

Changes of the pro-hormone levels of vitamin D 25(OH)D in patients with newly diagnosed pulmonary tuberculosis treatment failure

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In Ukraine the number of patients with newly diagnosed tuberculosis (NTDB) who successfully complete the course of treatment reaches 60–65 % today. This is while the World Health Organization (WHO) criteria for successful treatment of this category of patients is 85 %. Scientists around the world are studying the possible pathogenetic factors of treatment failure of antimycobacterial therapy in patients with tuberculosis. Nowadays, the impact of vitamin D has been widely studied in this area. Studying of the dynamics of this indicator in patients with NDTB with widespread destructive tuberculosis in the lungs and bacterial excretion with the purpose of finding new markers of progression of a specific process and failure of treatment, as well as finding possible ways of additional pathogenetic therapy to accompany patients is actual. This approach will prevent treatment failure and, as a consequence, improve treatment efficiency.

Purpose. To determine changes in the pro-hormone levels of vitamin D 25(OH)D in patients with NDTB treatment failure during the intensive phase of antimycobacterial therapy.

Materials and methods. A prospective study involving 58 patients with NDTB lungs was performed. The patients were divided into 2 groups: 28 patients with pulmonary NDTB treatment failure were included in the 1st group (the main group), 30 patients, who subsequently successfully completed the course of treatment were included in the 2nd group (comparison group). The control group consisted of 29 healthy volunteer-donors. All the patients had been in inpatient treatment in Communal Institution “Zaporizhzhia Regional TB Clinical dispensary” during 2017–2019 years. Scientific medical-laboratory center of Zaporizhzhia State Medical University researched changes of the level of 25(OH)D in the blood serum by method of enzyme linked immunosorbent assay using immunoassay analyser Sirio S with “DIAsource ImmunoAssays S.A.” kit (Belgium) (ng/ml). Blood sampling was made after an overnight fast. Blood was collected uniformly throughout the year in all patients and volunteers to avoid the effect of seasonal variability in vitamin D in the blood.

Results. While healthy volunteers have a reduction in the level of pro-hormone 25(OH)D only in 51.7 % of cases (deficiency in 13.8 % and insufficiency in 37.9 %), patients with NDTB with generalized specific process in the lungs, the presence of destruction of over 3 cm in diameter and bacterial excretion at the beginning of intensive phase of antimycobacterial therapy (0 doses), have its decrease in 96.5 % (81 % deficiency and 15.5 % insufficiency). 1/3 of patients (35.7 % at the 0th dose and 32.1 % at the 90th dose) with tuberculosis treatment failure have pro-hormone levels 25(OH)D less than 7 ng/ml, whereas in patients who successfully completed the course of treatment, this concentration of pro-hormone 25(OH)D was not even diagnosed. In the dynamics, after 3 months of intensive phase of antimycobacterial therapy (90 doses) in patients with NDTB treatment failure the levels of pro-hormone 25(OH)D continue to decrease significantly by 1.3 times relative to the initial values, which is 1.4 times lower than in patients who successfully completed the course of treatment.

Conclusions. In the vast majority of patients with NDTB of lungs with a risk of ineffective treatment, a pronounced deficiency of vitamin D (1/3 patients with pro-hormone levels 25(OH)D less than 7 ng/ml) is determined at the beginning of treatment, and after 3 months of the intensive phase of antimycobacterial chemotherapy exacerbates vitamin D deficiency. Therefore, this indicator can be used as a prognostic for the tuberculosis treatment failure and reducing the level of pro-hormone 25(OH)D in the dynamics require consideration of the problem of methods of its correction by the addition of vitamin D.

Ключові слова:

туберкульоз, невдача лікування, вітамін D.

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Зміни рівнів прогормона вітаміну D 25(OH)D у хворих на неефективно лікований уперше діагностований туберкульоз легень

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В Україні частка хворих на вперше діагностований туберкульоз (ВДТБ), які успішно завершують курс лікування, становить 60–65 %, а критерій Всесвітньої організації охорони здоров'я (ВООЗ) успішного лікування таких пацієнтів – 85 %. Світова наукова спільнота вивчає можливі патогенетичні чинники невдачі антимікобактеріальної терапії у хворих на туберкульоз. У цьому аспекті нині широко вивчають вплив вітаміну D. Актуальним є вивчення динаміки цього показника у хворих на ВДТБ із поширеним деструктивним туберкульозним процесом у легенях і бактеріовиділення для пошуку нових маркерів прогресування специфічного процесу та невдачі лікування, а також для з'ясування можливих шляхів додаткової патогенетичної терапії супроводу хворих. Такий підхід дає можливість запобігти невдачі лікування та, як наслідок, сприятиме підвищенню ефективності лікування.

Мета роботи – визначити зміни рівнів прогормона вітаміну D 25(OH)D у хворих на неефективно лікований ВДТБ легень у процесі інтенсивної фази антимікобактеріальної терапії.

Матеріали та методи. Виконали проспективне дослідження, в яке залучили 58 хворих на ВДТБ легень. Пацієнтів поділили на 2 групи: у 1 (основну) включили 28 осіб із неефективно лікованим ВДТБ легень, у 2 групу (порівняння) – 30

хворих, які згодом успішно завершили курс лікування. Контрольну групу утворили 29 здорових донорів-волонтерів. Усі пацієнти перебували на стаціонарному лікуванні в КУ «Запорізький обласний протитуберкульозний клінічний диспансер» у 2017–2019 рр. Дослідження рівнів прогормона вітаміну D 25(OH)D здійснили в Навчальному медико-лабораторному центрі Запорізького державного медичного університету методом твердофазного імуноферментного аналізу, використовуючи імуноферментний рідер Sirio S і набори «DIAsource ImmunoAssays S.A.» (Бельгія), (нг/мл). Зразки крові пацієнтів брали вранці натще. У всіх хворих та у волонтерів кров брали рівномірно протягом року для уникнення впливу сезонної варіабельності вітаміну D у крові.

Результати. У здорових волонтерів зниження рівня прогормона 25(OH)D визначили тільки у 51,7 % випадків (дефіцит – у 13,8 %, недостатність – у 37,9 %). У хворих на ВДТБ легень із поширеним специфічним процесом у легенях, наявністю деструкцій понад 3 см у діаметрі та бактеріовиділенням на початку інтенсивної фази антимікобактеріальної терапії (0 доз) зниження рівня прогормона 25(OH)D діагностували у 96,5 % (у 81 % – дефіцит, у 15,5 % – недостатність). 1/3 хворих (35,7 % на 0 дозі та 32,1 % на 90 дозі) з неефективно лікованим туберкульозом мають рівні прогормона 25(OH)D менші ніж 7 нг/мл, а у хворих, які успішно завершили курс лікування, таку концентрацію прогормона 25(OH)D навіть не визначали. У динаміці, через 3 місяці інтенсивної фази антимікобактеріальної терапії (90 доз), у хворих на неефективно лікований ВДТБ легень рівні прогормона 25(OH)D вірогідно продовжують знижуватися в 1,3 раза щодо початкових значень; це в 1,4 раза менше ніж показники пацієнтів, які успішно завершили курс лікування.

Висновки. У більшості хворих на ВДТБ легень із ризиком неефективного лікування визначали виразний дефіцит вітаміну D (у 1/3 хворих рівні прогормона 25(OH)D менші ніж 7 нг/мл) на початку лікування, а через 3 місяці інтенсивної фази антимікобактеріальної хімотерапії поглиблюється дефіцит вітаміну D. Отже, цей показник можна застосовувати як прогностичний щодо неефективного лікування туберкульозу, а зниження рівня прогормона 25(OH)D у динаміці потребує з'ясування доцільності методів його корекції шляхом додавання препаратів вітаміну D.

Изменения уровней прогормона витамина D 25(OH)D у больных неэффективно леченным впервые диагностированным туберкулезом легких

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В Украине доля больных с впервые диагностированным туберкулезом легких (ВДТБ), которые успешно заканчивают курс лечения, составляет 60–65 %, а критерий Всемирной организации здравоохранения (ВОЗ) успешного лечения этой категории пациентов составляет 85 %. Ученые всего мира изучают возможные патогенетические факторы неудачи антимикобактериальной терапии у больных туберкулезом. В этом аспекте широко изучают влияние витамина D. Актуально изучение динамики этого показателя у больных ВДТБ с распространенным деструктивным туберкулезным процессом в легких и бактериовыделением для поиска новых маркеров прогрессирования специфического процесса и неэффективного лечения, а также установления возможных путей дополнительной патогенетической терапии сопровождения больных. Такой подход позволит предупредить неудачу лечения и, как следствие, будет способствовать повышению эффективности лечения.

Цель работы – определить изменения уровней прогормона витамина D 25(OH)D у больных с неэффективно леченным ВДТБ легких в процессе интенсивной фазы антимикобактериальной терапии.

Материалы и методы. Выполнено проспективное исследование, в которое вошли 58 больных ВДТБ легких. Пациентов поделили на 2 группы: 1 (основная) – 28 пациентов с неэффективно леченным ВДТБ легких; 2 группа (сравнения) – 30 пациентов, которые потом успешно завершили курс лечения. Контрольную группу составили 29 здоровых доноров-волонтеров. Все пациенты находились на стационарном лечении в КУ «Запорожский областной противотуберкулезный клинический диспансер» в период 2017–2019 гг. Исследование уровней прогормона витамина D 25(OH)D выполнили в Учебном медико-лабораторном центре Запорожского государственного медицинского университета методом твердофазного иммуноферментного анализа с использованием иммуноферментного ридера Sirio S и наборов «DIAsource ImmunoAssays S.A.» (Бельгия), (нг/мл). Образцы крови пациентов брали утром натощак. У всех больных и у волонтеров кровь собирали равномерно в течение года для избегания влияния сезонной вариабельности витамина D в крови.

Результаты. У здоровых волонтеров снижение уровня прогормона 25(OH)D установлено только в 51,7 % случаев (дефицит – в 13,8 %, недостаточность – в 37,9 %). У больных ВДТБ с распространенным специфическим процессом в легких, с наличием деструкций более 3 см в диаметре и бактериовыделением в начале интенсивной фазы антимикобактериальной терапии (0 доз) снижение прогормона 25(OH)D установлено у 96,5 % (у 81 % – дефицит, у 15,5 % – недостаточность). 1/3 больных (35,7 % на 0 дозе и 32,1 % на 90 дозе) с неэффективно леченным туберкулезом имеют уровни прогормона 25(OH)D меньше 7 нг/мл. У больных, которые успешно завершили курс лечения, такая концентрация прогормона 25(OH)D даже не диагностирована. В динамике, через 3 месяца интенсивной фазы антимикобактериальной терапии (90 доз), у больных с неэффективно леченным ВДТБ легких уровни прогормона 25(OH)D достоверно продолжают снижаться в 1,3 раза относительно начальных значений; это в 1,4 раза ниже относительно показателей пациентов, которые успешно завершили курс лечения.

Выводы. У большинства больных ВДТБ легких с риском неэффективного лечения установлен выраженный дефицит витамина D (у 1/3 пациентов уровни прогормона 25(OH)D меньше 7 нг/мл) в начале лечения, а через 3 месяца интенсивной фазы антимикобактериальной химиотерапии усугубляется дефицит витамина D. Таким образом, этот показатель можно использовать как прогностический касательно неэффективного лечения туберкулеза, а снижение уровня прогормона 25(OH)D в динамике обуславливает необходимость рассмотрения вопроса целесообразности методов его коррекции путем добавления препаратов витамина D.

Ключевые слова:
туберкулез,
неудача лечения,
витамин D.

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Table 1. The study groups distribution by age and gender

Indicator	The 1 st group (n = 28)	The 2 nd group (n = 30)	The control group (n = 29)
Men	20 (71.4 %)	23 (76.7 %)	19 (65.6 %)
Women	8 (28.6 %)	7 (23.3 %)	11 (34.4 %)
Average age, years	46.04 ± 2.09	43.0 ± 3.48	42.2 ± 2.9

Newly diagnosed tuberculosis (NTDB) treatment failure is established in the patient according to the Ukrainian unified clinical guide of medical care (UUCGMC) "Tuberculosis" [1]. In Ukraine the number of patients with NDTB who successfully complete the course of treatment reaches 60–65 % today [2]. This is while the World Health Organization (WHO) criteria for successful treatment of this category of patients is 85 %. The most important of causes of treatment failure are lack of adherence to treatment [2] and late detection of tuberculosis (when patients are diagnosed with massive bacterial excretion, a generalized process in the lungs and destructions) [3]. Ukrainian scientists mention [4] that changing the structure of clinical forms of tuberculosis toward widespread and acute-progressing forms will further reduce the effectiveness of treatment. At the same time, scientists around the world are studying the possible pathogenetic factors of treatment failure of antimycobacterial therapy (AMBT) in patients with tuberculosis. Nowadays, the impact of vitamin D has been widely studied in this area.

The following mechanisms of regulation of the immune response by vitamin D in patients with tuberculosis have been established: activates macrophages, promotes the enhancement of antimycobacterial action of cathelicidin and γ -interferon, activates oxidative stress [5]. It is believed that the gold standard for determining the content of this vitamin is the evaluating of the concentration of pro-hormone vitamin D – 25(OH)D [6].

Povorozniuk V. V et al. indicate that the vast majority of the population of Ukraine (81.8 %) has a deficiency of vitamin D and 4.6 % inhabitants – insufficiency [6].

When comparing the levels of vitamin D pro-hormone in infected individuals and patients with active tuberculosis, the findings of the scientists have differences. Aibana O. et al. [5] and Gurjav U. et al. [7] on the basis of the obtained data argue that low levels of vitamin D in people with latent tuberculosis infection contribute to the development of active disease. Hong Y. et al. [8] note significantly lower levels of 25(OH)D in patients than in infected individuals. Ashenafi S. et al. [9] indicate that there is no difference between vitamin D pro-hormone levels between the compared contingents.

Wang Q. Z. et al. [10] indicate that patients with active tuberculosis with very low pro-hormone 25(OH)D levels (less than 8.5 ng/ml) have more severe disease symptoms. Memon A. et al. [11] detect a deficiency of pro-hormone vitamin D in the blood of patients with pulmonary tuberculosis with bacterial excretion and the presence of destructions.

In contrast to foreign authors, the role of vitamin D in the course of tuberculosis in children [12] and in adults with comorbid tuberculosis/chronic obstructive pulmonary disease [13] has been studied by Ukrainian scientists.

Both articles point to the important role of vitamin D in pathogenesis of tuberculosis. However, there are no data available in domestic literature about the dynamics of vitamin D levels in treatment failure newly diagnosed tuberculosis patients in dynamics.

Thus, due to the data on the predominantly low levels of vitamin D in Ukrainian population and the effect of pro-hormone 25(OH)D on the course of tuberculosis, studying of the dynamics of this indicator in patients with NDTB with widespread destructive tuberculosis in the lungs and bacterial excretion with the purpose of finding new markers of progression of a specific process and failure of treatment, as well as finding possible ways of additional pathogenetic therapy to accompany patients is actual. This approach will prevent treatment failure and, as a consequence, improve treatment efficiency.

Aim

To determine changes in the pro-hormone levels of vitamin D 25(OH)D in patients with NDTB treatment failure during the intensive phase of AMBT.

Materials and methods

A prospective study involving 58 patients with NDTB lungs was performed. The patients were divided into 2 groups: 28 patients with pulmonary NDTB treatment failure were included in the 1st group (the main group), 30 patients, who subsequently successfully completed the course of treatment were included in the 2nd group (comparison group). The control group consisted of 29 healthy volunteer-donors.

The age and gender of people in groups did not differ significantly (Table 1).

All the patients had been in inpatient treatment in Communal Institution "Zaporizhzhia Regional TB Clinical dispensary" during 2017–2019 years. Patients had been included in the study after signing the informed and voluntary consent. The study was approved by Commission for Bioethics of Zaporizhzhia State Medical University (Protocol № 1 of 02.02.2017).

Scientific medical-laboratory center of Zaporizhzhia State Medical University researched changes the level of 25(OH)D in the blood serum by method of enzyme linked immunosorbent assay using immunoassay analyser Sirio S with "DIAsource ImmunoAssays S.A." kit (Belgium) (ng/ml). Blood sampling was made after an overnight fast. Blood was collected uniformly throughout the year in all patients and volunteers to avoid the effect of seasonal variability in vitamin D in the blood.

Entry criteria: newly diagnosed pulmonary tuberculosis, widespread pulmonary tuberculosis process (infiltrative and disseminated), destructions in the pulmonary tissue over than 3 cm long and bacteriological proof.

Exclusionary criteria: other cases of the 2nd categoria [1], chemoresistant tuberculosis, co-infection (TB/HIV), comorbidities, age over 70 years, non-compliance for treatment.

Since the widespread pulmonary tuberculosis process was diagnosed in the 1st and 2nd groups' patients, an intensive phase (IP) for patients was 90

Table 2. Distribution of patients in groups depending on the concentration of pro-hormone 25(OH)D at its low values

Concentration of pro-hormone 25(OH)D	The 1 st group (n = 28)				The 2 nd group (n = 30)			
	0 doses		90 doses		0 doses		90 doses	
	abs.	%	abs.	%	abs.	%	abs.	%
<10 ng/ml	11	39.3	11	39.3	8	26.7	8	26.7
<9 ng/ml	10	35.7	10	35.7	4	13.3	8	26.7
<8 ng/ml	10	35.7	10	35.7	4	13.3	6	20
<7 ng/ml	10	35.7*	9	32.1#	0	0	0	0

*: a significant difference between indicators of groups at the 0 doses, $P < 0.05$; #: a significant difference between indicators of groups at the 90 doses, $P < 0.05$.

doses. Therefore, treatment efficacy was evaluated in 3 months according to the Unified medical care protocol "Tuberculosis" [1].

Pro-hormone vitamin D 25(OH)D level was conducted at the beginning of IP of the treatment (0 doses) and at the end of IP (after 3 months of the treatment – 90 doses).

Statistica for Windows 13.0 (Copyright 1984–2018 TIBCO Software Inc. All rights reserved. Licence № JPZ8041382130ARCN10-J) software was used for the statistical analysis. Normality of distribution of the quantitative indicators was performed by Shapiro–Wilk test. Research evidence are submitted in a form $M \pm m$, where M stands for average mean, m stands for mean error. The statistical significance of differences between groups was determined using Student's T-test (since the normality of distribution of the quantitative indicators was performed). The significance of the difference in the distribution of indicators (the distribution of patients in study groups in dynamics of treatment depending on the status of pro-hormone 25(OH)D) between groups was determined by comparison of frequencies. To compare qualitative indicators (distribution of patients in groups depending on the concentration of pro-hormone 25(OH)D at its low values) used the method of χ -squares with Yates correction. The results considered to be significant only if the P-value was lower than 0.05.

Results

Given that the concentration of pro-hormone 25(OH)D less than 20 ng/ml is a deficiency of vitamin D, and the concentration of 21–29 ng/ml is its insufficiency [5], the distribution of patients in the study groups during treatment depending on the status of pro-hormone 25(OH)D was done (Fig. 1).

As we can see, healthy volunteers had pro-hormone 25(OH)D deficiency only in 4 people (13.8 %) and its insufficiency in 11 (37.9 %). This indicator was normal in almost half of the people – 17 (48.3 %). Analyzing the data of patients, it was found that the frequency of both pro-hormone 25(OH)D deficiency and its insufficiency was almost the same and did not differ significantly in patients of both groups 1 and 2 at the beginning of IP of AMBT (0 doses). Thus, in the vast majority of the 1st and 2nd groups' patients there was a pro-hormone 25(OH)D deficiency (in 22 (78.6 %) and 25 (89.3 %) patients, respectively), which is significantly more frequent than in healthy volunteers: by 5.6 times ($P < 0.01$) in the 1st group and by 5.3 times ($P < 0.01$) in the 2nd group. However, the frequency of pro-hormone 25(OH)D insufficiency in patients of the 1st

and 2nd groups was lower but not significantly than in healthy volunteers: by 2.6 times in the 1st group and by 2.2 times in the 2nd group (in 4 (14.3 %) in the 1st group and in 5 (16.7 %) in the 2nd group versus 11 (37.9 %) in control group, $P > 0.05$).

At the end of IP of AMBT (90 doses) there were no patients with vitamin D insufficiency in the 1st group who had treatment failure ($P < 0.05$ compared to control group), on the other hand, the frequency of its deficiency increased by 10.7 (25 (89.3 % compared to 22 (78.3 %); $P > 0.05$) and this index normalized by 3.6 % (3 (10.7 %) against 2 (7.1 %); $P > 0.05$).

In patients who successfully completed IP of AMBT (90 doses) the frequency of persons with normal level of pro-hormone 25(OH)D was decreased by 3.3 % (2 patients (6.7 %) versus 3 (10 %); $P > 0.05$) and frequency of sick people with its insufficiency was reduced by 3.4 % (4 (13.3 %) against 5 (16.7 %); $P > 0.05$), instead the frequency of its deficit increased by 6.7 % (24 patients (80 %) at the beginning against 22 (73.3 %) at the end of IP; $P > 0.05$).

Based on the data of previous studies [10], that in patients with active tuberculosis with very low values of pro-hormone 25(OH)D (less than 8.5 ng/ml) more severe symptoms occur, the distribution of patients in groups depending on the concentration of pro-hormone 25(OH)D at its low values was done (Table 2). The proportion of patients with an appropriate concentration 10 ng/ml and below was evaluated. The concentration of pro-hormone 25(OH)D 10 ng/ml and below was not diagnosed in healthy volunteers.

It was found that the number of patients in group 1 with 25(OH)D level less than 7 ng/ml at the beginning of treatment and after 3 months reached more than 1/3 of patients (35.7 % and 32.1 % respectively), which is reliable distinguished patients from those who successfully completed the course of treatment (group 2), where such a concentration of pro-hormone 25(OH)D (<7 ng/ml) was not even diagnosed.

Comparing the levels of pro-hormone 25(OH)D in patients at the beginning of treatment (0 doses), it was found that they were reduced by 2.1 times in group 1 and by 1.7 times – in group 2 of patients relative to the corresponding indicator in the control (14.5 ± 2.55 ng/ml and 18.28 ± 2.77 ng/ml versus 31.04 ± 2.73 ng/ml; $P < 0.01$), (Fig. 2).

The dynamics showed a decrease in the levels of pro-hormone 25(OH)D in both groups, but a significant decrease by 1.3 times occurred in patients of 1 group (14.5 ± 2.55 ng/ml versus 10.9 ± 1.18 ng/ml; $P < 0.05$ and 18.28 ± 2.77 ng/ml versus 15.48 ± 2.3 ng/ml; $P > 0.05$).

After 3 months of treatment (90 doses), the levels of pro-hormone 25(OH)D remained lower in both groups

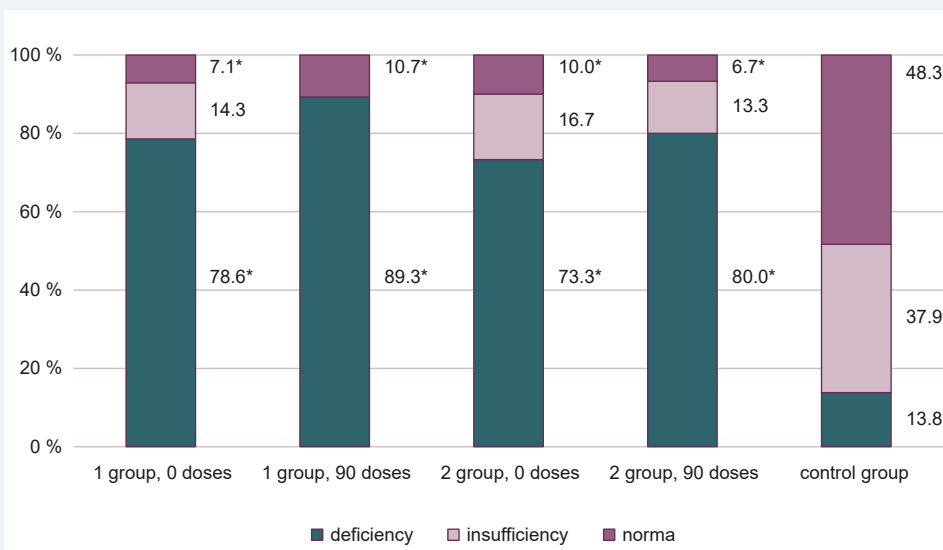


Fig. 1. Distribution of patients in groups in dynamics depending on pro-hormone 25(OH)D status, %.

*: a significant difference between indicators related to the control group, $P < 0.05$.

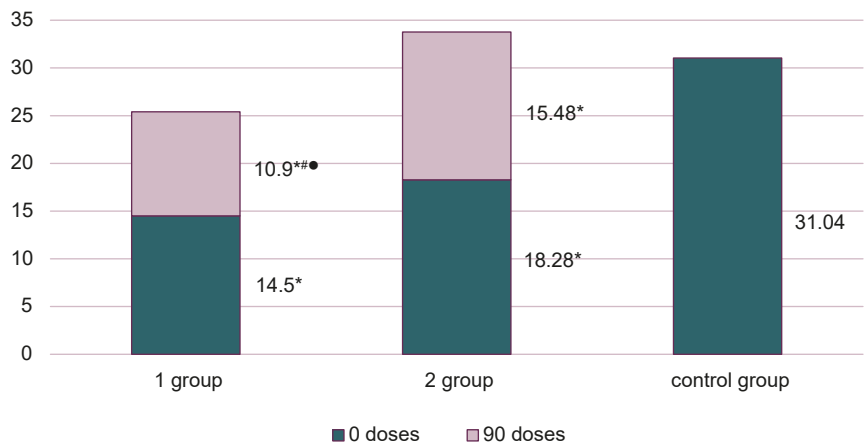


Fig. 2. Pro-hormone 25(OH)D levels in groups during treatment, ng/ml.

*: significant difference between indicators at the 0 and 90 doses related to the control group, $P < 0.05$;

#: significant difference between indicators in dynamics within one group, $P < 0.05$;

*#: significant difference between indicators at the 0 and 90 doses between 1 and 2 groups, $P < 0.05$.

compared to controls: by 2.8 times for 1 group and by 2 times for 2 group (10.9 ± 1.18 ng/ml and 15.48 ± 2.3 ng/ml against 31.04 ± 2.73 ng/ml; $P < 0.001$).

Comparing the levels of pro-hormone 25(OH)D after 3 months of treatment (90 doses) between 1 and 2 groups, it was found that in 1 group it was by 1.4 times lower: 10.9 ± 1.18 ng/ml against 15.48 ± 2.3 ng/ml; $P < 0.05$.

Discussion

It was found that there are 56 (96.5 %) patients with low levels of pro-hormone 25(OH)D, of which 47 people (81 %) have a deficiency and 9 (15.5 %) have an insufficiency among 58 patients with NDTB of lungs with generalized pulmonary involvement, destruction of lung tissue over 3 cm in diameter and with bacteriological proof (which is a risk of treatment failure) at the beginning of IP of AMBT (0 doses). These results confirmed the findings of previous studies [11], but Memon A. et al. determined this indicator in patients with NDTB with bacterial excretion and the presence of destruction, regardless of the size of affected lungs' areas. At the same time, we found that more than 1/3

of patients who will have treatment failure have levels of 25(OH)D below 7 ng/ml.

A further significant decrease in the level of pro-hormone 25(OH)D by 1.3 times in patients with treatment failure and a its decrease (but not significant) in patients who successfully completed the course of treatment in dynamics in patients with NDTB of lungs was determined. Tukvadze N. et al. [14] found that the levels of pro-hormone 25(OH)D did not change during treatment in patients receiving AMBT (both at the 60th and 90th doses), but the researchers examined patients with bacterial excretion, which in 78.8 % of cases had no destruction in the lungs. Mily A. et al. [15] also did not detect changes in vitamin D pro-hormone levels after IP of AMBT completion (90 doses). The opposite results were obtained by Sloan D. J. et al. [16] and Tostmann A. et al. [17], who received data that after 2 months of IP of AMBT (60 doses) vitamin D levels increased in patients. The authors attribute this to the fact that in the course of treatment in patients improves nutrition and general clinical condition, which contributes to an increase in time spent on the street and, as a consequence, increases the supply of vitamin D to the body.

Hazan Z. et al. [18] obtained results similar to ours, they found that pro-hormone 25(OH)D levels in patients

with bacterial excretion were significantly reduced within 3 months in patients who had deficiency, insufficiency, and normal values. The authors explained this effect by antimycobacterial drugs of the first line (isoniazid, rifampicin, pyrazinamide, ethambutol) impact on the metabolism of vitamin D. However, data on this effect on vitamin D metabolism are controversial. Thus, some researchers have found that isoniazid and rifampicin promote the increase in serum levels of pro-hormone 25(OH)D [19]. Others have found that first-line drugs so affect the metabolism of vitamin D, which reduce the vitamin D-induced production of cathelicidin by macrophages [20].

Considering the fact that the pro-hormone 25(OH)D levels after 3 months of IP of AMBT (90 doses) in patients who failed treatment were 1.4 times lower than in patients who successfully completed the course of treatment. This is despite the fact that all patients received the same standardized AMBT. Therefore, it is likely that not only drugs have an effect on vitamin D metabolism. We believe that due to the generalized tuberculosis and presence of the destruction over 3 cm and bacterial excretion, vitamin D is actively involved in the protection against tuberculosis and therefore the concentration of pro-hormone 25(OH)D in the serum is reduced, especially if immune answer is insufficient to stabilize the process after 3 months of treatment with antimycobacterial drugs and treatment failure is diagnosed.

Conclusions

1. While healthy volunteers have a reduction in the level of pro-hormone 25(OH)D only in 51.7 % of cases (deficiency in 13.8 % and insufficiency in 37.9 %), patients with NDTB with generalized specific process in the lungs, the presence of destruction of over 3 cm in diameter and bacterial excretion at the beginning of IP of AMBT (0 doses), have its decrease in 96.5 % (81 % deficiency and 15.5 % insufficiency).

2. 1/3 of patients (35.7 % at the 0th dose and 32.1 % at the 90th dose) with tuberculosis treatment failure have pro-hormone levels 25(OH)D less than 7 ng/ml, whereas in patients who successfully completed the course of treatment, this concentration of pro-hormone 25(OH)D was not even diagnosed.

3. In the dynamics, after 3 months of IP of AMBT (90 doses) in patients with NDTB treatment failure the levels of pro-hormone 25(OH)D continue to decrease significantly by 1.3 times relative to the initial values, which is 1.4 times lower than in patients who successfully completed the course of treatment.

Thus, in the vast majority of patients with NDTB of lungs with a risk of ineffective treatment, a pronounced deficiency of vitamin D (1/3 patients with pro-hormone levels 25(OH)D less than 7 ng/ml) is determined at the beginning of treatment, and after 3 months of the intensive phase of antimycobacterial chemotherapy exacerbates vitamin D deficiency. Therefore, this indicator can be used as a prognostic for the tuberculosis treatment failure and reducing the level of pro-hormone 25(OH)D in the dynamics require consideration of the problem of methods of its correction by the addition of vitamin D.

Prospects for further scientific research. To develop an algorithm for managing this category of patients in order to reduce the number of treatment failures and increase the effectiveness of antimycobacterial therapy.

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