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Review Article

Osteoporosis in Patients with Primary Biliary Cholangitis

I. Nakhcha.[1], I. Ben el barhdadi.[1], G. ouariaghlia.[1], F.Z.Ajana.[1]

[1]Gastroenterology Department C, Ibn Sina Hospital, Rabat, Morocco

*Corresponding Author
I. Nakhcha

Abstract: Metabolic bone disease has been recognized as an important complication of chronic liver disease particularly in cholestatic disorders [primary biliary cholangitis (PBC) and primary sclerosing cholangitis] and after liver transplantation. It includes osteoporosis and more rarely osteomalacia, which is more frequent in severe malabsorption and advanced liver disease. The pathogenesis of this disorder is complex and is likely to be multifactorial. Regardless of the etiology of osteoporosis in PBC patients, they have an increased risk of spontaneous or low-trauma fracturing leading to significant patient morbidity, deterioration of quality of life, and even patient mortality. The development of bone densitometry has allowed assessment of bone mass and then contributed in estimating the fracture risk. The gold standard of bone mineral density measurement is currently the dual- energy X-ray absorptiometry. Recommendations formulated by the World Health Organization have reported the diagnostic ranges of osteoporosis based on the t-score: patient with osteoporosis has a t-score less than – 2.5 SD, osteopenia has a t-score between – 1.0 and – 2.5 SD and a normal individual has a t-score more than – 1.0 SD. The risk of fracture shows a correlation with bone mineral density but no fracture threshold was determined and the best site of characterizing the hip fracture risk is the measure of the bone mineral density of the proximal femur. The treatment of osteoporosis in patients with PBC is largely based on trials of patients with postmenopausal osteoporosis as there are a few and smaller studies of osteoporotic patients with PBC. Bisphosphonates seem to be effective in biliary disease and are more tolerated.

Keywords: osteoporosis, primary biliary cholangitis.

Pathogenesis

Mechanisms of osteoporosis in primary biliary cirrhosis (PBC) are still unclear and are poorly understood. Potential inciting factors that either directly or indirectly alter bone mass include insulin growth factor-1 (IGF-1) deficiency, hyperbilirubinemia, hypogonadism, and excess alcohol intake. In addition, subnormal vitamin D levels, vitamin D receptor genotype (Pares, A. *et al.,* 2005), osteoprotegerin (OPG) deficiency, and immunosuppressive therapy before and after transplantation were also evocated (Sambrook, P., & Cooper, C. 2006). IGF-1 seems to play a key role in the process of bone remodeling and maintenance of bone mass. Low levels of IGF-1 in patients with cirrhosis and advanced liver disease were related to reduced bone formation. However, no direct relationship between IGF-1 levels and osteoporosis has been established (Rouillard, S., & Lane, N.E. 2001; Lakatos, P. L. *et al.,* 2004). OPG secreted by osteoblasts is a member of the tumor necrosis factor receptor super family and has recently been found to regulate bone turnover. It inhibits osteoclast differentiation in vitro and in vivo but still the role of OPG in hepatic osteodystrophy and particularly in PBC is speculative (Moschen, A. R. *et al.*, 2005; Szalay, F. *et al.,* 2003). Recent studies in PBC show that the receptor activator of NF-kb (RANK) and the receptor activator of NF-kb ligand (RANKL) in addition to OPG have been shown to be involved in osteoclastic bone resorption (Moschen, A. R. *et al.*, 2005; Boyle, W.J. *et al.,* 2003). The exact role of RANK/RANKL in the pathogenesis of low bone turnover in this chronic liver disease remains unclear with conflicting findings on the levels of these proteins in serum. As known, unconjugated bilirubin inhibits osteoblast activity and function in vitro and in animal models. Nevertheless, no correlation between unconjugated, conjugated, and total bilirubin levels and bone mineral density (BMD) was found in some studies of patients undergoing liver transplantation. A recent study confirmed that elevated serum bilirubin alone is not a major contributory factor to hepatic osteodystrophy (Smith, D.L. *et al.*, 2006). Hypogonadism is an established risk factor of osteoporosis in PBC. Postmenopausal women presented

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a reduced trabecular bone volume in this cholestatic liver disease and more specifically patients with longer duration of the disease and decreased calcium absorption. Male patients with hypogonadism have decreased levels of estrogen, which are very important for maintenance of skeletal health in men (Rouillard, S., & Lane, N.E. 2001; Bell, H. *et al.*, 1995). Vitamin D deficiency is likely not to be implicated in the development of hepatic osteodystrophy (AGA Clinical Practice Committee. 2003; Diamond, T. *et al.*, 1989). Metabolism of vitamin D is normal in this hepatic disorder but calcium and vitamin D malabsorption can occur andcontribute to skeletal effects. Diamond *et al.*, (1989) compared the largest cohort of 107 patients with chronic liver disease (CLD) including primary cholestatic disorders with 40 age-matched controls, showing normal levels of vitamin D metabolites in the noncirrhotic patients. Cirrhotic patients showed a significant decrease in 25–hydoxy vitamin D and 1,25-dihydroxy vitamin D without histological features of osteomalacia. Hence, these findings confirmed that osteoblast dysfunction in CLD cannot be explained by abnormalities in vitamin D metabolites. In a recent study of PBC patients, vitamin D receptor genotype correlated with lumbar spine BMD with an allele dose effect. In this study, the risk of vertebral fractures increased from 2-3 folds with the presence of a t allele (Springer, J.E *et al.*, 2000). Corticosteroids are frequently used in patients with autoimmune hepatitis or even inflammatory disorders in PBC patients. Their role as a risk factor of osteoporosis in these patients was reported in some studies (AGA Clinical Practice Committee. 2003; Angulo, P. *et al.*, 2000; Angulo, P. *et al.*, 2000) but not in others (Leuschner, M. *et al.*, 1999). They are also used in combination with the other immunosuppressive therapy after liver transplantation. During the first 12 months of use of corticosteroids with doses exceeding 7.5 mg/day of prednisone, trabecular bone loss is accelerated. Corticosteroids increase osteoclast differentiation and activity by production of interleukins, specifically IL-1 and IL-6 and decrease osteoblast differentiation by suppressing differentiation, recruitment, and indirectly reducing the collagen synthesis. Consequently, corticosteroids are used with reduced dosage in addition to alternative immunosuppressive medication in all patients after liver transplantation to minimize the deleterious effect on bone metabolism. Prevalence of osteoporosis in primary biliary cirrhosis It has been shown that osteoporosis seemed to be more striking in patients with PBC than other patients with chronic liver disease with increased risk of fracture. The prevalence of osteoporosis in PBC patients as defined by the World Health Organization (World Health Organization Study Group.1994) is between 14.2 and 51.5%. The difference between studies is probably because of differences in patient selection, cirrhotic state, liver disease severity or hypogonadism.

PBC affects elderly women and who are naturally prone to osteoporosis. This bone complication can be the first manifestation of this cholestatic liver disease and then leading to screen the patients with PBC. In the largest controlled study of PBC to date (Eastell, R. *et al.*, 1991), lumbar z-score was reduced (mean z-score: – 0.66) and correlated significantly with a calculated risk score based on age, bilirubin level, prothrombin time, serum albumin level, and edema ($r = – 0.36$, $P < 0.0001$) and this result has been confirmed by other groups (Lindor, K.D. *et al.*, 1995). Menopausal status in patients with PBC is considered as an important risk factor for the development of osteoporosis. BMD is strongly affected by estrogen status; it is normal in premenopausal women but is most deficient in premature menopause (Bagur, A. *et al.*, 1998). For many years, the fact that menopausal patients with PBC are at higher risk of osteoporosis was considered as a controversial subject (AGA Clinical Practice Committee. 2003; Collier, J. 2007; Collier, J.D. 2002). However, in two recent studies the researchers confirmed a 4-fold increased risk of osteoporosis and a 2-fold increased risk of fractures in this group of patients compared with the age-matched controls. Guanˇabens *et al.*, (2005) in a study of 142 women with PBC have shown that the relative risk of osteoporosis was 3.83 (38% were osteoporotic versus 10% in the control group). Cirrhosis has been linked to increased risk of fracture by approximately 2-fold than noncirrhotic liver disease including PBC (Tsuneoka, K. *et al.*, 1996; Diamond, T. *et al.*, 1990), with a single exception (Olsson, R. *et al.*, 1994). Bone density in patients diagnosed recently, PBC before cirrhotic state is similar to healthy controls (Halmos, B. *et al.*, 2000). Among patients with cirrhosis, other variables such as severe clinical score (Child-Pugh), Mayo Risk Score, histological stage (Ludwig, Sheuer) and lower BMI showed progressive correlation with low BMD (Eastell, R. *et al.*, 1991; Lindor, K.D. *et al.*, 1995; Pereira, S.P. *et al.*, 1999; Crippin, J.S. *et al.*, 1994) with three exceptions (Bagur, A. *et al.*, 1998; Chen, C.C. *et al.*, 1996; Pietschmann, P. *et al.*, 1990). In a large cohort study of 930 patients with PBC compared with 9202 age and sexmatched controls (Solaymani-Dodaran, M. *et al.*, 2006), the absolute excess of fracture was 12.5 of 1000 individuals per year. PBC patients who are at the end stage of liver disease and in need of orthotopic liver transplantation have higher risk of osteoporosis and fractures (Guichelaar, M. *et al.*, 2007; Guichelaar, M.M.J. *et al.*, 2006). According to the Mayo Group, this risk has fallen over the last two decades. Patients (26%) with biliary disease (PBC; primary sclerosing cholangitis) listed for transplantation was osteoporotic between 1996 and 2000 versus 57% between 1985 and 1989. This result may be explained by the use of low-dose corticosteroids and better nutrition (Guichelaar, M.M.J. *et al.*, 2006). Liver transplantation As the rate of PBC patients who underwent orthotropic liver transplantation (OLT) increases, metabolic bone disease and particularly osteoporosis becomes a major cause of

morbidity (AGA Clinical Practice Committee. 2003; Cheung, A.M. 2001).The etiology is multifactorial: with the use of high-dose corticosteroids and other immunosuppressive therapy such as cyclosporine A and tacrolimus (FK506), immobility, and poor nutrition. All these factors contribute to the accelerated bone loss after the OLT. Boneloss follows typically a biphasic course after liver transplantation with the greatest decrease during the first 3-6 months and then spontaneous stabilization and even improvement of BMD during the ensuing 12 months and may continue for years (Guichelaar, M.M.J. *et al.,* 2006; Cheung, A.M. 2001). Early accelerated bone turnover is not only because of the well-known corticosteroids that affect the bone but also is attributed to immunosuppressive agents such as the calcinurin inhibitors. Their role in bone turnover after OLT is still controversial and because they are used in combination with corticosteroids the independent effects of these agents on bone metabolism is difficult to ascertain in humans. Fracture rates of 15–27% have been reported (Reeves, H.L. *et al.,* 1998; Ninkovic, M. *et al.,* 2000), but most of the fractures occur in the first year and less after 3 years of liver transplantation (Guichelaar, M. *et al.,* 2007). BMD decrease after OLT is insufficient to account for the high-early fracture risk. Nevertheless, pretransplant vertebral fracture and low BMD before OLT are more predictive for posttransplant fracture (Navasa, M. *et al.,* 1994; Rust, C. *et al.,* 2000). There is no consensus concerning the effects of type of liver disease before transplantation, sex and menopausal status on the risk of post-transplant fractures.

When To Measure Bone Mineral Density in Primary Biliary Cholangitis

Patients? A BMD measurement can be recommended to all patients with hepatic disorders. However, this would lead to a considerable number of unnecessary tests. Then, a BMD measurement should be interpreted in combination with the other risk factors of fracture. The American Gastroenterological Association guidelines (AGA Clinical Practice Committee. 2003) suggest that BMD should be considered in all patients with PBC at diagnosis, whereas other recommendations (Collier, J.D. 2002) limit BMD to patients with bilirubin greater than three times the upper limit of the normal individuals. Indeed, osteoporosis can be the first clinical manifestation in these patients and then leading to screen for antimitochondrial antibody in osteoporotic patients with both an elevated l-glutamyl transferase and serum alkaline phosphatase level (Heathcote, J. 1996). There is a clear consensus that BMD should be assessed in all patients with cirrhosis, those receiving long-term corticosteroids (> 3 months) or those who have experienced a fragility fracture and before liver transplantation. A shorter follow-up interval (approximately 1 year) is recommended for patients recently initiating highdose corticosteroid therapy and current recommendations are that treatment for osteoporosis should be started in patients older than 35 years with chronic liver disease including PBC patients and who are likely in need of high doses of corticosteroids (7.5 mg/day) for more than 3 months. In younger patients, treatment is indicated only if BMD shows a t-score of less than – 2.5 SD (Sambrook, P., & Cooper, C. 2006; Leuschner, M. *et al.,* 1999; Eastell, R. *et al.,* 1991; Collier, J.D. 2002). There is no need to use serum and urinary bone turnover markers to assess the risk for fracture, indicate a BMD measurement, or to evaluate the response to treatment.

Treatment of Osteoporosis In Primary Biliary Cholangitis

Therapy of osteoporosis in patients with PBC is based on studies and trials consisting of patients with postmenopausal osteoporosis. These small and few studies were as outcome measurements to improve BMD rather than more clinically important fracture rates (Guanabens, N. *et al.,* 20003).

Nonpharmacological measures should be taken into account in addition to pharmacological therapies for the management of osteoporosis in patients with PBC.

General Measures

Many reversible factors that affect bone loss should be eliminated such as alcohol intake, tobacco, caffeine ingestion, and corticosteroids dosages. Regular weight-bearing exercises and changes of life style are integral to maintain both muscle and bone mass.

Vitamin D and Calcium

Earlier studies did not show any beneficial effects of using calcium alone in reversing osteoporosis in patients with chronic liver disease. However, in patients with PBC, two studies (Camisasca, M. *et al.,* 1994; Rosen, H. 1995) showed calcium-improved bone mass in the patients who were vitamin D deficient. Patients with hepatic osteodystrophy including cholestatic liver disease, high-dose vitamin D or 25-hydroxy vitamin D, increased bone mass (Reed, J.S. *et al.,* 1980; Mobarhan, S.A. *et al.,* 1984) and reversed some of the osteomalacic changes of bone mass but still further studies of calcium and vitamin D supplement are warranted in patients with PBC. All patients should receive 1000–1200 mg of calcium daily and at least 400–800 IU of vitamin D daily. However, patients with malabsorption required higher doses of calcium and vitamin D (AGA Clinical Practice Committee. 2003).

Antiresorptive Therapies

Bisphosphonates: Risedronate, alendronate, etidronate, and ibandronate are bisphosphonates, which are used for treating postmenopausal osteoporosis. They are the main therapy for treating PBC patients with osteoporosis and are usually given with calcium and vitamin D. These drugs were studied in a small number of patients with CLD and especially patients with PBC

(Pares, A., & Guanabens, N. 2006). In PBC patients, alendronate increases bone mass; in a comparison study, the improvement of BMD was more marked in the alendronate group compared with etidronate given a 2-year period (Zein, C.O. *et al.,* 2005). In a further study, alendronate is better tolerated once weekly than once daily in PBC patients with osteoporosis. The effect of bisphosphonates (alendronate) was not able to show an effect on fracture rate (Zein, C.O. *et al.,* 2005). After liver transplantation, PBC patients are usuall treated with bisphosphonates, which have been studied in seven studies in an attempt to reduce the high fracture rate observed in these patients. Intravenous pamidronate have shown no effect on fracture risk in five studies. With concern to BMD, three studies showed an increase in the bone mass but it was mainly limited to trabecular bone (lumbar spine). Oral alendronate was only studied in an uncontrolled trial after liver transplantation. Zoledronic acid given within 7 days of transplantation and then 1, 3, 6, and 9 months reduced bone loss in the first 3 months. The lack of these results is the small size of the studies. Hence, a real effect on the fracture rate has not been shown.

Hormone Replacement Therapy

Hormone replacement therapy (HRT) has become the second-line therapy after bisphosphonates because of the risk of thromboembolic disease and gynecological malignancy. It may protect bones in older women with hepatic osteodystrophy. This drug was studied in only two small-randomized controlled trials of patients with PBC. Transdermal estrogen has shown to improve BMD after 2 years. However, no effect on fracture rate has been shown in the first trial (Pereira, S.P. *et al.,* 2004). In the second one, hormone replacement therapy reduced bone loss at the femoral neck of 31 patients (Boone, R.H. *et al.,* 2006). In another study of 18 patients with PBC, only one patient had to stop this therapy because of a hepatic toxicity (rising of aminotransferases) (Ormarsdottir, S. *et al.,* 2004).

Raloxifene

This is a selective estrogen receptor modulator that has less effect on bone turnover than bisphosphonates. There are a few studies on its effect on bone mass in PBC patients. One pilot study has suggested that it can prevent bone loss in PBC patients after 1 year (Levy, C. *et al.,* 2005). It is approved by the Food and Drug Administration for the prevention and treatment of osteoporosis in postmenopausal women (level D evidence in hepatic disease) (AGA Clinical Practice Committee. 2003). The participation of a bone disease specialist in the choice of raloxifene in patients with PBC is recommended.

Testosterone

This therapy is used in hypogonadal men patients with CLD (PBC) with the aim of stabilising hormone levels. Transdermal testosterone is preferred to prevent the exposure of the liver to surges in levels seen with oral or depot preparations. Other treatments Ranelate of strontium reduces vertebral and nonvertebral fracture in postmenopausal osteoporosis. To date, there have been no studies on its effect in PBC patients with osteoporosis. Its use can be an alternative in patients intolerant of bisphosphonates. Recombinant parathyroid hormone is reserved to patients intolerant of bisphosphonates to prevent fragility fractures. Its mechanism is stimulating bone formation (Wariaghli, G. *et al.,* 2010)

CONCLUSION

Osteoporosis still is the most clinically important form of bone disorders in PBC. Multiple factors contribute to the development of this bone disorder. With the increasing prevalence of patients with known PBC, there will be large numbers of patients with potential bone disease. Therefore, it is important to identify such individuals before they develop fractures. The widespread accessibility to DXA testing has led to an increased number of hepatology patients with diagnosis of osteopenia and osteoporosis. Furthermore, it is needed to define who among these disease groups are at greater risk for fracture. A lot of clinical risk factors such as corticosteroid use and hypogonadism should be taken into account when risk is assessed. The best course of management for these patients is to review the individual risk factors for osteoporosis, and prescribe age and disease-specific therapies. The evidence for treatment of osteoporosis in PBC patients is still based on large studies of postmenopausal women because of the few or small size studies of PBC. Bisphosphonates have shown an improvement in bone mass in this chronic hepatic disease and after liver transplantation and are more tolerated than other therapies but still a beneficial effect on fracture rate has not been shown.

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