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# *The influence of chronic obstructive pulmonary disease on the occurrence rate and intensification of osteoporosis*

Chronic obstructive pulmonary disease (COPD) and osteoporosis are significant medical and social problems. Both diseases are characteristic of middle and old age. In Poland, COPD occurs in 8-15% of men and in 3-5% women over 30 years of age. Patients suffer from progressive destruction of lung parenchyma, which leads to respiratory insufficiency, deterioration of health and life quality, and often to premature death. A principal risk factor of COPD is tobacco smoking, which also negatively affects bone density. At the same time, the protracted inflammatory state that COPD is stimulates the production of a number of factors capable of enhancing the process of bone mass loss.

## OBJECTIVE

The aim of the study was an evaluation of the relationship between osteopoenia, osteoporosis and COPD, evaluation of the frequency of occurrence and intensity of the disturbances of bone mass and density as well as an attempt to establish the cause-effect relations between the two diseases.

## MATERIAL

The group under investigation consisted of 77 patients (aged 38-90 years, on average 64.3 ± 9.7) suffering from COPD at different stages of its development (57 persons) and a control group (20 persons). Patients with COPD and those from the control group were recruited from an outpatients' clinic and from a hospital. The mean weight of the group examined was 74.1 kg (± 13.4 kg), height – 168.3 cm (± 7.1 cm), surface of the body - 1.84 $m^2$ (± 0.17 $m^2$) and the Body Mass Index – 26.2 $kg/m^2$ (± 4.6 $kg/m^2$). Patients with COPD were divided into groups depending on the advancement of the disease. 33 patients were treated with chronic corticosteroid therapy. 14 patients taking an inhaled steroid had the mean current dose of 400 mg/day, and the mean duration of use – 2 years. 19 patients were treated with oral corticosteroids. The mean dose of prednisone was 8 mg/day, while the mean duration of treatment was 3.7 years.

## METHODS

After informed consent, the patients were interviewed and examined. The interview included age, sex, duration of respiratory illness, activity level, smoking, concurrent illnesses, information on the use of drugs. All the patients underwent spirometric examination carried out by means of the abcPneumoRS system. Static and dynamic lung volumes were measured in all patients. All the patients (excluding the control group) underwent bronchodilator response tests with Fenoterol hydrobromide in the dose of 0.0004 g. The execution and interpretation of the lung function tests were based on the guidelines of the European Respiratory Society (9) and the Polish Society of Phthisiopneumonology (6). All the patients underwent bone densitometry, carried out by means of the A/S Osteometer and using the DEXA method. Such densitometric parameters as the bone mass content (BMC), bone mineral density (BMD) and T-score (number of standard deviations below peak bone mass) were determined by examining the patients' distal forearm section. Interpretation of bone densitometry was based on the guidelines of the World Health Organisation (2).

## STATISTICS

All the calculations were done by using the STATISTICA software, with particular regard for the t-Student test. Differences between groups were analysed with the Kolmogorov-Smirnov test, Lilliefors test and Leven test, as well as non-parametric tests (Mann-Whitney, Wolf-Wadowitz). The differences in the mean values were examined by using

the Kruskall-Wallis test and the analysis of variance. Also used were Pearson's test and the $\chi^2$ test. The value of $p<0.05$ was accepted as statistically significant.

## RESULTS

The mean age, weight, height, body surface and Body Mass Index (BMI) did not markedly differ between the two groups. Nor did the mean values of BMD, BMC and T-score differ significantly between the groups. However, the osteoporosis frequency rate was much higher among patients with COPD, particularly in women (46%) (Table 1). BMD decreased progressively with age in women, but was higher in the group with

Table 1. The relationship between the osteoporosis and osteopoenia frequency rates and the patients' sex and presence of COPD

| | Normal | Osteopoenia | Osteoporosis |
|---|---|---|---|
| All patients | | | |
| Without chronic obstructive pulmonary disease | 45% | 30% | 25% |
| With chronic obstructive pulmonary disease | 36% | 30% | 34% |
| Women | | | |
| Without chronic obstructive pulmonary disease | 50% | 33% | 17% |
| With chronic obstructive pulmonary disease | 45% | 9% | 46% |
| Men | | | |
| Without chronic obstructive pulmonary disease | 43% | 29% | 28% |
| With chronic obstructive pulmonary disease | 34% | 34% | 32% |

COPD than in the group without it. A similar tendency was also observed in men, but the rate of bone loss was much slower (Figs 2 and 3). Significant differences in osteoporosis

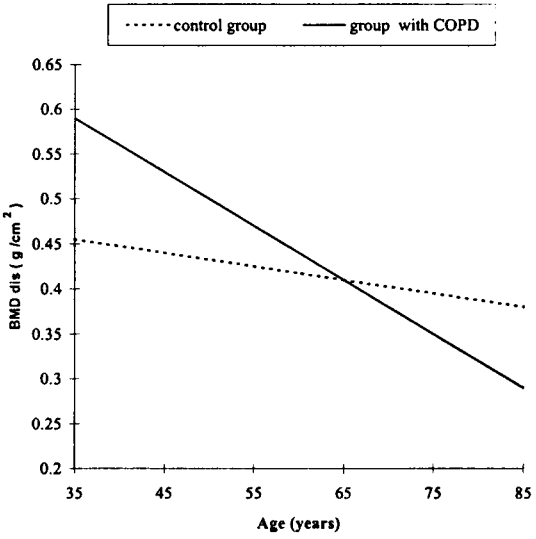


Fig. 1. The relationship between bone mass density, age and the presence of COPD in women

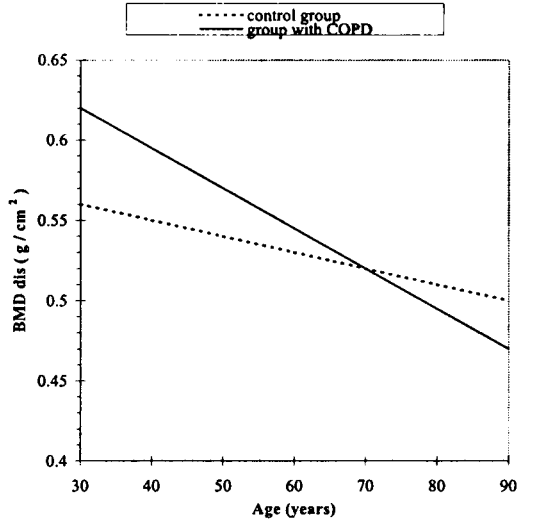


Fig. 2. The relationship between bone mass density, age and the presence of COPD in men

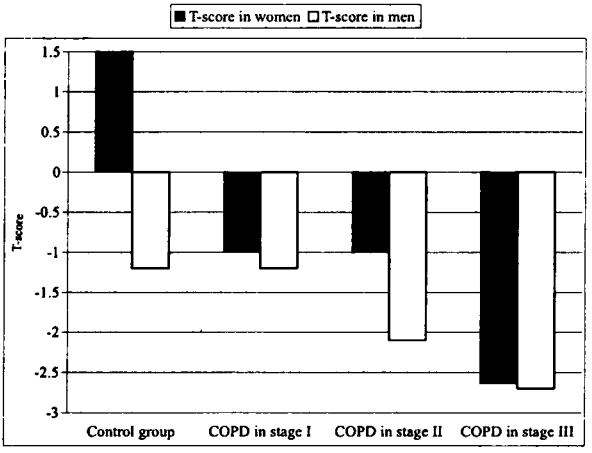


Fig. 3. The relationship between T-score in women and men and the different degree of COPD

frequency rate were observed in patients with different stages of the chronic obstructive pulmonary disease progression. BMD and BMC in both groups did not differ, but the T-score was much lower in stage III of COPD in both men and women. Smoking frequency increased in patients with COPD, particularly in stage III of the disease. Furthermore, the T-score was the lowest in men and women in stage III of COPD ($p=0.012$). Significant differences were observed in BMD, BMC and T-score in patients with different values of $FEV_1$. The patients with lower $FEV_1$ and weight had a lower BMC and T-score, but patients with lower weight and highest $FEV_1$ had high values of BMC and T-score. Furthermore, $FEV_1$ reversibility rate determined by means of the bronchodilatator response had a considerable influence on bone mass. T-scores between ± 1.0 and -1.4, which represent normal bone mass or osteopoenia, were present in patients with $FEV_1$ under 50% and a higher bronchodilatator response (over 15%). In patients with $FEV_1$ under 50% and low bronchodilatator response (from 0% to 7%) T-scores were within osteoporotic range (from -3.0 to -3.4). Similarly, in patients in stage I and II of COPD with a higher bronchodilatator of $FEV_1$ response, higher T-scores were observed than in patients with a low percentage change.

## DISCUSSION

Many factors can accelerate development of osteoporosis in patients with COPD. Factors like cigarette smoking, physical inactivity, increased level of TNF-alpha and other cytokines, glucocorticoids therapy in patients with COPD can lead to excessive decrease of bone mass. This study shows that in patients with COPD osteoporosis frequency rate

is higher, particularly in women, smokers and patients in stage III of COPD. These observations concerning patients with COPD are consistent with other reports in the literature.

Riaucho et al. (7) studied 44 male patients with COPD who had never received glucocorticoids. No differences in vertebral fractures, serum osteocalcin (index of bone formation), urinary hydroxyproline (index of bone resorption), 1.25-dihydroxyvitamin D and parathyroid hormone were found between the control and the main group. But calcitonin concentrations were higher in the patients than in the control group. Also, serum 259 hydroxyvitamin D was increased in patients with COPD. The authors suggest that increased concentrations of calcitonin may protect the bones from the effect of hypovitaminosis D.

Nashimura et al. (5) studied 21 patients with COPD, measuring BMC by the DEXA method. Patients showed significantly ($p<0.05$) lower BMC which was significantly correlated with body weight.

Shane et al. (8) examined 70 patients with end-stage pulmonary disease who were awaiting lung transplantation. Patients were grouped into categories by diagnosis and patients with COPD accounted for 40 percent (28 persons). Each patient was evaluated with BMD of the lumbar spine, hip and nondominant forearm as measured by DEXA. Also, the authors measured serum osteocalcin, serum levels of 25-hydroxyvitamin D and 1.25 dihydroxyvitamin D. A subset of 50 patients had a standard set of radiographs of the thoracic and lumbar spine to detect undiagnosed compression. Osteoporosis was present in 49 percent of the patients and osteopoenia in 35 percent when the lumbar spine was examined. Osteoporosis was present in 49 percent and osteopoenia was present in 31 percent at the femoral neck. The prevalence rate of vertebral fractures was 29 percent in patients with COPD and they tended to have lower lumbar spine and femoral neck BMD than those without fractures. Similar to the study of Riaucho et al. study, serum levels of 25-hydroxyvitamin D were decreased in all groups of patients.

The results of these investigations indicate that osteoporosis is much more common in patients with COPD. The increased risk of osteoporosis in COPD is associated with a variety of disorders, not only with lower serum levels of 25-hydroxyvitamin D. Chronic obstructive pulmonary disease is a disorder characterised by chronic inflammation. The important factors implicated in the pathogenesis of the bone loss are circulating cytokines, TNF-alpha, IL-1 and IL-6, produced by the inflammatory process. TNF-alpha is a potent inhibitor of bone collagen synthesis and a stimulator of osteoclastic bone resorption. Patients with COPD commonly have low body weight. Current understanding of the pathophysiology of cachexia attributes much of anorexia and weight loss to the effects of tumour necrosis factor alpha.

Cigarette smoking is one of the most important risk factors of osteoporosis and COPD. An association between smoking and osteoporosis has been found in many studies. In a 12-year prospective study, Cornuz et al. analysed 116,229 female nurses, 34 to 59 years of age (1). Smokers were at an increased risk of hip fracture and the risk increased linearly with greater cigarette consumption. In a meta-analysis of 29 cross-sec-

tional studies, Law et al. (4) demonstrated that in premenopausal women bone density was similar in smokers and non-smokers. Bone loss in the postmenopausal period was greater in current smokers than in non-smokers and the risk of hip fracture was greater at the age of 60. The results of these investigations concern only women. Vogel et al. (10) examined 1,303 men (Hawaii Osteoporosis Study) categorised as current cigarette smokers, past smokers, and non-smokers. The mean length of follow-up was 5 years. In all those investigated, bone mass density was measured at the distal radius and was greater at 1.8-3.3% in the current smokers than the never-smokers. The mechanisms of bone loss in smokers are uncertain. Smoking may reduce calcium absorption, endogenous oestrogen and testosterone, while increasing the level of cortisol, IL-6, TNF or direct toxic effect on the bones. The relationship of smoking to rates of BMD change and to intestinal calcium absorption was examined in men and women by Krall et al. (3) Smokers had the lowest mean absorption fraction with calcium and vitamin D.

To sum up, patients with COPD are at a higher risk of osteoporosis. This association seems to be important because it represents a risk factor that is at least partly modifiable.

## CONCLUSIONS

The research confirmed the relationship between the patients' bone mass and density and their age, sex, weight and body surface. Osteoporosis frequency rate was much higher among patients with COPD, particularly women. The following relationship was observed between the progression of the disease and the mass and mineral density of the bones: the more advanced was the airflow obstruction, the lower were the osseous mass coefficients. Forced expiratory volume during the first second and airflow obstruction reversibility rate determined by means of bronchodilatator response also had a considerable influence on osseous mass coefficients.

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## SUMMARY

The aim of this study was the estimation of the relationship between osteopenia and osteoporosis and chronic obstructive pulmonary disease (COPD). The group under investigation consisted of 77 people suffering from chronic obstructive pulmonary disease in different stages of its development and control group. All the patients underwent spirometry carried out by means of abcPneumoRS system and bone densitometry carried out by means of Osteometer A/S using the DEXA method; the results were compared with those of the reference groups. Static and dynamic lung volumnes were measured in all patients. By means of densitometry the mass, bone mineral density and T-score were determined in all patients' distal forearm. The research confirmed the relationship between the mass and density of bones and patients' age, sex, weight and body surface. Osteoporosis frequency rate was much higher among patients with chronic obstructive pulmonary disease, particularly women. The following relationship between the degree of disease progression and the mass and mineral density of the bones was observed: the more advanced airflow obstruction was, the lower osseous mass coefficients were. Forced expiratory volume during the first second and airflow obstruction reversibility rate determined by means of bronchodilatator response also had a considerable influence on osseous mass coefficients.

Wpływ przewlekłej obturacyjnej choroby płuc na częstość i nasilenie osteoporozy

Celem pracy była ocena związków osteopenii i osteoporozy z przewlekłą obturacyjną chorobą płuc, ocena częstości występowania i nasilenia zaburzeń masy i gęstości kości w tym schorzeniu oraz próba oceny relacji przyczynowo-skutkowych między obu chorobami. Badana grupa składała się z 77 osób chorych na POChP w różnych stadiach zaawansowania choroby i grupy kontrolnej. U wszystkich badanych wykonano badanie spirometryczne aparatem abcPneumoRS oraz badanie densytometryczne aparatem Osteometr A/S, wykorzystując metodę DEXA, a wyniki odniesiono do grup referencyjnych. Mierzono parametry spirometryczne statyczne i dynamiczne. Densytometrycznie oznaczano masę, gęstość mineralną kości, wskaźnik T, a badanym odcinkiem kości był dystalny odcinek kości promieniowej i łokciowej. W badaniach własnych potwierdzono zależność masy i gęstości kości od wieku, płci, masy i powierzchni ciała. Częstość osteoporozy była większa w grupie pacjentów z POChP, szczególnie wśród kobiet. Stwierdzono zależność pomiędzy stopniem zaawansowania POChP a masą i gęstością mineralną kości. Im obturacja bardziej nasilona, tym niższe były wskaźniki masy kostnej. Na kształtowanie się wskaźników masy kostnej istotnie wpływała wielkość natężonej pojemności wydechowej pierwszosekundowej oraz stopień odwracalności obturacji, wykazany testem z beta-mimetykiem.