OSTEOPOROSIS – A SILENT EPIDEMIC OF XXI CENTURY: SECONDARY FORMS
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Abstract. The objective of the study was to determine the main causes of osteoporosis in chronic kidney disease, chronic obstructive pulmonary disease, pulmonary sarcoidosis and understand how the disease develops in these conditions.

Materials and Methods. To study the mechanisms of developing secondary osteoporosis, a literature review was conducted.

Results. Secondary forms of osteoporosis account for approximately 15-20% of reported cases and result mainly from concomitant diseases or from using drugs that have a negative effect on bone tissue. Despite its inert and stable appearance, bone tissue is a metabolically active, continuously renewing system. Throughout life, it continuously undergoes remodeling cycles involving the two main processes: the first one is called bone resorption and involves the breakdown of old bone followed by the destruction and removal of both the mineral substance and the organic matrix from resorption sites; the second one is called new bone formation and involves bone matrix synthesis and its subsequent mineralization. The imbalance between these two processes, the predominance of bone resorption over bone formation, is the key link in the pathogenesis of osteoporosis. Such an imbalance reflects the impairment of the major mechanisms of systemic hormonal and local (cytokine) regulation of cellular activity and occurs in secondary osteoporosis.

Conclusions. To date, at the stage of providing medical care to patients with chronic bronchopulmonary diseases and chronic kidney disease, inadequate attention is paid to timely diagnosis and treatment of concomitant osteoporosis. The latter often develops as a secondary condition due to systemic inflammation, severe hypoxia, low physical activity, taking inhaled and systemic glucocorticoids. Its signs are not clinically apparent; hence, it is referred to as the ‘silent epidemic’. Since osteoporosis has no pathognomonic symptoms and its clinical presentation is rather vague, in patients with chronic bronchopulmonary diseases and chronic kidney disease, its early diagnosis by determining mineral bone density is recommended to prevent the development of severe complications, including low-energy fractures.

Keywords: Osteoporosis; Chronic Kidney Disease; Chronic Obstructive Pulmonary Disease; Pulmonary Sarcoidosis.

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References. A comprehensive list of references is provided in the final version of the manuscript.

Conclusions. The study provides important insights into the pathogenesis of secondary osteoporosis in chronic kidney disease and chronic obstructive pulmonary disease. It highlights the need for improved diagnostic and therapeutic strategies to prevent the development of severe complications associated with osteoporosis.

Implications. The findings of this study have significant implications for clinical practice and public health, as they underscore the importance of early detection and intervention in preventing osteoporosis-related fractures.
Introduction

The World Health Organization defines osteoporosis (OP) as a skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fractures. OP has been considered as a separate nosological entity since 1940 and in the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10), it belongs to class XIII diseases, codes M80-82.

Literally, OP means ‘porous bones.’ In OP, bones become weak and brittle, so brittle that a slight fall, blow, or even a sudden movement or coughing, a fall from standing height or less can cause their fracture. OP-related fractures are seen in the bones with low bone mineral density (BMD) after low-energy trauma [1-4]. Due to the high risk of fractures, OP ranks fourth after cardiovascular diseases, cancers, and diabetes mellitus in terms of medical and social significance [5]. OP is currently divided into two types [6]: primary OP which develops as a separate condition; secondary OP which occurs due to the presence of underlying disease.

Primary OP is classified as follows:
• postmenopausal OP which is caused by hormonal changes during the menopausal transition period;
• juvenile OP which affects children or adolescents and manifests itself by pain in the lower back, hips, and feet, difficulty walking, and multiple bone lesions;
• senile OP which is associated with aging and results in significantly diminished bone mass, brittle and fragile bones;
• idiopathic OP which may occur at any age; the underlying cause of its development is unknown.

Secondary OP causes are classified as non-modifiable and modifiable.

Modifiable causes involve the following [7,8]:
• calcium deficiency (inadequate calcium intake is associated with low bone density, low bone mass, and high risk of fractures);
• vitamin D deficiency (as much as 81.8% of the Ukrainian population have been found to have vitamin D deficiency; the risk factors for its developing are female gender, obesity (body mass index (BMI) over 35 kg/m²), being underweight (BMI less than 18.5 kg/m², winter season) and not living in the southern part of country;
• low physical activity (people living a sedentary lifestyle are at higher risk of developing OP; any weight-bearing exercises, especially walking, running, jumping, dancing, and weightlifting are the best for bones, while swimming, despite its usefulness, prevents OP to a lesser extent, since in water, there is almost no axial loading on bones); smoking, alcohol consumption (smoking is fairly known to weaken bones, and excessive alcohol is likely to interfere with the body’s ability to absorb calcium; therefore, regular drinking increases the risk of OP);
• low body weight.

Non-modifiable causes (those that cannot be changed) involve:
• genetics;
• age-related changes;
• female gender;
• body constitution (men and women of asthenic body type and too low body weight (BMI of 19 kg/m² and less) tend to be at higher risk of OP as they naturally have less bone mass);
• taking glucocorticoids (GCs) used for treating bronchial asthma and rheumatic diseases;
• endocrine disorders, including diabetes mellitus, thyroid dysfunction, gonadal dysfunction;
• past or chronic gastrointestinal disorders;
• kidney diseases, kidney failure;
• blood disorders;
• rheumatic diseases, including systemic sclerosis, systemic lupus erythematosus, ankylosing spondylitis, rheumatoid arthritis;
• prolonged bed rest (after surgery, trauma);
• fractures.

At the present stage of providing medical care to patients presenting with various diseases, inadequate attention is paid to the diagnosis and treatment of concomitant OP which has no pathognomonic clinical signs. Its clinical signs are unclear; hence, it is referred to as the ‘silent epidemic’ [3,9]. In most cases, back pain, including thoracic pain, lumbosacral spine pain, or sacral bone pain, is the early warning sign of OP. In addition, patients usually complain of fatigue and the need for multiple rests during the day in a lying position. The first presentation is often a distal radius fracture or a kyphotic spinal deformity which develops long before pain and, as a rule, is not considered by patients as disease manifestation. The vertebral bodies are capable of gradual accumulating microfractures in the form of ‘creeping deformities’ which usually do not manifest themselves; therefore, it is the spine that is most affected in OP. Unlike osteoporotic fractures of other localizations, most spinal fractures do not occur from falls, they result from compressive loading, e.g.,

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Pain intensity may differ among patients, as well as a single patient may experience various types and levels of pain occurring at different time intervals, ranging from severe short-term or debilitating chronic pain to mild pain that comes and goes. Pain in OP is characterized by trabecular microfractures in the vertebral bodies, an irritation of the periosteum with the porous mass of deformable vertebrae. In addition, pain syndrome can result from periosteal hemorrhages, muscle tension at the fracture or deformity site. Although pain in OP is less intense than pain in osteomalacia, in some cases, it is that leaves patients bedridden.

A common presentation of OP is a decline in patients' body height. As the height of the trunk reduces, pronounced skin folds are formed on the lateral chest and the costal arches descend to the wings of the ilium. Movements of the lumbar spine are limited. Shuffling, unsteady gait with feet wide apart, which is often seen in patients with steroid-induced OP, involves no bone fractures and is caused by concomitant conditions and muscle weakness.

Thus, warning signs of OP include:
- lumbosacral spine pain or thoracic pain;
- interscapular pain;
- back muscle fatigue;
- extreme tiredness;
- need for multiple rests during the day in a lying position;
- gait abnormalities, lameness;
- decline in body height by more than 4 cm (late manifestation of OP);
- fractures (late manifestation of OP).

Secondary forms of OP account for approximately 15-20% of reported OP cases and result mostly from concomitant diseases or from using drugs that have a negative effect on bone tissue [10,11]. Thus, OP is fairly common in chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), and pulmonary sarcoidosis.

CKD is one of the major challenges to modern medicine due to its widespread prevalence, progressive clinical course with the development of chronic kidney failure (CKF), frequent complications, need for high-cost renal replacement therapy in end-stage renal disease, frequent patient disability, and high mortality rates [12].

Over 850 million people suffer from CKD around the world, and to date, it is one of the most common diseases worldwide [13].

Despite the achievements of modern nephrology, CKF remains a severe disabling condition due to the development of complications. Disorders of bone metabolism and bone remodeling are important complications occurring in the early stages of CKD and progressing with deterioration in renal function [14].

Under normal conditions, the secretion of parathyroid hormone (PTH) by the parathyroid glands which respond to changes in the level of circulating ionized calcium due to the calcium-sensing receptor located on the chief cells of the parathyroid glands is the key process in the regulation of calcium metabolism [15]. When the level of circulating ionized calcium decreases, the level of PTH increases and provides for the three main functions helping in achieving normocalcemia: the receptor-mediated reabsorption of calcium in the renal tubules; the stimulation of osteoclastic resorption to release skeletal calcium; increasing renal hydroxylase activity that results in the formation of 1,25-dihydroxyvitamin D3 and increased intestinal calcium absorption. In response to these PTH-mediated effects, elevated calcium level, acting as a feedback mechanism, reduces PHT secretion [16].

In CKD, the reduction in the number of functional nephrons causes a cascade of complications, including vitamin D deficiency, hyperphosphatemia, altered function of the calcium-sensing receptor of the parathyroid glands, reduced intestinal calcium absorption, increased PTH synthesis, hypertrophy, and hyperplasia of parathyroid chief cells [17]. Prolonging life of CKF patients through renal replacement therapy led to increased incidence of the musculoskeletal system involvement, and the studies, that found a close relationship among disorders of phosphorus-calcium metabolism, bone changes, and end-stage CKF patients' mortality, determined an increasing interest for studying this problem [12]. In such patients, these disorders are associated with the development of secondary hyperparathyroidism (SHPT), the main components of which are hypocalcemia, hyperphosphatemia, and reducing synthesis of active 1,25-dihydroxyvitamin D3 [18].

The main indicator of hyperparathyroidism is elevated PTH level. In CKF progression, especially when starting hemodialysis treatment, the compensatory mechanisms for disturbed homeostasis become ineffective and exacerbate pathological changes. Due to drastically decreased filtration, the tubular mechanisms are not capable of restoring calcium and phosphorus balance. The kidneys are not capable of synthesizing active vitamin D3 that plays a role in hypocalcemia and hyperplasia of the parathyroid glands [19]. Bone resorption induced by excess PTH results in the formation of sparingly soluble calcium phosphate compounds and their deposition in the vascular wall, myocardium, soft tissues, thereby leading to irreversible ischemic changes in organs and tissues, which greatly increases the risk of patients' death [18].

In this case, tertiary hyperparathyroidism develops, which results from SHPT progression and presents with autonomous parathyroid hyperfunction and impaired
feedback mechanisms among calcium level, PTH secretion level, and morphological gland restructuring with adenoma formation [20].

OP is the only manifestation of hyperparathyroidism which is diagnosed in asymptomatic or minimally asymptomatic disease forms. However, in all forms involving hyperparathyroidism, BMD decreases and 72% of patients are diagnosed with OP. At the same time, the manifestation of SHPT characterizes its neglected phase as at that moment, organs and systems undergo irreversible changes resulting in severe disability, and in some cases, even in death. Therefore, there is a need for the early detection of hyperparathyroidism which should be based on laboratory results rather than clinical symptoms. The early diagnosis of impaired BMD and rapid bone mass loss using densitometry techniques may be reasonable [18].

The Kidney Disease Improving Global Outcomes (KDIGO) introduced the term ‘chronic kidney disease - mineral and bone disorder’ (CKD-MBD) and its classification [14]. According to the KDIGO guidelines, this term should be used if at least one of the following signs is present:
- abnormal biochemical parameters of calcium, phosphorus, PTH, or vitamin D metabolism;
- abnormalities in bone turnover, mineralization, volume, linear growth, or strength;
- vascular or other soft-tissue calcification [21].

According to research evidence collected over many years, the pathogenesis of developing mineral and bone abnormalities is complex and multifactorial. PHT, vitamin D, and calcitonin have been found to be the three major hormones regulating calcium and phosphorus homeostasis. With a reduction in glomerular filtration rate (GFR) to below 60 ml/min/1.73 m2, the filtered load of phosphorus decreases and its serum level increases, resulting in high PHT secretion [22].

According to the latest research findings, hyperphosphatemia stimulates the secretion of fibroblast growth factor (FGF) 23 by osteocytes. Recently, FGF23 has been shown to inhibit renal tubular phosphate reabsorption by increasing its clearance that suppresses PHT secretion in the early stages of kidney diseases. Progressive deterioration of kidney function leads to reduced response to elevated FGF23 level, and, hence, serum phosphate level increases [23].

End-stage CKD patients are at an extremely high risk of bone fractures due to the high incidence of uremic OP and mineral bone disorders [24]. Uremic patients are more prone to be diagnosed with abnormal bone metabolism, a disarranged bone microarchitecture, lower bone mass, and musculoskeletal fragility than healthy individuals [25]. The concept of ‘uremic OP’ has been recently introduced by Fukagawa et al. to explain the role of uremic toxins in affecting bone quality in CKD patients [26]. Accumulated uremic toxins have a noxious effect on bone metabolism and functions by impairing the quality and quantity of bone mass.

Since disorders of calcium and phosphorus metabolism often occur during the early stages of CKD, worsen in impaired kidney function, deteriorate life quality, become an additional cause of disability, and increase the mortality rate among nephrology patients, further study of the pathogenetic mechanisms of the formation of mineral metabolism disorders and parathyroid dysfunction in CKD patients, as well as the development of new methods for the prevention and effective correction of these abnormalities are necessary.

COPD is a socially significant multifactorial pathology, with exogenous, endogenous, epigenetic, and stochastic factors being involved in its development and formation. COPD develops gradually, resulting from a combination of risk factors (tobacco exposure from active smoking or passive exposure to second-hand smoke, occupational factors, air pollution) [27]. Aging is an important risk factor for COPD as well, as disease develops mainly in middle-aged adults and elderly people [28]. At the same time, COPD patients taking GCs for a prolong period of time have been found to be at risk of mineral metabolism disorders. The structure and function of the skeletal system, the activity of metabolic processes, and the intensity of bone remodeling are interconnected. The systemic inflammatory process and metabolic disorders in COPD patients accelerate bone resorption, especially in elderly people and postmenopausal women.

Several studies have found that the progressive loss of alveolar bone height in individuals with periodontal diseases is indirectly caused by both the effects of local pathological factors and the presence of systemic diseases [29]. The active resorptive and destructive processes in the alveolar bone of patients with generalized periodontitis are associated with accelerated bone mass loss, impaired bone metabolism, unbalanced remodulation processes, and the predominance of resorption processes over osteosynthesis. Therefore, a BMD test is considered as the most reliable method for studying the structure and function of the skeletal system in such patients. Currently, several studies have found that COPD patients develop generalized periodontitis and systemic OP earlier than individuals without somatic pathology [27,29]. Therefore, studies on the relationship between the density of the spongy substance of the alveolar bone and OP in such cohort of patients are ongoing.

In patients with bronchopulmonary pathology, OP is considered as a secondary condition. In such patients, inflammatory processes relevant to the underlying condition directly affect bone resorption. Pro-inflammatory cytokines activated in COPD patients play an important role in the regulation of bone metabolism. Due to this, COPD patients develop an imbalance be-
tween inflammatory mediators suppressing osteoclastogenesis (tumor necrosis factor alpha (TNF-α), interleukin 1 (IL-1), IL-3) and activating bone metabolism (IL-11, macrophage colony-stimulating factor). Thus, the relationship among the inflammatory process in the bronchopulmonary system, bone remodeling, and bone mass loss is explained [30,31].

In addition, another important risk factor for OP in COPD patients is taking inhaled GCs which, according to the generally accepted recommendations, should be included in the background therapy for Stage III and Stage IV COPD. Developing OP in adults and affecting linear growth in children are the proven systemic effects that occur in response to high doses of inhaled GCs (daily doses of over 1,000 μg of beclomethasone dipropionate and 750 μg of fluticasone). CG-induced OP results from enhanced bone resorption and reduced bone formation [30,32].

To diagnose OP in COPD patients, accurate collection of medical history and some laboratory findings, including complete blood count, biochemical profile (serum calcium and phosphorus, alkaline phosphatase, osteocalcin, and serum 25(OH) D3 for excluding vitamin D deficiency) are essential. The examinations should be carried out at the time of diagnosis, prior to pathogenetic therapy, and once a year after therapy. Dual energy x-ray absorptiometry (DXA) is considered to be gold standard for diagnosing OP; in addition, thoracic and lumbar spine x-rays in anterior and lateral projections, as well as the Fracture Risk Assessment Tool (FRAX) are useful.

In recent years, an increase in the morbidity and mortality among patients with sarcoidosis has been observed as well. Young patients with sarcoidosis who take GCs often develop osteopenia. The degree of reducing BMD increases proportionally to reducing the vital capacity (VC). Moreover, there is a negative correlation between BMD characteristics and the level of reducing BMD increases proportionally to reducing the vital capacity (VC). Moreover, there is a negative correlation between BMD characteristics and the level of reducing BMD increases proportionally to reducing the vital capacity (VC). Moreover, there is a negative correlation between BMD characteristics and the level of reducing BMD increases proportionally to reducing the vital capacity (VC). Moreover, there is a negative correlation between BMD characteristics and the level of reducing BMD increases proportionally to reducing the vital capacity (VC). Moreover, there is a negative correlation between BMD characteristics and the level of reducing BMD increases proportionally to reducing the vital capacity (VC). Moreover, there is a negative correlation between BMD characteristics and the level of reducing BMD increases proportionally to reducing the vital capacity (VC). Moreover, there is a negative correlation between BMD characteristics and the level of reducing BMD increases proportionally to reducing the vital capacity (VC). Moreover, there is a negative correlation between BMD characteristics and the level of reducing BMD increases proportionally to reducing the vital capacity (VC).

An important strategy for sarcoidosis treatment is using GCs, the effectiveness of which has been proven by several randomized trials [33,34]. At the same time, studying the remote outcomes of long-term GC therapy indicates the high rate of recurrences occurring within a year after therapy and high risk of secondary OP [35]. This implies the need for monitoring BMD and drug treatment of calcium metabolism disorders, if necessary.

**Conclusions**

Hence, OP is the most common and dramatic in terms of consequences bone disease. Its development is clinically determined by numerous factors, including age, body weight, menopausal status, taking GCs and other drugs affecting bone metabolism, comitant

conditions, etc. At the tissue level, these factors lead to the imbalance between osteoclast-mediated bone resorption and osteoclast-mediated bone formation, with impaired bone homeostasis, thereby resulting in bone mass loss.

Therefore, patients with CKD, COPD, and pulmonary sarcoidosis are at higher risk of secondary OP. Such patients more frequently present with low-energy fractures, especially in case of unjustified prescriptions of GCs. The use of inhaled GCs reduces adverse effects but does not eliminate them. In this regard, in patients with chronic pulmonary diseases and CKD, bone density should be measured and in case of low MBD values, further short-term preventive and strategic recommendations should be given.

**References**

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