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CLINICAL-DIAGNOSTIC PROPERTIES OF DIABETES MELLITUS 2 TYPE IN ASSOCIATION WITH TUBERCULOSIS AND DISORDER OF VITAMIN B12 AND D HEMOSTAS

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ABSTRACT
This article presents the results of the researchon clinical-diagnostic properties of diabetes mellitus. Diabetes and tuberculosis are that diseases which have more connection with death around the world. People who have tuberculosis more suffer from diabetes mellitus. As known, diabetes inhibits the immunological response, which contributes to the development of infectious diseases, including infection with tuberculosis mycobacteria [18].Tuberculosis is the third leading cause of death among infection diseases, whereas among non infection diseases diabetes is one of the most important [12]. The relationship between diabetes and tuberculosis has already been the subject of many studies, but at the same time, the relationship between these two diseases remains not fully understood.

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Diabetes, tuberculosis, chronic obstructive pulmonary disease, chromatography, Vitamin B12,Vitamin D, hemoglobin, insulin, Mantoux test.

INTRODUCTION

According to the National Clinical Protocols for the Management of Patients with Respiratory Tuberculosis in Adults (2020), patients with diabetes mellitus are included in a group where have increased risk of tuberculosis incidence. According to Boillat-Blanco N. et all (2016), vitamin D levels are inversely associated with tuberculosis (TB) and diabetes (DM). Vitamin D can mediate the relationship between tuberculosis and type 2 diabetes, that is, low 25 (OH) D can increase the risk of tuberculosis in patients with diabetes [5].

A number of scientists who studied 306 patients with tuberculosis and diabetes revealed a low content of vitamin D in patients. with both prediabetes and diabetes [20]

Recent studies have shown that in patients with type 2 diabetes and low serum vitamin D levels monocyte function is impaired, therefore, the ability to limit the intracellular growth of Mycobacterium tuberculosis is reduced, and this may be one of the factors linking diabetes with an increased risk of developing TB [9] .

According to Stevenson CR, Critchley JA, Forouhi NG [13] and Herrera MT, Gonzalez Y., Hernández-Sánchez F. [9], diabetes is associated with a three-fold increase in the risk of developing tuberculosis (TB) compared with the general population [2, 3]. For example, in 2012, the worldwide share diabetes among adults in cases of adult TB was estimated at 15%, and the number of adult cases of TB associated with diabetes was 1,042,000 [1-4].

For several decades, there has been evidence that vitamin D deficiency contributes to a higher risk of developing active tuberculosis compared with those with normal levels of vitamin D [22]. In turn, patients with tuberculosis as a whole also have a higher likelihood of vitamin D deficiency compared with normal control [7]. A small study in urban China using liquid chromatography and tandem mass spectrometry showed significant differences in vitamin D levels between patients with TB,

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patients with TB and prediabetes, and patients with TB and diabetes [18].

Type 2 diabetes mellitus (DM) increases the risk of developing tuberculosis (TB), and the level of TB is higher in people with diabetes than in the general population. Diabetes mellitus is also associated with adverse treatment outcomes for tuberculosis. Given the epidemiological transition in many countries of the world, current forecasts indicate that the prevalence of diabetes will reach 552 million people till 2030. Although the link between diabetes and tuberculosis has been known for several decades, [5.6] an unprecedented global increase of diabetes has led WHO and the International Union to Fight Tuberculosis and Lung Diseases in 2011 made a global recommendation that all tuberculosis patients should be tested for diabetes and vice versa [14]. Moreover countries, including China and India, have begun screening programs for TB patients for diabetes [7–9]. Despite this, the global response to the crisis was difficult due to a lack of knowledge regarding the most suitable screening methods and technologies for use in TB conditions [4]. The need for the develop and evaluate more accurate, quicker, non-invasive and cost-effective point-of-care (POC) diagnostic and control tests, including measurements of blood glucose and glycosylated hemoglobin (A1c) was recognized as the most relevant in 2011 at a consultation meeting of global experts on tuberculosis and diabetes. [1].

According to Zhao X. (2018) a large-scale study in China showed that 84% of patients with diabetes mellitus have vitamin D deficiency or acute deficiency, and these proportions are higher in patients living in the designated poverty zone , compared to other areas. Those with long diabetes history and HbA1c ≥10% had a higher risk of vitamin D deficiency [20, 21].

As you know, Vitamin B12 is necessary for the normal development of red blood cells, for the development and life of neurons (including the brain, especially the frontal lobes), and for DNA synthesis. Vitamin B12 is also needed for the work of methionine synthase, which stimulates the conversion of homocysteine to methionine. Therefore, with a deficiency of vitamin B12, homocysteine in blood tests increases [22].

At the same time, many issues remain controversial regarding the features of homeostasis in patients with type 2 diabetes mellitus with vitamin B12 and vitamin D deficiency, new reliable data are still required on the features of endocrine complications in patients with type 2 diabetes associated with tuberculosis, and the duration of replacement therapy with vitamins B12 and D and questions of the quality of life of patients, etc.

Thus, the problem of studying the homeostasis of vitamins B12 and D in patients with type 2 diabetes associated with tuberculosis is one of the urgent problems of modern endocrinology.

All of the above was the reason for the present study.

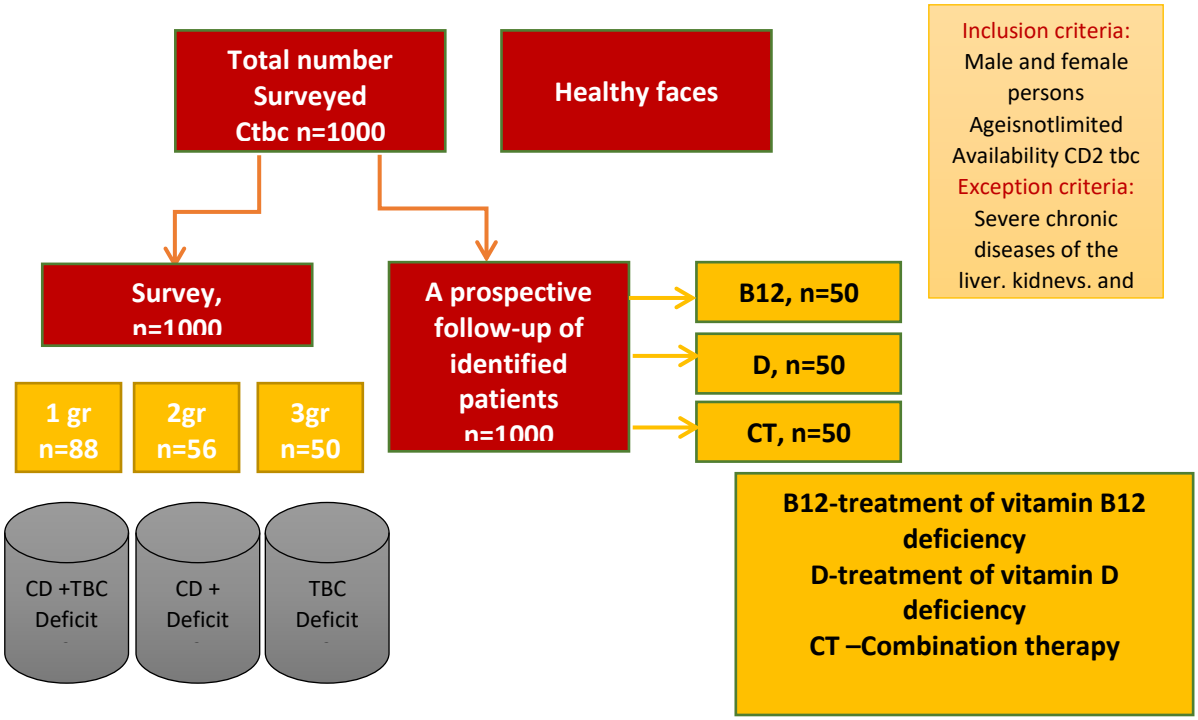

Figure 1. Design of experiment

Objective

To study the clinical and diagnostic features of type 2 diabetes mellitus associated with tuberculosis and impaired homeostasis of vitamins B12 and D.

Materials and methods research

The study involved 1,000 patients with tuberculosis who were examined by a screening method at the AMI for the period 2018-2019. Of these, 622 were men, 378 were women. The age of patients ranged from 16 to 70 years, while the average age of men was -58.2 ± 8.2 years, whereas the average age of women was -52.8 ± 2.7 years.

In the next step, we selected 188 patients (of which 94 were men and 93 were women) and consequently were divided into 3 groups as follows:

Group 1 - 88 patients with type 2 diabetes mellitus and pulmonary tuberculosis with a deficiency of vitamins B12 and D,

Group 2 - 56 patients with type 2 diabetes mellitus with a deficiency of vitamins B12 and D,

Group 3 - 50 patients with pulmonary tuberculosis with a deficiency of vitamins B12 and D.

The control group consisted of 30 healthy individuals of the corresponding age and gender. Thus, there were 138 patients with pulmonary tuberculosis.

In fig. 1 is shown a screening of TB with a deficiency of vitamin B12 and vitamin D.

There were used medical history informations of in-patients with taking into account date of anamnesis, including epidemiological, clinical examination results, tuberculin diagnostics, X-ray tomography studies, bacteriological studies, laboratory data (general blood test, determination of blood sugar, glycemic profile glucose tolerance test, glycated hemoglobin, insulin, blood C-peptide). In addition, we calculated the leukocyte intoxication index (LII), the index of shift of blood leukocytes (ISBL) [1, 2].

The content of 25 (OH) D in adolescents with vitamin D deficiency ranged from 11.4 to 27.3 ng / ml. In vitamin D deficiency, level 25 (OH) D was 8.6 ng / ml.

According to the Clinical Recommendations (2016, Russia), the serum level of vitamin B12 can be divided into 3 values: 1) probable vitamin B12 deficiency: <148 pmol / l (<200 pg / ml), 2) possible vitamin B12 deficiency: 148 - 258 pmol / L (<201-350 pg / ml), 3) Unlikely vitamin B12 deficiency:> 258 pmol / L (> 350 pg / ml).

With a vitamin deficiency, vitamin D deficiency is defined as a concentration of 25 (OH) D <20 ng / ml (50 nmol / L), deficiency is a concentration of 25 (OH) D from 20 to 30 ng / ml (50 to 75 nmol / L), adequate levels are 30-100 ng / ml (75-250 nmol / l). Recommended target values of 25 (OH) D for correction of vitamin D deficiency are 30-60 ng / ml (75-150 nmol / L). (Level of evidence A I, Guidelines for the diagnosis and treatment of Vitamin B12 Deficiency, UK Society of Hematologists (2014)).

In the blood serum of these patients, the concentration of 25-hydroxy-cholecalciferol 25 (OH) D was determined - an indicator of the adequacy of providing a particular person with vitamin D. The analysis took into account nationality, diet, intake of vitamin D during the examination and earlier. All patients underwent anthropometry with the calculation of the BMI and determination of nutritional status.

The inclusion criteria for patients are as follows: patients with a stably elevated blood glucose content, patients with a combination of type 2 and pulmonary tuberculosis.

Exclusion criteria: patients with chronic renal failure (CRF), severe liver disease, heart defects, acute myocardial infarction (AMI), acute cerebrovascular accident (stroke).

Statistical data processing was performed using the program VyuB1a1 for personal computers. When comparing the average values in normally distributed sets of quantitative data, the Student t-test was calculated. Differences were considered statistically significant at a significance level of $p<0.05$

Random characteristics are presented as average ± error of average. When testing statistical hypotheses in computer software packages, not only the value of the statistical criterion (Student's t-test, Fisher's criterion, etc.) was calculated, but also the achieved (critical) significance level was directly calculated to evaluate the criterion used.

Results And Discussions

Table 1 shows the distribution of patients by gender and age.

The first group consisted of 37 men and 51 women, whose average age was 54.4 ± 2.2 / 55.5 ± 1.7 (m / f), respectively. The duration of diabetes in men was within 6.8 ± 1.4 years, and in women 4.6 ± 0.7 years. The duration of tuberculosis in men were 1.8 ± 0.3, and in women 1.9 ± 0.2 years.

The average HbA1C content was in the range of 8.9 ± 0.50 / 9.9 ± 0.51, and glucose 10.6 ± 0.61 / 15.0 ± 0.82 nmol / L in the 1st group patients . The average insulin level was 11.3 ± 2.09 / 11.7 ± 2.2 pg / ml, and Vit B12 403 ± 33.7 / 407 ± 45.7 (normal 193-982 pg / ml, on average 450 pg / ml), the content of Vit D was in the range of 13.1 ± 2.1 / 11.1 ± 3.08 ng / ml, respectively (normally from 30-100 ng / ml).

The second group consisted of 26 men and 30 women, the average age was 49.5 ± 5.2 / 45.0 ± 8.0 years. The duration of tuberculosis in this group was 1.8 ± 0.4 / 1.0 ± 0.2 years. The average HbA1C content was in the range 8.1 ± 0.2 / 8.9 ± 0.7, and the glucose content was 8.9 ± 0.1 / 9.8 ± 0.4 nmol / L in the 2nd group patients . The average insulin level was 9.6 ± 1.9 / 16.3 ± 1.3 pg / ml, and Vit B12

376.7 ± 91.1 / 402.0 ± 13.3 (normal, 193-982 pg / ml, average 450 pg / ml), the content of vit D was in the range of 14.5 ± 1.4 / 11.6 ± 1.7 ng / ml, respectively (normally from 30-100 ng / ml).
The third group consisted of 19 men and 31 women, the average age was 47, 8 ± 6.3 / 47.0 ± 5.0 years. The duration of tuberculosis in this group was 2.7 ± 0.4 / 1.9 ± 0.3 years. The average content of HbA1C was in the range 4.1 ± 0.2 / 4.9 ± 0.7, and glucose 5.1 ± 0.1 / 5.8 ± 0.4 nmol / L in patients of the 1st group. The average insulin level was 8.2 ± 1.3 / 12.7 ± 1.3 pg / ml, and Vit B12 137.7 ± 8.1 / 123.0 ± 10.3 (normal, 193-982 pg / ml, average 450 pg / ml), the content of Vit D was in the range of 12.3 ± 0.4 / 8.2 ± 0.7 ng / ml, respectively (normally from 30-100 ng / ml).

Table 1: Distribution of patients by gender and age (WHO classification)

Age	Number of men	Number of women
11-15 years	5	**7**
18 – 29	15	15
30-44	22	19
45-59	23	26
60-74	17	13
75 and older	12	13
Total : n = 188	**94**	**93**

A clinical and anamnestic research showed that newly diagnosed tuberculosis was found in 54 of 138 patients with pulmonary tuberculosis (39.1%), and relapse of the tuberculosis process was observed in 6 of 138 (4.3%) patients. Moreover, in the majority of patients, pulmonary tuberculosis was detected during preventive examination - 47 out of 138 people (34.05%), while seeking medical help - in 13 patients out of 138 (9.3%). Infiltrative pulmonary tuberculosis was more detected in 49 cases (35.5%), while fibrous-cavernous was registered in 6 people (4.3%), tuberculoma was detected in 4 people (2.8%) and disseminated tuberculosis in 1 person (0.7%), in 2 cases (1.4%), the process was combined with pleural tuberculosis and in 4 cases (2.8%) with extra pulmonary lesions-generalized tuberculosis. In general, a common process was recorded - 36 people (26%). In the main part of patients, the tuberculosis process was accompanied by bacterial excretion - 37 people (26.8%). Drug resistance was observed in 13 (9.4%) patients, of which multiple drug resistance was observed in 12 patients. (8.6%).
The majority of patients had type 2 diabetes mellitus - these were patients of groups 1 and 2 - 144 cases (76.5%). According to the severity of diabetes, the patients were divided as follows: with moderate severity - 132 patients out of 144 (91.6%) and with a severe degree - 12 patients (8.4%).
Depending on the compensation form of diabetes mellitus, the distribution was as follows: compensated - 5 people. (3.5%), subcompensated - 93 people. (64.9%) and decompensated diabetes mellitus - 46 people.(31.9%). It was also found that 63 (43.3%) patients had various complications of diabetes.
Further, according to the anamnesis, we specified additional risk factors for the development of tuberculosis in patients with type 2 diabetes. Assessing social factors, we found that the majority of patients were unemployed - 143 out of 188 patients (77%), while 74 (39.3%) people had secondary education, 74 (39.3%) had secondary education and higher - 40 (21.2%). Most patients rated their living conditions as satisfactory - 176 people (93%), while in 12 patients (6.3%) they were unsatisfactory. 80 (42.5%) people had bad habits, 30 of them (37.5%) regularly drank alcohol, 168 patients (89.3%) smoked, 6 patients (3.1%) were addicted. Previously, 13 (6.9%) patients with combined pathology were in prison.
Assessing medical risk factors, it was found that in 96 patients (51.7%), simultaneously with type 2 diabetes and tuberculosis, chronic obstructive pulmonary disease (COPD) occurred, in 74 - myocarditis (39.3%), in 47 - ischemic disease heart and arterial hypertension (25%) . Moreover 38 patients had chronic hepatitis (20, 1%), 26 cases chronic pancreatitis (13.8%) and 22 cases gastritis (11.7%). There another thing which should be noted that 22 had atherosclerosis lower extremities (11.7%), 20 - alcoholism (10.6%), 16 - chronic cholecystitis (8.5%), 16 - chronic pyelonephritis (8.5%), 16 - encephalopathy of mixed origin (8.5%), 12 - widespread osteochondrosis of the spine (6.4%), 6 - hypothyroidism (3.1%), 6 - oncopathology (3.1%).Clarifying the epidemiological history, it was found that only every 4 patients had contact with a patient with tuberculosis (25%), in other cases, either patients denied contact (17 - 28.3%) or did not know about it (28 - 46.7 %).In table 2 presents the average values of anthropometric indicators for groups.

Table 2: The average values of weight, height and BMI for groups

Group	Height	Weight	BMI
1 group n= 88	174,8± 3,8	63,4±6,4	20,6± 3,8
2 group n= 56	174,5± 2,5	82,75±5,3*	27,35± 7,8*
3 group n= 50	170,4± 8,3	72± 7,8*	24,50± 8,3*
Control n= 30	176,5 ± 2,6	67,4 ±6,3	19,7± 2,1

Note: P - significance of differences compared with control data, where * - p <0.05.

As can be seen from table 2, significant differences from the control were by weight and BMI in all groups of patients.

When the tuberculous process was detected, most patients had clinical symptoms due to the manifestation of the inflammatory process: intoxication syndrome was observed in 32 (17.0%) patients, bronchopulmonary syndrome - in 16 (8.5%), a combination of these syndromes - in 116 patients (61 , 7%), and only 25 (13.3%) patients did not suffer from complications. The degree of intoxication was calculated by the leukocyte intoxication index, while the average level of the indicator was 2.01 ± 0.2 units, In normal condition it is 0.5-1.5 units.

According to the results of a clinical blood test, ESR acceleration was more often recorded in 120 cases (64%), anemia in 66 (35.1%), lymphopenia in 60 cases (31.7%), there were no changes in 25 cases (13, 3%). Upon receipt, blood sugar averaged 11.8 ± 1.1 mmol / L.

The Mantoux test was performed on admission to 35 patients; it was negative in 6 patients (3.1%), positive normergic in most patients - 165 (87.7%), and positive hyperergic in 16 patients (8.5%). The average size of the infiltrate during the Mantoux test was 14.1 ± 0.7 mm, which indicated a pronounced response to tuberculin.

Then we studied the biochemical parameters in groups. Table 3 shows the average values of biochemical parameters in groups.

Table 3: The average values of biochemical parameters of groups

Group	Blood glucose, on an empty stomach, mmol / L	HbA1C, %	GFR, ml / min
1 group n= 88	9,7*± 0,8 (from 7,4 to14,5)	7,8* ± 0,4 (from 5,4 to12,2)	73,25*± 3,1 (from 67 to 98)
	8,9*± 0,6 (from 8,5 to 13,9)	9,3* ± 0,4 (from 6,3 to 11,4)	91,3*± 3,5 (from 76 to 101)
2 group n= 56	9,37*± 0,2 (from 8 to 13,8)	8,62*± 0,2 (from 6,6 to 10,7)	64,96* ± 3,8 (from 58 to 70,4)
	8,76 *± 0,5 (from 9 to 16.3)	8,88* ± 0,7 (from 7,9 to 11)	63,75 ± 2,6 (from 51 to 72)
3 group n= 50	4,63± 0,02* (from 4,4 to 4,7)	4,7* ± 0,4 (from 4,2 to 5,1)	105,8*± 4,3 (from 92 to 110)
	4,5 ± 0,03* (from 4,7 to 4,9)	4,7* ± 0,5 (from 4,7 to 5,8)	106, 4 *± 3,7 (from 96 to 114)
Control n= 30	4,4 ± 0,6	5,1 ±0,8	121,4 ± 9,6

Note: P - significance of differences compared with control data, where * - p <0.05. GFR - glomerular filtration rate, ml / min; HbA1C - glycated hemoglobin.

As can be seen from table 3, in groups 1 and 2 of patients there were a significant increase in fasting glycemia, HbA1C, GFR (p <0.05), while in patients of group 3 indicators did not differ from the norm and the control group.

Of the 138 patients of groups 1 and 3 participating in the study, 41 (29.7%) people had sufficient vitamin D in their blood serum, and 97 patients (70.2%) had vitamin D deficiency. In the 2nd group of patients (56 patients with type 2 diabetes), 12 (21.4%) patients had a sufficient serum vitamin D content, and vitamin D deficiency was observed in 44 patients (78.5%).

Of the 138 patients of groups 1 and 3 participating in the study of patients with pulmonary tuberculosis and type 2 diabetes, 36 (26.0%) people had sufficient vitamin B12 in their blood serum, and 102 patients (73.9%) had vitamin B12 deficiency. In the 2nd group of patients (56 patients with type 2 diabetes), 16 (28.6%) patients had sufficient vitamin B12 in their blood serum, and B12 hypovitaminosis was observed in 40 patients (71.4%).

Table 4 presents the average values of biochemical and hormonal blood tests of groups.

Table 4: The average values of biochemical and hormonal blood tests of groups.

Indicators	1 group	2 group	3 group	Control	Norm
ИРИ, mcED / ml	9,98 ±0,71	21,48±5,73	23,5±4,5	6,5±1,3	3-30
C peptide mmol / L	214,83±56,2	247,25±132,8	382,33±123,3	148±20,5	0,01-400
Vit. B12	123,8 ±6,6*	111,8 ± 4,5*	125,7 ±0,5*	435,4 ±8,3	400-500 pg/ml
Vit. Д	14,4±1,3*	16,5±1,6*	13,5± 2,3*	64,1± 7,1	30-100 ng/ml

Note: P - significance of differences compared with control data, where * - p <0.05.

As can be seen from table 4, the average values of vitamins B12 and D were significantly reduced in all groups compared with the control (p <0.05).

Given the effectiveness of anti-TB treatment, the following tuberculosis outcomes were recorded: with deterioration in 30 cases (15.9%), no change in 18 cases (9.5%), with improvement in most cases - 135 (71.7%), of in 25 cases (18.6%) they underwent surgical treatment and a significant improvement in 5 cases (3.7%).

Thus, despite the low level of body reactivity in patients with tuberculosis and type 2 diabetes, we observed the high effectiveness of ongoing anti-tuberculosis therapy.

Conclusion

1) Of the 138 patients of groups 1 and 3 participating in the study of patients with pulmonary tuberculosis and type 2 diabetes, 41 (29.7%) people had sufficient vitamin D in their blood serum, and 97 patients (70.2%) had vitamin D deficiency. In the 2nd group of patients (56 patients with type 2 diabetes), 12 (21.4%) patients had a sufficient serum vitamin D content , and vitamin D deficiency was observed in 44 patients (78.5%).

2) Of the 138 patients of groups 1 and 3 were selected for research , 36 (26.0%) people had sufficient vitamin B12 in their blood serum; 102 patients (73.9%) had vitamin B12 . In the 2nd group of patients (56 patients with type 2 diabetes), 16 (28.6%) patients had sufficient vitamin B12 in their blood serum, and B12 hypovitaminosis was observed in 40 patients (71.4%).

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