THERAPEUTIC ALTERNATIVES IN OSTEOPOROSIS AFTER LIVER TRANSPLANT

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Abstract. Hepatic osteodistrophy, one of the consequences of the continuous deterioration of liver function and chronic cholestasis, represents an important morbidity factor for patients waiting for liver transplant. Bone mineral density continues to decrease after transplant explaining the high incidence of fractures. Pretransplant osteodistrophy screening is mandatory and prophylaxis and treatment should be started as soon as possible to prevent further deterioration of BMD after transplant. Due to the specific problems encountered in liver cirrhosis, therapeutic alternatives must be carefully selected with a special regard to risk-benefit ratio.

Keywords: liver, transplant, osteodistrophy, treatment, vitamin D, biphosphonates

Introduction

Hepatic osteodistrophy is one of the less discussed complication of chronic liver diseases, though it represents an important morbidity factor for these patients. The continuous deterioration of the liver function and chronic cholestasis are followed by important alterations of calcium, vitamins D and K metabolism. Some of the essential factors for bone metabolism are also impaired in liver failure, for example insulin-like growth factor (IGF-1) and IGF binding proteins, fibronectin [1], leading to a decrease of bone mineral density, especially in patients with advanced liver disease, waiting for transplant. In these patients the prevalence of osteodistrophy (mainly osteoporosis, more frequent than osteomalacia) is high, varying between 37-53% [2]. During the first 6 months after liver transplant a supplementary decrease of DMO occurs, due to the unfavourable effects of corticotherapy, immunosuppressants, malnutrition and prolonged immobilisation. These patients have also a high incidence of postransplant fractures, between 17%-65% [3,4].

Taking into account the above-mentioned problems, it is necessary to perform a screening before transplant, including BMD measurement, using DEXA (dual energy X ray absorbiometry) and to identify the possible supplementary and potentially correctable risk factors for secondary osteoporosis [5,6]. Besides comorbidities, BMD can be altered also by medication, for example chronic use of diuretics and anticoagulants [7], and after transplant by large doses of corticosteroids and immunosuppressants.

In 2002, J D Collier and colab developed guidelines for the treatment of osteoporosis associated with chronic liver diseases, but there are no special issues regarding liver transplant recipients [8]. Therapeutic measures addressed to these patients were based on the above-mentioned guide and on the American College Of Rheumatology recommendations [9]. In Romania, post-transplant osteodistrophy has not been studied yet, though there are few studies regarding this complication in patients with advanced liver disease [10,11].

It is necessary to inform transplanted patients about the benefits of simple lifestyle measures: sun exposure, physical exercise, nutrition (proteins, diary, milk) [8]. Drug prophylaxis includes supplementation of calcium and vitamin D and metabolites of vitamin D, biphosphonates and calcitonine [8].

Vitamin D and its metabolites increase the intestinal absorption of calcium partially antagonizing the effects of corticosteroids and indirectly inhibiting the release of PTH. Vitamin D has a controversial efficiency in preventing the post transplant bone mineral density decrease [12]. Metabolites of vitamin D (calcidiol- 25-hydroxyvitamin D,
alfacalcifol-1α-hydroxyvitamin D and calcitriol-1,25-dihydroxyvitamin D) seem to be more efficient, but with the risk of increasing calcemia and calciuria which have to be monitored during treatment [13]. Calcitriol has a supplementary advantage: it has also an immunonmodulatory effect, allowing a decrease of immunosuppressant doses [14, 15]. Collier and colab [8] recommend daily supplements of 1-1.5 g calcium and 800 iu vitamin D3 in patients with low levels of vitamin D (< 20–30 ng/ml). In patients with established osteoporosis, calcium and vitamin D administered alone are not capable to improve BMD [16, 17]. This is not surprising taking into consideration the fact that pathogenesis of hepatic osteodistrophy is complex, involving many different factors, besides abnormalities in calcium-vitamin D metabolism [18].

**Estrogen replacement therapy** is used with caution in patients with chronic liver diseases, due to the risk of influencing cell proliferation and releasing of oxygen free radicals, which have carcinogenic effects [19], but there are no sufficient data to contraindicate estrogens in these patients and in addition, some studies showing good results of estrogen treatment in women with primary biliary cirrhosis and autoimmune hepatitis without an aggravation of cholestasis [20, 21]. A study referring to a small group of postmenopausal liver transplanted women, who were treated with transdermal estrogen, demonstrated a 4% increase of lumbar spine and femoral BMD, without thrombotic events [22].

In hypogonadal men with hepatic osteodistrophy, testosterone supplement may improve BMD with the risk of hepatoma occurrence [20].

**Raloxifene**, a selective modulator of estrogenic receptor [23], is an alternative to estrogens. Due to the fact that this drug is metabolized primarily in the liver, concentration of Raloxifene was 2.5 higher in cirrhotic patients than in healthy volunteers [23], suggesting the importance of using lower doses and of monitoring adverse effects in these patients. In a study which included patients with PBC, raloxifene appears safe and of benefit in improving BMD [16, 17]. A better understanding of the benefits of antiresorptive therapy in post transplant osteodistrophy, can be made through meta-analysis, which indicate favorable effects of bisphosphonates associated with an active metabolite of vitamin D and calcium [32], with an additionally decrease of fractures incidence in the first year after liver transplant [33].

**Strontium ranelat** is an antiresorptive drug with an stimulant effect on osteoblast, inducing bone formation [34]. Its efficiency in liver diseases is not yet communicated, though it may be an alternative due to the preponderant renal excretion and better digestive tolerability.

**Calcitonine** binds itself on membrane receptors of osteoclasts, decreasing the population of osteoclasts and their secretory capacity, thus inhibiting bone resorption. This drug is efficient in preventing corticotherapy induced osteoporosis, and seems to have also a protective effect against bone demineralisation caused by cyclosporine. It has limited indications: in patients who cannot tolerate hormonal substitutive treatment and bisphosphonats, or if BMD show no amelioration during treatment with the above mentioned drugs [35,36,37], but a study of efficacy demonstrated no benefit on prevention of bone loss and no significant reduction in fracture incidence in the first 6 months after liver transplant [38].

**Teriparatide** (recombinant hormone PTH1-34) is the active fragment of endogenous PTH (an important activator of osteogenesis), which is recently used in osteoporosis treatment. There are no data...
regarding teriparatide in hepatic osteodystrophy, but a recent study on patients with kidney transplant showed no amelioration of bone turn-over or bone mineralization in these patients [39].

Conclusions

Osteoporosis has a higher prevalence in patients waiting for liver transplant, due to the continuous deterioration of liver function and association of other risk factors, with unfavorable consequences on bone mineral density. BMD and supplementary risk factors for osteodystrophy must be evaluated before transplant, and treatment must be initiated as soon as possible, taking into account the trend of post transplant BMD decrease. Most of the studies recommend supplements of vitamin D metabolites, calcium in association with intravenous bisphosphonates, but the risk and benefits are difficult to assess due to the small number of cases.

References


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