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A Review on the Diagnosis and Treatment of Osteoporosis in Primary Biliary Cholangitis

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Abstract: Osteoporosis (OP) is a common extrahepatic manifestation of primary biliary cholangitis (PBC), with a high incidence rate and damage, which seriously affects patients' long-term prognosis. Early diagnosis and intervention are crucial for improving the prognosis of PBC patients. This article reviews the OP screening methods, treatment indications, and clinical treatment for PBC patients based on relevant domestic and foreign literature.

Keywords: Primary biliary cholangitis; Osteoporosis; Screening; Diagnosis; Treatment

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1. Introduction

Primary biliary cholangitis (PBC) is a common disease in clinics, with osteoporosis (OP) as an important extrahepatic manifestation of PBC, affecting patients' physical and mental health and long-term prognosis [1,2]. As the incidence of PBC increases, so does the prevalence of OP [2,3], and early diagnosis and intervention are essential to improve the prognosis of PBC patients [4]. This article reviews the screening methods and clinical treatment of OP in patients with PBC, aiming at early detection, diagnosis, and intervention to improve their prognosis.

2. Prevalence of OP in patients with PBC

Previous studies have shown that the prevalence of OP in patients with PBC is 20% to 52% [5]. Fan *et al.* conducted a meta-analysis of eight articles on 1,643 patients with PBC and 10,921 controls and showed that the relative risk of OP in patients with PBC was 2.79 (95% CI 1.26 to 6.16) [6]. Data show that OP can occur in all stages of PBC, and the abnormal rate of bone mineral density (BMD) in patients with advanced PBC is as high as 80.0% [3,7]. OP is directly associated with brittle fractures, which have been shown to occur in 22% to 23% of patients with advanced PBC [8]. As a result, the literature [3,8] clearly states that all patients with PBC, including those with first visit, should be routinely screened and assessed for OP and fracture risk, and timely anti-OP intervention should be given.

3. OP risk assessment in PBC patients

3.1. OP risk screening tools

The current clinical tools for screening OP risk include the One-Minute Osteoporosis Risk Test and the Osteoporosis Self-Assessment Tool for Asians (OSTA).

The One-Minute Osteoporosis Risk Test is a rapid screening tool for OP risk developed by the International Osteoporosis Foundation (IOF) and is currently recognized as a common OP screening tool in clinical settings [7,9,10]. The method is simple, rapid, widely used, and has high accuracy in predicting OP risk. The disadvantage is that this test can only be used to screen for OP risk and not to diagnose OP.

OSTA is a commonly used screening tool for OP in Asians and can also be used for the simple assessment of fragile fractures in patients with PBC [11]. OSTA index = (body mass in kg – age in years) × 0.2. When the OSTA index is between -1 and -4, indicating a risk of OP, it is necessary to enhance BMD testing to confirm the diagnosis of OP. When high-risk patients have an OSTA index of less than -4, further testing with the fracture risk assessment tool (FRAX) and BMD is not required, and they can be treated directly with anti-OP therapy [12]. OSTA is simpler and more practical than the One-Minute Osteoporosis Risk Test [12,13].

3.2. Risk assessment of PBC

The risk of brittle fractures, also known as OP fractures, can be assessed using FRAX. The tool, first published in 2008 by academics such as Kanis of the University of Sheffield, UK [14], is now included in more than 80 global guidelines covering more than 80% of the world's population; it has been recommended by the World Health Organization (WHO) as a predictive tool for assessing the risk of OP fractures in patients over the next 10 years, the appropriate population is those aged 40 to 90 years who are at risk for OP fractures but do not have fractures [15,16]. When FRAX predicted ≥ 3% probability of hip fracture or ≥ 20% probability of OP fracture in any major bone, it is defined as patients at high risk of OP fracture [17]. When FRAX assessment thresholds are reached in patients at high risk of fracture, anti-OP therapy can be administered without the need for BMD testing [15,17]. Chandrana *et al.* showed good concordance between the OSTA and FRAX methods for assessing OP in their study involving 1,056 postmenopausal women [12]. The tool is currently available online.

4. BMD detection and OP diagnosis

BMD is currently recognized both domestically and internationally as the primary diagnostic indicator for OP. It is also considered a reliable indicator for assessing the efficacy of anti-OP treatment [18,19]. BMD detection techniques include dual-energy X-ray absorptiometry (DXA) and quantitative computed tomography (QCT) [19].

4.1. DXA

DXA is currently the most widely used BMD test in the diagnosis of OP, fracture risk assessment, and follow-up of patients with PBC [20,21], with lumbar and hip BMD testing being the gold standard for the diagnosis of OP. At present, the majority of diagnostic criteria for OP are recommended by the WHO. According to these guidelines, a T-score between -1.0 and -2.5 indicates osteopenia, while a T-score of -2.5 or lower confirms a diagnosis of osteoporosis. The advantages of DXA are non-invasive, quantitative, and wide detection sites. Its disadvantages are the influence of factors such as BMD receptor weight measured by DXA, scoliosis, hyperosteogeny, vertebral fracture, and vascular calcification [21].

4.2. QCT

QCT is a method to measure BMD with clinical CT data, quality control, and analysis system of QCT. QCT can

be used to detect multiple sites, with the spine and hip being the most commonly used, and it measures BMD comparable to that measured by DXA [22]. The characteristics are not affected by spinal degeneration, scoliosis, and body weight, and can clearly show the fine structure of bone. Vertebral QCT < 80 mg/cm^3 and 80–120 mg/cm^3 are equivalent to WHO-recommended OP and osteopenia, respectively [23]. Domestic scholars consider that the above criteria are applicable to the diagnosis of OP in the Chinese population [24]. The limitation is that the radiation dose is high and the low dose technique should be used in clinical application.

4.3. Other techniques

Other detection techniques include peripheral dual-energy X-ray absorptiometry (pDXA), single X-ray absorptiometry (SXA), peripheral quantitative computed tomography (pQCT), quantitative ultrasound (QUS), etc. However, none of these tests can be used to diagnose osteoporosis directly. Instead, they are primarily used for screening osteoporosis risk and assessing the risk of osteoporosis-related fractures [19,25], with relatively little clinical application.

5. OP treatment

Patients with PBC who have a confirmed diagnosis of OP, a history of brittle fractures, or are at high risk of fractures based on OSTA or FRAX assessments require anti-OP therapy [20]. There is no specific drug for the treatment of PBC with OP and the optimal treatment strategy is the combination of calcium and vitamin D with anti-OP on the basis of treating the primary disease and improving liver function [20,26].

5.1. Calcium and vitamin D

Calcium is an important nutrient for maintaining bone health in humans, and rational supplementation of calcium and vitamin D can effectively prevent bone loss and reduce the incidence of brittle fractures [27]. Patients with PBC complicated with OP should be given 1000–1500 mg of calcium and 800–1000 IU of vitamin D daily [28]. The data show that when the serum vitamin D concentration is maintained above 30 μg/l, anti-OP drugs will exert better therapeutic effects [29]. A recent meta-analysis of 26 randomized controlled trials (RCTs) from 2016 to 2022 carried out by Voulgaridou *et al.* showed that calcium plus vitamin D was more beneficial than vitamin D alone in improving BMD [30]. Calcium and vitamin D have been listed by the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) as basic treatments for PBC patients with OP [20,31].

5.2. Bisphosphonates

Bisphosphonates are selective anti-resorptives that are effective in the general population [30,31]. Bansal *et al.* treated 215 cirrhotic patients with 150 mg ibandronate orally for 6 months and showed a significant improvement in BMD [32]. However, a meta-analysis of the use of bisphosphonates in PBC patients with OP showed no high-quality evidence of a significant improvement in BMD [33]. This is because current anti-OP therapies for PBC patients are based on experiences with postmenopausal osteoporosis, which primarily address increased bone resorption, rather than targeting the PBC-specific mechanism of reduced bone formation [34]. Clinically, bisphosphonates remain the first-line treatment recommended by AASLD and EASL, despite their relatively weak effect in patients with PBC complicated by OP [31,35]. The main adverse effects of oral bisphosphonates are acid reflux, abdominal pain, and esophageal ulcers, which increase the risk of bleeding in cirrhotic patients with esophageal gastric varices. Studies [32,36] followed up 215 and 120 cirrhotic patients treated with bisphosphonates and risedronate for 6 months and 1 year, respectively, bisphosphonates did not increase the risk of bleeding. In a 2-year clinical observation,

Guañabens *et al.* showed that none of the patients treated with bisphosphonates had adverse effects such as liver damage or cholestasis [37], suggesting that the use of bisphosphonates in the treatment of PBC, including cirrhotic patients with esophageal gastric varices, is beneficial.

5.3. Receptor activator of nuclear factor-κB ligand (RANKL) monoclonal antibody

Denosumab is the representative drug of RANKL. The first human monoclonal antibody of RANKL to be approved was denosumab, which improves BMD by inhibiting osteoclast activity to reduce bone resorption [38]. Saeki *et al.* treated 60 patients with chronic liver disease complicated with OP with denosumab for 1 year and found that no matter sex, age, or presence of liver cirrhosis, the BMD of patients with chronic liver disease was significantly improved by denosumab [39]. A 3-year follow-up study of 6 patients with PBC and 4 patients with autoimmune hepatitis (AIH) showed significant improvement in BMD in all autoimmune hepatitis, with no related adverse events such as hypocalcemia, osteonecrosis of the femur or jaw occurred [40], suggesting that the treatment of PBC with OP with denosumab is safe and effective. Denosumab has the potential to be an effective therapeutic drug to improve the long-term quality of life of patients with PBC [38].

5.4. Other anti-OP drugs

Other anti-OP drugs are not suitable for the treatment of patients with PBC because of their effects of inducing or aggravating liver damage, such as calcitonin, hormone replacement therapy and selective estrogen receptor modulators (SERMs), parathyroid hormone analogs, and ESR1 monoclonal antibody [41,42].

6. Conclusion

OP is a common extrahepatic manifestation of PBC with high incidence and damage, which seriously affects the long-term prognosis of patients. In the early 2000s, the American College of Gastroenterology (ACG) guidelines recommended that all patients with PBC should be routinely screened for OP. The One-Minute Osteoporosis Risk Test, OSTA, and FRAX are commonly used tools for screening and risk assessment of OP, while BMD is the gold standard for the diagnosis of OP. At present, the best treatment strategy for PBC with OP is based on the treatment of primary disease, improvement of liver function, and supplement of calcium and vitamin D, most patients are treated with bisphosphonate or denosumab. The clinical application of salmon calcitonin and monoclonal antibody in PBC is not mature, lacking reports on large samples. Estrogen replacement therapy, SERMs, and PTH analogs are not suitable for PBC patients because of the adverse effects such as inducing or aggravating liver injury, reducing portal blood flow, and increasing portal vein thrombosis.

Disclosure statement

The authors declare no conflict of interest.

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