment of bone disease is difficult because of heterogeneous study populations and different methodologies. Also the sample sizes are small and lack control groups. Table 1 summarizes the results of previous studies to prevent bone loss in patients with PBC [11–22].

<table>
<thead>
<tr>
<th>Drug</th>
<th>Author</th>
<th>Number of patients</th>
<th>Study design</th>
<th>Duration</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcitriol</td>
<td>Comisso et al. [11]</td>
<td>25</td>
<td>Prospective, CO</td>
<td>6 months</td>
<td>Negative</td>
</tr>
<tr>
<td>Calcitriol</td>
<td>Floreni et al. [12]</td>
<td>23</td>
<td>OL</td>
<td>3 years</td>
<td>BMD stable compared to untreated patients</td>
</tr>
<tr>
<td>UDCA</td>
<td>Lindor et al. [14]</td>
<td>96</td>
<td>RCT</td>
<td>3 years</td>
<td>Negative</td>
</tr>
<tr>
<td>Estrogen</td>
<td>Oleson et al. [15]</td>
<td>10</td>
<td>OL</td>
<td>2 years</td>
<td>Improvement in BMD</td>
</tr>
<tr>
<td>Estrogen</td>
<td>Coppo et al. [16]</td>
<td>10</td>
<td>Retrospective</td>
<td>1 year</td>
<td>Improvement in BMD</td>
</tr>
<tr>
<td>Fluoroide</td>
<td>Guarabeni et al. [17]</td>
<td>22</td>
<td>RCT</td>
<td>2 years</td>
<td>BMD stable compared to patients on placebo</td>
</tr>
<tr>
<td>Estrogen</td>
<td>Wolfagen et al. [18]</td>
<td>12</td>
<td>Randomized, uncontrolled</td>
<td>1 year</td>
<td>BMD stable compared to untreated</td>
</tr>
<tr>
<td>Estrogen</td>
<td>Guarabeni et al. [19]</td>
<td>32</td>
<td>Randomized</td>
<td>2 years</td>
<td>Lumbar spine and femoral neck BMD better in estrogen group</td>
</tr>
<tr>
<td>Estrogen vs fluoroide</td>
<td>Guarabeni et al. [20]</td>
<td>26</td>
<td>Randomized</td>
<td>1 year</td>
<td>BMD better in estrogen group</td>
</tr>
<tr>
<td>Estrogen vs alendronate</td>
<td>Flax et al. [21]</td>
<td>67</td>
<td>RCT</td>
<td>60 completed 1 year, 14 completed 2 years</td>
<td>No change in BMD compared to placebo</td>
</tr>
<tr>
<td>Vitamin K2 vs placebo</td>
<td>Lindor et al. [22]</td>
<td>25</td>
<td>RCT</td>
<td>2 years</td>
<td>BMD stable compared to patients on placebo</td>
</tr>
</tbody>
</table>

| Abbreviations: RCT, randomized controlled trial; CO, crossover; OL, open label; BMD, bone mineral density. |

**Calcium and vitamin D supplementation**

The administration of calcium and vitamin D seems reasonable to prevent osteomalacia, but it does not prevent bone loss or improve lumbar mineral density in the presence of osteoporosis [16,23,24]. Other investigators have shown less bone loss with vitamin D through dual-energy X-ray absorptiometry [25], but this study was limited by a small sample size, absence of standard therapy (calcium supplementation) in the control group, and variable follow-up time not accounted for in the final analysis. Calcium 1.5g/day and vitamin D 800 IU/day are recommended routinely for patients with normal BMD.
**Ursodeoxycholic acid**

Ursodeoxycholic acid (UDCA) was prospectively evaluated over a 3-year period in a randomized, double blind, controlled trial involving 88 patients with PBC [14]. After the study period, there was no difference in the lumbar spine bone density between the UDCA-treated and the placebo-treated patients. Therefore, specific therapy for osteoporosis is needed in addition to UDCA.

**Hormone replacement therapy**

Estrogen replacement has been used in postmenopausal women with PBC with improvement of BMD and without worsening of underlying cholestasis. In one study, a retrospective analysis of bone densitometries of 16 women who had been treated with estrogen replacement revealed an increase in the lumbar spine BMD at 1 year [16]. A prospective study of 10 postmenopausal women with PBC given HRT for 2 years showed a significant increase in lumbar spine and total body BMD, while age-matched controls had a significant decrease in both lumbar spine and total body BMD [15]. Again, hepatotoxicity was not observed during this trial. However, given recent results of HERS II trial (heart and estrogen/progestin replacement study follow-up), which showed an increased rate of hip fractures among women on hormone therapy without the benefit of cardiovascular protection [26], the use of hormone replacement therapy is discouraged.

**Calcitonin**

Calcitonin is an antiresorptive agent with proven efficacy in post-menopausal osteoporosis. Although it failed to show beneficial effects in one small prospective cross-over trial involving 25 PBC patients [11], its use was reevaluated in combination with calcium and vitamin D supplementation in a pilot study of 3-years duration [12]. In that study involving 59 osteoporotic women with PBC, calcitonin was said to be effective in the treatment of severe osteodystrophy, but methodologic limitations make it difficult to analyze the data.

**Sodium fluoride**

Fluoride stimulates bone formation. In postmenopausal osteoporotic women, it caused an increase in BMD without decreasing the fracture rate in 22 PBC patients prospectively followed in a randomized double blind placebo controlled trial over a 2-year period [17]. All patients also received calcium and vitamin D. Although only 15 patients completed the trial, those on the active treatment maintained a stable BMD, whereas patients who received placebo had a significant drop in BMD. Nevertheless, bisphosphonates proved to be better than fluoride in the prevention of bone loss in PBC patients (see later in the discussion).

**Bisphosphonates**

Cyclical etidronate, a bisphosphonate drug with antiresorptive properties that had been proven effective in postmenopausal osteoporotic women, was first used in PBC patients who were participating in a controlled trial of prednisone or azathioprine versus placebo [18]. Twenty-four patients were randomized to receive etidronate and calcium or calcium alone. Of those, 12 patients were on immunosuppressants and were analyzed separately. Cyclic etidronate was noted to prevent bone loss in steroid-treated patients. Later, fluoride was
compared with cyclical etidronate, showing that the BMD increased in the lumbar spine and was unchanged in the femoral neck of patients who received etidronate, whereas the lumbar spine BMD was unchanged and the femoral neck BMD decreased in those who received fluoride [19]. Of note, two fractures were reported in the fluoride group and none in the etidronate group. Etidronate was also compared with alendronate, another bisphosphonate, in a randomized trial involving 26 women with PBC [20]. Alendronate was found to be superior to etidronate, with improvement in spinal and femoral BMD after 1 year of therapy.

The best data regarding efficacy of etidronate comes from a randomized double blind placebo controlled data including 67 patients with PBC [21]. Although etidronate use was correlated with a significant reduction in markers of bone turnover, no change was observed in the lumbar spine or femoral BMD compared with placebo. Unfortunately, etidronate did not improve BMD in patients with PBC and its routine use is not recommended. Other, more potent, bisphosphonates are currently being evaluated in the authors' institution.

**Vitamin K**

The effects of vitamin K administration were assessed in patients with PBC in a randomized controlled trial using dual-energy X-ray absorptiometry to evaluate 27 patients before and after 2 years of therapy [22]. At the end of the study, BMD remained significantly higher in the treated patients compared with the placebo group. This agent seems promising, but it may be difficult to design and conduct further studies as patients may be using over the counter preparations that contain vitamin K or may affect its metabolism.

**Summary and treatment recommendations**

In summary, there is a paucity of treatment options for osteoporosis in patients with PBC. There are only a few randomized controlled trials, all with a small sample size. Most of the available trials examined lumbar spine or femoral neck bone mineral density as the primary goal, whereas it is known that BMD is still a poor predictor of fractures [27]. Ideally, studies should be designed to evaluate the rate of new bone fractures instead of BMD, implying both a significantly longer follow-up period and larger sample sizes.

Even though in well-conducted clinical trials in postmenopausal osteoporotic women without liver disease alendronate was shown to decrease the fracture rate [28], patients with esophageal varices should not receive therapy with oral bisphosphonates because of the risk of pill esophagitis prompting a variceal bleeding. Unfortunately, osteoporosis is far more common in patients with stages III and IV of disease than it is with stages I and II PBC, highlighting the urgent need for the evaluation of new drugs. It is possible that the use of once-a-week or injectable bisphosphonates will emerge as a better option in this situation.

Future perspectives include new trials with vitamin K, alendronate, and raloxifene, a selective estrogen receptor modulator. Raloxifene has been shown to prevent bone loss and decrease serum total cholesterol without stimulating reproductive tissues [29,30]. In a large multicentric randomized controlled trial involving postmenopausal osteoporotic women without liver disease, raloxifene use for 3 years led to an increase in lumbar spine bone mineral density and a reduction in the risk of vertebral fractures [31,32] without significant adverse effects. A small pilot study, in the authors' institution, involving 9 postmenopausal
women with PBC also demonstrated that lumbar spine bone mineral density increased with raloxifene (data not published). No hepatotoxicity was observed.

Treatment of osteoporosis must therefore be individualized. Based on the scarce amount of data currently available, it seems that calcium and vitamin D supplementation and exercise are the first choice of therapy in patients with PBC and osteoporosis. Bisphosphonates, vitamin K, and raloxifene may emerge as future validated options.

**Fat soluble vitamin deficiencies**

Fat-soluble vitamin deficiencies have been reported in PBC patients with variable prevalence. Data obtained from 180 patients previously enrolled in the UDCA trial at the Mayo Clinic revealed that the proportion of patients with vitamin A, D, E, or K deficiency was 33.5%, 13.2%, 1.9% and 7.8%, respectively [33]. A low serum albumin correlated with low serum levels of vitamin D. Similarly, advanced histologic stage, high Mayo risk score, and low total cholesterol levels were independently associated with vitamin A deficiency in a multivariate analysis. A Mayo risk score of greater than or equal to 5 had the highest sensitivity and specificity in identifying patients at risk for vitamin A deficiency. These findings are in agreement with previous studies where vitamin A and D deficiencies had been associated with more advanced disease and severe cholestasis [34]. It has been postulated that the low serum vitamin A levels result from a defective mobilization of this vitamin from the liver in patients with PBC, because their liver biopsy specimens exhibit the same amount of vitamin A as controls [35].

Patients with the above mentioned risk factors, namely Mayo risk of greater than or equal to 5, low cholesterol or albumin levels, and advanced disease stage, need to be screened for fat-soluble vitamin deficiencies.

**Treatment**

**Vitamin A**

For patients with visual symptoms secondary to vitamin A deficiency, namely nocturnal blindness or abnormal dark adaptation, supplementation can be done orally with 50,000 IU (15 mg) per day for 1 month or 25,000 to 50,000 IU three times a week for 6 months. These can be followed by a maintenance dose that should be determined according to serum retinol levels. It must be remembered that excess vitamin A is hepatotoxic.

**Vitamin D**

Vitamin D and calcium supplementation is suggested independent of a vitamin deficiency. For individuals older than 51 years of age, it is recommended 600 to 800 IU/day of vitamin D and 1200 to 1500 mg of calcium for prevention of osteoporosis. If a deficiency is present, 25,000 to 50,000 IU can be given orally 2 to 3 times per week.

**Vitamin E**
Patients with symptomatic vitamin E deficiency should be treated with 800 to 1200 mg of alpha-tocopherol per day. This rare deficiency would be clinically manifested as ataxia, ophthalmoplegia, myopathies, or pigmented retinopathy.

**Vitamin K**

In adults, vitamin K deficiency manifests as hemorrhage or, possibly, bone osteodystrophy. Although this diagnosis can be made directly, hypovitaminosis K is usually based on an abnormally elevated prothrombin time. The preferred treatment in chronic malabsorptive disorders is 5 mg/day orally.

**Hyperlipidemia**

Disturbances of lipid metabolism, with hyperlipidemia and xanthomathia formation, are part of the spectrum of clinical features associated with prolonged cholestasis. They are thought to be the result of abnormal activities of enzymes, such as lecithin cholesterol acyl transferase (LCAT) and hepatic lipase. In PBC, the specific lipoprotein abnormalities seem to be related to the stage of disease. Elevations of low density lipoproteins (LDL) and high density lipoproteins (HDL) are seen in patients with histologic stages 1 and 2, whereas marked elevation of LDL with a decrease in HDL are noted in patients with the more advanced histologic stages 3 and 4 [36]. In late disease, there is also appearance of lipoprotein X, a LDL particle rich in phospholipids and free cholesterol but low in triglycerides. The hyperlipidemia associated with PBC does not seem to lead to an increased risk of atherosclerosis, possibly because of a higher than normal concentration of lipoprotein A1 particles [37,38].

The management of hyperlipidemia in this population is an issue of concern. Many patients with PBC use cholestyramine for pruritus. However, a defined role for this drug in treating hypercholesterolemia has never been established. Clofibrate, a drug more frequently used for hypertriglyceridemia, was noted to cause paradoxical elevation of serum cholesterol in two small case series of patients with PBC [39,40]. UDCA has been observed to lower serum cholesterol [41–43], especially in those with the highest baseline levels. Regardless of such effects, many patients with PBC who are taking UDCA have persistent hyperlipidemia possibly requiring further therapy. Balan et al [43] demonstrated that the magnitude of improvement in serum cholesterol by UDCA is greatest in patients who have the highest baseline serum total cholesterol and in those with the highest baseline serum total bilirubin values.

The efficacy of bezafibrate, a fibric acid derivative used to treat hyperlipidemia, in improving serum markers of PBC has been assessed in small pilot studies [44–47], but the specific end-point of lipid abnormalities in PBC was never addressed by these investigators.

More recently, the use of simvastatin has been evaluated in 6 patients with early stage PBC and hypercholesterolemia, who were on long term UDCA treatment (10–15 mg/kg/day) [48]. All patients had a decrease in serum LDL levels (average 25%), whereas HDL remained largely unchanged after 2 months of therapy. Worsening of serum liver biochemistries was not observed. In fact, there was a statistically significant improvement of alkaline phosphatase and gamma-glutamyl transferase. The significance of this finding is unclear, as only six patients were analyzed, but it sets the precedent for future studies.
Summary

Osteoporosis is several times more common in patients with PBC compared with the general population.维持adequate intake of calcium and vitamin D is important for prevention of bone loss. The use of bisphosphonates or vitamin K to improve bone mineral density in osteopenic patients seems promising and needs to be further evaluated.

Patients with PBC may develop fat-soluble vitamin deficiencies, especially vitamins A and D; serum levels should be investigated in patients considered at risk with the aim of recommending appropriate replacement therapy.

Finally, hyperlipidemia in PBC does not seem to be associated with an increased risk of atherogenesis. New therapies in this patient population are currently under investigation.

References


