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PATHOPHYSIOLOGICAL ASPECTS OF PULMONOGENIC OSTEOPENIA

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Abstract: It has been established that a decrease in bone density is diagnosed in 78% of patients with chronic obstructive pulmonary disease (COPD). The incidence of osteoporosis (OP) was higher in pulmonary emphysema than in chronic obstructive bronchitis, and the degree of bone density decrease is largely determined by the severity of bronchial obstruction. In 73.6% of cases, there is an increase in bone resorption with relatively stable bone formation. body weight deficiency, the incidence of OP is significantly higher than in patients with a normal body mass index. The presence of close correlations between pro-inflammatory cytokines, bone density and markers of bone metabolism in patients with COPD determine a significant role of cytokine-mediated mechanisms in the pathogenesis of pulmonogenic osteopenia.

Introduction. The physiological meaning of bone remodeling is its constant renewal to preserve the mechanical resistance of the bone matrix, which in turn is the basis for the functional adaptation of bone tissue to everyday load [1]. Bone metabolism takes place with the participation of osteoclasts (OCs), which are responsible for the resorption of the old calcified matrix, and osteoblasts (OBs), which occupy a central place in the processes of bone tissue synthesis [6].

Bone remodeling is a complex, continuous process [5] and in a normally functioning organism is mediated by the conjugate activity of the OC and OB, the functional activity of which is regulated by a whole complex of systemic and local mechanisms. Their disruption leads to an imbalance between the processes of formation and resorption, the reaction of bone tissue to the presented effects goes beyond the limits of physiological parameters. All this disrupts the quantitative and qualitative composition of bone tissue, contributes to the development of osteoporosis (OP) and related fractures [6].

The most informative way to assess bone metabolism is to determine the level of enzymes reflecting osteoblastic and osteoclastic activity. The study of the latter in clinical practice is used to identify patients with rapid bone loss and determine the type and rate of bone metabolism, which is essential for clarifying the pathogenetic mechanisms of various forms of OP, choosing adequate treatment and monitoring its effectiveness.

In recent years, some progress has been made in understanding the pathophysiological mechanisms of primary and secondary forms of OP [11, 12]. Among the latter, a special place belongs to changes in bone metabolism in chronic obstructive pulmonary diseases (COPD). Thus, according to our data, 75.9% of patients with chronic obstructive bronchitis (COPD) develop osteopenic syndrome [3]. In the pathogenesis of pulmonogenic osteopenias, in addition to the known resorptive effects of glucocorticoids (GC) used in the treatment of some COPD variants, other, non-iatrogenic factors are of particular importance: hypoxia,

altered cytokine profile, hypodynamia, myopathy, etc. [2, 7, 17]. At the same time, the study of this problem is still fragmentary, which prompted us to a more detailed analysis of some of its aspects.

The aim of the study was to comprehensively assess the cytokine profile, biochemical markers of resorption and bone tissue formation in comparison with its density in order to clarify the features of bone metabolism in the main variants of COPD.

Materials and methods. A total of 95 patients with COPD (30 women, 65 men) were examined, with an average age of 54.2±1.4 years, and a disease duration of 4 to 22 years. When making the diagnosis, we were guided by the recommendations of the European Respiratory Union (the level of reduction in forced expiratory volume in 1 second. (FEV1) in relation to due values) [21]. Mild COPD (group 1 - FEV1>70% of the proper values) was diagnosed in 21 patients, moderate (group 2 - FEV1 5069%) - in 44, severe (group 3 - FEV1<50%) - in 30 patients.

According to the known clinical and functional criteria, 2 main clinical variants of COPD have been verified: mainly emphysematous and bronchitis [9]. The clinical picture of the first (57 patients) was dominated by manifestations of pulmonary emphysema (EL). The second variant (38 patients) was characterized by typical signs of COPD.

External respiration function (AHF) assessment in all patients was carried out using the spiroanalyzer "Spirosift-500" (Fucuda, Japan); To determine the reversibility of bronchial obstruction, a discharge test with inhalation of 200 μg of salbut-mol was used, which was considered positive with an increase in FEV1 by 12% or more [8].

Persons receiving GC therapy as the basic therapy, having other concomitant diseases that could have an independent effect on bone metabolism were excluded from the examination. Prior to the start of the examination, the patients did not receive antiresorptive therapy.

Bone density (BCT) was measured by ultrasonic densitometry using the Sound Scan Compact device (Myriad Ultrasound System LTD, Israel) and expressed in standard deviations (SD) from the standard values of peak bone mass (T-test). Normal PCT was diagnosed at T-score values from 1SD to -1SD inclusive, osteopenia (preclinical OP) - from -1SD to -2.5 SD, clinically expressed OP - at SD less than -2.5. Diagnostically significant indicators for severe OP were a decrease in the T-score less than -2.5 SD and the presence of one or more fractures without a significant history of trauma [5].

The state of bone metabolism was judged by the concentration in the blood serum of biochemical markers of bone formation (total alkaline phosphatase - ALP, osteocalcin - OCC - non-collagen protein synthesized by OB specific to bone tissue) and markers of bone resorption (CrossLaps - ^ - a component of C-terminal body peptide of collagen type I). In all patients, basal secretion of parathyroid hormone (PTH) in blood serum was also examined. Blood was taken from the ulnar vein in the morning after a 12-hour fast. The activity of ALP was determined on the biochemical analyzer "COBAS MIRA S" (Switzerland) and expressed in IU/L. The content of OCC, ^, PTH in the blood serum was determined by the enzyme-linked immunosorbent method using kits manufactured by "HOFFMAN LA ROSHE" (Switzerland) on the "ELECSIS" apparatus of the same company.

The determination of interleukins (IL-1P, IL-6, IL-8, tumor-necrotic factor - TNF-a) was carried out using reagents from R&D Diagnostics Inc. (USA) by enzyme-linked immunosorbent assay in the Sen-Dwich version, according to the attached instructions. The results were recorded on the enzyme-linked immunosorbent analyzer "Multiscan" (Finland). Calculations of the number of cytokines (ng/ml) were carried out by constructing a calibration curve using a special computer program. The patients' body mass index (BMI) was calculated according to the generally accepted formula: BMI = body weight in kilograms / square of height in meters. The control group consisted of 50 healthy individuals of similar age and sex.

The results obtained during the study were processed on a personal computer in Microsoft Excel using a statistical data processing package.

Results and discussion. The PCT study showed that the majority of COPD patients develop osteopenic syndrome of varying severity. Thus, in the group as a whole, a decrease in PCT was detected in 74 (77.8%) patients. Moreover, osteopenia was diagnosed in 51.5% of cases, clinically expressed OP in 16.8%, severe OP in 9.4%. Spontaneous fractures occurred in 16.8% of the examined. Fractures were most often localized in the thoracic spine and ribs. This confirms the data that bones with a trabecular structure are affected in OP [14, 22].

The most significant factor determining the degree of PCT decrease was the severity of ventilation disorders (Table). We found that an increase in the degree of FEV1 decrease is accompanied by a regular decrease in PCT ($r=-0.86$, $p<0.01$). In all patients with mild COPD, where the FEV1 level was 80.6±2.2%, densitometric parameters were within the normal range, but significantly lower than the control values ($p<0.05$). PCT values in groups 2 and 3 (FEV, 64.3±1.7% and 35.7 ±1.8%, respectively) were in the range characteristic of osteopenia, reaching minimal values in the latter case. Depending on the clinical form of COPD, there were also certain differences in the structure of osteopenic syndrome. Thus, according to ultrasound densitometry, in 24.5% of patients with COPD, PCT values corresponded to normal values, in 64.9% osteopenia was detected, and only in 12.2% - OP. At the same time, all patients with EL had deviations towards a decrease in PCT, and in 57.8% of cases to the level of osteopenia, in 42.2% - to the level of OP. Despite the absence of significant differences in the incidence of preclinical OP in both groups, the number of patients with a decrease in bone density characteristic of clinically expressed OP significantly increases in EL. At the same time, the majority of EL patients were diagnosed with severe OP complicated by fractures.

The analysis of changes in biochemical markers of bone metabolism significantly expands the understanding of the pathophysiological mechanisms of osteopenic syndrome in patients with COPD. It was established that in the examined, the concentration of C sharply increases, exceeding the same indicator in the control by almost 3 times. At the same time, the degree of elevation of this marker also depended on the clinical variant of COPD: the concentration of COPD was maximum in patients with EL (0.944±0.04 ng/ml, in COPD -0.646±0.06 ng/ml, $p<0.01$).

According to the literature, it is known that SI reliably characterizes the severity of osteopenic syndrome and is important for the identification of patients with rapid bone loss [18, 22]. This is confirmed in our study. Thus, a close inverse correlation was established between the level of S and the PCT value both in COPD ($r = -0.64$, $p<0.05$) and in EL ($r = -0.78$, $p<0.01$). A sharp increase in this parameter in blood serum and its closer relationship with a decrease in PCT in EL also indicates a more pronounced bone resorption in this category of patients. The analysis of changes in the concentration of CF depending on the severity of COPD showed a consistent decrease in it as FEV1 decreased ($g = -0.72$, $p<0.01$). Thus, the maximum level of this indicator was registered in patients of group 3, characterized by a sharp limitation of the ventilation function of the lungs. Therefore, the aggravation of respiratory disorders in COPD is accompanied by a significant increase in bone loss.

The mean values of serum OCC for the entire group of COPD patients did not differ significantly from those in the control group ($p<0.05$), which indicates the preservation of the function of the OB. However, intragroup analysis showed differences in the behavior of this indicator.

Thus, in patients with EL, there was a tendency to reduce the BCC compared to the control values ($p>0.05$), while in COPD its concentration exceeded the same parameter in the control ($p<0.05$). There was a certain dynamics of changes in the GCC depending on the severity of COPD. In the mild form, the content of the OCC exceeded the control values (39.3±2.2 ng/ml, $p<0.05$), and in the moderate course, its concentration

was significantly lower than in the severe course ($p<0.05$). Probably, this phenomenon is explained by a significant spread of individual values of BCC in the blood serum. At the same time, attention is drawn to the features of the relationship between the OCC and the SC, which are grouped into several variants. Thus, in 15 (15.8%) patients, there was a clear increase in both parameters compared to the control values (BCC - 48.96 ±4.9 ng/ml, $p<0.05$, SC - 0.827±0.1 ng/ml, $p<0.01$). In 10 (10.5%) patients, a decrease in the GCC level was accompanied by an increase in the concentration of SC. Among the other patients (73.6%), the GCC values did not differ from the control values, and the SC was elevated.

The peculiar profile of bone metabolism markers in COPD indicates a different direction and intensity of bone remodeling, which in the first case is associated with a symmetrical increase in the processes of resorption and formation, and in the second case is accompanied by a weakening of bone creation against the background of increased bone loss. In other cases, there is a third variant of bone remodeling disorders, which is associated with the intensification of bone resorption with relatively stable bone formation.

The activity of ALP in the blood serum in patients with COPD was reduced compared to the control group (37.64±1.7 U/L and 64.2±2.4 U/L, respectively, $p<0.01$), but its level in none of the cases exceeded the norm. There were no deviations from the norm in the basal secretion of PTH, as well as intragroup differences in this parameter.

Among the possible causes of bone remodeling disorders in COPD, body weight deficit is also discussed, which is considered a strong determinant of bone density [7, 10]. It is known that as COPD worsens and respiratory failure increases, its complications associated with increased catabolic processes come to the fore in clinical symptoms, one of the manifestations of which is significant weight loss, myopathy, etc. [9]. In this regard, in patients with COPD, the dependence of bone density on BMI was considered. The range of this indicator in the examined ranged from 17.9 to 23.8 kg/m2. Depending on the value of BMI, all patients were ranked into 3 groups. With a BMI in the range of 17.5 to 18.4 kg/m2, corresponding to a body weight deficit, there were 9 (9.5%) people; with BMI = 18.5-19.4 kg/m2, corresponding to low nutrition - 27 (28.4%). Normal height-to-weight ratio was observed in 59 (62%) patients (BMI above 19.5 kg/m2). It should be noted that patients with COPD were characterized by a higher BMI (19.6±0.2 kg/m2) compared to that of EL (18.1±0.1 kg/m2, $p<0.01$). It was found that in patients with COPD and body weight deficit (BMI = 17.8±0.1), the incidence of OP is significantly higher than in patients with normal BMI ($p<0.001$), and in patients with reduced nutrition, the average densitometric parameters correspond to osteopenia. A close negative relationship between BMI and serum concentration of C was revealed ($g = -0.74$, $p<0.01$). Therefore, a low BMI can be considered an additional risk factor for the development of osteopenic syndrome in COPD.

A comprehensive analysis of PCT and biochemical markers showed that in most patients, the minimum values of bone density coincide with the corresponding pathological changes in bone metabolism. Extreme manifestations of these changes are osteoporetic fractures. At the same time, in 7 patients with COPD with fractures of various localization, the decrease in PCT did not reach the densitometric criteria of clinically expressed OP, but the concentration of SC in the blood serum was increased. It is likely that an increase in bone resorption significantly increases the risk of fractures regardless of the baseline, often high PCT, which is consistent with data from other studies [5, 18, 22]. This can be explained by the fact that bone fragility in OP is determined not only by its density, but to a large extent by disturbances in the microarchitectonics of bone tissue, the severity of which can be assessed using biochemical markers of bone resorption [5]. Thus, markers of bone metabolism are reliable predictors not only of the rate of bone loss, but also of the risk of fractures.

In recent years, new data have emerged regarding the relationship between inflammatory mediators, which include some cytokines and OPs. It is believed that cytokines play an important role not only in initiating the inflammatory process, but also in regulating the activity of OC and OB [4, 12]. Therefore,

immunopathological mechanisms, which also occupy a certain place in the pathogenesis of COPD, are considered from the point of view of their possible impact on bone tissue remodeling [13, 20]. In response to hypoxia, the concentration of IL-1P, IL-6, IL-8 and TNo-a in the blood serum increases. According to some authors, these cytokines initiate osteoclast-mediated resorption, and IL-1R is one of its most potent stimulators [5, 12, 20]. We have established a close correlation between this indicator and PCT ($r = -0.71$, $p<0.01$) and with the marker of bone resorption C ($r = 0.62$, $p<0.01$). A similar level of correlation with PCT and SC was noted for IL-6, the increase in the concentration of which was maximum as COPD became more severe. The concentration of TNo-a in the blood also increased markedly, which reached peak values in severe COPD. It is interesting to note that in patients with EL this parameter was significantly higher than in patients with COPD ($p<0.01$). It is known that TNo-a is referred to as a molecular marker of myopathies (cachexines), and at the same time it plays an important role in the process of bone tissue resorption [19]. A more significant loss of body weight in patients with EL against the background of more noticeable bone losses is apparently associated with cytokine-mediated mechanisms, which is confirmed by the correlation of TNo-a with PCT ($r = -0.74$, $p<0.01$), BMI ($r = -0.84$, $p<0.001$) and C ($r = 0.71$, $p<0.01$). Interestingly, the increase in IL-8 in all COPD patients correlates only with the value of the BCC ($r = -0.55$, $p<0.05$) and is not correlated with the level of SC. To date, the ability of serum IL-8 to affect bone resorption has not been proven, and its participation in the process of bone remodeling is debatable [7, 16]. Apparently, cytokine-mediated bone resorption is not so much associated with partial hypercytokinemia, but is more due to their systemic synergistic effect on bone tissue [4], which occurs in COPD.

Findings.

1. According to the results of osteodensitometry, a decrease in bone density is diagnosed in 78% of patients with COPD. Preclinical osteoporosis (osteopenia) occurs in 51.5% of patients, and clinically pronounced osteoporosis occurs in 16.8%. The incidence of osteoporosis is higher in pulmonary emphysema than in chronic obstructive bronchitis. The degree of decrease in bone density is largely determined by the severity of bronchial obstruction.

2. Analysis of markers of bone metabolism made it possible to establish several variants of bone remodeling disorders. Increased bone resorption with relatively stable bone formation was observed in 73.6% of patients, increased resorption and formation processes in 15.8%, intensification of resorption and weakening of bone formation in 10.5%.

3. Body mass index is an additional marker of osteopenic syndrome in COPD, which is confirmed by close correlations between this indicator and bone density.

4. The presence of close correlations between pro-inflammatory cytokines, bone density, and markers of bone metabolism in patients with COPD emphasizes the significant role of cytokine-mediated mechanisms in the pathogenesis of pulmonogenic osteopenias.

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