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Features of etiology and pathogenesis of osteoporosis in patients with chronic obstructive pulmonary disease

Key words: *chronic obstructive pulmonary disease, osteoporosis, pathogenesis.*

Chronic obstructive pulmonary disease (COPD) accompanied by related pathology is one of the greatest pressing medical and social problems worldwide. It is due to the high level of incidence, invalidization and lethality resulting both from the main disease as well as from the related pathologies. COPD leads to decrease in the quality of life and loss of labor capacity among the population. At the same time the development of COPD worsens severely when compounded by any related diseases [1].

Epidemiological research data shows that COPD prevalence rate in the world is 7,6 %, in Europe 7,4 %. Among the smoking population this rate reaches 11 % [17].

COPD remains one of the few diseases with a mortality rate that is not decreasing but continuously growing. The World Health Organization (WHO) forecasts that by the year 2030 COPD will be, among other things, the number 4 cause of death amounting to nearly 4,7 billion lethal incidents per year [1].

COPD results in high financial expenses – both direct (healthcare budget for diagnosis and treatment) as well as indirect (economic expenses due to invalidization, sick pay, premature mortality, additional family expenditures when caring of the sick). Within the European Union the general direct costs for the respiratory diseases amount to about 6 % of the total healthcare budget, 56 % of which goes to COPD [17].

According to GOLD (Global Initiative for Chronic Obstructive Lung Disease) definition, COPD is a preventable and treatable disease featuring persistent obstruction of airways, normally progressing and associated with unusual inflammatory response of the lungs to the harmful particles or gases. Aggravation or related diseases exacerbate the general critical condition of a patient leading to uncontrolled development of COPD [4, 17].

Many COPD patients show systemic (extrapulmonary) developments significantly effecting both quality of life and

viability. Clear airway obstruction, especially lung hyperinflation, have an adverse effect on cardiac function. Fatigue, anorexia and weight loss due to muscle loss – all belong to normal symptoms among patients with severe COPD. Body mass index (BMI) of such patients may drop to < 20. Inflammatory mediators persistence in the blood flow leads to muscle loss and to a drop in weight, which leads to development of cachexia, worsening of ischemic heart disease, heart failure, osteoporosis, diabetes mellitus, depression, sexual activity reduction [1, 4, 5, 17].

Therefore GOLD has included in its recommendation for 2011 a new COPD classification that is based on a change in the attitude to clinical assessment of a patient. Thus, the COPD clinical assessment should be based on the following: 1) estimation of intensity of the clinical symptoms; 2) complications risk forecast; 3) severity of spirometric disorders; 4) detection of severe related diseases and pathologic conditions (ischemic heart disease, heart failure, cardiac fibrillation, arterial hypertension, osteoporosis, anxiety and depressive disorders, lung cancer, diabetes mellitus, liver failure, chronic infections) [1, 17].

Osteoporosis deserves special attention. In COPD patients it is a secondary development that appears as a result of a systemic inflammatory process, metabolic disorders, long-term hypoxia arising on the background of respiratory failure and decreased physical activity and is systemic in its nature [4, 12, 13, 18].

As reported by some epidemiologic researches the incidence of osteopenia and osteoporosis in COPD patients is up to 60 %. In case of a long-term development and progression of COPD, osteoporosis has more frequent occurrence [5].

Osteoporosis (OP) – is a progressive systemic skeletal disease, characterized by reduced bone mass and disorders in microarchitectonics of bone tissue leading to increased bone fragility and risk of fracture [8].

The most frequent sites of pathologic fracture preconditioned by osteoporosis are vertebrae, ribs, wrists, hip (femoral neck), proximal part of humerus, pelvic bones. Such fractures often lead to patient disability or fatality [3, 9, 11, 14].

At present, when offering medical help to COPD patients, the attention to diagnosis and treatment of related osteoporosis is insufficient.

In 2008 a group of WHO experts developed a tool for risk assessment of osteoporosis and its complications among men and women with and without estimation of bone mineral density (BMD) [5]. The use of FRAX (Fracture Risk Assessment Tool) when estimating risk of fracture has been supported by other organizations involved in the osteoporosis issue, such as International Osteoporosis Foundation, National Osteoporosis Foundation, the American Society for Bone and Mineral Research, the International Society for Clinical Densitometry etc. [2, 6].

FRAX is a method (a tool) for a 10-year risk assessment of fractures of the hip bone and of other significant osteoporotic fractures (radius, humerus, clinically significant fractures of the vertebrae and femur) developed on the basis of consideration of age, body mass index and clinical risk factors of fractures with or without a research of BMD of femoral neck in men and women [16].

Unfortunately, up till now the use of FRAX algorithm for Ukrainian population as well as for other CIS countries is possible only with the use of data from other countries due to the fact that, despite the epidemiological research conducted within the recent decades by Ukrainian scientific and medical center for osteoporosis, the official statistical data is insufficient for determination of the FRAX values [6, 16, 20].

Conducting large-scale epidemiological studies will reveal regional differences in osteoporosis-related fractures in different areas of the country and determine the 10-year probability of osteoporotic fracture risk for the population of Ukraine. In the event of inability to use own (country-specific) data to calculate fracture risk the International Association of Osteoporosis recommends using data of a population that is geographically, ethnically and otherwise (frequency of osteoporosis and fractures occurrence) closest to the studied sample.

Nevertheless, like any other method, FRAX algorithm has some limitations that should not be neglected [6, 10, 16, 20].

1. For patients under 65 years of age, the therapeutic approach should be determined on the basis of the combination of risk factors and densitometry outcomes.

2. FRAX should not be used for women at pre-menopause, men under 50 years of age and children.

3. The FRAX method allows making an estimation of fracture risk rate, but offers no direct answer whether "to treat or not to treat". A clinician makes the decision as to the beginning of a treatment.

4. Despite the fact that most clinical risk factors have a dose-related influence on the fracture risk, FRAX provides only «yes» or «no» answers, which could result in under- or overestimation of real fracture risk. Unlike other risk estimation tools (Garvan nomogram), the FRAX model considers the risk factor but not the level of its severity (for example:

the dose and duration of glucocorticosteroid (GCS) administration, the number and type of previous fractures, duration and actual circumstances as to alcohol intake and smoking) that could influence the criteria under research.

5. As of now the FRAX method tolerance has not been established.

6. The FRAX model includes only BMD indicators of the hip bone and does not employ BMD indicators for lumbar spine and peripheral skeleton, which limits risk calculations for other fractures.

7. The FRAX model does not include BMD indicators for biochemical markers of bone remodeling that speak of the intensity of the remodeling of bone tissue and the extent of its loss.

8. As of today, the FRAX model has not been established for all countries nor ethnic population groups, which limits its application.

9. The majority of patients researched for fracture risk rate under the FRAX algorithm were women.

10. FRAX may not be used for patients undergoing anti-osteoporotic treatment (may not be used to estimate the treatment effectiveness).

Besides, FRAX (Fracture Risk Assessment Tool) [16], that lays foundation for ACR (American College of Rheumatology) 2010 recommendation and European League Against Rheumatism (EULAR) recommendation on osteoporosis treatment as well as IOF (International Osteoporosis Foundation) recommendations, does not reflect the actual issues of etiology and pathogenesis of secondary osteoporosis in COPD patients, and thus FRAX may not be effectively applied to this patients contingency. As an alternative to the FRAX system, ACR suggests using fracture risk estimation chart based on the results of X-ray densitometry.

Table 1 shows general questions from the FRAX questionnaire. However, essentially they do not reflect the pathogenesis of COPD development and its complications which include osteoporosis [1]. Thus, in order to reveal secondary osteoporosis during COPD, it would be useful to consider duration and severity of the disease, frequency of exacerbations, its clinical and functional characteristics, the doses, duration and ways of administration of GCS.

The FRAX questionnaire is largely targeted at menopausal women and men over 50 years of age [6, 7, 16]. However, with COPD there is a different consistent pattern. There is a greater occurrence rate among men rather than women, age 40 and up, primarily among the smokers or those who used to smoke at some earlier point in life. Among urban residents it is almost twice as often as among rural population. Besides, the actual COPD diagnosis rate is rather low. According to population-based screening studies, among patients with first-time COPD only 20 % were previously diagnosed with it. The situation also impairs diagnosing of secondary osteoporosis conditioned by COPD [1].

COPD belongs to environmentally-caused diseases developing under a variety of factors, smoking being the greatest one [1, 17]. Epidemiological research supports that active tobacco smoking is the major factor for the risk of COPD development as well as for secondary osteoporosis in the future. If a patient smokes or used to smoke in the past,

Questions from the FRAX Questionnaire			Table 1
No	Question	Answer	
1	Age	Input data here	
2	Gender	1 - male; 2 - female	
3	Body mass, kg	Input data here	
4	Height, cm	Input data here	
5	Have you ever had bone fractures?	No – 1; yes – 2	
6	Did your parents ever have femoral neck fractures?	No – 1; yes – 2	
7	Do you smoke?	No – 1; yes – 2	
8	Are you taking glucocorticosteroids?	No – 1; yes – 2	
9	Have you ever had rheumatic arthritis?	No – 1; yes – 2	
10	Do you have secondary osteoporosis?	No – 1; yes – 2	
11	Are you taking alcohol (3 or more ounces* per 24 hours)?	No – 1; yes – 2	
12	Femoral neck BMD indicator	Input data here	
Note: In different countries 1 ounce of alcohol equals 8 to 10 ml of alcohol that amounts to one standard glass of beer (285 ml), one measuring cup of dehydrated alcohol (30 ml), a medium-size glass of wine (120 ml), one measuring cup of aperitif (60 ml).			

the smoking intensity needs to be estimated in order to calculate the smoking index (SI).

$SI \text{ (pack-years)} = \text{number of cigarettes per day} \times \text{smoking experience (years)} / 20.$

The smoking index exceeding 10 pack-years is the most important factor for risk of COPD and its complications.

It has been determined that COPD-induced morphological changes mainly affect distal airways, pulmonary and vessel parenchyma causing emphysema.

Tobacco smoke or any other inhaled aggressive substances cause lung inflammation that, given the COPD, develops into pathology. Oxidative stress and proteinase excess in the lungs are considered the main COPD development mechanisms. Oxidants generated by the tobacco smoke or other harmful particles are released from the activated inflammation cells – macrophages and neutrophils. Biomarkers of oxidative stress can be detected in expired breath condensate, sputum and blood circulation system of COPD patients. The oxidative stress increases dramatically at exacerbation of the disease. Numerous researches prove a proteinase misbalance in the lungs of COPD patients between those that destroy components of the connective tissue and those that fight against the process. A proteinase-dependent destruction of elastin – the main component of the connective tissue – is the leading factor for development of emphysema.

Inflammation in COPD has a systemic nature. The inflammation mediators appearing in COPD employ inflammation cells from the circulation (chemotactic effects), aggravate the inflammation process (proinflammatory cytokines) and induce structural changes (growth factors). As a result pathomorphological changes specific to COPD emerge: mucus hypersecretion, airflow speed limitation, and «air traps» that lead to hyperinflation of the lungs. Morphologically, early

stages of COPD show a nonsuppurative inflammation and hypersecretion of mucus in the bronchi greater than 2 mm in diameter, less pronounced productive inflammation – in the bronchioles of smaller diameter with the absence of pathological changes in the area of acini. Characteristic features of inflammation in COPD are: increased number of neutrophils, macrophages, lymphocytes CD8⁺ and Tsl-lymphocytes, which are detected only in smokers. The degree of inflammation, exudation and fibrosis in the distal bronchi correlates with a decrease in forced expiratory volume within the first second (FEV₁) and the ratio of forced expiratory volume within the first second to forced vital capacity of the lungs (FVC) – FEV₁ / FVC. The reduction of the ratio of FEV₁ / FVC to less than 70 % after inhalation of 400 mcg of salbutamol (reversibility test) is the diagnostic criterion for COPD [22]. The severity of the obstruction is evaluated in accordance with the FEV₁ value after a test with a bronchial spasmolytic (table 2).

Identification of an obstruction that persists after administration of the bronchial spasmolytic confirms COPD [1, 17, 22]. In addition the 2011 GOLD documents observed that the I - II severity stages (FEV₁ > 50 %) provided a low risk of systemic complications, and at III-IV stages (FEV₁ < 50 %) – a high risk.

Also the number of exacerbations experienced within the last year should be taken into account. Two or more COPD exacerbations requiring treatment within the last 12 months serve as a reliable prediction of frequent exacerbations and hospitalization in the future. Therefore, exacerbation and systemic complication risk forecast in COPD patients is assessed according to and depends on clinical symptoms of the disease, spirometric values and exacerbations experienced earlier.

Stage Signs (Grade of Severity of Development) of COPD		Table 2
The Stage and Severity of COPD Development	COPD Signs	
I, Mild	- $FEV_1/FVC < 70\%$; - $FEV_1 \geq 80\%$ of the normal value; - Usual, but not always, chronic cough, sputum discharge	
II, Moderate	- $FEV_1/FVC < 70\%$; - $50\% \leq FEV_1 < 80\%$ of the normal value; - Symptoms progress, dyspnea on physical exertion and during exacerbations	
III, Severe	- $FEV_1/FVC < 70\%$; - $30\% \leq FEV_1 < 50\%$ of the normal value; - Increasing dyspnea, recurrent exacerbation, worsening of the quality of life of the patients	
IV, Very severe	- $FEV_1/FVC < 70\%*$, $FEV_1 < 30\%$ of the normal value, or $FEV_1 < 50\%$ of the normal value accompanied by chronic pulmonary disease; - Further symptoms progression, dramatic drop in the quality of life, exacerbations may be life-threatening	
Note: * – In case of a very severe course of COPD and significant drop in FVC ratio the FEV_1/FVC increases and loses its diagnostic value.		

Peripheral obstruction leads to airflow speed limitation and progressive increase of «air traps» during exhalation and the formation of lung hyperinflation. The hyperinflation develops on the earlier stages of COPD and is the leading mechanism for the development of expiratory dyspnea. Dynamic (on physical exertion) hyperinflation leads to increased dyspnea and decrease in physical exercise tolerance.

Development of centrilobular (mainly in the upper segments of the lungs) emphysema, begins devastation of the capillary bed, as well as thickening of the walls of the arteries due to intimal proliferation, and in the areas of emphysema – of their muscular walls as well. The gradual destruction of lung parenchyma, which is caused by emphysema, increases «air traps» during exhalation. Bronchodilators reduce «air traps», and thus improve the clinical picture and exercise tolerance in COPD [3, 15, 19].

Moreover, one of the most important factors for osteoporosis in patients with COPD is vitamin D deficiency [23], which also needs to be considered when diagnosing and treating patients with comorbidity.

For objective evaluation of physical exercise tolerance the 6-minute walking test is used (table 3).

The 6-Minute Walking Test for Physical Exercise Tolerance		Table 3
Functional class	6-minute distance, m	
0	550	
I	426–549	
II	301–425	
III	151–300	
IV	< 150	

In order to assess the degree of clinical symptoms, GOLD 2011 recommends using the Modified Medical Research Council Dyspnea Scale (MMRC) (table 4) or the simple questionnaire of COPD Assessment Test (CAT) (table 5).

Using CAT-Assessment Test is preferred because it gives a fuller description of the functional condition of a patient. It is needless to use both charts.

When MMRC score is ≥ 2 or CAT test score is ≥ 10 the patient is considered to have severe symptoms and great risk of complications.

Based on the assessment of clinical symptoms, functional parameters and the risk of possible complications it is proposed to allocate four clinical groups of patients with COPD – A, B, C and D (table 6).

Therefore, the clinical groups C and D have the greatest risk of exacerbation and systemic complications, and thus require mandatory examination for detection of secondary osteoporosis.

The strategic focus of the COPD drug therapy is to control symptoms of bronchial obstruction, inflammation, disorders of mucociliary clearance (at basic pharmacotherapy), cessation of relapses that occurred and prevention of recurrent exacerbations, which will allow for slowing down of the progression of the disease.

The bronchodilators (bronchial spasmolytics) that combine several groups of pharmacological medications take a leading role in comprehensive pharmacotherapy of COPD. These are the following: short- and long-acting β_2 -agonists, short- and long-acting anticholinergic drugs for inhalation use, as well as methylxanthines (or phosphodiesterase inhibitors).

GCS take a special place in COPD therapy [19]. GCS do not affect the neutrophilic inflammation in the bronchi in COPD and do not have direct bronchodilator effect, but may have indirect effect: reduce swelling of the mucous membrane of the bronchi and thus improve the clarity of airways, increase the sensitivity of β_2 -receptors of the bronchi to the respective drugs, stimulate the production of surfactant, reduce the taxis

Modified Medical Research Council Dyspnea Scale (MMRC)		Table 4
Degree of dyspnea	Clinical profile	
0	The dyspnea appears only during considerable physical exertion.	
1 (mild)	The dyspnea appears only during brisk walking or walking up-hill.	
2 (moderate)	The dyspnea causes to slow down the walking as compared to peers or forces one to make stops while walking at a normal pace on flat terrain.	
3 (severe)	The dyspnea makes one make stops in walking a distance of up to 100 m or after a few minutes of walking on flat terrain	
4 (very severe)	The dyspnea makes it impossible to leave one's home or appears when dressing and undressing.	

CAT-Assessment Test									Table 5
Statement	Score (gradation)						Statement	Total	
I never cough	0	1	2	3	4	5	I cough all the time		
I never spit sputum at all	0	1	2	3	4	5	My chest is packed with sputum		
I do not have a constraint feeling in my chest	0	1	2	3	4	5	I feel my chest to be very constricted		
I do not experience dyspnea when walking up-hill or walking up one flights of stairs	0	1	2	3	4	5	When I walk up-hill or walking up one flight of stairs I experience acute dyspnea		
I am not limited in my everyday activity	0	1	2	3	4	5	I am greatly limited in my everyday activity		
I can easily leave my house without paying much attention to my lungs	0	1	2	3	4	5	I am greatly concerned when I leave my house due to my lung condition		
I sleep without waking up (due to breathing problems)	0	1	2	3	4	5	I wake up due to breathing problems		
I am full of energy	0	1	2	3	4	5	I have no energy at all		
Total score									

of polymorphonuclear leukocytes to the lungs, increase the activity of protease inhibitors in bronchial secretions, reduce the secretion of bronchial mucus glands and goblet cells. If administered regularly, inhaled glucocorticosteroids (IGCS) improve clinical symptoms, the lung function, the quality of life and reduce the frequency of exacerbations in patients with $FEV_1 < 60\%$. Their combination with long-acting β_2 -agonists provides additional clinical benefit [1, 17].

During COPD exacerbation the following therapy algorithm is recommended:

1) High doses of inhaled bronchial spasmolytics (short-acting β_2 -agonists or short-acting anticholinergic drugs, or a combination of the two); a spacer or a nebulizer may be used for their administration;

2) High doses of systemic GCS, equivalent of 30–40 mg of prednisolone, administered orally or parenterally for 7–14 days;

3) Antibacterial medications, in the event of purulent sputum.

Therefore, with patients receiving inhaled or oral GCS within their comprehensive treatment for COPD one should always take into account their equivalent dose in prednisolone to determine the risk of osteoporosis [21].

Radiographic changes specific to osteoporosis are detectable when bones lose 20–40 % of calcium. Some authors point out that in many cases the severity of osteopenia on radiographs does not correlate with fractures of the spine [1].

Therefore, to determine the final diagnosis of secondary osteoporosis and monitor the effectiveness of the treatment it is advisable to use X-ray bone densitometry.

The following types belong among the methods of X-ray densitometry: dual energy X-ray densitometry (absorptiometry), peripheral bone densitometry, double-photon absorptiometry [2]. However, due to the high cost and lack of appropriate equipment in most medical institutions of Ukraine, these methods remain scarcely available for mass screening of patients with COPD.

Classification and Clinical Group Allocation Chart for COPD (A, B, C, D - depending on severity of symptoms and risk of complications)

Table 6

Group	Description	Spirometric severity of obstruction	Exacerbations per year	Dyspnea according to MMRC	Functional status according to CAT
A	Low risk, mild clinical symptoms	1–2 (FEV ₁ ≥ 50 %)	≤ 1	0–1	< 10
B	Low risk, considerable clinical symptoms	1–2 (FEV ₁ ≥ 50 %)	≤ 1	≥ 2	≥ 10
C	High risk, mild clinical symptoms	3–4 (FEV ₁ < 50 %)	≥ 2	0–1	< 10
D	High risk, considerable clinical symptoms	3–4 (FEV ₁ < 50 %)	≥ 2	≥ 2	≥ 10

Conclusion

Osteoporosis occurs secondary to COPD, as a result of complications of the underlying disease, and therefore is closely related to the pathogenesis of COPD.

The FRAX questionnaire cannot be used effectively to diagnose osteoporosis in patients with COPD because it does not take into account the major pathogenetic mechanisms of secondary osteoporosis in this pathology, namely: the presence of chronic systemic inflammation and systemic complications, the course of the underlying disease, the clinical group of the patient, effects of harmful factors that influence the occurrence and course of the disease (smoking index), the doses of inhaled or systemic GCS administered to the patient that may also influence the development of osteoporosis. Therefore, the scale of the diagnosis of secondary osteoporosis should include specific clinical and functional parameters characterizing the severity of COPD and the likelihood of development of osteoporosis.

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**ОСОБЛИВОСТІ ЕТІОЛОГІЇ ТА ПАТОГЕНЕЗУ
ОСТЕОПОРОЗУ У ХВОРИХ НА ХРОНІЧНЕ
ОБСТРУКТИВНЕ ЗАХВОРЮВАННЯ ЛЕГЕНЬ**

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Резюме

В статті висвітлені актуальні питання пов'язані з особливостями етіології і патогенезу остеопорозу у хворих на хронічне обструктивне захворювання легень (ХОЗЛ).

Остеопороз при ХОЗЛ виникає вторинно, як наслідок ускладнення основного захворювання, а тому тісно пов'язаний з патогенезом ХОЗЛ.

Для оцінки ризику виникнення вторинного остеопорозу при ХОЗЛ необхідно враховувати наступні фактори: вираженість хронічного системного запалення і системних ускладнень, тривалість перебігу основного захворювання, клінічну групу, до якої відноситься хворий, дії ушкоджуючих факторів, які впливають на виникнення і перебіг захворювання (індекс паління), дози інгаляційних або системних глюкокортикостероїдів, які отримує хворий і які можуть також впливати на розвиток остеопорозу. Тому до шкали діагностики вторинного остеопорозу доцільно включати конкретні клініко-функціональні показники, які характеризують ступінь тяжкості ХОЗЛ і вірогідність розвитку остеопорозу.

Ключові слова: хронічне обструктивне захворювання легень, остеопороз, патогенез.

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**FEATURES OF ETIOLOGY AND PATHOGENESIS
OF OSTEOPOROSIS IN PATIENTS WITH CHRONIC
OBSTRUCTIVE PULMONARY DISEASE**

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Summary

The article illuminated current issues related to the characteristics of the etiology and pathogenesis of osteoporosis in patients with chronic obstructive pulmonary disease (COPD).

Osteoporosis occurs secondary to COPD, as a result of complications of the underlying disease, and therefore is closely related to the pathogenesis of COPD.

To assess the risk of secondary osteoporosis in COPD one should consider the following factors: expression of chronic systemic inflammation and systemic complications, duration of the underlying disease, the clinical group to which the patient belongs, the dose of damaging factors that influence the occurrence and course of the disease (an index of smoking), dose of inhaled or systemic corticosteroids, administered to the patient and which can also affect the development of osteoporosis. Therefore, the scale of the secondary diagnosis of osteoporosis is appropriate to include specific clinical and functional parameters that characterize the severity of COPD and the accuracy of osteoporosis.

Key words: chronic obstructive pulmonary disease, osteoporosis, pathogenesis.

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