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SECONDARY OSTEOPOROSIS IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY PATHOLOGY

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Abstract
Osteoporosis (OP) is a progressive multifactorial systemic disease of the skeleton, characterized by a decrease in bone mass and a violation of the structure (microarchitectonics) of bone tissue. Among the diseases that contribute to the development of osteoporosis, a special place is given to chronic obstructive pulmonary diseases: chronic obstructive pulmonary disease (COPD) and bronchial asthma (AD).

Keywords: Osteoporosis, obstructive pulmonary diseases, calcium and vitamin D preparations, antiosteoporetic drugs.

Introduction

Osteoporosis (OP) is a progressive multifactorial systemic disease of the skeleton, characterized by a decrease in bone mass and a violation of the structure (microarchitectonics) of bone tissue. Among the risk factors for the development of osteoporosis, non-modifiable (genetic), modifiable factors and drug effects can be distinguished. On the one hand, the role of hereditary predisposition to this disease is undoubted, on the other hand, the importance of such "exogenous" risk factors as a deficiency of protein, calcium and vitamin D intake, smoking, alcohol abuse, physical inactivity, low body weight, early menopause in women has been reliably proven. development of osteoporosis, a special place is given to chronic obstructive pulmonary diseases: chronic obstructive pulmonary disease (COPD) and bronchial asthma (BA). This is due to the commonality of many exogenous risk factors for the development of osteoporosis and chronic obstructive pulmonary pathology, the commonality of pathogenesis mechanisms, as well as the influence of drug therapy used to treat COPD and AD. It should be emphasized that in patients with COPD and AD, the development of OP occurs even in the absence of GC therapy. The Bone Mineral Density (BMD) study performed by Praet J.P. et al. in 1992 revealed a lower BMD value in patients with chronic bronchitis compared to a control group comparable in age. More recent studies have also found a high incidence (up to 60%) of osteopenia and osteoporosis in COPD patients (Incalzi R.A. et al., 2000), and as COPD progressed, it increased. Among patients with lung diseases (mainly COPD with FEV1 below 80% of the proper level) who had never received GC, osteoporosis (according to the T-score) was registered 4 times more often than in the control. Vertebral fractures were observed in 12.4% of COPD patients with moderate functional impairment (FEV1 70% of the due value) who did not receive GC. A decrease in BMD was also found in 42.8% of patients with bronchial asthma aged 20-49 years who had not previously received hormonal therapy.

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Osteoporosis in COPD patients belongs to the category of secondary osteoporosis. Steroid OP is the second (after postmenopausal) most common form of OP and the most common form of secondary OP associated with the use of drugs. According to the US National Center for Health Statistics, in 20% of patients suffering from OP, the cause of bone damage is the use of corticosteroids.

Osteoporosis in patients with bronchopulmonary pathology is due to the fact that the inflammatory process can have a direct impact on bone metabolism. A large number of pro-inflammatory cytokines, which play an important role in the pathogenesis of obstructive pulmonary diseases, are involved in the regulation of bone resorption. TNF-a contributes to the increase in the number and maturation of osteoclast precursors. IL-1 and IL-6 are powerful mediators of osteoclastogenesis (according to in vitro data, IL-1 is a 4-fold stronger bone resorption factor than parathyroid hormone). Thus, these and other cytokines (including IL-11 and monocyte-macrophageal colony-stimulating factor) may provide a link between the inflammatory process in the bronchopulmonary system and bone remodeling and contribute to bone loss.

According to international consensus documents (GINA, 2013), inhaled glucocorticoids are the basic anti-inflammatory drugs used to treat patients with bronchial asthma. Patients with severe and extremely severe COPD according to GOLD (2013) also receive inhaled corticosteroids in complex basic therapy. Proven systemic effects that develop in response to the use of high doses of inhaled glucocorticosteroids (over 1,000 μg/day for beclamethasone dipropionate and over 750 μg/day for fluticasone) include osteoporosis in adults and effects on linear growth in children. If inhaled glucocorticoid therapy is ineffective, patients with bronchopulmonary diseases may require systemic (oral) therapy with glucocorticoid hormones to stabilize the condition. Treatment with low doses (<5 mg/day) of HA is currently considered to have no significant effect on bone mass. However, a meta-analysis of the results of controlled trials showed that the administration of even minimal (2.5 mg/day) doses of HA can have an undesirable effect on bone metabolism. The most rapid loss of bone tissue develops during the first 6-12 months. GC therapy, subsequently the decrease is less pronounced, but persists throughout the entire period of GC use.

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The main feature of steroid osteoporosis is the effect of corticosteroids on both processes that form the basis of bone remodeling: attenuation of osteoblast-mediated formation and increase of osteoclast-mediated bone resorption. GCs are able to induce apoptosis (programmed death) and inhibit the formation and activity of osteoblasts by reducing the synthesis of prostaglandin E2 (PGE2). The effect of GC on osteoblasts can be direct - through activation or inhibition of gene expression of osteoblasts themselves, or indirect - through a change in the expression or activity of osteoblast growth factors. HA increases the excretion of calcium in the urine and causes impaired tubular reabsorption of calcium and phosphorus, lowers the content of active forms of vitamin D metabolites and vitamin^-bound protein involved in the processes of intestinal absorption of calcium. At the same time, HA inhibits only active intestinal absorption of calcium, while passive diffusion through the intestinal wall slightly increases and becomes the main mechanism of calcium intake into the body of patients treated with GC. Secondary hyperparathyroidism, which develops in response to decreased intestinal calcium absorption and increased urinary calcium excretion, may stimulate osteoclast-mediated bone resorption. One of

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the main factors in the development of osteoporosis is currently considered to be the suppression of GC secretion of sex hormones, which play a decisive role in bone metabolism. Other important factors underlying the development of steroid osteoporosis are a decrease in the synthesis of collagen and non-collagen proteins, as well as local bone growth factors (IPGF-1, TGF-K, etc.).
HA has a negative effect not only on the "quantity" (bone mineral density - BMD), but also on the "quality" of the bone. This results in a lower "fracture threshold" in individuals receiving GC than in individuals not receiving these drugs. That is why steroid osteoporosis is diagnosed according to the T-test of osteodensitometry not at 2.5, but at 1.5 standard deviations from the peak bone mass of persons of the corresponding sex. A feature of steroid osteoporosis is a more pronounced lesion of trabecular (spine, greater trochanter) than cortical (long bones) bone tissue. In addition, it is known that the relative risk of fractures of the bones of the skeleton (spine, femur) increases in a dose-dependent manner.
The most important factors determining bone loss during GC treatment are the cumulative dose of GC, age over 50 years, and the postmenopausal period. Probable risk factors for the development of steroid osteoporosis include long-term use and high daily dose of HA, low body weight, decreased physical activity, inflammatory diseases and other general risk factors for the development of OP, which were mentioned earlier.
The fact that steroid osteoporosis is reversible is extremely important, which predetermines the need for prevention and early treatment of this condition.
The process of osteoporosis is characterized by a slow increase in bone loss and deformity of the vertebrae and can be asymptomatic for a long time. The clinical significance of OP is determined primarily by the risk of developing skeletal bone fractures. The most characteristic are fractures of the spine, distal radius and proximal femur (femoral neck fracture) that occur after minimal trauma (non-traumatic). Pain syndrome in OP is explained by small bone microfractures and periostal irritation. Patients may have a change in gait (the so-called "duck" gait). Acute intense pain in the affected part of the spine is associated with compression of the bodies of one or more vertebrae, sharply restricts the range of motion and is often the cause of severe depression. Pain in the affected thoracic spine may limit respiratory excursions and increase respiratory failure in patients with chronic bronchopulmonary pathology.
Characteristic of OP is also a decrease in the height of adult patients, which is usually compared with height at a young age. At the same time, thoracic kyphosis increases and the pelvis tilts anteriorly.
Diagnostic search for suspected osteoporosis involves the establishment of osteopenia (a symptom of reduced bone density), the identification of its complications (bone fractures), the assessment of the metabolic rate in bone tissue (which is of auxiliary importance), as well as the clarification of the causes of osteopenia and a differential diagnosis with other forms of metabolic osteopathy.
The main methods for diagnosing OP are bone X-ray and osteodensitometry.
Standard radiography, the most widespread and generally accepted method of diagnosing OP, allows you to reliably recognize the disease, but determines only the pronounced stages of OP (when up to 20-30% of bone mass is lost) and is not suitable for assessing the dynamics of changes in bone tissue.
Currently, various methods of bone densitometry (isotope, ultrasound, and X-ray, including dual-energy absorptiometry, which is the gold standard for diagnosing osteoporosis) are used for the early diagnosis of OP. These methods make it possible to identify already 2-5% of bone mass loss,

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to assess the dynamics of bone density during the development of the disease or the effectiveness of treatment.

It is advisable to emphasize that osteodensitometry in itself does not make it possible to make a nosological diagnosis and does not replace a classical X-ray examination.

In recent years, the priority in the diagnosis of patients with BMD disorders is not the fact of the presence of OP, but the assessment of the risk of developing its complications: fractures. According to the recommendations of the International Association for Bone Fragility (IL) and WHO, the risk of fracture associated with bone fragility should be expressed as a short-term absolute risk (AR), i.e. the probability of an event over a 10-year period of time. At present, a method (tool) has been developed to assess the 10-year risk of major osteoporotic fractures (radius, humerus, clinically significant fractures of the vertebral bodies and femur) in individuals aged 40 to 90 years, based on the use of age, BMI and clinical RF of fractures with or without BMD of the femoral neck in men and women. This method is called the FRAT (fracture risk assessment tool) calculator, and its use allows you to determine the need for active treatment tactics even in cases where densitometry is difficult to perform for some reason.

When determining biochemical markers of bone metabolism, it should be remembered that the markers of bone formation include the activity of total alkaline phosphate in the blood and its bone isoenzyme, osteocalcin, and human collagen pro-peptide type 1. Markers of bone resorption include urinary excretion of oxyproline, acid tartrate-resistant phosphatase activity, and determination of collagen breakdown products: pyridinoline, deoxypyridinoline, N-terminal telopeptide in fasting urine, C-telopeptide in blood. The most informative markers of bone resorption are deoxypyridine-lin and telopeptides.

Osteoporosis prevention begins with a set of measures aimed at eliminating or reducing the severity of risk factors for osteoporosis. Primary prevention measures include therapeutic exercises, isometric exercises, swimming, a diet high in calcium and vitamin D (dairy products) and relatively low in phosphates, table salt and fiber, quitting smoking, excessive alcohol and caffeine, avoiding heavy physical activity, as well as eliminating risk factors for accidental loss of balance (taking sleeping pills, sedatives, etc.) and protecting the hip joint.

For the purpose of secondary prevention of osteoporosis, all patients with risk factors must receive at least 1,500 mg of elemental calcium in combination with vitamin D (400-800 IU) or its active metabolites (calcitriol and especially alfacalcidol) per day. This combination should be prescribed as soon as possible from the time of diagnosis of osteopenia and/or the start of ongoing therapy with systemic GC.

In recent years, after the introduction of the FRAT instrument into clinical practice, the degree of risk of fractures must be taken into account when prescribing treatment to patients with bone metabolism disorders. The algorithm for choosing treatment tactics is presented in Figure 1.

The FRAT calculator can also be used to decide whether densitometry is necessary. In this case, the risk of fractures is initially assessed. In case of high risk, treatment with anti-osteoporetic drugs is immediately started. If the risk is assessed as medium, it is recommended to perform densitometry, according to the results of which the risk is reassessed. If the risk is assessed as high (a decrease in BMD according to the T-test below -2.5), then the patient is prescribed anti-osteoporetic therapy. In case of low risk, a set of preventive measures is carried out.

According to modern ideas, the drugs of choice for secondary osteoporosis are bisphosphonates, pyrophosphate analogues, which bind to hydroxyapatite at the sites of bone remodeling and inhibit

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bone resorption. The Russian pharmaceutical market offers bisphosphonates of almost all groups, both in the form of original drugs and in the form of generics.

An alternative method of treating secondary osteoporosis is pharmacotherapy with salmon calcitonin preparations. The drug reduces the risk of both vertebral fractures and femoral neck fractures, in addition, it has an analgesic effect, which is especially important in patients with GC-induced compression fractures.

Hormone replacement therapy (HRT) with female sex hormones is highly effective in postmenopausal women with low mineral density (osteopenia) or osteoporosis in preventing vertebral fractures and other fractures, including femoral necks (recommendation level A). However, it is known that the risks may outweigh the benefits. Thus, it has been shown that long-term use (more than 5 years) is associated with the risk of developing breast cancer, coronary artery disease and stroke (recommendation level A). In addition, one of the serious side effects of HRT is venous thrombosis (A). Therefore, when prescribing this treatment, the patient should be warned about possible complications. The efficacy of HRT in patients with secondary osteoporosis has not been proven.

Selective estrogen receptor modulators are a relatively new group of synthetic drugs used in the treatment of osteoporosis. The first and so far the only drug with proven efficacy from this group - raloxifene - has the effect of an estrogen agonist in relation to bone and lipid metabolism, and an estrogen antagonist - in relation to the uterus and mammary gland. Data regarding the efficacy of estrogen receptor modulators (safer than standard HRT) in steroid osteoporosis are currently lacking.

Proven systemic effects that develop in response to the use of high doses of inhaled glucocorticosteroids include osteoporosis in adults and the effect on the linear growth of children

An undoubted success in the treatment of patients with OP is the creation of new drugs directed against various pathogenetic mechanisms of the formation of bone metabolism disorders. These drugs include denosumab, which is recommended for the treatment of post-menopausal osteoporosis in women at increased risk of bone fractures. Denosumab selectively binds the regulator of osteoclast formation (RANK ligand), resulting in a decrease in the rate of bone destruction, an increase in BMD, and a significantly reduced likelihood of new vertebral, extravertebral, and femoral neck fractures.

Thus, in all patients with chronic obstructive pulmonary pathology, it is necessary to assess the risk factors for OP, determine the risk of fractures using the FRAT calculator, conduct a densitometric study of BMD, determine the concentration of serum calcium, phosphorus and ALP (if abnormalities are detected, exclude bone diseases) and the concentration of calcium in daily urine. In addition to a set of non-drug preventive measures related to lifestyle and physical activity, all patients with osteopenia need to take calcium and vitamin D preparations, this combination should be prescribed as early as possible. In case of a decrease in bone mineral density below the age norm, antiosteoporetic drugs should be added to therapy. Proper treatment of the underlying disease (COPD) is of great importance, since a decrease in the activity of the inflammatory process will inevitably lead to the normalization of bone remodeling processes. (Yk)

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