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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

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საქართველოს სამედიცინო სიახლენი

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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

ТБИЛИСИ - НЬЮ-ЙОРК

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2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

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3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

Содержание:

რეზიუმე

ოსცილომეტრიით განსაზღვრული აორტის პულსური ტალღის სიჩქარის, გაძლიერების ინდექსის და აორტაში სისხლის ცენტრალური წნევის მაჩვენებლების შედარება პაციენტებში მწვავე და ქრონიკული კორონარული სინდრომით

[1]ზ.ლომინაძე, [2,3]კ.ჭელიძე, [2]ლ.ჭელიძე, [2]ე.ლომინაძე

[1]შპს კლინიკა-LJ, ქუთაისი; [2]თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი (თსსუ); [3]ინგოროყვას მაღალი სამედიცინო ტექნოლოგიების საუნივერსიტეტო კლინიკა, თსსუ, შინაგანი დაავადებათა დეპარტამენტი, თბილისი, საქართველო

ბოლო პერიოდის კვლევებით გამოვლინდა მძლავრი ასოციაცია კორონარული არტერიების დაავადებასა და არტერიული რიგიდობის ისეთ მაჩვენებელს შორის, როგორიცაა აორტის პულსური ტალღის სიჩქარე (PWV). კვლევების აბსოლუტურ უმრავლესობაში გამოყენებულია არტერიული რიგიდობის შეფასების ისეთი მეთოდები, როგორებიცაა: კაროტიდულ-ფემორალური PWV (cfPWV) ან მხარ-წვივის PWV (baPWV). რამდენიმე კვლევამ გამოავლინა ოსცილომეტრული პულსური ტალღის სიჩქარის, როგორც ათეროსკლეროზული კარდიოვასკულური დაავადების დამოუკიდებელი მარკერის როლი.

წინამდებარე კვლევის მიზანს წარმოადგენდა არტერიული რიგიდობის მაჩვენებლების შედარება მწვავე კორონარული სინდრომის და გულის სტაბილური იშემიური დაავადების მქონე პაციენტებში.

მწვავე კორონარული სინდრომით 100 პაციენტში (ჯგუფი 1) და ქრონიკული კორონარული სინდრომით 91 პაციენტში (ჯგუფი 2) ოსცილომეტრული მეთოდით შეფასებული იყო არტერიული რიგიდობის პარამეტრები.

მძლავრი ასოციაცია გამოვლინდა აორტის პულსური წნევის სიჩქარესა (PWVao) და მწვავე კორონარული სინდრომის ინციდენტობას შორის [OR=9.41; 95% CI (4.86, 18.2)]. გაძლიერების ინდქსისთვის (Aix) და აორტაში სისხლის ცენტრალური სისტოლური წნევისთვის ასოციაციის ხარისხი განაწილდა შემდეგნაირად: OR=5.11; 95% CI (2.65, 9.86) და OR =3.15; 95% CI (1.63, 6.1), შესაბამისად.

არტერიული რიგიდობის ოსცილომეტრიით განსაზღვრული ისეთი პარამეტრები, როგორებიცაა: აორტის პულსური წნევის სიჩქარე (PWVao), გაძლიერების ინდექსი (AIx) და სისხლის ცენტრალური სისტოლური წნევა (SBPao) შეიძლება გამოყენებული იყოს მწვავე კორონარული სინდრომის რისკის ადრეული სტრატიფიკაციისა და პრევენციისთვის.

BONE FORMATION MARKERS (N-TERMINAL PROPEPTIDE TYPE I ROCOLLAGEN, OSTEOCALCIN AND VITAMIN D) AS EARLY PREDICTORS OF OSTEOPOROSIS IN PATIENTS SUFFERING FROM CHRONIC OBSTRUCTIVE LUNG DISEASE

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According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), chronic obstructive lung disease (COLD) is characterized by multiple extrapulmonary manifestations which in most patients result in the extended hospitalization period as well as constitute risk factors regarding unfavourable short-term and long-term prognosis and increased mortality [2, 8, 12]. According to the concept of syntropic pathology, the most common diseases and pathological conditions in patients suffering from COPD are cardiovascular diseases, skeletal muscle dysfunction, metabolic syndrome, osteoporosis, depression and lung cancer [6, 8, 12].

Interest in the comorbidity of COPD and osteoporosis is not accidental as both diseases are among the most common human diseases. In Europe, the USA and Japan, osteoporosis affects about 75 million people [29]. Thus, according to Povorozniuk V.V., Ukraine has passed the limit of 3 million patients suffering osteoporosis, i.e. every second adult citizen of Ukraine has osteopenia and every fourth person suffers from osteoporosis [20, 29].

COPD affects about 251 million people [17]. Prevalence of COPD fluctuates in different countries ranging from 7.8 to 19.7%, increases with the age of patients and reaches a peak at the age of over 60 years [8].

At the same time, osteoporosis is one of the most common comorbidities in patients suffering from COPD. According to various authors, the prevalence rate ranges from 4 to 59% [18, 31], 22% - 44% [37] in the population. According to our information, an increase in the incidence of osteoporosis and osteopenia along with an increasing severity of COPD has been established: it ranges from 10.1% and 49.3% respectively, in patients with GOLD I up to 50.0% and 27.7% in patients with GOLD IV [24].

Comorbidity between COPD and osteoporosis can be predictable not only due to the widespread prevalence of both pathologies, but also due to the presence of similar etiopathogenetic and risk factors as well as individual elements of such mechanisms [20]. Systemic inflammation can be a potential mechanism in COPD. Thus, the flow of anti-inflammatory cy-

tokines into the systemic blood flow, increase in the systemic oxidative stress, development of endothelial dysfunction, activation of matrix metalloproteinases result in the development of comorbid pathology having an «extrapulmonary» origin. Alveolar destruction, decreased vascular elasticity and bone matrix loss may have common mechanisms, including overproduction of inflammatory cytokines such as IL-6, IL-1 and TNF-α [18, 27]. In addition, TNF-α and IL-1 can stimulate the processes of macrophage differentiation into osteoclasts, and IL-1, IL-11 and macrophage colony-stimulating factor are stronger triggers of bone resorption than parathyroid hormone [18, 37]. Hypoxia also can also stimulate the synthesis of ICAM-1 molecules, activate TNF-α as well as core transcription factor (NF-kB) in bronchial smooth muscle cells while resulting in NF-kB-dependent chronization of inflammatory process in COPD [16].

Other possible mechanisms which are not mutually exclusive may include general genetic predisposition, physical inertia and chronic hypoxia [19].

Osteoporosis in patients suffering COPD often remains undiagnosed because it develops gradually and remains asymptomatic for a long time [18, 29]. Based on this, both successive processes (i.e. a «chain of diseases») and long-term coexistence of two pathologies can be observed [20].

However, depending on whichever of these two points of view we take, the question which arises today is: what mechanisms of bone remodelling are affected by COPD? Remodelling processes constantly occur in normal bone. The pathogenesis of osteoporosis is based on an imbalance of these processes: increased resorption and reduced bone formation. Our aim was to find out whether markers of bone formation may be early predictors of osteoporosis in patients with COPD.

Material and methods. The study involved 66 patients suffering from COPD with a disease duration of 10 to 30 years. Each patient signed an informed consent for participation in the study (as recommended by the ethical committees on biomedical research, public health legislation of Ukraine and the Helsinki Declaration of 2000).

The selection of patients was carried out under the following criteria: hospitalization due to exacerbation of COPD during the autumn-winter period; COPD was diagnosed at least 6 months before the study; the age was >27 years; FEV1 was <80% of the proper level and FEV1/FVC was<70%; an increase in FEV1 after inhalation of short-acting β2-agonist was less than 12% (<200 ml) compared to the output data.

Verification of the COPD diagnosis and its formulation was carried out in accordance with GOLD recommendations and the order of the Ministry of Health of Ukraine No. 555 dated 27.06.2013 «On the approval and implementation of medical and technological documents for standardization of medical care for chronic obstructive pulmonary disease» [26]. Shortness of breath was assessed using the mMRC scale (Modified Medical Research Council scale) and the COPD assessment test (CAT) [8]. According to the results of testing, all patients were divided into clinical groups (Table 1).

The mean age of patients was (53.59±12.83) years. Males and females were distributed evenly - 50.0% (33 people each). 37 (66.06%) patients smoked, their index of pack / years made up (29.08±16.62).

Various biomarkers are currently available for specific and sensitive assessment of bone metabolism. Bone formation markers are the products of osteoblast activity, and namely serum procollagen type I aminoterminal propeptide (PINP), osteocalcin [30]. 25(OH)D is the only metabolite of vitamin D which is used to determine its content in the body. Vitamin D deficiency was defined as 25 (OH) D level constituting less than 50 nmol/l, vitamin D deficiency was 50.1-74.9 nmol/l of 25 (OH) D. The level of 25(OH)D above 75.0 nmol/l was within normal range [5].

In order to determine the markers of bone formation in the serum of patients with COPD, blood was taken from the ulnar vein in the morning on an empty stomach after a 12-hour fast in a total volume of 20 ml on the next day after hospitalization. The study was performed using the electrochemiluminescence method on the Eleksys 2010 analyser (Roche Diagnostics, Germany) with Cobas test systems.

Control group included 24 healthy people who, at the time of examination, had no signs of somatic pathology manifestation and had the age of (52.31±1.62) years. There were 17 males (70.6%) and females (27.3%).

Statistical processing of the study results was carried out using licensed software packages Microsoft Office 2010, Microsoft Excel 6.1/prof and Statistica 6.1. minus the arithmetic mean (M) and the standard error of the mean (SD). At a small number of observations (n<30), the assessment of the difference probability between the parameters of the mentioned groups was performed on the basis of comparing the result not with the margin values of the Student's test, but with its tabular values for the corresponding number of observations.

Results and discussion. Content of P1NP, serum osteocalcin and vitamin D determined on the basis of age, sex and severity of COPD.

The obtained results of P1NP concentration indicate a decrease in its content with age of patients. Thus, in the group of subjects under the age of 45 years, the content of P1NP was 48.75% higher compared with the group of patients aged 75 years and older ($p<0.001$) (Table 2). In men and women with COPD, no significant difference in P1NP (35.42±15.42) and (39.83±11.99) ng/ml, respectively) ($p >0.05$). A significant relationship was found between the age of patients and the level of P1NP ($r=-0.46$; $p<0.05$), which confirms the role of age as an inhibitory factor in the formation of bone tissue in patients with COPD.

The study of osteocalcin levels revealed a decrease in its content in the serum of patients suffering from COPD in the elderly compared with control group by 2.72 times and in 1.88 times in young people. Thus, the level of osteocalcin in the control group ranged from (29.82±0.33) to (34.21±0.44) ng/ml, while in young patients it was (21.94±0.98) ng/ml, whereas with age it decreased up to (16.23±0.41) ng/ml in elderly patients and up to (11.78±0.75) ng/ml in persons of old age ($p<0.05$) (Table 2). Significant differences were found in the level of this indicator between the groups of young and mature people $p=0.032$), young people and the elderly ($p=0.033$) and young and old people ($p=0.037$), as well as in comparison with the control group ($p=0.001$).

A study of 25(OH)D concentration showed that all patients with COPD had vitamin D deficiency, while 23.08% of patients under the age of 45 had a severe form of deficiency. Among patients of advanced age, severe deficiency of vitamin D was diagnosed in 70.59% of people, while among the elderly people it was diagnosed in 100% of cases (Table 2).

Table 1. Distribution of patients with COPD by severity

Groups	n	Clinical characteristics
group A, GOLD I	15	mMRC = 0–1 and / or for CAT<10 points and up to 1 COPD exacerbation over the last year
group B, GOLD II	25	mMRC ≥ 2 and / or CAT ≥ 10 points and / or 0–1 COPD exacerbation over the last year
group C, GOLD III	20	mMRC = 0–1 and / or CAT<10 points and 2 or more COPD exacerbations over the last year
Group D, GOLD IV	6	mMRC ≥ 2 and / or CAT ≥ 10 points and 2 or more COPD exacerbations over the last year

Table 2. Markers of bone formation depending on the age of patients with COPD (M±SD)

Age	P1NP (ng/ml)	Osteocalcin (ng/ml)	Vitamin D (nmol/)
up to 45 years, n=13 (young age)	38.65±0.64	21.94±0.98	30.04±0.50
45-59 years, n=21 (mature age)	38.78±0.57	15.71±0.51*	25.17±0.36
t p_1	0.449 0.661	2.032 0.03	1.909 0.080
60-74 years, n=17 (grow old)	35.53±0.64*	16.23±0.41*	24.28±0.89*
t p_2	2.747 0.011	2.047 0.033	3.432 0.005
≥ 75 years, n=9 (very old)	25.81±0.56*	11.78±0.75*	7.59±0.51*
t p_3	4.471 0.0007	2.207 0.034	7.243 0.00001
Total, n=66	37.29±0.34	15.87±0.36	25.52±0.30
Control group, n=24	37.63±0.78	32.015±0.36	66.88±5.11

*Notes: 1) the sign * indicates a probable difference in parameters compared with patients with COPD at a young age (p<0,05);*
2) p_1 - the reliability of difference between groups of young and mature people;
3) p_2 - the significance of difference between groups of young people and the elderly;
4) p_3 - the significance of difference between groups of young people and the elderly.

Table 3. Markers of bone formation depending on the severity of COPD (M±SD)

COPD severity	P1NP (ng/ml)	Osteocalcin (ng/ml)	Vitamin D (nmol/l)
GOLD I n=15	37.77±0.29	25.63±0.94#	27.19±0.42#
GOLD II n=25	38.60±0.51*	21.11±0.68#	27.87±0.44#
GOLD III n=20	38.57±0.95*	13.84±0.36* #	26.33±0.58#
GOLD IV n=6	29.65±1.22* #	13.15±0.46* #	15.51±0.78* #
Control group n=24	37.63±0.78	32.015±0.36	6.88±5.11

*Notes: 1) The sign * indicates a probable difference in parameters compared with patients with COPD I (p<0.05);*
2) The sign # indicates a probable difference in parameters compared to the control group (p<0.05).

The study of bone formation markers in patients with COPD depending on the severity of the disease revealed a decrease in P1NP by 27.39% in patients with GOLD IV compared with GOLD I (Table 3). Among patients with GOLD I, the number of patients with a decrease in P1NP made up 40.0%, among patients with GOLD II it made up 48.0%, among patients with GOLD III it made up 45.0% and among patients with GOLD IV such a decrease was in 66.67% of patients. Statistically significant changes in the level of propeptides were observed when comparing GOLD I and GOLD II (p=0.005), GOLD I and GOLD III (p=0.045), and GOLD I and GOLD IV (p =0.002).

Osteocalcin dynamics also decreased significantly in parallel with the progression of the disease. Thus, the concentration of osteocalcin ranged from (25.63±0.94) ng/ml in patients with GOLD I to (13.15±0.46) ng/ml in patients with GOLD IV (p=0.0036) (table 3). Among patients with GOLD I, the number of patients with a decrease in osteocalcin made up 66.67%, among patients with GOLD II, it made up 89.0%, in patients with GOLD III it made up 85.0% and in patients with GOLD IV such a decrease was found in all (100%) patients. The results indicate a significant decrease in bone formation process in patients with COPD, which is also confirmed by the established negative correlation between the level of osteocalcin and the severity of COPD (r=-0.36; p<0.05).

There was a deepening of vitamin D deficiency with an increasing severity of COPD. Thus, among representatives of

GOLD IV the level of vitamin D decreased 1.75 times compared with patients with GOLD I. Severe form of vitamin D deficiency was found in 46.67% of patients with GOLD I, in 40.0% of patients with GOLD II, in 65.0% of patients with GOLD III and in 100% of patients with GOLD IV (Table 3). Statistically significant changes in vitamin D levels were observed while comparing GOLD I and IV ($t=5.51$, $p=0.0002$). It was found that vitamin D deficiency depends on COPD severity, which is confirmed by the established feedback ($r=-0.48$; $p<0.05$).

We compared the levels of bone formation markers depending on the presence of such a causative factor of COPD as smoking. Thus, P1NP level was significantly reduced in 8 (21.62%), vitamin D in 12 (32.33%) and osteocalcin in 14 (37.84%) patients with COPD who are smokers. Osteocalcin level was (14.67±0.45) ng/ml in smokers compared with (16.38±0.38) ng/ml in non-smokers ($t=2.90$, $p<0.01$); vitamin D level was (24.26±0.35) nmol/l in smokers compared with (26.74±0.49) nmol/l in non-smokers ($t=4.11$, $p<0.01$); P1NP level in smokers was (34.82±0.57) ng/ml compared to (39.88±0.39) ng / ml, ($t=7.33$, $p<0.001$).

The received data show that along with an increasing age and increasing severity of COPD there is an inhibition of bone formation markers. Such processes occur on the background of vitamin D deficiency. Such an imbalance results in the creation of favourable conditions leading towards the development of osteoporosis.

All bone markers are products of bone collagen degradation [4]. Approximately 90% of organic bone matrix synthesized as procollagen consist of collagen of the first type [1]. P1NP in the serum directly depends on the amount of newly formed collagen which is deposited in the bone. Thus, P1NP is a true bone formation marker [4, 37].

Results of multiple studies suggest that P1NP assessment may be an additional tool in identifying high risk groups for bone loss [31], for preventing fractures and predicting the risk of their occurrence, as well as for monitoring the effectiveness of osteotropic therapy in patients suffering from osteoporosis [30]. In addition, P1NP does not have hormonal activity which may give it an advantage over osteocalcin [34].

Some works have shown a likely impact of age on the variability in serum levels of PINP. A study of healthy children demonstrated the highest P1NP level over the first year of life with a gradual decrease in its level up to puberty. There was no postnatal P1NP peak; however, its levels remained higher than reference norms for adults [4]. Determination of P1NP level in the serum of healthy individuals of different ages showed a probable decrease in women and men under 45 years (47.74±21.31 ng/ml, $p=0.02$), followed by an increase in PINP in women aged 50-59 years (51.91±26.82 ng/ml, $p=0.03$), which corresponds to late postmenopausal period in Ukraine [30]. At the same time, P1NP level remained stable or slightly increased after the age of 70 years [7, 33]. In contrast, our study showed a progressive decrease in P1NP levels with age in patients with COPD.

Further studies have revealed a link between P1NP levels and the severity of fibrotic lesions [13, 22, 38]. P1NP levels in serum have been shown not only to be significantly higher than those in the control group, but also increased according to the severity of pulmonary fibrosis [13], liver fibrosis [38] and in patients with subclinical interstitial lung disease [22]. It shows that the reconstruction of the extracellular matrix may accompany subclinical fibrosis before the onset of clinically obvious disease which led to the high level of P1NP as a marker of fibrogenesis.

Our data are consistent with the results of other studies which showed low levels of osteocalcin in 41% of patients suffering from COPD [36]. Some authors have suggested that the severity of COPD in middle-aged and older men is associated with decreased bone formation, low metabolism and osteogenesis dysfunction [35]. The authors have established that serum osteocalcin and P1NP are independent variables up to percent FEV1. On the contrary, another study found no significant differences in serum levels of P1NP, osteocalcin in men with stable COPD, whereas in women there were significant differences in P1NP [25].

Numerous studies have revealed that vitamin D deficiency is relatively common in patients suffering from COPD and is associated with increased respiratory symptoms, decreased pulmonary function, increased frequency of severe exacerbations [14, 19, 21, 23, 32], thickening of the airway walls on the computed tomography of the chest [11], as well as suppression of Th1 and Th17 reactions, which are involved in the pathogenesis of COPD [19]. Comparison of the obtained values between the groups shows that the decrease in the level of 25(OH)D in the serum of patients with COPD occurs gradually from 1 to 2 degrees of COPD and is inversely correlated with inflammatory cytokines [9], exacerbation and age of patients [3] consistent with our results.

It has been established that the mucous membrane of the respiratory tract is a place where local synthesis of the active metabolite of vitamin D(1.25 (OH)2D) occurs, i.e. the process which can be influenced by inflammatory mediators. As a consequence, mucositis and other factors associated with COPD may modulate the protective effects of 1.25(OH)2D [32]. However, the link between clinical signs of COPD and vitamin D levels remains controversial, so vitamin D is not yet considered a representative biomarker for COPD phenotypes [28].

The literature describes that vitamin D used in patients with COPD improves pulmonary function (FEV1, FEV1/FVC), 6-minute walk test and reduces acute exacerbation, sputum volume and CAT [21] as well as significantly reduces inflammation due to a decrease in serum levels of RANKL, TNF-α and IL-1 and an increase in IL-10, which simultaneously reduces bone loss [15]. Several studies have shown that vitamin D status correlates with bone mineral density in patients with COPD. Thus, at the beginning of the study 100 patients with stable COPD and vitamin D deficiency showed the risk of osteoporosis increased by 7.5 times over a 3-year follow-up period [25]. Taking into account the presence of hypovitaminosis D in the structure of bone metabolism, there is a predominance of resorption processes over bone neoplasms resulting in the deposition of osteoid in the absence of adequate mineralization [5]. On the contrary, a 6-month supplement to the standard treatment with vitamin D in the volume of 200,000 IU per month did not show additional clinical benefits among patients with COPD [10].

Therefore, it seems likely that COPD is associated with a decreased function of bone-forming osteoblasts which leads to low bone metabolism. It should be still noted that there exist many factors which may alter bone metabolism to varying degrees in patients suffering from COPD, including glucocorticoid use, hypoxia, vitamin D deficiency etc. The study provides evidence that bone formation disorders are a result of a combination of several mutually aggravating factors: age, smoking and COPD severity. Taking into account that the first signs of these disorders, and namely a decrease in vitamin D and osteocalcin levels, are diagnosed as early as GOLD I, it can be argued that COPD is the leading factor.

Conclusions:

1. Disorders of bone metabolism in patients with COPD are associated with a number of factors with an increase in the degree of COPD severity, presence of adverse etiological factors and the age of patients.
2. In patients with COPD revealed a decrease in markers of bone formation which are directly dependent on the severity of COPD. Thus, P1NP level decreased by 27.39% in patients with COPD, stage IV, compared with patients with stage I ($p<0.05$). 66.67% of patients with GOLD I and 100% with GOLD IV showed a decrease in osteocalcin.
3. Disorders of bone metabolism occur on the background of vitamin D deficiency which is diagnosed in all patients with COPD. It should be noted that the level of vitamin D in patients with GOLD IV decreased by 1.75 times compared with patients with GOLD I ($p<0,05$).
4. Patients with COPD who smoke show a suppression of bone formation which is reflected in the number of patients with decreased levels of P1NP, osteocalcin and vitamin D (21.62%, 37.84% and 32.33%, respectively).

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SUMMARY

BONE FORMATION MARKERS (N-TERMINAL PROPEPTIDE TYPE I PROCOLLAGEN, OSTEOCALCIN AND VITAMIN D) AS EARLY PREDICTORS OF OSTEOPOROSIS IN PATIENTS SUFFERING FROM CHRONIC OBSTRUCTIVE LUNG DISEASE

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The aim of the work was to find out whether markers of bone formation can be early predictors of osteoporosis in patients with COPD.

The study involved 66 patients with COPD with disease duration from 10 to 30 years, age 53.59±12.83 years. 37 (66.06%) patients smoked, the pack / year index was (29.08±16.62). According to the results of CAT testing, all patients were divided into 4 clinical groups: GOLD I-IV. The content of serum markers of bone formation was determined: N-terminal procollagen type I propeptide (PINP), osteocalcin and vitamin D depending on the age and severity of COPD.

A decrease in all markers of bone formation was found with the age of patients and the severity of COPD. Thus, in patients under 45 years, the P1NP level was 48.75% higher than in patients aged 75 and older ($p<0.001$). A significant relationship was established between the age of patients and the P1NP level ($r= -0.46$; $p=<0.05$). With GOLD I, a decrease in the P1NP content was observed in 40.0% of patients, with GOLD II - 48.0%, GOLD III - in 45.0%, and with GOLD IV, such a decrease was in 66.67% of patients.

The level of osteocalcin decreased in patients with COPD of old age compared with the control by 2.72 times and in young people - by 1.88 times. With GOLD I, a decrease in osteocalcin

content was observed in 66.67%, with GOLD II - 89.0%, GOLD III - in 85.0%, and with GOLD IV, a decrease was observed in all (100%) patients.

The concentration of vitamin D was reduced in all patients with COPD, and severe vitamin D deficiency was diagnosed in 23.08% of patients under 45 years, in 70.59% of elderly patients, in 100% of elderly people. Among the representatives of GOLD IV, the level of vitamin D decreased by 1.75 times as compared with patients with GOLD I. A severe form of vitamin D deficiency was diagnosed in 46.67% of patients with GOLD I, 40.0% in GOLD II, 65.0% in GOLD III, and in 100% of patients with GOLD IV.

The data obtained indicate that with increasing age and increasing severity of COPD, the formation of markers of bone tissue formation is inhibited. These processes occur against the background of vitamin D deficiency. As a result of this imbalance, favorable conditions are created for the development of osteoporosis. Considering that the first signs of these disorders, in particular a decrease in the levels of vitamin D and osteocalcin, are diagnosed already with GOLD I, it can be argued that COPD is the leading factor.

Keywords: chronic obstructive pulmonary disease (COPD), osteoporosis, markers of bone tissue formation, N-terminal propeptide of type I procollagen, osteocalcin, vitamin D.

РЕЗЮМЕ

МАРКЕРЫ ФОРМИРОВАНИЯ КОСТНОЙ ТКАНИ (N-ТЕРМИНАЛЬНЫЙ ПРОПЕПТИД ПРОКОЛЛАГЕНА I ТИПА, ОСТЕОКАЛЬЦИН И ВИТАМИН D) КАК РАННИЕ ПРЕДИКТОРЫ ОСТЕОПОРОЗА У БОЛЬНЫХ ХРОНИЧЕСКОЙ ОБСТРУКТИВНОЙ БОЛЕЗНЬЮ ЛЕГКИХ

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Цель исследования - определить, являются ли маркеры костного формирования ранними предикторами остеопороза у больных хронической обструктивной болезнью легких.

Обследовано 66 больных хронической обструктивной болезнью легких (ХОБЛ) длительностью заболевания от 10 до 30 лет, в возрасте 53,59±12,83 лет. 37 (66,06%) пациентов курили, индекс пачко/лет составил 29,08±16,62. По результатам тестирования CAT всех больных разделили на 4 клинические группы: GOLD I-IV. Определяли содержание сывороточных маркеров образования кости: N-терминальный пропептид проколлагена первого типа (P1NP), остеокальцин и витамин D в зависимости от возраста и тяжести ХОБЛ.

Установлено снижение всех маркеров формирования кости в зависимости от возраста больных и тяжести заболевания. У больных в возрасте до 45 лет уровень P1NP был на 48,75% выше в сравнении с больными в возрасте 75 лет и старше (p<0,001). Установлена достоверная связь между возрастом больных и уровнем P1NP (r=-0,46; p=<0,05). При GOLD I снижение содержания P1NP выявлено у 6 (40,0%) пациентов, при GOLD II – у 12 (48,0%), GOLD III – у 9 (45,0%) и при GOLD IV такое снижение было у 4 (66,67%) пациентов.

Уровень остеокальцина понизился у больных ХОБЛ старческого возраста в сравнении с контролем в 2,72 раз и лицами молодого возраста - в 1,88 раза. При GOLD I снижение содержания остеокальцина наблюдалось у 10 (66,67%), при GOLD II – у 22 (89,0%), GOLD III - у 17 (85,0%) и при GOLD IV снижение было у всех 6 (100%) пациентов.

Концентрация витамина D была снижена у всех больных ХОБЛ, а тяжелый дефицит витамина D диагностирован у 23,08% пациентов в возрасте до 45 лет, у 70,59% больных пожилого возраста и у всех лиц старческого возраста. У представителей GOLD IV уровень витамина D был снижен в 1,75 раз в сравнении с больными GOLD I. Тяжелую форму дефицита витамина D диагностировали у 7 (46,67%) больных GOLD I, у 10 (40,0%) - GOLD II, у 13 (65,0%)- GOLD III и у всех пациентов GOLD IV.

Полученные данные свидетельствуют, что с увеличением возраста и усилением тяжести ХОБЛ отмечается угнетение образования маркеров формирования костной ткани. Эти процессы происходят на фоне дефицита витамина D. В результате такого дисбаланса создаются благоприятные условия для развития остеопороза. Учитывая, что первые признаки этих нарушений, в частности уменьшение уровней витамина D и остеокальцина, диагностируются уже при GOLD I – можно утверждать, что фактор ХОБЛ является ведущим.

რეზიუმე

ძვლოვანი ქსოვილის ფორმირების მარკერები (I ტიპის პროკოლაგენის N-ტერმინალური პოლიპეპტიდი, ოსტეოკალცინი და ვიტამინი D), როგორც ოსტეოპოროზის ადრეული პრედიქტორები პაციენტებში ფილტვების ქრონიკული ობსტრუქციული დაავადებით

ნ.მასიკი, ნ.მატვიიჩუკი, ო.მასიკი

ვინიცას ნ.პიროგოვის სახ. ეროვნული სამედიცინო უნივერსიტეტი, უკრაინა

კვლევის მიზანს წარმოადგენდა განსაზღვრა იმისა, თუ რამდენად წარმოადგენს ძვლოვანი ქსოვილის ფორმირების მარკერები ოსტეოპოროზის ადრეულ პრედიქტორებს პაციენტებში ფილტვების ქრონიკული ობსტრუქციული დაავადებით (ფქოდ).

გამოკვლეულია 66 პაციენტი ფქოდ-ით, დაავადების ხანგრძლივობა – 10-30 წელი, პაციენტების ასაკი - 53,59±12,83 წელი. 37 (66,06%) პაციენტი ეწეოდა სიგარეტს, კოლოფი/წლის ინდექსი - 29,08±16,62. CAT-ტესტირების შედეგების მიხედვით ყველა პაციენტი დაიყო 4 კლინიკურ ჯგუფად: GOLD I - IV. პაციენტის ასაკის და ფქოდ-ის სიმძიმის მიხედვით განისაზღვრა ძვლის წარმოქმნის შრატისმიერი მარკერები: I ტიპის პროკოლაგენის N-ტერმინალური პოლიპეპტიდი (P1NP), ოსტეოკალცინი და ვიტამინი D.

დადგენილია ძვლის ფორმირების ყველა მარკერის შემცირება პაციენტების ასაკის და დაავადების სიმძიმისაგან დამოკიდებულებით. 45 წლამდე ასაკის პაციენტების P1NP-ის დონე შეადგენდა 48,75%-ით მეტს 75 წლის და მეტი ასაკის პაციენტებთან შედარებით (p<0,001). დადგენილია სარწმუნო კავშირი პაციენტების ასაკსა და P1NP-ის დონეს შორის (r=-0,46; p<0,05). GOLD I -ში P1NP-ის შემცველობის შემცირება გამოუვლინდა 6 (40,0%) პაციენტს, GOLD II –ში - 12-ს (48,0%), GOLD III–ში – 9-ს (45,0%), GOLD IV–ში - 4-ს (66,67%).

ოსტეოკალცინის დონე ხანდაზმული ასაკის პაციენ-

ტებში ფქოდ-ით, საკონტროლოსთან შედარებით, შემცირდა 2,72-ჯერ, ახალგაზრდა ასაკის პაციენტებთან შედარებით კი – 1,88-ჯერ. GOLD I –ში ოსტეოკალცინის შემცველობის შემცირება აღინიშნა 10 (66,67%) პაციენტში, GOLD II –ში - 22-ში (89,0%),GOLD III–ში – 17-ში (85,0%), GOLD IV–ში - ექვსივე (100%) პაციენტში.

ვიტამინი D-ს კონცენტრაცია შემცირებული იყო ყველა პაციენტში ფქოდ-ით, ხოლო ვიტამინი D-ს მძიმე დეფიციტი დიაგნოსტირდა 45 წლამდე ასაკის პაციენტთა 23,08%-ში, ხანდაზმული ასაკის პაციენტების 70,59%-ში და მოხუცებულობითი ასაკის ყველა პაციენტში.

GOLD IV–ში ვიტამინი D-ს დონე შემცირებული იყო 1,75-ჯერ, GOLD I-თან შედარებით. ვიტამინი D-ს მძიმე დეფიციტი დიაგნოსტირდა: GOLD I –ში - 7 (46,67%) პაციენტში, GOLD II –ში - 10 (40,0%), GOLD III–ში – 13 (65,0%), GOLD IV–ში – ყველა პაციენტში.

მიღებული შედეგები მიუთითებს, რომ ასაკის მატებასთან და ფქოდ-ის დამძიმებასთან ერთად აღინიშნება ძვლოვანი ქსოვილის ფორმირების მარკერების წარმოქმნის დათრგუნვა. ეს პროცესები მიმდინარეობს ვიტამინ D-ს დეფიციტის ფონზე. ასეთი დისბალანსი ქმნის ხელსაყრელ პირობებს ოსტეოპოროზის განვითარებისათვის. იმის გათვალისწინებით, რომ ამ დარღვევების პირველი ნიშნები, კერძოდ - ვიტამინ D-ს და ოსტეოკალცინის დონის შემცირება, დიაგნოსტირდება უკვე GOLD I –ში, შეიძლება გაკეთდეს დასკვნა, რომ ფქოდ წარმოადგენს წამყვან ფაქტორს.

CLINICAL CHARACTERISTICS OF ALS IN GEORGIAN PATIENTS

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"Does it take place through simple propagation, extending gradually across the neuroglia?" [1] This is what French Neurologist -J.M Charcot has been questioning regarding amyotrophic lateral sclerosis progression in his lectures on the diseases of the nervous system in 1877. It's been 145 years since, even though many questions have been answered, the cause of amyotrophic lateral sclerosis (ALS) remains today unknown for most of the patients with the disease. the aim of this article is to describe the clinical characteristics of Georgian ALS patients. ALS onset and progression vary greatly among individuals, so these data provide additional insight into the phenotypic differences within a national population. An understanding of symptoms of ALS onset may help clinicians make a quicker diagnosis, which could lead to earlier therapeutic interventions.

Material and methods. Overall 47 patients with ALS were investigated, among them 24 male (51.06%), 23 female (48.9%), aged 25-84 (Table 1) we documented clinical manifestations of the disease in those patients, age at diagnosis, Patient survey of clinical symptoms was taken using Mayo Clinic Lab. Neurology patient form , Cognitive changes assessed via Addenbrooke Cognitive Examination scale (ACE III), and frontal behavioral inventory, diagnosis of FTD was based on Strong criteria of FTD. Patient functional status was assessed with ALSFRS-R. Diagnosis of ALS was based on the new Gold coast criteria -incorporating progressive motor impairment documented by history or repeated clinical assessment, preceded by normal motor function, and presence of upper and lower motor neuron dysfunction in at least 1 body region, (with upper and lower motor neuron dysfunction noted in the same body region if only one body region is involved) or lower motor neuron dysfunction in at least 2 body regions, most importantly excluding other diseases.[7] All patients underwent nerve conduction studies and needle electromyography , In patients with signs of dementia or suspicion of other diseases MRI of Head and Spine was done. Those with unexplained sensory signs or symptoms, abnormal nerve conduction studies, weakness in the distribution of individual motor nerves, or any abnormality on cervical or head MRI suggestive of an alternate diagnosis such as spinal stenosis or cervical myelopathy, multiple sclerosis were not included in the study. Patients diagnosed with conditions such as spinal muscular atrophy, Kennedy syndrome, monomelic amyotrophy, Hirayama syndrome, or multifocal motor neuropathy were excluded from the study.

Results and discussion. *Age of onset*. Recent studies have shown that the mean age of ALS onset is between 51 and 66 years [4]. When compared with patients from Asian countries , ALS usually strikes patients in Europe later in life. The greater age at ALS onset in Europe may be partly explained by the use of population-based studies [4,5] the mean age at ALS onset in Georgian was found to be 58.30 years, patients were aged 26 to 84 years, 63.8% of the patients were 50–69 years old (Table 1) ALS begins with nonspecific symptoms that can mimic those of other neuromuscular diseases. ALS diagnosis can therefore be delayed if a misdiagnosis occurs in the early stages. Due to the lack of valid diagnostic biomarkers, diagnostic delay is marked. ALS is diagnosed clinically through progressive symptoms, which takes time to demonstrate. According to recent studies, diagnostic delays typically range from 9 to 24 months in different populations [6,8,9]. According to our data, the average time to diagnose ALS was 6 to 15 months from onset of symptoms, key factors for diagnostic delay were referrals to specialists rather than neurologists, and consequent misdiagnosis resulting in unnecessary procedures, patients with a bulbar onset were diagnosed earlier than those with spinal onset.