ORIGINAL ARTICLE

IMPACT OF NUTRITIONAL CORRECTION OF PROTEIN METABOLISM DISORDERS ON THE CLINICAL COURSE OF PULMONARY TUBERCULOSIS

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ABSTRACT

The aim: To study the impact of nutritional correction of protein metabolism disorders on the clinical course of pulmonary tuberculosis.

Materials and methods: The study involved 67 patients with pulmonary tuberculosis, which were divided into two groups: group I – 35 patients who underwent nutritional correction of protein metabolism disorders against the background of antimycobacterial therapy (AMBT) and group II – 32 patients who received standard AMBT. An assessment of clinical indicators and the condition of protein metabolism (PM) was conducted by determining the concentration of individual non-essential, essential amino acids and their total amount.

Results: The proposed correction scheme includes food products containing essential nutrients and biologically active compounds that have a positive impact on the corresponding links of pathogenesis and can be used throughout all phases of treatment. Its application had a positive impact on the indicators of PM (significant ($p<0.05$) increase in total amount of essential amino acids (TAEAA), total amount of non-essential amino acids (TANEAA) and total amount of amino acids (TAAA) in blood serum and the concentration of individual essential and non-essential amino acids (significantly reached the level of indicators in healthy individuals) and clinical course of tuberculosis (intoxication syndrome disappeared earlier by 10.8 ± 0.97 days, and respiratory one by 8.95 ± 1.68 days), there was an increase in the frequency of healing of decay cavities at the time of completion of treatment by 34.0% and a significant ($p<0.05$) reduction in the average duration of treatment by 21.1 ± 2.91 days.

Conclusions: The application of nutritional correction of protein metabolism in the complex treatment of patients with pulmonary tuberculosis made it possible to obtain a pronounced positive impact on the clinical course of the disease and the condition of protein metabolism, which contributed to an increase in the effectiveness of treatment and rehabilitation.

KEY WORDS: amino acid composition of blood serum, nutrients, complex treatment of tuberculosis

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INTRODUCTION

Ukraine is in second place in the European region by the incidence rate of tuberculosis (TB), about 65.0% of new cases of the disease occur in vulnerable and marginalized groups of the population. The high prevalence of TB is due to the presence of a number of challenges that have negatively affected the health of the population. Most of the population is on the verge of poverty, does not have the opportunity to eat a rationally and balanced, accordingly, does not receive the needfull amount of proteins, the structural elements of which are amino acids [1-3]. TB leads to significant disorders of tissue metabolism, there was a tendency to reduce the overall concentration level of amino acids in the acute phase of the tuberculosis process, not only due to essential amino acids, but also non-essential ones, which was explained by insufficient synthesis and overuse of them for the energy and plastic needs of the body [4-6]. Intensive AMBT, which acts directly on the causative agent of the disease, remains the main and obligatory component of the modern approach to the treatment of this pathology. Pathogenetic therapy in TB patients is aimed at correcting metabolic processes and dysfunctions of various organs and systems, at normalizing existing metabolic disorders [7-9].

Imbalance in the diet of TB patients before the onset of the disease leads to a deficiency of the most biologically active nutrients, which contributes to the development of the pathological process and creates the basis for a complicated course of the disease [10-12]. Today, there are no modern dietary guidelines, available and understandable recommendations for the nutrition of TB patients, which can be used throughout all phases of treatment and will meet the physiological needs of patients and offer a list of food products, containing biologically active compounds which, in turn, have a positive impact on reducing inflammation, normalizing metabolic disorders caused by inflammation and long-term AMBT, on the activation of reparative mechanisms, the correction of psycho-emotional status.

THE AIM

Study of the impact of nutritional correction of protein metabolism disorders (NCPMD) on the clinical course of pulmonary tuberculosis.

MATERIALS AND METHODS

The studies were conducted in accordance with the principles of bioethics in compliance with the WHO regulations, World Medical Association Declaration of Helsinki. The study protocol was approved by the Bioethics commission of the Bogomolets National Medical University. Informed consent was obtained from all study participants. The study involved 67 patients with newly diagnosed pulmonary tuberculosis. Among them there were 53 men (79.1%), 14 women (20.9%). The average age of patients is 38.4±1.8 years. All patients were divided into two groups: group I – 35 patients who underwent NCPMD on the background of AMBT and Group II – 32 patients receiving standard AMBT, no statistically significant difference between groups by sex and age ($p > 0.05$). Within 5 days after hospitalization a multipurpose evaluation was conducted in accordance with diagnostic examination plan, required for persons with pulmonary pathology. The criteria for exclusion from the study were diseases of the gastrointestinal tract, hepatobiliary disease, diabetes mellitus, HIV infection, viral hepatitis, under 18 years of age.

Before the start of treatment, 32 (91.4%) persons of group I and 29 (90.6%) ones of group II had intoxication syndrome (IS). Respiratory syndrome (RS) was detected in 31 (88.6%) patients of group I and 29 (90.6%) patients of group II. Weight loss was determined in 21 (70.0%) patients of group I and 26 (70.2%) patients of group II. In 23 (76.7%) patients of group I and 29 (78.4%) ones of group II, the tuberculous process occupied more than three lungs segments, decay cavities were present in 24 (80.0%) patients of group I and 23 (82.1%) ones of group II. Bacterial excretion was present in 29 (82.9%) patients of group I and in 27 (84.4%) patients of group II. It should be noted that patients with massive bacterial excretion prevailed in both groups: in 16 (45.7%) patients of group I and in 15 (46.9%) patients of group II.

For study the condition of protein metabolism (BU) the concentration of individual non-essential amino acids (NEAA) (ornithine, aspartic acid, serine, glutamic acid, proline, glycine, alanine, cysteine, tyrosine, and glutamine), essential amino acids (EAA) (lysine, histidine, arginine, threonine, valine, methionine, isoleucine, phenylalanine, and leucine) and their total amount (TAAA) (mg per 100 ml of blood serum) were determined. The studies were carried out on an empty stomach. The material was venous blood; precipitation of protein samples was carried out by the method of deproteinization of samples with sulfosalicylic acid. The studies were carried out on an automatic analyzer of amino acids AAA-339-T, by the method of ion-exchange column chromatography on the basis of the laboratory of technology of biological products (chromatography group) of O. V. Palladin Institute of Biochemistry.

Before to the start of treatment, patients of both groups had PM disorders, manifested by a decrease in the total amount of essential amino acids (TAEAA) by 1.2 times (group I up to 8.5 ±0.5 mg and group II up to 8.8 ±0.4 mg per 100 ml of blood serum) compared with the control group (10.9 ±0.7 mg per 100 ml of blood serum). Also, in patients of both groups, the level of the total amount of non-essential amino acids (TANEAA) was reduced by 1.2 times (group I to 15.9±0.4 mg and group II to 15.9±0.4 mg per 100 ml of blood serum) compared with the control group (19.7±0.9 mg per 100 ml of blood serum). Which led to a decrease in TAAA in patients of both groups by 1.2 times (group I to 24.4±0.5 mg and group II to 24.7±0.8 mg in 100 ml of blood serum) compared with the control group (30.6±2.4 mg in 100 ml of blood serum). The control group consisted of 30 healthy individuals aged 18 to 55 years, men – 16 (53.0%), women – 14 (47.0%).

Etiotropic AMBT in both groups was performed according to current guidelines. The treatment regimen in the intensive phase included the use of isoniazid, rifampicin, pyrazinamide, ethambutol for 2 months (60 doses). The drugs in all studied groups of patients were administered once in a daily dose under the supervision of medical personnel in accordance with the prescribed treatment regimen.

An individual approach was used in the design of the diet and differentiation was carried out taking into account the phase of development of the tuberculosis process and the general condition of the body, NCPMD was produced by enriching the diets of patients with the appropriate products listed in Table I.

Statistical data analysis was performed using Statistica 10.0 and Microsoft Excel. Data are given as arithmetic mean ± standard deviation (M±SD) with normal distribution of variables. The significance of the difference in indicators was calculated by Student's t-test with a normal distribution of values. The results of comparisons were considered reliable if the error probability was less than $p<0.05$.

RESULTS

At the end of the intensive phase of treatment it was found the disappearance of IS during the first month of treatment was observed in 26 (81.3%) patients of group I and only in 17 (58.6%) patients of group II. At 2 months of treatment, IS disappeared in 5 (15.6%) patients of group I and in 7 (24.1%) patients of group II. Sustained normalization of body temperature, improvement in appetite, the disappearance of night sweats was observed on average after 19.75±3.2 days in patients of I group and 30.55±4.1 days in patients of group II after the start of treatment ($p<0.05$). After 1 month of treatment, disappearance of RS was observed in 17 (54.8%) patients of group I and only in 12 (41.4%) patients of group II, at 2 months of treatment RS disappeared in 11 (35.5%) patients of group I and in 11 (37.9%) patients of group II. The cessation of coughing, a significant decrease in shortness of breath from the start of treatment in patients of group I was observed on aver-

Table I. Pathogenetic nutritional correction of the diet for patients with newly diagnosed pulmonary tuberculosis

№	Links of pathogenesis	Biologically active compounds	Products nutrition
1	2	3	4
1.	Reduction of inflammation		
	- activation of immunometabolic processes	Protein	Sour-milk, dairy products, meat, eggs
	- decreased expression of anti-inflammatory cytokines, increased activity of phagocytes	Vitamin D	Sea fish, eggs
	- protection of mucous membranes from bacteria, activation of cellular antibacterial immunity	Secretory immunoglobulin A Lactobacillus acidophilus	Dairy products – prebiotics. Acidophilus
	- interleukin synthesis	PUFAs W-3	Sea fish, walnuts
	- tissue antioxidant protection	Vitamins and provitamins	
		Ascorbic acid	Citrus fruits, cabbage, green onions, parsley, dill, currants, horseradish, wild rose
		α-Tocopherol	Unrefined vegetable oils, nuts, legumes
		Retinol	Beef liver, whole milk, eggs
		Alpha-, beta-, gamma-carotenes	Carrots, pumpkin, persimmon, oranges
		Trace elements	
		Selenium	Garlic, seafood
		Copper	Fish, marine aquatic organisms
		Magnesium	Groats, almonds
		Zinc	Meat, pumpkin seeds
		Cobalt	Meat, seafood
		Manganese	Cereals
		Plant antioxidants	
		Ubiquinone	Pistachios, sesame
		Anthocyanins	Red grapes, cranberries, blueberries, red cabbage
		Catechins	Green and black tea, blueberry, sea buckthorn
		Coumarins	Cinnamon, mint, green tea, blueberries
		Chlorophils	Green parts of plants, garden greens
		Polyphenols	Green tea, red grapes, onions, apples, strawberries, raspberries
	- antiseptic action	Bioflavonoids, quercetin, rutin	Plums, cherries, blueberries, apples, apricots, red peppers, green tea
		Salicylates Ascorbic acid	Cherry, raspberry Citrus fruits, cabbage, green onions, parsley, dill, currants, horseradish, wild rose
		Malic acid Cinnamic acid Phytoncides	Apples, dogwood Cinnamon Onion, garlic, horseradish, currant, citrus
		Terpenes Hydroquinone	Dill, coriander, mint, cumin Lingonberry, pear, wild strawberry, cranberry, blueberry
		Benzoic acid Benzaldehyde Eugenol	Cranberry, lingonberry Elderberry, almond Clove, basil
	- anti-inflammatory, desensitizing effect	Calcium	Sour-milk, dairy products
	- specific bacteriostatic action	Essential oils	Thyme, mint, cloves
2.	Normalization of metabolic disorders caused by inflammation and long-term chemotherapy		
	- increase in appetite	Choleretic effect	Cherries, apples, cabbage, onions, parsley, celery, dried fruits, chicory, mint, wild rose
	- enzyme inducers	Synthesis of liver benzpyrene hydroxylase, intestinal and liver monooxygenases	White cabbage, Brussels sprouts, cauliflower, spinach
	- prevention of the negative impact of specific therapy	B vitamins	Beef liver, poultry, fish, whole grain bread, wheat bran
3.	Completion of inflammation, activation of reparative mechanisms		
	- acceleration of epithelization	Vitamin A	Beef liver, whole milk, eggs
		Calcium	Dairy products
	- rebuilding the gut microbiota ecosystem	Vitamins B1, B2, B6, B12, PP	Natural yogurt
4	Correction of psycho-emotional status		
		Vegetative phyto- regulators	Lemons, oranges, vanilla, cinnamon, bananas
		Probiotics	Natural yogurt

Table II. Indicators of the concentration of essential amino acids in blood serum in patients of groups I and II in the dynamics and in the control group (x ± SD)

Amino acid (mg in 100 ml of blood serum)	Control group (healthy individuals) n= 30	Group I (n= 35)	Group 2 (n= 32)
Lysine	2,2±0,2	2,1±0,022	1,7±0,1
Histidine	1,1±0,1	1,0±0,022	0,8±0,11,2
Arginine	1,2±0,1	1,1±0,022	1,0±0,031,2
Threonine	1,2±0,1	1,2±0,12	1,0±0,031,2
Valine	1,9 ±0,2	1,9 ±0,03	1,9±0,1
Methionine	0,4±0,04	0,3±0,02	0,3±0,021
Isoleucine	0,7±0,1	0,7±0,03	0,7±0,04
Phenylalanine	0,7±0,04	0,7±0,022	0,6±0,031
Leucine	1,2±0,1	1,2±0,1	1,2±0,07
The total amount of essential amino acids	10,9±0,7	10,1±0,12	9,1±0,21,2

Note. 1 - p<0,05 when comparing with indicators of healthy individuals;
2 - p<0,05 when comparing I and II groups of patients

Table III. The concentration of non-essential amino acids in blood serum in patients of groups I and II in dynamics and in the control group (x ± SD)

Amino acid (mg in 100 ml of blood serum)	Control group (healthy individuals) n= 30	Group I (n= 35)	Group 2 (n= 32)
Ornithine	0,7±0,1	0,7±0,02	0,7±0,02
Aspartic acid	0,1±0,01	0,1±0,01	0,1±0,01
Serine	0,9±0,1	1,1±0,052	0,9±0,01
Glutamic acid	0,7±0,1	0,8±0,022	0,5±0,021,2
Proline	1,8 ±0,2	1,7 ±0,02	1,7±0,1
Glycine	1,5±0,1	1,6±0,12	1,3±0,04
Alanine	3,3±0,3	3,1±0,3	3,0±0,1
Cysteine	0,8±0,1	0,8±0,1	0,8±0,1
Tyrosine	1,5±0,1	1,5±0,03	1,5±0,1
Glutamine	8,5±0,8	8,3±0,052	7,6±0,1
The total amount of non-essential amino acids	19,7±0,9	19,8±0,12	18,1±0,2

Note. 1 - p<0,05 when comparing with indicators of healthy individuals;
2 - p<0,05 when comparing I and II groups of patients

age after 37.24±5.12 days and in group II after 46.19±3.44 days. Indicators of the termination of bacterial excretion did not differ statistically in both studied groups (group I – 17 (58.6%) patients, group II – 14 (51.9%) ones). The frequency of healing of decay cavities in both study groups differed from each other, in favor of group I – 10 (31.25%) patients versus 4 (13.3%) ones.

After 2 months of treatment assay of the dynamics of PM indicators showed that patients of group I have a significantly (p <0.05) higher concentration of individual EAA and, accordingly, a higher concentration level of TAEAA compared to indicators in group II. Significantly (p <0.05) higher concentration of such EAA as: lysine, histidine, arginine, threonine in patients of group I compared with the corresponding indicators in group II. And also, significantly (p <0.05) higher TAEAA in patients of group I (10.1±0.1 mg compared with the corresponding indicator in group II 9.1±0.2 mg in 100 ml of blood serum) and it is significantly did not differ from that in the control group (Table II).

At the same time, in patients of group II, there is a significantly lower concentration of such amino acids as histidine (1.4 times), arginine (1.2 times), threonine (1.2 times), methionine (1.3 times), phenylalanine (1.2 times) compared with the corresponding indicators in the control group. Therefore, a decrease in the concentration of individual EAA led to a significant (p<0.05) decrease (1.2 times) in TAEAA compared with the corresponding indicator in the control group 10.9±0.68 mg per 100 ml of blood serum.

Analyzing the concentration of individual NEAA and their total amount in patients of groups I and II in dynamics and in the control group after 2 months of treatment, it should be noted that in patients of group I, compared with the corresponding indicators in group II, there is a signifi-

cantly ($p<0.05$) higher the concentration of such NEAA as: serine, glutamic acid, glycine, glutamine, and TANEAA was 19.8±0.10 mg, which is significantly ($p<0.05$) higher compared to the corresponding indicator of 18.1±0.20 mg in 100 ml of blood serum in patients of group II (Table III).

This indicates that in patients of group I there was a normalization of the indicators of the concentration of NEAA, and they did not significantly differ from those in the control group. At the same time, in patients of group II, there is an unreliable, but significantly lower concentration of some NEAA and, accordingly, lower TANEAA 18.1±0.20 mg per 100 ml compared to the corresponding indicator in the control group 19.7±0.90 mg per 100 ml blood serum. In patients of group I, there is a significantly ($p<0.05$) higher concentration level of TAAA 29.9±0.20 mg compared with the corresponding indicators in group II 27.2±0.50 mg per 100 ml of blood serum and it does not significantly differ from indicator in the control group.

DISCUSSION

The changes in the amino acid spectrum of blood serum in patients with TB before the start of treatment that we have identified represent PM disorders in general and can be considered an integral consequence of various causes. They have a negative impact on the metabolic processes of the body in totaly and the clinical course of TB, which is manifested by prolonged IS and RS, the possible development of complications, and a lengthening of the rehabilitation period. Our hypothesis that the use of AMBT alone will not be enough for the full normalization of PM indicators (achieving the indicators of healthy individuals) have been confirmed, this is indicated by an amino acid imbalance, a decrease in TAAA and individual NEAA and EAA in blood serum [8,9]. The obtained data allowed us to determine the priority clinical indicators for the inclusion of NCPMD in the complex treatment of patients with TB: – the presence of risk factors in the patient (socially vulnerable patients, the unemployed, retired employees, homeless people, released from prison); – long-term development of the disease, accompanied by prolonged IS and RS, which contributed to the emaciation of the body and the development of metabolic disorders; – loss of body weight; – lesion of large parts of lung tissue by the pathological process accompanied by its decay; – bacterial excretion; – signs of protein metabolism disorders[8,9,13,14]. The proposed correction scheme includes food products containing essential nutrients and biologically active compounds that have a positive impact on the corresponding links of pathogenesis (reduction of inflammation, normalization of metabolic disorders caused by inflammation and long-term AMBT, activation of reparative mechanisms, correction of psycho-emotional status) and can be used throughout all phases of treatment. Which had a positive impact on the PM indicators (significant ($p<0.05$) increase in blood serum TAEAA, TANEAA and TAAA blood serum and the concentration of individual EAA and NEAA (significantly reached the level of indicators in healthy individuals) and the clinical course of TB. There was a positive trend in the disappearance of IS (disappeared faster by 10.8±0.97 days) and RS (disappeared faster by 8.95±1.68 days), an increase in the frequency of healing of decay cavities at the time of completion of treatment by 34.0% and a significant reduction in the average duration of treatment by 21.1±2.91 days in these patients ($p<0.05$). Further studies to improve the NCPD scheme in the complex treatment of patients with TB are promising, since the method can provide a significant additional therapeutic and preventive potential without drug overload of patients, promote the level of social rehabilitation of TB patients.

CONCLUSIONS

The inclusion of nutritional correction of protein metabolism disorders in the standard regimen of treatment with antimycobacterial drugs made it possible to obtain a pronounced positive impact on the clinical course of the disease and the condition of protein metabolism, which contributed to an increase in the effectiveness of treatment and rehabilitation of patients with pulmonary tuberculosis.

Conflicts of Interest: authors have no conflict of interest to declare.

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Conflict of interest
The Authors declare no conflict of interest.

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