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THE ROLE OF VITAMIN D IN THE PROGRESSION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE.

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Abstract: Vitamin D deficiency is one of the important indicators determining the pathogenetic mechanisms that aggravate the course of COPD, supporting the extremely strong influence of COPD on the patient's life and 2.4 times more often with a 4-year survival rate of 18%. The use of a therapeutic dose of vitamin D in the complex of COPD treatment standards determined the therapeutic effectiveness after treatment in the form of a 2.1-fold decrease in the degree of shortness of breath, a 45.9% decrease in the severity of bronchial obstruction, and a 41.0% decrease in the effect of the disease on the patient's health and life. There was a significant decrease compared to the control of course doses of steroids (by 48%) and the length of hospital stay (by 29.8%).
Keywords: chronic obstructive pulmonary disease,vit D, markers of progression, BODE index, CAT test, phenotypes.

Objective of the study. To assess the prognostic and clinical significance of vitamin D insufficiency/deficiency as a marker of frequent exacerbations and progression of COPD.

Material and methods. The study included 116 patients with COPD who were hospitalized in the pulmonology department of the Tashkent City Clinical Hospital No. 1, where they underwent comprehensive clinical, laboratory and functional studies within the framework of the objectives.

Results. Vitamin D deficiency is one of the important indicators that determines the pathogenetic mechanisms that aggravate the course of COPD, supporting the extremely strong impact of COPD on the patient's life and 2.4 times more often the percentage of 4-year survival of 18%. The use of a therapeutic dose of vitamin D in a set of COPD treatment standards determined the therapeutic efficacy after treatment in the form of a 2.1-fold decrease in the degree of dyspnea, a 45.9% decrease in the severity of bronchial obstruction, and a 41.0% decrease in the impact of the disease on the patient's health and life. A reliable decrease in the course doses of steroids (by 48%) and the length of hospital stay (by 29.8%) was noted compared to the control. According to WHO, vitamin D deficiency is pandemic in nature, affecting over 1 billion people on the planet [Glyadelova N.P., 2017]. Epidemiological statistics on vitamin D deficiency are associated with an increased incidence and risk of diseases mediated by infectious processes, such as acute respiratory infections, pulmonary tuberculosis, inflammatory bowel diseases, and demonstrate a close relationship between low vitamin D levels and adverse outcomes, including morbidity and mortality indicators, in severe infectious and immune-mediated diseases [Ibraeva

L.K. et al., 2022; Velikaya O.V. et al., 2020; Dolgo-Saburova Yu.V. et al., 2021; Aibana O. et al., 2019; Vipul P. et al., 2017]. Low vitamin D levels are not the cause of the disease, but a marker or even a consequence of its complicated progressive course [Lee Y.H. et al., 2016; Vipul P. et al., 2017]. Multifactorial development of vitamin D deficiency, determined by unbalanced poor nutrition, functional age-related decrease in vitamin D synthesis by aging skin, limited time outdoors and exposure to sunlight, decreased physical activity, drug load of steroid therapy, providing deficiency due to increased catabolism of glucocorticoids, systemic non-respiratory manifestations of COPD with impaired activation due to renal dysfunction and cachexia with lower storage capacity in muscles or fat due to exhaustion [Forli L. et al., 2004.], is often observed in patients with COPD, which may explain the causes of vitamin D deficiency. COPD patients have potential prerequisites for impaired consumption, synthesis, storage and metabolism of vitamin D, leading to the formation of insufficiency and deficiency of vitamin D and determining deep homeostatic disorders at the cellular, organ and organism levels.

Early diagnosis of vitamin D deficiency will ensure the need for mandatory measures aimed at therapeutic and preventive treatment programs for patients with vitamin D deficiency, ensuring increased treatment efficiency of COPD treatment standards and the quality of life of COPD patients.

Objective - To assess the prognostic and clinical significance of vitamin D insufficiency/deficiency as a marker of frequent exacerbations and progression of COPD.

Materials and methods.

To achieve our goal, the study included 116 COPD patients who were inpatients in the pulmonology department of Tashkent City Clinical Hospital No. 1, where they underwent comprehensive clinical, laboratory and functional studies within the framework of the objectives.

The type of COPD exacerbation is classified according to Anthonisen et al. (1987), where type I determines the presence of 3 large criteria: "the appearance or increase in shortness of breath; an increase in the volume of sputum, an increase in the "purulence" of sputum"; Type II - the presence of the first 2 major criteria; Type III: the presence of 1 major and at least 1 minor criterion, including: upper respiratory tract infection, an increase in body temperature above 380C, increased cough, wheezing [Anthonisen N.R., 2002]. The degree of dyspnea was interpreted according to the discriminatory scale of dyspnea MRC (Medical Research Council) [Nena Milačić et al, 2015; Bestall J.C. et al, 1999]. The impact of COPD on the patient's daily life and health was assessed using the CAT test (COPD Assessment Test) recommended by GOLD [Mahler D.A. et al., 1992; Gruffydd-Jones K. et al, 2013], where 0-10 points are insignificant impact; 11-20 points are moderate; 21-30 points - pronounced and 31-40 points - serious impact of the disease. In assessing the outcome of the disease, reflecting the percentage of 4-year survival, the BODE index was used [Celli B.R., 2006], where the sum of points determines 0-2 points - 80%, 3-4 points 67%, 5-6 points -57% and 7-10 points -18%. The 6-minute step test, determining tolerance to physical activity, was assessed in accordance with the standard protocol and recommendations of P.L.Enright (1998) [Enright P.L. et al.,

1998], where the expected value for men 6 MWD (i) with the lower limit of the norm was 153 m and for women - 139 m.

The calculation of the diaphragm fatigue index was carried out using the discriminant equation of Yu. M. Perelman et al. (1998) F = 17.3 x MOS50 (l / s) [Perelman Yu. M. et al., 1998], where at F < 65.1, the state of diaphragm fatigue was diagnosed.

Vitamin D was determined by immunochemiluminescent analysis (ICLA) using a kit manufactured by Beckman Coulter.

The level of cytokines (interleukins (IL)-1; -4; -6; -10; -17; -21; TNF-α; TGF-B) in the serum was carried out by the ELISA method on a Mindray Mr-96A spectrophotometer. Specific tissue antibodies to lung tissue were determined by the passive hemagglutination reaction according to the generally accepted standardized method [https://chem21.info/info/1399408].

Statistical analysis was performed using the STATISTICA 13.3 program (developer - StatSoft, Inc). All values in the tables are presented as the arithmetic mean of the variation series ± the error of the mean (M ± m). Values with a level of $p < 0.05$ and $p < 0.01$ (with a confidence probability of 95.5% and 99%) were used as a statistical hypothesis.

Results and discussion. An analysis of the assessment of vitamin D levels in patients with COPD showed that 42 of 116 patients (36.2%) had a deficient level of vitamin D (9.1±0.26 ng/ml), 40 (34.5%) patients had vitamin D deficiency (17.2±0.4 ng/ml), and 34 (29.3%) had a normal level of vitamin D (24.8±0.6 ng/ml).

The results of assessing the vitamin D level in patients with COPD with different phenotypic components are presented in Table 1, which shows that the overwhelming majority of COPD patients with vitamin D insufficiency/deficiency are noted in the cohort of patients over 70 years old (80.4%), smokers - (73.5%) with a smoking history of more than 40 years (83.4%), the number of cigarettes smoked more than 20 pcs per day - (75.5%) and an increase in deficiency states with a smoking index of more than 50 packs / year (42.9%). Vitamin D deficiency is more pronounced in COPD patients (85.7%) with a pronounced violation of the nutritional status according to BMI.

Table 1. Vitamin D level in cohort groups of patients with COPD

Signs and criteria		**n**	**M±m**	**уровень витамина D,%**		
				Norm	**Failure**	**deficit**
Age, years	Up to 50 years	5	19,0±2,2	2(40,0±24,5)	3(60,0±24,5)	-
	50-70 years	60	17,5±0,9	22(36,7±6,2)	19(31,7±6,0)	19(31,7±6,0)
	>70 years old	51	15,1±1,0	10(19,6±5,6)	18(35,3±6,7)	23(45,1±7,0)
sex	Female	29	16,8±1,4	10(34,5±9,0)	7(24,1±8,1)	12(41,4±9,3)
	Male	87	16,4±0,7	24(27,6±4,5)	33(37,9±5,2)	30(34,5±6,6)
Factor	Yes	83	16,6±0,7	22(26,5±4,8)	34(41,0±5,4)	27(32,5±5,1)

smoking	No	33	16,3±1,4	12(36,4±8,4)	6(18,2±6,7)	15(45,4±8,7)
Smoking experience, years	Up to 20 years	9	19,4±2,8	3(33,4±16,7)	4(44,4±17,6)	2(22,2±14,7)
	20-40 years	62	16,9±0,8	17(27,4±5,7)	28(45,2±6,3)	17(27,4±5,7)
	40 years and over	12	12,9±1,8	2(16,7±11,2)	2(16,7±11,2)	8(66,7±14,2)
Smoking intensity, pcs per day	Up to 20 pcs.	15	15,3±1,2	2(13,3±9,1)	7(46,7±13,3)	5(33,3±12,6)
	20-40 pcs	53	16,6±0,8	13(24,5±5,9)	25(47,2±6,8)	15(28,3±6,2)
	40 pcs and more	15	15,5±1,6	6(40,0±13,1)	2(13,3±9,1)	7(46,7±13,3)
Smoking index	0-14 pack/years	32	16,1±1,4	10(31,3±8,2)	6(18,8±6,9)	16(50,0±8,8)
	15-24 packs/years	16	18,2±1,4	3(18,8±10,1)	12(75,0±11,2)	1(6,2±6,2)
	25-49 pack/years	54	16,1±0,9	12(22,2±5,6)	22(40,7±6,7)	20(37,0±6,6)
	>50 pack/year	14	17,1±1,4	7(50,0±13,9)	1(7,1±7,1)	6(42,9±13,7)
Body mass index	<18,5	7	12,8±3,8	1(14,3±11,4)	-	6(85,7±11,4)
	18,5-25,0	34	14,7±1,2	7(20,6±6,9)	12(35,3±8,2)	15(44,1±8,5)
	25,0-30,0	52	17,2±0,9	15(28,8±6,3)	21(40,4±6,8)	16(30,8±6,4)
	>30	23	18,6±1,3	11(47,8±9,6)	7(30,4±9,8)	5(21,7±8,8)
Seasonality of COPD exacerbation	Winter-spring	83	14,6±0,7	18(21,7±4,5)	28(33,7±5,2)	37(44,6±5,4)
	Summer-autumn	33	16,3±1,4	15(45,4±8,7)	12(36,4±8,4)	6(18,2±6,7)
Use of steroid therapy	Systematic	75	14,8±0,7	21(28,0±5,2)	26(34,7±5,5)	35(46,7±5,8)
	Episodic	41	17,3±1,4	26(63,4±7,5)	7(17,1±5,9)	8(19,5±6,2)

The results of the study showed that in COPD patients with a seasonal pattern of exacerbations "Winter-spring", the proportion of vitamin D insufficiency/deficiency was significantly higher, amounting to 78%. A significant proportion of vitamin D insufficiency/deficiency was also noted among COPD patients systematically taking steroid therapy drugs (81.4%). The obtained results demonstrated that COPD patients are a high-risk group for vitamin D deficiency/deficiency conditions, where prophylactic doses of vitamin D should be prescribed in the early period of treatment with the following phenotypic criteria: age, smoking history and intensity, severe nutritional deficiency, systemic steroid therapy, and seasonality of exacerbations.

Based on generally accepted criteria for the progression, outcome of COPD, and the impact of the disease on the patient's daily life and health, which included criteria

for the severity of obstruction, severity of dyspnea, exercise tolerance, degree of diaphragmatic fatigue, severity of mucociliary insufficiency and insufficiency of the local immune response, bronchodilator and steroid refractoriness, duration of inpatient treatment, and the number of exacerbations per year, we compared the incidence of unfavorable indicators in COPD patients with comorbid status for vitamin D deficiency (Table 2).

The results of the study showed that among COPD patients with vitamin D deficiency, indicators that determine the progression of the disease and an unfavorable outcome of COPD were noted 2.2 times more often in patients with type I exacerbation of COPD, 2.4 times with a mixed (bronchitis-emphysematous) phenotype, 2.2 times in COPD patients with diaphragm fatigue syndrome, 3.9 times in COPD individuals with sIgA deficiency, 2.1 times with bronchodilator and 1.9 times with steroid refractoriness, 1.6 times with extremely severe obstructive disorders and 1.8 times with lower exercise tolerance. It is noted that COPD patients with vitamin D deficiency are characterized by a 2.0 times higher frequency of COPD exacerbations more than 4 times a year and a 3.5 times higher duration of inpatient treatment more than 40 days a year. The clinical and functional "portrait" of COPD patients with vitamin D deficiency is determined by a 1.8 times extremely strong impact of COPD on the patient's life and is 2.4 times more often characterized by a 4-year survival rate of 18%.

Table 2. The nature of indicators of progression of the course and unfavorable outcome

Indicators	Gradations	COPD patients		OR
		Vitamin D deficiency, n=42	Vitamin norm D, n=34	
Type of COPD exacerbation	Type 1	19(45,2±7,7)	7(20,6±6,9)	2,2
	Type 2	16(38,1±7,5)	12(35,3±8,2)	1,1
	Type 3	7(16,7±5,7)	15(44,1±8,5)	0,4
MRC, балл	<2	14(33,3±7,3)	19(55,9±8,5)	0,6
	≥2	28(66,7±7,3)	15 (44,1±8,5)	1,5
ОФВ$_1$,%	>50	6(14,3±5,4)	12(35,3±8,2)	0,4
	30-50	16(38,1±7,5)	12(35,3±8,2)	1,1
	<30	20(47,6±7,5)	10(29,4±7,8)	1,6
Фенотип ХОБЛ	Bronchitis	4(9,5±4,5)	9(26,5±7,6)	0,7
	Emphysematous	20(47,6±7,7)	11(32,3±8,0)	1,5
	bronchitis-emphysematous	12(28,6±7,0)	4(11,8±5,5)	2,4
6-МШТ,м	>350	9(26,2±6,8)	20(58,8±8,4)	0,4
	<350	33(73,8±6,8)	14(41,2±8,4)	1,8
Diaphragm Fatigue Index	>65,1	10(23,8±7,3)	22(64,7±8,2)	0,4
	<65,1	32(76,2±7,3)	12(35,3±8,2)	2,2
CAT, балл	<10	2(4,8±3,3)	8(23,5±7,3)	0,2

	11-20	8(19,0±6,0)	7(20,6±6,9)	0,9
	21-30	14(33,3±7,3)	10(29,4±7,8)	1,1
	31-40	20(47,6±7,7)	9(26,5±7,6)	1,8
Index BODE, points	0-2	5(11,9±5,0)	12(35,3±8,2)	0,3
	3-4	10(23,8±6,6)	10(29,4±7,8)	0,8
	5-6	15(35,7±7,4)	8(23,5±7,3)	1,5
	7-10	12(28,6±7,0)	4(11,8±5,5)	2,4
MCC, min	≥25	28(66,7±7,3)	13(38,2±8,3)	1,7
	<25	14(33,3±7,3)	21(61,8±8,3)	0,5
sIgA, g/l	≥1	18(42,8±7,6)	29(85,3±6,1)	0,5
	<1	24(57,2±7,6)	5(14,7±6,1)	3,9
Bronchodilator refractoriness (increase in FEV1 with treatment,%)	<10	28(66,7±7,3)	11(32,3±8,0)	2,1
	≥10	14(33,3±7,3)	23(67,6±8,0)	0,5
Steroid refractoriness (daily dose of steroids, mg)	≤30	18(42,8±7,6)	24(70,6±7,8)	0,6
	>30	24(57,2±7,6)	10(29,4±7,8)	1,9
Number of exacerbations per year, times	Up to 2 times	8(19,0±6,0)	14(41,2±8,4)	0,5
	2-4 times	14(28,6±7,3)	12(35,3±8,2)	0,8
	More than 4 times	20(47,6±7,7)	8(23,5±7,3)	2,0
Duration of inpatient treatment, per year	before 20 days	6(14,3±5,4)	18(52,9±8,6)	0,3
	20-40 days	14(28,6±7,3)	11(32,3±8,0)	0,9
	more 40 days	22(52,4±7,7)	5(14,8±6,1)	3,5

The assessment of the obtained indicators reflects that the cohort of patients with vitamin D deficiency is a high-risk group for progressive course and unfavorable outcome of COPD, which occurs in 7 out of 10 COPD patients.

Taking into account the established features of the course of COPD against the background of vitamin D deficiency, we considered approaches to drug correction of vitamin D. COPD patients with high-risk indicators of vitamin D deficiency were prescribed therapeutic doses of vitamin D at 10,000 IU per day for 2 weeks, followed by a transition to a dose of 5,000 IU per day for 6 weeks and then taking vitamin D 2,000 IU per day.

The results of the evaluation of the effectiveness of the use of a therapeutic dose of vitamin D in 25 patients with COPD with vitamin D deficiency, who were prescribed 10,000 IU per day, and the control group are presented in Table 3, where short-term indicators after treatment are assessed: the severity of dyspnea, the course dose of steroids for relieving an exacerbation, and the duration of inpatient treatment for an exacerbation.

Table 3. Efficacy of the therapeutic dose of vitamin D in patients with COPD

Short-term treatment indicators		COPD patients with vitamin D deficiency	
		Therapeutic doses of vitamin D, n=25	Control, n=15
MRC, score	before	3,6±0,6	3,2±0,4
	after	1,7±0,2	2,3±0,8
ОФВ1	before	31,8±1,7	33,5±1,9
	after	46,4±1,2	38,4±2,2
CAT, score	before	34,6±2,5	33,9±1,5
	after	20,4±1,8	25,4±2,1
BODE score	before	6,6±1,3	6,9±1,5
	after	4,2±1,1	5,4±1,6
Course dose of steroids for relief of exacerbation, mg		165,4±10,8	315,6±20,6
Duration of inpatient stay, days		10,6±1,4	15,1±2,0

Evaluation of the effectiveness of using a therapeutic dose of vitamin D in a set of standards for the treatment of COPD determined therapeutic effectiveness in the form of a decrease in the degree of dyspnea, bronchial obstruction, the impact of the disease on the health and life of the patient, course doses of steroids and the duration of hospital stay, which reliably improved the quality of life and reduced the risks in the prognosis of 4-year survival. Thus, vitamin D deficiency is one of the important indicators that determine the pathogenetic mechanisms aggravating the course of COPD, supporting an extremely strong impact of COPD on the life of the patient and 2.4 times more often the percentage of 4-year survival of 18%. The use of a therapeutic dose of vitamin D in a set of standards for the treatment of COPD determined therapeutic effectiveness after treatment in the form of a decrease in the degree of dyspnea by 2.1 times, a decrease in the severity of bronchial obstruction by 45.9%, a decrease in the impact of the disease on the health and life of the patient by 41.0%. A significant decrease in the course doses of steroids (by 48%) and the length of hospital stay (by 29.8%) was noted compared to the control group.

The data emphasize that the examination of COPD patients for the level of vitamin D should be a mandatory point in the practice of a pulmonologist, especially in the cohort of patients over 70 years old, smokers with a smoking history of more than 40 years, the number of cigarettes smoked more than 20 pcs per day or a smoking index of more than 50 packs / year, a body mass index <18.5 kg / m2 and systematic intake of steroid hormones. Early diagnosis of vitamin D deficiency status will ensure the need for mandatory measures aimed at therapeutic and preventive programs for the treatment of vitamin D deficiency, ensuring increased treatment efficiency of COPD treatment standards and the quality of life of COPD patients.

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