REVIEWS

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IN MEMORIAM OF PROFESSOR WANDA HORST-SIKORSKA

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Osteoporosis in Gastrointestinal Diseases*

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article

Abstract

Secondary osteoporosis occurs as an isolated pathology or co-exists with types I and II osteoporosis. The gastroenterologist may come across osteoporosis or osteopenia in a patient with a gastrointestinal disease. This is often a young patient in whom investigations should be carried out and appropriate treatment initiated, aimed at preventing bone fractures and the formation of the best peak bone mass. Osteoporosis occurs in patients with the following conditions: Crohn's disease, ulcerative colitis, celiac disease, post gastrectomy patients, patients with short bowel syndrome, chronic hepatitis and cirrhosis, treated with steroids (steroid-induced osteoporosis) and patients using proton pump inhibitors chronically (state of achlorhydria). It is therefore necessary to approve a list of risk factors of secondary osteoporosis, the presence of which would be an indication for screening for osteoporosis, including a DXA study and the development of a separate algorithm for the therapeutic management of secondary osteoporosis accompanying gastrointestinal diseases, especially in premenopausal young women and young men, because there are currently no registered drugs with proven antifracture activity for this group of patients (**Adv Clin Exp Med 2016, 25, 1, 185–190**).

Key words: bone mineral density, osteoporosis, gastrointestinal disorders.

Definition and Diagnosis of Osteoporosis

According to WHO definition, osteoporosis is a systemic skeletal disorder that is characterised by low bone mass, micro-architectural deterioration with increased bone fragility and susceptibility to fracture. Osteoporosis is diagnosed based on bone densitometry studies (DEXA); according to WHO criteria osteoporosis is present when the T-score of the femoral neck is less than or equal to –2.5. This definition also extends to the study of the spinal L1–L4 segment. For the diagnosis of secondary osteoporosis, it is useful to determine the Z-score, which compares the patient's BMD with that of persons of the same gender and age. A Z-score of less than –2.0 is suggestive of secondary osteoporosis. A major complication of osteoporosis is bone fracture, hence the emphasis on the analysis of the risk factors of fractures. The introduced overall fracture risk calculator FRAX, estimates fracture risks based on the body mass index (BMI), bone mineral density (BMD) and risk factors such as age, sex, body weight, height, history of osteoporotic bone fracture, history of osteoporotic hip fracture in parents, current smoking habit, alcohol abuse, chronic treatment with glucocorticoids, the actual presence of diseases that cause secondary osteoporosis, e.g. food malabsorption, chronic malnutrition, chronic liver disease and diagnosed rheumatoid arthritis. According to the statistics in Poland, osteoporosis affects 25 to 30% of women and 8 to 12% of men. The incidence of osteoporosis in gastrointestinal diseases has not been determined; the statistics applies only to individual diseases. Secondary osteoporosis during the perimenopausal period is 30–40% in women and 50–80% in men.

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Non-Specific Inflammatory Bowel Diseases and Osteoporosis

Of significance to bone metabolism is RANKL (receptor activator for nuclear factor κB ligand = ligand receptor activator of nuclear factor κB), which participates in the activation of osteoclasts. It belongs to the family of tumour necrosis factors and in humans it is encoded by the *TNFSF11* gene [1]. RANK acts in conjunction with osteoprotegerin (OPG), which is a protein in the family of tumour necrosis factor receptors (TNFR). The level of OPG gene expression is affected by many factors, such as: cytokines (TNF-a, IL-1a, IL-18, TNF-b), bone morphogenic proteins, 17b-estradiol and bone mechanical loads – they enhance expression; whereas, glucocorticoids (GCs), immunosuppressants, PTH, PGE2, FGF (fibroblast growth factor) decrease gene expression. As a result, RANKL increases the pool of active osteoclasts, stimulating bone resorption, while OPG has the opposite effect. Proinflammatory cytokines may induce osteopenia and osteoporosis. TNF-alpha, IL-1, IL-6, IL-7 and IL-17 increase the ratio of RANKL to OPG, thereby promoting bone resorption. IL-4, on the other hand, inhibits the activity of IL-17 and RANKL [2]. Therefore, bone loss is to be expected in all processes associated with chronic inflammation. The absorption of calcium and other macro- and microelements essential for bone metabolism takes place in the gastrointestinal tract. Hence, malabsorption caused by an inflammatory bowel disease or poor diet may lead to the impairment of bone metabolism. Vitamin 1,25 $(OH)_2$-D_3 regulates bone metabolism and its deficiency is associated with the risk of developing osteoporosis. In target organ cells, 1,25(OH)2-D_3 binds with its specific nuclear receptor VDR (vitamin D receptor) in a complex with retinoid X receptor and through the modulation of appropriate genes exerts its biological effect [3]. In inflammatory bowel diseases, the incidence of osteopenia in men and women is 22% and 59% respectively and osteoporosis 5% and 41% respectively. The incidence of spinal osteopenia is 54% and osteoporosis 18% respectively. In the proximal femur, osteopenia is present in 78% and 29% osteoporosis. In Crohn's disease, osteoporosis occurs in 15–40% of adult patients [4, 5]. Increased risk of bone fractures is associated with low bone mineral density. It is 1.4 times higher in patients with celiac disease than in healthy population, and 1.3 to 14 times higher in patients with Crohn's disease than in patients with ulcerative colitis. Elderly patients and patients with ulcerative colitis have a high risk of bone fractures [6]. An analysis involving 6,027 Canadian patients with inflammatory bowel diseases showed a 40% increase in the risk of bone fractures compared to the general population [7]. An interesting study was conducted in the Netherlands, where an assessment of the incidence of bone fracture in patients with inflammatory bowel diseases examined about 231,000 cases of fracture. The incidence of bone fractures was 156 and 282 cases per 100,000 of patients with Crohn's disease and ulcerative colitis respectively. The risk of spinal fracture was estimated at 1.72 and 1.59 for fracture of the hip, in comparison to the control group. The risk of fractures was higher in patients with Crohn's disease than in patients with ulcerative colitis. Only 13% of patients with a history of fracture received anti-fracture treatment [8]. A Danish study involving 7,072 patients with Crohn's disease and 8,323 patients with ulcerative colitis did not show an increase in the risk of bone fractures in the course of the diseases, except for a slight increase in risk during the period of diagnosis. The risk of bone fracture in the course of Crohn's disease was slightly higher than in ulcerative colitis [9]. Risk factors of osteoporosis in Crohn's disease, according to Frei [10] include: high daily dose of GCs and prolonged treatment period, young age at the time of diagnosis (usually a higher disease activity), history of bowel resection, the use of azathioprine as well as low body weight. A major and common problem in patients with IBD is vitamin D deficiency. In a study by Bours et al., which included 316 patients, vitamin D deficiency was present in 39% of the patients during summer and 57% of the patients during winter [11]. Indications for DEXA testing according to the British Society of Gastroenterology may be: persistent active inflammatory bowel disease, > 10% weight loss, BMI of < 20 kg/m^2, age > 70 years of age, treatment with GCs for a period of six months, patients < 65 years of age, in whom treatment with glucocorticoids is planned, if there are other known risk factors for osteoporosis. Treatment with bisphosphonates in patients treated with GCs with a T-score of –1.5, as well as in all patients over 65 years of age treated with GCs, regardless of the result of the DEXA study. The indication for treatment is osteoporotic fracture or reduced T-score (< 1.5); bisphosphonates, teriparatide and intranasal calcitonin are recommended [12].

Osteoporosis in Celiac Disease

In 15% of cases, osteoporosis accompanies celiac disease. Celiac disease can affect the development of bone metabolism disorders at any age.

The incidence of biopsy-proven celiac disease in patients with osteoporosis is × 17 higher than in subjects with normal bone mass (3.4% and 0.2% respectively) [13]. Children with celiac disease in the Polish population have a reduction in bone mineral density by 40.5% (13.5% in osteoporosis and 27% in osteopenia). Osteopenia occurs in almost all untreated patients, with noticeable improvements after the use of a gluten-free diet [14]. The pathogenesis of bone metabolism disorders in celiac disease include the impaired absorption of calcium and vitamin D, with secondary hyperparathyroidism, zinc deficiency with a reduction in IGF-1, increase in the levels of pro-inflammatory cytokines and the presence of autoantibodies against tissue transglutaminase as well as sex hormone deficiency.

Post-Gastrectomy Osteoporosis

In post-gastrectomy patients, osteomalacia occurs in 10–20% of patients, and osteoporosis of the L1–L4 lumbar spine in 22–42% and of the femoral neck in 61% of patients. The incidence and severity of osteopenia increase with the passage of time after gastrectomy. Thirty years after gastrectomy, the risk of hip fracture increases 2.5 fold and the risk of vertebral fracture increases by 4.4 fold. The risk of a metabolic bone disease is similar regardless of the surgical method (whether Billroth I or Billroth II) [15]. Of importance in the pathogenesis of osteoporosis is an acceleration of the passage of food content (often bypassing the duodenum) and the impairment of calcium and vitamin D absorption. DXA study is recommended in: patients at least 10 years after gastrectomy, postmenopausal women, men over 50 years of age and patients with hypogonadism and with a history of osteoporotic fracture.

Osteoporosis in Short Bowel Syndrome

The prevalence of osteoporosis in patients with short bowel syndrome ranges from 21–67%. Symptoms of short bowel syndrome are the result of malabsorption, and occur when the remaining length of the small intestine does not exceed 200 cm. Jejunoileal bypass surgeries, used in the treatment of pathological obesity, cause less absorption impairment. Malabsorption of macro- and micronutrients, impairment of enterohepatic circulation of D metabolites, leading to impairment in the absorption of calcium and vitamin D, magnesium, zinc, vitamin B12, especially with fatty diarrhea.

Osteoporosis in Liver Diseases

The following occur in chronic liver diseases: malabsorption of calcium and phosphate, reduced concentration of 25OH D, increase in PTH level, reduction in the number and activity of osteoblasts as a result of a decrease in the production of IGF-1 in the hepatocytes and an increase in the apoptosis of hepatocytes. As a result of hormonal disorders, there is a reduction of serum free testosterone. In primary biliary cirrhosis (PBC), unconjugated bilirubin interferes with the proliferation of osteoblasts. Some role in the development of bone metabolism disorders in patients with chronic liver diseases has been attributed to leptin, which stimulates the activation of osteoblasts and inhibits their apoptosis when administered peripherally. A lower serum leptin level has been observed in patients with primary biliary cirrhosis in comparison to the control group. The risk of bone fractures in patients with primary biliary cirrhosis after liver transplant is about 37% (6). A two-fold increase in risk of the overall fracture of bones and fracture of the proximal femur and the forearm was observed in a group of 930 patients with primary biliary cirrhosis, in comparison to the general population (n = 9.202) [16]. Low-energy fractures occur in 14–21% of patients with chronic hepatitis and patients with liver cirrhosis and 45% in patients with end-stage liver failure referred for liver transplant [17]. Osteoporosis occurred in 36.6% and osteopenia in 48.1% of a group of 243 patients with chronic liver disease in the preparatory period for liver transplant [18]. After liver transplantation, an osteoporotic bone is exposed to additional risks, even to the immunosuppressive therapy the patient has to take for life. The patients require calcium and vitamin D supplementation [19]. American Society of Gastroenterology recommends performing a DXA study in patients with chronic liver disease: after an osteoporotic bone fracture, in postmenopausal women, in patients chronically treated with glucocorticoids for more than 3 months, after a diagnosis of PBC and in patients with cirrhosis of the liver, prior to liver transplantation. Follow-up DXA is recommended each year in patients chronically treated with glucocorticoids, until the stabilisation of BMD results and after 2–3 years in patients with normal DXA [20].

Drug-Induced Osteoporosis in Gastroenterology

Glucocorticoids

At physiological concentrations, cortisol stimulates the synthesis of collagen by osteoblasts. Higher concentrations cause delayed maturation of the osteoblasts, inhibit the synthesis of collagen, osteocalcin and alkaline phosphatase, and impairs bone matrix mineralisation. This leads to the damage of the developing cytoskeleton of actin filaments, as a result of which the cell changes its shape and undergoes apoptosis. GCs stimulate the synthesis of collagenase III – a metalloprotease involved in the degradation of the bone matrix. GCs inhibit the synthesis of insulin-like growth factors (IGF-1, IGF-2) and the expression of the receptor for IGF-2; they also have an impact on the synthesis of IGF-binding proteins. They modulate the response of osteoblasts to PTH, 1,25(OH)2D3 and cytokines. They alter the metabolism of vitamin D and reduce the number of receptors for this vitamin. They increase the loss of calcium with urine and reduce the intestinal absorption of calcium [21]. As a result of the above changes in every bone remodelling cycle, there is approximately 30% less tissue formed than under normal conditions [22, 23]. The greatest loss of bone mass occurs in the first 6–12 months of treatment and particularly affects bones with trabecular structure, most often the vertebral bodies. According to literature, the short-term use of GCs for three months is not likely to adversely affect BMD (bone mineral density). GCs induce osteoporosis through the modulation of the osteoblast response to PTH, vitamin 1,25(OH)2D3 and cytokines. These drugs alter the metabolism of vitamin D and reduce the number of receptors for this vitamin. The immediate effect of GCs on bone tissue reconstruction is the increase of RANKL and decrease of OPG (< 10 mg of prednisone per day), thereby increasing the activity of osteoclasts [24]. Prevention of osteoporosis during treatment with GCs occurs through the supplementation of vitamin D – 25(OH)D at a dose of 20–60 μg/day or 1,25(OH)2D – at a dose of 0.5–1.5 μg/day and the supplementation of calcium (1,000–1,500–2,000 mg of calcium carbonate/day). Institution of bisphosphonate treatment when the T-score is < 1.5 or there is an existing bone fracture. Bisphosphonates (alendronate, other bisphosphonates also intravenously), adjuvant calcitonin and teriparatide.

Proton Pump Inhibitors

The second group of drugs often used are PPIs. Their negative effect on the bone tissue is increasingly being raised, though further studies are needed in order to arrive at definitive conclusions. Epidemiological studies indicate an association between the use of PPIs, low bone density and the risk of fractures. A reduction of the gastric pH causes a decrease in calcium absorption, although this theory has been questioned. Consider the long-term use of PPIs, especially in patients at risk of osteoporosis, 161,806 postmenopausal women (aged 50 to 79 years) with no history of fractures were included in a prospective analysis. The primary endpoints of the study were: fractures of the hip, spine, forearm or wrist as well as the densitometric evaluation of BMD over a span of three years. The use of PPIs was not associated with an increased risk of femoral neck fracture; there were also no significant differences in BMD between the groups during the three-year period of follow-up. However, there was an increase in the risk of fractures of the spine, forearm and wrist [25].

Treatment of Osteoporosis Coexisting with Gastrointestinal Diseases

The prophylaxis and treatment of osteoporosis which occurs in the course of gastrointestinal diseases is the elimination or reduction of risk factors and treatment with drugs that inhibit bone resorption and/or stimulate bone formation. Antiresorptive drugs are effective only with low bone mass and a T-score below –2.0; there is the need, therefore, to monitor the bone density in the femoral neck using the DEXA method before their commencement. Diet and physical activity in the prevention and treatment of osteoporosis entails a reasonable supply of protein, carbohydrates, fats, vitamins and minerals, calcium intake for life in an amount suitable for age and gender, maintaining an appropriate Ca:P ratio of 1 : 1 in the diet. An important element is to combat salting, smoking and excessive alcohol consumption; reduction in the consumption of coffee and tea and regular daily physical activity, tailored to the physical condition of the patient. Drugs used in the treatment of osteoporosis include: bisphosphonates e.g. alendronate sodium, ibandronic acid, zoledronic acid and risedronate sodium. The question remains – how long the treatment is to last? In the case of alendronate, the bone mineral density must be monitored every year by means of a DXA study; after 5 years of treatment, the effectiveness and safety of further administration should be verified, and consideration given to the inclusion of other drugs. Other

drugs used include: strontium ranelate, denosumab, calcitonin, raloxifene, teriparatide or rhPTH (1-34); the use of parathormone (PTH 1-84) is being considered [26–28]. The effect of anti-TNF-alpha monoclonal antibodies, infliximab and adalimumab on bone tissue in patients with Crohn's disease was assessed in individual studies (the addition of these drugs to bisphosphonate caused a greater BMD increase than the use of bisphosphonate alone). Treatment directed against TNF-alpha may be beneficial to bone formation in patients with non-specific bowel diseases; however, more extensive studies need to be carried out in this area [29]. Also noteworthy is denosumab, a human monoclonal antibody directed against the receptor activator of nuclear factor kappa-B [NFkappaB] ligand (RANKL), which has a reversible anti-resorption effect and is an alternative to bisphosphonates [30–34].

Summary

The risk of osteoporosis and osteoporotic fractures in gastrointestinal diseases depends on the type of disease and a whole range of risk factors which may be present in a patient. There are indications to develop a separate algorithm for the diagnosis and treatment of people with secondary osteoporosis, especially young patients, since there are currently no registered drugs with proven antifracture activity for this group of patients. Currently, we are forced to follow the generally accepted principles, as in primary osteoporosis. This is difficult even if only because of the registration of drugs for the treatment of postmenopausal osteoporosis alone. The principles of the treatment of osteoporosis are similar in all diseases of the gastrointestinal tract. For prophylaxis, consideration should be given to the adequate intake of 1,200 mg/day of Ca and 800–1,000 IU/day of vitamin D in the diet. Patients should carry out regular physical exercises, stop smoking and avoid excessive consumption of alcohol. The dose of corticosteroids should be reduced to a minimum [35].

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