The quality of bone tissue and its mineral density in patients with chronic obstructive pulmonary disease

Abstract. Background. The objective of the work is to study the effect of chronic obstructive pulmonary disease (COPD) on mineral density (BMD) and trabecular bone score (TBS), depending on the degree of severity and women’s age. Materials and methods. We have examined 30 women aged 57.43 ± 7.87 years, patients with COPD of various stages (GOLD 1–4). We have studied the BMD Total, BMD the lumbar spine (L1–L4), BMD Femur, and BMD Radius by means of dual-energy X-ray absorptiometry (DEXA). TBS of the lumbar spine (L1–L4) was determined by the TBS iNsight method (Med-Imaps, Pessac, France). Results. A significant decrease of the BMD was found at every skeletal area starting from GOLD 3, whereas at the L1–L4 level the BMD began to decrease at GOLD 2. The correlation was found between the severity of COPD and BMD Femur (r = –0.75, p < 0.05), BMD Radius (r = –0.73, p < 0.05), BMD L1–L4 (r = –0.80, p < 0.05) BMD Total (r = –0.73, p < 0.05). Starting from GOLD 2, the values of TBS significantly decreased and corresponded to the partial bone quality loss. The most pronounced changes occurred at the level of TBS L, and corresponded to a significant bone quality loss already at GOLD 2. The TBS progressively decreased and at GOLD 3–4 corresponded to a significant loss of bone quality. The correlation was found between the severity of COPD and TBS of the spine at the level of L1–L4 (r = –0.76, p<0.05), TBS of the spine at the level of L2–L4 (r = –0.75, p<0.05). Conclusions. Age equally affects both BMD and TBS in women with COPD, and from the age of 45, these rates progressively decrease. The effect of COPD on bone tissue according to the severity of the disease is heterogeneous at different segments of the axial skeleton. The earliest changes concern the decrease in BMD L1-L4 (1.19 ± 0.05) g/cm² compared to GOLD 1 (1.39 ± 0.05) g/cm² (p < 0.05) and TBS L1 (1.17 ± 0.06) in comparison with GOLD 1 (1.34 ± 0.06; p < 0.05), whose decrease is observed already at GOLD 2.

Keywords: chronic obstructive pulmonary disease; trabecular bone score; bone mineral density

Introduction

The chronic obstructive pulmonary disease (COPD) is one of the most common and widely-spread chronic diseases in the world (7.6 %) associated with a heavy economic burden [1]. According to the recent analysis of pathogenesis, the COPD is considered a multi-system disorder or systemically manifested disorder, since a long-standing chronic inflammation of the respiratory pathways, as well as chronic disorders of pulmonary ventilation, provokes a cascade of pathogenic modifications in the pulmonary tissue, other organs and systems including the cardiovascular, locomotor and other ones [2-4].
metabolic syndrome [9], atherosclerosis, cachexia, anorexia and osteoporosis (OP) [10].

The simultaneous course of COPD and OP will always be accompanied by a syndrome of “mutual encumbrance”, due to the activated chronic infection [11], smoking effect [12, 13], bronchial permeability disorder, developed hypoxia and oxidative stress [14], as well as systemic steroidal treatment [4, 6, 9, 15].

At the moment, there are two opinions as to the interaction between COPD and attending disorders. On one hand, the comorbid pathology arises out of the collateral systemic inflammation resulting from a series of inflammatory and reparative events occurring in the lungs during the COPD [6, 15]. Further on, the OP develops as a secondary COPD systemic effect. On the other hand, the OP may develop independently from the COPD or, in case of the overall developmental factors, one disease increases the risk of other development [13].

The osteoporosis is a wide-spread systemic skeletal disease characterized by a bone loss and structural changes of bone tissue [16]. The bone state depends on various factors; one of the key determinants of its strength and fracture risk being the bone mineral density (BMD) [17], however, the latter is able to predict only up to 60% fracture risk [18]. The bone strength and fracture risk is found to depend on other parameters: structural make-up and existing micro-damage, mineralization and bone metabolism rate [16].

The bone tissue is a dynamic open system with a complex multi-level individual and variable morphological make-up, physic-mechanical properties, chemical composition and biological potential [19]. During the adaptive remodeling, the bone may change its structure and properties due to the regulatory system and local conditions under which it exists, and “according to the biological principle of bone number and function correspondence” [19-21].

The trabecular bone metabolism happens much faster (8 times faster) than the cortical one [18]. Due to this fact, the trabecular microarchitecture’s evaluation increases the precision and sensitivity of bone quality evaluation and fracture risk in the clinical practice.

In case of the extant bone pathology, there is a more precise criterion to evaluate its solidity, as the stiffness and strength depend not only on the mineral content determining the X-ray absorbance [20]. It is the nature of structural-functional disorders and the degree of elementary disorganization of its microstructure which affects the pathological changes of the bone. The biological parameters of the bone tissue such as the quality and presence of osteogenic precursor cells and their colony-forming abilities are no less varied [21]. All of these parameters equally determine the bone quality. They are interdependent, though the character of those ties is very complex; it is thus barely possible to predict the special reactions of bone tissue to the metabolic changes of the ailing body affected by COPD, for instance, using only one criterion (namely the BMD). Because of that, during the recent years there is an increasing number of new diagnostic tools helping to determine the trabecular bone quality, and further, to forecast the risk of low-energy fractures in other population groups.

The aim of this study is to explore the COPD influence on BMD and bone quality depending on the disease severity and women’s age.

Materials and methods

In order to achieve the given aim, there was an open observation cohort study performed at the Department of Clinical Physiology and Pathology of Locomotor Apparatus by the SI “D. F. Chebotaryov Institute of Gerontology” by the NAMS of Ukraine, examining 30 female patients with COPD aged 57.43 ± 7.87 years old (age range: 40–70 years). Their participation was voluntary, all the examined subjects obtained detailed information about the study and signed a consent form.

The study involved patients with a verified COPD diagnosis of over-3 year standing. The COPD diagnosis is made in accordance to the GOLD recommendations and the Healthcare Ministry of Ukraine’s Order #555 as of 27.06.2013 [13, 23]. All the examined subjects were distributed into groups depending on the COPD severity (Table 1). The GOLD 1 (light degree) group is made of patients with FEV1/FVC ≥80 – <90% of the values required after the bronchodilator treatment, the GOLD 2 (medium degree) group – ≥50 – <80%; the GOLD 3 (severe) group – ≥30 – <50%; the GOLD 4 (very severe) group – <30 [4, 13, 23]. Correlation analysis revealed a significant association between COPD severity of illness and its duration (r = 0.78; p < 0.05).

Determination of BMD was performed using dual-energy X-ray absorptiometry (DEXA) (Lunar, 2005, USA). Since osteoporotic changes develop unevenly in different parts of the skeleton, we analyzed the results of DEXA of the total skeleton (Total), the lumbar spine (L1-L4), the femoral neck (Femur), ultra-distal radius (Radius) and total mineral content area (Bone Mineral Content, BMC, g) of the entire skeleton (BMC Total).

| Table 1. The group characteristics of COPD-afflicted patients depending on its severity (M ± SD) |
|---|---|---|---|---|
| Groups | Mean age, years | Height, cm | Weight, kg | Disease duration, years |
| GOLD 1. n = 6 | 47.82 ± 13.54 | 161.00 ± 5.23 | 66.00 ± 6.29 | 10.14 ± 7.24 |
| GOLD 2. n = 6 | 55.71 ± 14.95 | 164.20 ± 10.86 | 71.83 ± 14.93 | 14.09 ± 7.40 |
| GOLD 3. n = 12 | 61.55 ± 13.57 | 165.67 ± 8.24 | 77.75 ± 10.42 | 19.80 ± 10.42* |
| GOLD 4. n = 6 | 60.89 ± 11.97 | 163.50 ± 4.46 | 73.00 ± 14.85 | 23.08 ± 8.55* |

Note. The asterisk * marks significant differences of values in comparison to GOLD 1 (p < 0.05).
Trabecular Bone Score (TBS) was determined by the TBS iNsight method (Med-Imaps, Pessac, France). The software package was installed on a computer osteodensitometer to assess the microarchitecture of the trabecular bone on densitometric images of the lumbar spine (L₁–L₄) (http://www.med-imaps.com) [24–26]. To compare TBS indicators, we used the criteria of their evaluation, created by the Working Group of TBS experts from different countries, by analogy with three categories of BMD assessment for postmenopausal women, namely: normal BMD, osteopenia and osteoporosis [19, 24]. TBS values of 1.35 and more are considered normal, values from 1.2 to 1.35 correspond to a partially disturbed microarchitecture of trabecular bone tissue, and 1.2 or less – a significant violation of it [19].

Statistical processing of the obtained research results was carried out on the basis of the computer program “Statistica 6.1.” (Stat Soft Inc., USA) [27]. The arithmetic mean (M), standard deviation (SD), number of studies (n) were determined. Using parametric and nonparametric statistical methods (Student’s test and Wilcoxon’s W-test for independent small samples). The results of the study were calculated using the metric statistical methods (Student’s test and Wilcoxon’s W-test for independent small samples). The results of the study were calculated using the metric statistical methods (Student’s test and Wilcoxon’s W-test for independent small samples). The results of the study were calculated using the metric statistical methods (Student’s test and Wilcoxon’s W-test for independent small samples).

Results

According to DEXA measurements, 4 (13.33%) patients had normal BMD, 18 (60.0%) were diagnosed with osteopenia, and 8 (26.67%) had osteoporosis.

The assessment of BMD depending on age revealed a decrease in this indicator in the age group 45–59 years at the level of L₁–L₄: 1.12 ± 0.05 g/cm² against 1.15 ± 0.04 g/cm² (t = 0.85; p = 1.48). There was a further decrease in BMD of the relevant areas of the skeleton in the age group 45–59 years at the level of L₁–L₄: 1.12 ± 0.05 g/cm² against 1.31 ± 0.04 g/cm² (t = 0.71; p = 1, 55), BMD Radius – 0.88 ± 0.03 g/cm² against 0.91 ± 0.05 g/cm² (t = 0.85; p = 1.48). There was a further decrease in BMD in the relevant areas of the skeleton in the age group of women 60 years and older: 0.99 ± 0.04 g/cm² (t = 6.13; p = 0.02), 1.14 ± 0.02 g/cm² (t = 4.75; p = 0.04), 0.76 ± 0.02 g/cm² (t = 5.03; p = 0.03), respectively, compared to persons younger than 45 years.

When comparing patients with COPD, distributed according to the severity of the disease, a significant decrease in BMD and T-score in the studied areas of the axial skeleton. No statistically significant differences were found when comparing the GOLD 1 and GOLD 2 groups for BMD Total, Femur and Radius, as well as when comparing the GOLD 1 and GOLD 3 groups for BMD Total and BMC Total (Table 2).

The bone evaluation according to the L₁–L₄ BMD and T-score revealed a significant reduction from GOLD 1 to GOLD 2 (p = 0.021), from GOLD 1 to GOLD 3 and GOLD 4 (p<0.001 for both values). The BMD L₁–L₄ reduction amounted to 49.5 % compared to GOLD 1 and GOLD 4 (p<0.01). The BMD and T-score Femur are significantly diminished in case of GOLD 3 and GOLD 4, especially in comparison with GOLD 1 (p = 0.003 and p = 0.004). The BMD and T-score Radius measurements revealed significant differences of values when GOLD 1 and GOLD 3 were compared (p = 0.037) with GOLD 4 (p = 0.0001). The studies of BMD and T-score Total revealed a significant decrease of values with various levels of evidence-based reliability when GOLD 1 and GOLD 3 were compared (p = 0.005) with GOLD 4 (p = 0.004). The BMC Total index did not reveal any significant changes from GOLD 1 to GOLD 2 (p = 0.975) and GOLD 3 (p = 0.052) while the degree of evidence-based reliability was rather high with GOLD 4 (p = 0.009).

The study of COPD’s degree of severity and how it correlated with the axial skeleton BMD demonstrated a close reverse correlation with the axial skeleton BMD (r = -0.71, p<0.05); BMD Total (r = -0.73, p<0.05); BMD Pelvis (r = -0.71, p<0.05); BMD Total spine (r = -0.72, p<0.05); BMD L₁–L₄ (r = -0.80, p<0.05); BMD Femur (r = -0.75, p<0.05) and BMD Radius (r = -0.73, p<0.05).

The results of our study show that the women afflicted with COPD demonstrate a progressive age-related lumbar spine BMD reduction starting at the age of 45. The evaluation of axial skeleton state depending on the dis-

<table>
<thead>
<tr>
<th>Indicators</th>
<th>GOLD 1, n = 6</th>
<th>GOLD 2, n = 6</th>
<th>GOLD 3, n = 12</th>
<th>GOLD 4, n = 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMD L₁–L₄, g/cm²</td>
<td>1.39 ± 0.05</td>
<td>1.19 ± 0.049*</td>
<td>1.05 ± 0.03*</td>
<td>0.93 ± 0.07*</td>
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<tr>
<td>T-score L₁–L₄, SD</td>
<td>1.90 ± 0.26</td>
<td>-0.17 ± 0.29*</td>
<td>-1.23 ± 0.16*</td>
<td>-2.13 ± 0.38*</td>
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<tr>
<td>BMD Femur, g/cm²</td>
<td>0.96 ± 0.03</td>
<td>0.89 ± 0.05</td>
<td>0.67 ± 0.04*</td>
<td>0.64 ± 0.06*</td>
</tr>
<tr>
<td>T-score Femur, SD</td>
<td>0.38 ± 0.42</td>
<td>-0.23 ± 0.20</td>
<td>-1.93 ± 0.16*</td>
<td>-2.08 ± 0.27*</td>
</tr>
<tr>
<td>BMD Radius, g/cm²</td>
<td>0.58 ± 0.02</td>
<td>0.55±0.04</td>
<td>0.51 ± 0.03*</td>
<td>0.40 ± 0.03*</td>
</tr>
<tr>
<td>T-score Radius, SD</td>
<td>0.58 ± 0.43</td>
<td>-0.37 ± 0.17</td>
<td>-1.11 ± 0.25*</td>
<td>-3.10 ± 0.25*</td>
</tr>
<tr>
<td>BMD Total, g/cm²</td>
<td>1.20 ± 0.04</td>
<td>1.18 ± 0.04</td>
<td>1.10 ± 0.02*</td>
<td>1.01 ± 0.03*</td>
</tr>
<tr>
<td>T-score Total, SD</td>
<td>1.36 ± 0.38</td>
<td>0.33 ± 0.68</td>
<td>-0.71 ± 0.23*</td>
<td>-1.45 ± 0.29*</td>
</tr>
<tr>
<td>BMC Total, g</td>
<td>2853.48 ± 2.54</td>
<td>2843.33 ± 5.51</td>
<td>2501.90 ± 1.99</td>
<td>2214.83 ± 2.44*</td>
</tr>
</tbody>
</table>

Note. The asterisk * marks significant differences of values in comparison to GOLD 1 (p<0.05).
ease severity reflected statistically significant BMD and T-score values of all the studied sites for women with GOLD 3, which were continuously growing; the smallest values were obtained with GOLD 4. Furthermore, the structural-functional bone state changes were inconsistent at various skeletal sites for every individual subject; they were revealed at the lumbar spine level first of all, and this fact is confirmed by the significant L₁-L₄ changes of GOLD 2 patients.

However, there are clinical cases where this parameter’s use for evaluation of vertebral bone quality is restricted [28]. For instance, when there were distinct degenerative-dystrophic changes at the lumbar spine, osteophytes and/or scoliotic deformation, the BMD values are growing. It is also well-known that when the glucocorticoids (GCs) were taken, the risk of vertebral deformation is independent from BMD [29, 30]. Taking into account this information, we were evaluating TBS of the COPD patients as the BMD-independent factor. The obtained findings were then compared with the researcher-suggested normative TBS values [19, 26].

Our studies demonstrate that TBS of lumbar spine was within normal ranges in the GOLD I patients. Starting with GOLD 2, the TBS L₁, TBS L₂, TBS L₁-L₄ and TBS L₁-L₄ values, though corresponding to a partial bone quality deterioration level, revealed a significant reduction in comparison with GOLD 1. The most pronounced changes were observed at the TBS L₁ level and corresponded to significant bone quality deterioration typical of GOLD 2. With GOLD 3, all the examined parameters were significantly reduced, while the GOLD 4 patients had TBS values corresponding to a significant bone quality disorder at all spinal sites, no higher than 1.27 (Table 3).

The study of correlations between the degrees of COPD severity and lumbar spine TBS revealed a close inverse correlation between the GOLD stage and TBS L₁-L₄ (r = -0.76, p<0.05) and TBS L₁-L₄ (r = -0.75; p<0.05).

Analysis of lumbar spine TBS values in relation to the COPD patients’ age brought normal values for the younger women. Starting with 45 years, TBS L₂, TBS L₃, TBS L₄, TBS L₁-L₄ and TBS L₂-L₄ decreased significantly in comparison with the ones obtained from the younger women and corresponded to a partial deterioration of bone quality. Furthermore, women of 60 years and older had the TBS values corresponding to a significant deterioration of bone quality. Based on our findings, the most prominent changes are observed with TBS L₁. It starts to decrease significantly after the age of 45 years, amounting to 1.17 ± 0.04 against 1.49 ± 0.03 of women younger than 45 years (p = 0.003). With advancing age, this parameter continues to decrease, and at 60 years and over it amounts to 1.03 ± 0.05 (p = 0.003, compared with women younger than 45 years (Table 4)).

Thus, lumbar spine TBS is a major diagnostic tool for the evaluation of COPD patients’ bone quality as it helps diagnose structural-functional bone disorders from the age of 45 and with GOLD 2.

Discussion

Our findings coincide with the reference data from the international sources on the clinical value of the lumbar spine TBS index [16-18, 20, 22, 24-26]. We’ve also obtained data which are partially coinciding with other study findings. For instance, the study by Casado E. et al. (2016) reported the TBS values in the COPD patients to be lower in those individuals who had a medium (2.57 ± 1.34) or advanced (2.54 ± 1.34) degree of severity than in those who had a slight degree of severity (2.19 ± 1.32, p<0.05). The GC use and a high GC cumulative dose in those patients are associated with the reduced TBS values (p = 0.002 and p = 0.013, respectively) [28]. The study of postmenopausal female patients with COPD demonstrated the association of the reduced TBS with a low number of trabecular structures, their thickness, connections and increased trabecular space [29].

The TBS study of patients with bronchial asthma confirms its connection with the degree of respiratory pathway obstruction, bronchial hyperreactivity and the inhalator GCS doses [30], while another study reports age, advanced asthma and frequency of systemic GCS use to be more important predictors of TBS values [31].

Watanabe R. et al. (2018) observe that TBS was much lower at the more advanced GOLD stages rather than GOLD 1. A multivariate regression analysis shows that

<table>
<thead>
<tr>
<th>Indices</th>
<th>TBS L₁</th>
<th>TBS L₂</th>
<th>TBS L₃</th>
<th>TBS L₄</th>
<th>TBS L₁-L₄</th>
<th>TBS L₂-L₄</th>
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<tr>
<td>GOLD 1</td>
<td>1.34 ± 0.06</td>
<td>1.42 ± 0.03</td>
<td>1.46 ± 0.04</td>
<td>1.43 ± 0.05</td>
<td>1.42 ± 0.04</td>
<td>1.44 ± 0.03</td>
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<tr>
<td>GOLD 2</td>
<td>1.17 ± 0.06*</td>
<td>1.29 ± 0.04*</td>
<td>1.28 ± 0.05*</td>
<td>1.31 ± 0.04</td>
<td>1.26 ± 0.04*</td>
<td>1.29 ± 0.04*</td>
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<tr>
<td>p₁₂</td>
<td>0.05</td>
<td>0.01</td>
<td>0.005</td>
<td>0.062</td>
<td>0.005</td>
<td>0.003</td>
</tr>
<tr>
<td>GOLD 3</td>
<td>1.07 ± 0.04*</td>
<td>1.21 ± 0.03*</td>
<td>1.31 ± 0.02*</td>
<td>1.27 ± 0.06*</td>
<td>1.21 ± 0.02*</td>
<td>1.26 ± 0.02*</td>
</tr>
<tr>
<td>p₁₂</td>
<td>0.0002</td>
<td>0.001</td>
<td>0.001</td>
<td>0.017</td>
<td>0.001</td>
<td>0.0002</td>
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<tr>
<td>GOLD 4</td>
<td>1.08 ± 0.09*</td>
<td>1.18 ± 0.07*</td>
<td>1.27 ± 0.07*</td>
<td>1.24 ± 0.03*</td>
<td>1.21 ± 0.07*</td>
<td>1.25 ± 0.06*</td>
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<tr>
<td>p₁₄</td>
<td>0.02</td>
<td>0.002</td>
<td>0.02</td>
<td>0.004</td>
<td>0.009</td>
<td>0.005</td>
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</tbody>
</table>

Note. The asterisk * marks significant differences of values in comparison to GOLD 1 (p < 0.05); p₁₂ – significance of differences between GOLD 1 and GOLD 2 groups; p₁₄ – significance of differences between GOLD 1 and GOLD 3 groups; p₁₄ – significance of differences between GOLD 1 and GOLD 4 groups.
the BMD and TBS are independent factors; furthermore, the TBS is associated with a systemic inflammation marker, reflected in an increased C-reactive protein rate, while the reduced BMD is most closely associated with a reduced body weight and 25-hydroxyvitamin D rate in the blood serum [32]. Shevroja E. et al. (2017) report that the reduced lumbar spine TBS values are associated with a history of fractures, independently of the FRAX questionnaire data [33].

Our study reveals the fact that the age has an equally important influence on the BMD and TBS of COPD-afflicted female patients. Starting from the age of 45 years, those values are progressively falling. The COPD impact on the bone tissue varies at various sites of axial spine and depending on the degree of severity. The initial changes concern the TBS L1 values whose decrease starts with GOLD 2. This is why TBS index may have a considerable diagnostic value for the structural-functional bone tissue state under the COPD.

Conclusions
Bone mineral density of the axial spine is decreasing significantly when the COPD degree reaches GOLD 3. The most vulnerable site lumbar spine with the significant reduction of BMD L₁–L₄ is observed when the degree of severity reaches GOLD 2 (1.19 ± 0.05) g/cm² rather than GOLD 1 (1.39 ± 0.05) g/cm² (p < 0.05).

For the women older than 45 years old, the trabecular bone score (TBS) decreases significantly at GOLD 2. Furthermore, the more advanced changes concern TBS L₁, and at GOLD 2 the obtained findings reflect significant bone destruction.

The combined study of BMD and TBS has an important diagnostic value for the analysis of structural-functional bone state in the COPD patients and considerably improves osteoporotic diagnostics.

The present study has the following restrictions: its design (cross-sectional study) and lack of control group. In the future, the longitudinal observations involving the COPD patients of both sexes will help us evaluate the BMD and TBS changes in a more detailed manner.

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Information on the individual author’s contribution:
V.V. Povoroznyuk. Concept and design of the study; N.P. Masik. Collection and processing of the materials. Analysis of the obtained data. Writing and formatting of the text; N.I. Dzerovych. Processing of the materials. Editing of the text.

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Якість кісткової тканини та її мінеральна щільність у хворих на хронічне обструктивне захворювання легень

Резюме. Мета — вивчення впливу хронічного обструктивного захворювання легень (ХОЗЛ) на мінеральну щільність кісткової тканини (МЩКТ) та її якість залежно від тяжкості захворювання та віку жінок. Матеріали та методи. Обстежено 30 жінок віком 57,43 ± 7,87 року, хворих на ХОЗЛ різної тяжкості (GOLD I–4). Досліджували МЩКТ юсугого скелета, поперекового відділу хребта, шийки стегнової кістки та дистального відділу кісток передпліччя за допомогою двохенергетичної рентгенівської абсорбціометрії (DEXA). Показник trabecular bone score (TBS) поперекового відділу хребта (L1–L4) визначали за допомогою методики TBS iNsight (Med-Imaps, Pessac, Франція). Результати. Установлено вірогідне зменшення МЩКТ усіх досліджуваних залежно від тяжкості захворювання та віку жінок. Значення TBS, починаючи з GOLD 2, а також у жінок віком старше 45 років відповідали частковому порушенню якості кістки, прогресивно знижувався і при GOLD 4 та в осіб старше 60 років відповідали значній втраті якості кістки. Найбільш виражені зміни відбувались на рівні TBS L1 і відповідали значній втраті якості кістки вже при GOLD 2. Установлено кореляційні зв’язки тяжкості ХОЗЛ і TBS L1–L4 (r = −0,76, p < 0,05) і TBS L2–L4 (r = −0,75, p < 0,05).

Ключові слова: хронічне обструктивне захворювання легень; якість кісткової тканини; мінеральна щільність кісткової тканини.