Osteoporosis in primary biliary cirrhosis of the liver

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Abstract

Osteoporosis is a metabolic bone disease associated with a reduction in bone mass and deterioration of bone architecture, leading to increased fragility and subsequent low-trauma fractures in the vertebral column, hip, forearm and other bones. In literature, metabolic bone diseases such as osteoporosis and osteomalacia have been recognised as a complication of chronic liver disease, although the mechanisms of this association remain unclear. An increasing body of research data indicates a strong relationship between osteoporosis and primary biliary cirrhosis (PBC), which mainly results from early diagnosis of the disease, usually when it is still asymptomatic. The incidence of osteoporosis in PBC ranges from 20% to 44% and increases with the progression of the disease. Similarly, the incidence of bone fractures is high in this group of patients (10–20%). In this article, current knowledge on risk factors, pathogenesis, diagnosis and treatment of osteoporosis in PBC is reviewed.

Primary biliary cirrhosis

Primary biliary cirrhosis (PBC) is a chronic autoimmune liver disease in which the inflammatory process occurs in the intrahepatic bile ducts. Its incidence is estimated to be 5 : 100,000 persons/year, while the prevalence is 50–250 per million [1]. Primary biliary cirrhosis represents approximately 1% of all cases of cirrhosis; it occurs only in adults, mostly in women and with a peak in the 5th and 6th decades of life. Primary biliary cirrhosis is relatively often found among family members, which is commonly associated with the presence of HLA-DR3, HLA-DR8 and HLA-DR52a antigens. The number of cases of primary biliary cirrhosis is gradually increasing, and nowadays it is usually diagnosed in earlier stages, before fully developed cirrhosis and liver failure. Although the progression of the disease can be significantly inhibited by increasing recognition of the related problems of reduced bone mineral density (BMD) and low-trauma osteoporotic fractures.

Hepatic osteodystrophy

The term ‘hepatic osteodystrophy’ was first introduced in 1960 and refers to a metabolic bone disease (MBD) in patients with chronic liver diseases. It used to be believed that MBD occurs only in patients with chronic cholestasis, but it is now known that MBD can also occur in other chronic liver diseases, with a severity dependent on the duration and severity of the liver disease. Hepatic osteodystrophy comprises two types of change in the bone: 1) osteoporosis, which is similar to primary osteoporosis but affects the trabecular bone more often than the cortical bone, and 2) osteomalacia, which predominates in advanced liver disease, particularly those caused by malnutrition [2]. In advanced stages of PBC, both these conditions may overlap, although osteomalacia (“soft” bone) is difficult to diagnose (only through invasive bone biopsy). There are also discrepancies in the assessment of the importance of osteomalacia and osteoporosis as factors leading to hepatic osteodystrophy [2].
Osteoporosis

Osteoporosis is a systemic skeletal disease associated with low bone mineral density and impaired spatial structure which increases the risk of low-trauma fractures, especially in the vertebral column, proximal femur and forearm bones. As defined by the World Health Organisation [3], osteoporosis is diagnosed on the basis of a densitometry test result in which bone mineral density (BMD) is lower by at least 2.5 standard deviations (SD) from the peak bone density of healthy young subjects (T-score). The term osteopaenia refers to persons with bone mineral density (BMD) between –1 SD and –2.5 SD of the T-score.

The commonly recognised risk factors for osteoporosis in the general population include age, female sex, previous fractures, treatment with steroids, smoking and alcohol abuse, low physical activity, low intake of vitamin D and low body weight. For example, the average risk of bone fracture in a 50-year-old Caucasian woman is about 40% compared to only 13% in men of the same age. In addition, a fracture of the femoral epiphysis is associated with a 20% risk of death within 6 months mainly due to pneumonia, venous thrombosis and pulmonary embolism. Low-trauma fractures are the most serious consequence of osteoporosis; regardless of the cause of osteoporosis, vertebral fractures in the lower thoracic and lumbar spine are the most frequent [4]. The systematic increase in the incidence of osteoporosis in the world is associated not only with longer human life, but also with a sedentary lifestyle and low-calcium diet.

Osteoporosis in primary biliary cirrhosis

Osteoporosis is a disease that often accompanies PBC. Its prevalence in recent years has increased, which is mainly associated with the increasingly early diagnosis of this liver disease. In cross-sectional studies on patients with PBC, osteoporosis incidence has been diagnosed with densitometry ranges from 20% to 44% (Table I) and increases with the progress of the disease [10, 12]. It is estimated that in the advanced stages of PBC, only about 20% of patients may have normal BMD [11]. However, precise determination of the prevalence of osteoporosis/osteopaenia is difficult because the aforementioned studies evaluate populations differently in terms of gender, race, age or severity of disease, as well as using different diagnostic criteria for the diagnosis of osteoporosis (T-score or z-score). There are also discrepancies in the literature as to whether osteoporosis occurs in patients with PBC more frequently than in the general population. Guañabens et al. observed a greater incidence of osteoporosis in patients with PBC in large groups tested in two studies [10, 13], similar to Mounach et al. [14], but contrary to Newton et al., who observed no such relationship [8]. Despite these discrepancies, as well as methodological limitations, studies performed to date suggest that patients with PBC display abnormal densitometry results more often than in the general population. The incidence of bone fractures is equally high in this group of patients (10–20%), although the severity of the disease seems to have no significant effect there [12, 15].

Just as in the general population, risk factors for osteoporosis in PBC include age, female gender, smoking, excessive alcohol consumption, underweight (body mass index in adulthood < 19.0 kg/m²), early menopause (before 45 years of age), positive family history and treatment with steroids. In addition, patients with PBC often have low physical activity and are more likely to fall [9], and also generally have lower levels of vitamin D than healthy people [16, 17]. Some studies indicate that in contrast to the general population, women with PBC are less predisposed to osteoporosis by menopause than by increased cholestasis and the severity of histological changes in the liver [10].

The pathogenesis of osteoporosis in PBC is suggested to include the influence of both the severity of bone resorption and a slowdown in internal modelling. Bone remodelling is largely controlled by the system: osteoprotegerin (OPG) – receptor activator of nuclear factor NF-κB – ligand (RANKL), the role of which has yet to be explained in disorders of bone metabolism in PBC. The RANKL is a transmembrane ligand present on stromal cells and osteoblasts; it binds to RANK, forming a complex that strongly stimulates osteoclasts. Osteoprotegerin, produced for example in the liver, is capable of binding to RANKL as its soluble receptor. This combination prevents the binding of RANKL to RANK, which

| Autor [ref.] | Number of patients | Average age [years] | Incidence of osteoporosis (%) |
|-------------|--------------------|---------------------|-------------------------------|
| Springer [5] | 72                 | 55 (34–81)          | 24                            |
| Parés [6]    | 61                 | 54 ±1.1             | 21                            |
| Menon [7]    | 176                | 53 (29–72)          | 20                            |
| Newton [8]   | 272                | 62 ±11              | 31                            |
| Solerio [9]  | 133                | 53 (21–81)          | 35                            |
| Guañabens [10]| 142               | 54 ±0.8             | 31                            |
| Guichelaar [11]| 156              | 53 ±0.7             | 44                            |
| Guañabens [12]| 185               | 56 (28–79)          | 32                            |
| Average      | 149                | 55                  | 30                            |
slows down the pathway of osteoclast maturation and consequently inhibits osteoclastic bone resorption.

In studies on healthy individuals OPG expression increases with age, while other dependencies are less
distinct. Patients with osteoporosis are usually observed to have increased OPG, although its low levels have also
been found in postmenopausal women with vertebral fractures [16]. Other studies report an increased risk of
fractures of the forearm and hip in women with high concentrations of OPG [10]. Some researchers even believe
that low RANKL and high OPG levels are good markers of increased risk of all low-trauma fractures [14].

In a few studies, patients with PBC also had elevated levels of OPG and reduced RANKL [18, 19]. It is not
known whether that is a primary phenomenon, or rather a consequence of increased bone resorption in the
early stages of PBC. It is possible that it is not PBC-specific and can only be regarded as a marker of chronic
inflammation [19]. Furthermore, in PBC no link has been found between increased levels of OPG and low RANKL
and the risk of osteoporosis or changes in markers of bone remodelling activity [18].

Most studies indicate that the development of osteoporosis in PBC is less associated with a slow down in
bone formation than with the severity of bone resorption [13, 20]. The impaired function of osteoblasts may
be the effect of cirrhosis-related (i.e. not solely PBC-related) reduction in the production of certain growth fac-
tors (especially IGF-1), increased synthesis of oncofoetal fibronectin, or the direct toxic effect of unconjugated
bilirubin and lithocholic acid on precursors and osteo-
blasts [4, 21]. Slowing down of the remodelling process
due to impaired bone formation is illustrated in a few
studies on PBC that show low levels of osteocalcin [22],
a non-collagen protein which is a biochemical marker
of osteoclast function. On the other hand, some histo-
morphometric studies suggest that PBC does not impair
bone formation, but, on the contrary, it increases the
rate of remodelling and bone resorption [23].

Other factors predisposing to bone metabolism
disorders in PBC include malnutrition and vitamin defi-
ciences, especially vitamins D and K. Reduced hepatic
synthesis of vitamin D binding proteins, reduced activity of 25-hydroxylase activity and reduced concentra-
tions of the vitamin D receptor, inducing peripheral resistance to the hormone, may cause secondary hyperparathy-
roidism, which increases bone resorption and deepens the deficit of calcium ions. In turn, vitamin K deficiency,
frequently observed in cholestasis, impairs osteoclast
maturation and function. This vitamin inhibits the ex-
pression of RANKL [4] and is necessary for the synthe-
sis of osteocalcin. Supplementation with vitamin K pre-
vents the loss of bone in PBC [4].

The importance of genetic factors in disorders of
bone metabolism in PBC remains uncertain. Springer
et al [14] evaluated the effect of BsmI polymorphism
of the vitamin D receptor gene on BMD in patients with
PBC. They found only a weak negative correlation with
BMD of the lumbar spine, and those results have not
yet been confirmed. Other studies in this group of pa-
tients tried to establish a relationship between BMD
and polymorphism of the insulin growth factor IGF-1
gene and collagen type I gene. However, the results of
those studies are inconclusive [15].

Osteoporosis and adipokines

Body weight is an important predictor of BMD at dif-
erent skeletal sites, influencing bone density, for exam-
ple by mechanical stress (concerning especially cortical
bone elements), as well as via hormones and adipose
tissue cytokines. Adipokines not only modulate the pro-
cesses related to diet, energy expenditure and glucose
metabolism, insulin sensitivity, free fatty acid oxidation,
or reproductive function and regulation of the cardio-
vascular system, but they also affect bone metabolism.
The best known is the effect of leptin on bone mass,
which occurs via a specialised population of hypotha-
lamic neurons as well as by receptors of β2-adrenergic
osteoblasts. Leptin inhibits osteoclastogenesis by reduc-
ing the synthesis of RANK and RANKL, and increasing
levels of OPG. In one study, leptin levels were signific-
antly lower in women with PBC than in healthy sub-
jects, with no significant correlation found between the
risk of osteoporosis and the concentration of leptin, its
soluble receptor, liver function test results or the histo-
logical severity of liver disease in women with PBC [24].
Similarly reduced leptin levels in the serum of women
with PBC and malnutrition were reported by Ben-Ari
et al [25], although the leptin levels did not correlate
with the severity of the liver disease. García-Suárez
et al. also reported decreased levels of leptin in PBC,
with the degree of reduction significantly associated
with the severity of histological changes in the liver [26].
In contrast to these reports, one study showed higher
levels of leptin in patients with PBC (class A Child-Pugh
score) than in healthy subjects [27]. In view of these
conflicting reports, it remains difficult to assess the
significance of changes in leptin concentration for the
pathogenesis of osteoporosis in PBC.

Adiponectin is another adipokine with a potential
effect on bone metabolism; it has an anti-inflammatory
effect, enhances insulin sensitivity and increases fatty
acid oxidation. In bone, adiponectin stimulates the pro-
duction of RANKL and inhibits OPG expression in os-
teoblasts, thereby indirectly promoting osteoclastogen-
esis. It is postulated that in healthy persons adiponectin
influences bone through three primary mechanisms: 1) positive, para/autocrine, 2) negative, direct endocrine and 3) positive, by enhancing the anabolic effect of insulin on bone tissue. The concentration of circulating adiponectin is negatively correlated with BMD and seems to be an independent predictor of low BMD [28–31]. The impact of adiponectin has not yet been assessed with regard to the risk of osteoporosis in PBC. In the only experiment on a group of patients, significantly elevated levels of the hormone were demonstrated regardless of age and body weight [32]. Given the negative relationship between adiponectin and BMD in healthy people, it can be expected that the share of adipokines may be significant in the pathogenesis of osteoporosis in PBC. There is a clear need for further research in this area.

Diagnosis of osteoporosis in primary biliary cirrhosis

The primary diagnostic tool for early detection of osteoporosis in PBC is dual X-ray absorptiometry (DXA) of the lumbar spine and proximal femur. In accordance with the recommendations of the European Association for the Study of the Liver, tests should be performed at diagnosis, and then at 1-year intervals [33]. Indications for DXA in PBC are summarised in Table II. Indications of therapeutic intervention (established for the general population) is too high in this group of patients. Given the much higher risk of osteoporosis in PBC than in healthy people, it can be expected that the share of adipokines may be significant in the pathogenesis of osteoporosis in PBC. There is a clear need for further research in this area.

Treatment

Treatment of osteoporosis in PBC poses two major difficulties. Firstly, for several years patients have been qualified for the treatment of primary osteoporosis according to a FRAX calculation of absolute 10-year risk of bone fracture (http://www.shef.ac.uk/FRAX/tool.jsp). In addition to the anthropometric and DXA test results (which are not absolutely required), FRAX computes information in which only one element is associated with PBC (questions about diseases predisposing to secondary osteoporosis, including chronic liver diseases). The usefulness of FRAX in PBC has not yet been evaluated. However, regardless of the result of the FRAX calculations, it seems that the use of an absolute risk of fracture > 20% as a threshold for the implementation of therapeutic intervention (established for the general population) is too high in this group of patients. Given the much higher risk of osteoporosis in PBC than the risk of primary and secondary osteoporosis not accompanied by PBC, it seems more reasonable to perform individual assessment of patients based on the age of onset, duration and severity of a disease, previous treatment with steroids, severity of cholestasis and qualification for a liver transplant. In practice, this means that in PBC diagnosis based on DXA results, osteoporosis therapy should be initiated at an early stage, i.e. in most patients with BMD between −1 SD and −2.5 SD, irrespective of the measurement site. In addition, studies show that the occurrence of fragility fractures is a risk factor for subsequent bone fractures, which that is independent of BMD. This means that after a fracture in the vertebral column, proximal epiphysis of the femoral neck or forearm loco typico fractures, even with an appropriate DXA test result, the patient should be subject to pharmacological treatment of osteoporosis.

Secondly, there is no specific method of treating osteoporosis in PBC, and therefore it is carried out in accordance with general rules. As far as possible, all patients should modify their lifestyle and eating habits; increase physical activity, withdraw stimulants and alcohol, avoid situations with a risk of falls, and increase the supply of calcium in the diet. Unless there are specific contraindications, most patients should introduce calcium and vitamin D supplementation so that the daily intake of calcium (including calcium contained in the diet) is 1000–1500 mg and vitamin D is 400–800 IU per day, preferably monitoring serum concentrations in order to achieve a target value > 30 ng/ml.

To date there have been no well-documented results of clinical trials evaluating fracture-risk efficacy and safety of pharmacological treatments of osteoporosis in PBC. The most frequent treatment includes bisphosphonates, administered orally or intravenously [33–35]. In this group of drugs, the most frequently analysed etidronate and alendronate in several months of therapy. Alendronate (at 70 mg/week) significantly improves bone mineral density after 1 year of use, with minimal side effects [4]. There is no data on the effect of zoledronic or ibandronic acid on osteoporosis in PBC. In the only (and pilot) study on raloxifene in PBC patients by Levy et al. [36], 9 patients who were given raloxifene exhibited a slight increase in BMD in the lumbar spine. Anabolic therapy with strontium ranelate and recombinant human parahormone (PTH 1-34) has not yet been used in PBC, although preliminary results of animal studies are promising [37]. Similarly, denosumab – IgG2 monoclonal antibody directed against RANKL –

Table II. Indications for densitometric examination in PBC

| At the time of diagnosis of PBC |
|--------------------------------|
| Rapid build-up of cholestasis  |
| Progressive malnutrition       |
| A history of low trauma fracture|
| Before liver transplantation   |
| A history of steroid treatment |
| The presence of other risk factors for osteoporosis |
has not yet been used in PBC. Denosumab, similarly to natural immunoglobulin, consists exclusively of amino acids and carbohydrates, and so is not eliminated from the body via the hepatic pathway. Furthermore, because of convenience in drug administration (subcutaneous injection every 6 months), denosumab may be an attractive alternative to bisphosphonate therapy in the prevention and treatment of osteoporosis in PBC [38].

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