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NUTRITIONAL CORRECTION OF PROTEIN METABOLISM AS A METHOD OF SECONDARY PREVENTION IN PATIENTS WITH PULMONARY TUBERCULOSIS

At present, Ukraine is one of the countries with a high incidence of tuberculosis – this figure is one of the highest among the countries of Central and Eastern Europe. According to the WHO, the European region has low rates of treatment effectiveness – 72% (in Ukraine – 67%). The effectiveness of treatment is influenced by many factors. One of them is disorders of various types of metabolism, which arise and develop under the direct influence of the tuberculosis process.[1]

Tuberculosis (TB) leads to significant disorders of protein metabolism, the development of dystrophic processes. There is a tendency to reduce the total level of amino acids in the acute phase of the tuberculosis process, due to essential amino acids (EAA), which is explained by their excessive use for energy and plastic needs of the body.[2] In addition, there is a link between the amino acid composition of the blood and pathological changes in TB (severity of the tuberculosis process, the presence of

1 World Health Organization, Global tuberculosis report 2019. In: Global tuberculosis report 2019; 2019; Gwenan M KNight, C Finn McQuaid, Peter J Dodd, Rein M G J Houben (2020). The Global Burden of Latent Tuberculosis Infection: A Re-estimation Using Mathematical Modelling. 13(10) Epub 2016 Oct 25. https://doi.org/10.1016/S1473-3099(19)30307-X; Туберкульоз. URL: //phc.org.ua/kontrol-zakhvoryuvan/tuberkuloz.

2 Musuenge, B.B.; Poda, G.G.; Chen, P.-C. Nutritional Status of Patients with Tuberculosis and Associated Factors in the Health Centre Region of Burkina Faso. Nutrients 2020; 12:2540. https://doi.org/10.3390/nu12092540; Lee D-Y, Kim E-H. Therapeutic Effects of Amino Acids in Liver Diseases: Current Studies and Future Perspectives. J Cancer Prevention. 2019;24(2):72–78. https://doi:10.15430/JCP.2019.24.2.72; Корж О.В., Тлустова Т.В., Цокурова О.В., Лазуткіна Д.М. Стан фактичного харчування та харчовий статус хворих на туберкульоз легень. Вестник гигиены и епидемиологии 2009; 1: 178–182.

symptoms of intoxication, the prevalence of the process in the lungs, the presence of decay cavities, bacterial excretion).[3] Current data on the state of protein metabolism (PM) (metabolism of essential and non-essential amino acids), the influence of the nature of nutrition, nutritional correction of metabolic processes and their relationship with PM in TB patients in modern epidemiological conditions in Ukraine, low material the provision of most patients is quite limited and contradictory.[4]

The above facts indicate that the study of the amino acid composition of blood serum (AAC BS), the study of PM, comparative assessment of PM depending on the clinical form and in comparison with healthy individuals, the study of the effects of antimycobacterial therapy (AMBT) on PM, study the effectiveness of nutritional correction of PM is a promising scientific field that has not only theoretical significance but also practical interest, as it opens opportunities for new approaches to diagnosis, reduction of treatment, secondary prevention of complications and increasing the level of social rehabilitation of patients with newly diagnosed tuberculosis (NDTB).

We conducted a clinical examination and determination of the state of PM in 102 patients with NDTB. To assess the state of PM was investigated the content of individual nonessential amino acids (nEAA) (ornithine, aspartic acid, serine, glutamic acid, proline, glycine, alanine, cysteine, tyrosine, glutamine) and EAA (lysine, histidine, arginine, threonine, valine), isoleucine, phenylalanine, leucine) serum amino acids, their total amount, as well as the content of ammonia (mg in 100 ml of blood serum) in patients with NDTB. Assessment of the functional state of the liver was performed based on the results of biochemical tests (level of total protein, total bilirubin, thymol test, level of ALT, AST, urea) by conventional methods. Upon admission to patients for treatment, a comprehensive examination was performed by he amount of diagnostic minimum required for persons with pulmonary pathology. The results of the study of PM in patients with NDTB showed a direct relationship between the degree of changes in PM with the prevalence of tuberculosis in the lungs. Patients with focal TB tend to decrease the total amount of amino acids (AATA), the

3 I.O. Galan, V.I. Petrenko, R.H. Protsyuk, S.T. Omelchuk, H.F. Marchenko Status of protein metabolism in patients with the first time diagnosed pulmonary tuberculosis depending of clinical form Ukrayins'kyy naukovo-praktychnyy zhurnal. Tuberkul'oz, lehenevi khvoroby, VIL-infektsiya 2018; 1(32):33-40. (Ukrainian) https://doi.org/10.30978/TB2018-1-33; Скорняков С.Н., Сабадаш Е.В., Медвинскии И.Д., Новиков Б.И., Павлов В.А. Аминокислотныи баланс плазмы крови и моноцитов у больных туберкулезом как фактор, отражающии тяжесть течения туберкулезного процесса. Медицинская иммунология. 2015;17(1):75-80. https://doi.org/10.15789/ 1563-0625-2015-1-75-80

4 Климович И. И., Дорошенко Е. М. Фонд свободных аминокислот в плазме крови больных активным туберкулёзом лёгких. Проблемы туберкулёза и болезней лёгких. 2003; 1:18 – 22; Grobler L, Nagpal S, Sudarsanam TD, Sinclair D. Nutritional supplements for people being treated for active tuberculosis. Cochrane Database Syst Rev. 2016 Jun; 2016(6): CD006086. Published online 2016 Jun 29. https://doi.org/10.1002/14651858.CD006086.pub4

total amount of nonessential amino acids (nEAA TA), and the total amount of essential amino acids (EAA TA) due to a decrease in the content of certain nEAA (glutamic acid, glutamine, alanine, methionine) and increased levels of ammonia ($p<0,05$) in blood serum. Patients with infiltrative TB have even more pronounced changes in PM: significant ($p<0.05$) increase in ammonia, decrease in AATA, EAA TA due to lysine, histidine, methionine, arginine, phenylalanine, and nEAA TA due to glutamic acid, glutamine. The largest changes were found in patients with disseminated TB: a significant ($p<0.05$) increase (2.7 times) in ammonia, a decrease (1.3 times) in AATA, a decrease in EAA TA by reducing the content of almost all EAA, a significant decrease in nEAA TA due to reducing the content of all nEAA. Deep disorders of PM, BAAP imbalance, accumulation of end products of protein breakdown in TB worsens the prognosis of the disease, which we observe in such patients (Table 1).

Table 1.

The content of essential and non-essential amino acids and blood serum ammonia in patients with newly diagnosed pulmonary tuberculosis depending on the clinical form and in comparison with healthy individuals

Amino acid (mg in 100 ml of blood serum)	Healthy people (n = 30)	Focal NDTB (n = 11)	Infiltrative NDTB (n=67)	Disseminated NDTB (n=24)
1	2	3	4	5
Ornithine	0,7±0,1	0,7±0,1	0,7±0,02	0,6±0,1
Aspartic acid	0,1±0,01	0,1±0,01	0,1±0,01	0,1±0,01
Serine	0,9±0,1	0,9±0,01	0,8±0,01	0,7±0,04**
Glutamic acid	0,7±0,1	0,6±0,1	0,5±0,02*	0,5±0,02*
Proline	1,8±0,2	1,8±0,1	1,5±0,1**	1,4±0,1**
Glycine	1,5±0,1	1,5±0,1	1,2±0,03*, **	1,1±0,04*, **
Alanine	3,3±0,3	3,1±0,1	3,0±0,1	2,9±0,03
Cysteine	0,8±0,1	0,8±0,1	0,8±0,03	0,8±0,02
Tyrosine	1,5±0,1	1,5±0,1	1,3±0,1	1,2±0,1*, **
Glutamine	8,5±0,8	7,8±0,1	6,2±0,4*, **	5,9±0,1*, **
The total amount of nonessential amino acids	**19,7±0,9**	**18,3±0,3**	**15,9±0,4*, ****	**15,3±0,2*, ****
Lysine	2,2±0,2	1,7±0,1*	1,7±0,1*	1,4±0,1*, **
Histidine	1,1±0,1	0,8±0,1*	0,8±0,1*	0,7±0,1*
Arginine	1,2±0,1	1,2±0,1	0,9±0,1*, **	0,7±0,1*, **
Threonine	1,2±0,1	1,0±0,1	1,0±0,1	0,8±0,1*
Valine	1,9±0,2	1,7±0,1	1,7±0,1	1,5±0,2
Methionine	0,4±0,04	0,3±0,02*	0,3±0,02*	0,2±0,03*, **

Continuation of the table 1.

1	2	3	4	5
Isoleucine	0,7±0,1	0,7±0,1	0,7±0,1	0,5±0,1
Phenylalanine	0,7±0,04	1,0±0,1*	0,6±0,03*, **	0,9±0,1**
Leucine	1,2±0,1	1,2±0,1	1,0±0,1	0,9±0,1*, **
The total amount of essential amino acids	**10,9±0,7**	**9,6±0,6**	**8,8±0,4***	**7,6±0,6*, ****
The total amount of amino acids	**30,6±2,4**	**28,4±0,8**	**24,7±0,8*, ****	**22,8±0,6*, ****
Ammonia	**0,7±0,1**	**0,9±0,1***	**1,5±0,1*, ****	**1,9±0,1*, ****

*Notes: * - significant discrepancies with the indicators of healthy individuals, p <0,05;*
*** - the intergroup value of the indicator differs significantly in patients with focal, infiltrative, disseminated TB, p <0,05.*

Thus, a comparative assessment of the state of PM in patients with NDTB depending on the clinical form and in comparison with healthy individuals indicates a pronounced violation of PM: amino acid imbalance, decrease in total and individual essential and essential amino acids, increased blood serum ammonia concentration, which became the basis for further research to select an effective way to correct these disorders. To study the dynamics of PM in patients with NDTB who received standard AMBT and to evaluate the effectiveness of prebiotics in combination with nutritional correction of protein metabolism in complex treatment, we selected a group of patients with infiltrative NDTB.

The analysis of the results of the dynamics of the indicators of the state of PM showed that under the influence of treatment with antimycobacterial drugs (AMBD) the content of most EAA and their total amount did not reach the indicators of healthy individuals. There was only a steady trend to increase EAA TA from 8.8±0.4 to 9.1±0.2 mg per 100 ml of blood serum compared to pre-treatment, which, in turn, was 16.5%, significantly lower (p <0.05) of the corresponding indicator in healthy individuals (10.9±0.7 mg in 100 ml of blood serum). Analysis of the dynamics of the results of studies of the content of nEAA showed that there was a significant (p <0,05) increase in nEAA TA by 12.2% (from 15.9±0.4 to 18.1±0.2 mg in 100 ml of blood serum) in comparison with the indicators before the beginning of treatment and there was a steady tendency to increase in comparison with the indicator in healthy individuals (19.7± 0.9 mg in 100 ml of blood serum). A reliable (p<0,05) increase in the concentration of four AA - serine, proline, glycine, glutamine in comparison with the corresponding indices before treatment has been established. And in comparison with the indicators of healthy donors, there was a steady tendency to increase the content of such nEAAs as

glycine, proline, glutamine. The content of other nEAAs remained virtually unchanged. Quite natural was a certain positive effect of AMBT on AATA, namely, there was a significant ($p<0.05$) increase of 9.2% (from 24,7±0,8 to 27,2±0,5 mg in 100 ml of blood serum) in comparison with the indicators before treatment, but in comparison with the indicator in healthy individuals there was only a steady tendency to increase it (30.6±2.4 mg in 100 ml of blood serum).

In patients with infiltrative NDTB before treatment, a significant increase in serum ammonia was observed. In our opinion, this is due to the pronounced phenomena of intoxication, the widespread tuberculous process in the lungs, and deep disorders of PM (massive protein breakdown). It should be noted that under the influence of AMBP treatment there was a significant ($p<0.05$) decrease in ammonia content by 40.4% (from 1.41±0.06 to 0.841±0.02 mg in 100 ml of blood serum) compared with an indicator before treatment, and there was a steady tendency to approach the figure in healthy individuals (0.7±0.1 mg in 100 ml of blood serum).

The obtained data convincingly show that the use of AMBT has a positive effect on some indicators of PM, but it is not enough for the full normalization of metabolic processes (achieving indicators of healthy people), namely the full recovery of all PM disorders (amino acid composition of blood serum) that occurred in patients on infiltrative NDTB.

Based on the data obtained, we have identified priority clinical indicators for the inclusion of nutritional correction of protein metabolism in the comprehensive treatment of patients with newly diagnosed tuberculosis: the patient has risk factors (socially vulnerable patients, unemployed, retired, homeless, from prison); prolonged development of the disease, accompanied by prolonged intoxication and respiratory syndrome; weight loss (weight loss up to 10 kg was in 55.2% of patients); lesions of the pathological process of large volumes of lung tissue, which is accompanied by its disintegration (65.7% of patients had darkening areas in the lungs with a diameter of 1 cm to the size of the lung lobe and more, 76.1% of them had decay cavities); bacterioexcretion (68.7% of patients were found to have Mycobacterium tuberculosis); signs of PM disorders (before treatment, some common changes were detected, which indicate a violation of PM, namely: - a significant decrease ($p<0.05$) EAA TA to 8,8±0,4 mg in 100 ml of serum and nEAA TA ($p<0.05$) to 15.9±0.4 mg in 100 ml of blood serum, which led to a significant decrease in AATA ($p<0.05$) by 19.3% (from 30.6±2,4 to 24,7±0.8 mg in 100 ml of blood serum), significant ($p <0,001$) increase in ammonia content by 2.1 times (from 0.7±00,1 to 1,41±0,06 mg in 100 ml of blood serum).

We then randomized 67 patients for infiltrating NDTB which were divided into two groups: the main group – 35 patients, who were given prebiotic based on lactulose and nutritious protein metabolic correction (NPMC) in the comprehensive treatment of tuberculosis and control group (II group) of 32 patients receiving standard AMBT. In terms of age, sex and clinical characteristics, the patients of the groups studied did not differ.

Although catabolic processes dominate anabolic processes in tuberculosis patients, as well as significant intoxication syndrome and AMBT admissions, patients have an urgent need for pathogenetic substantiation of the nutritional of correction of disorders of metabolic processes. Pathogenic mechanisms determine the direction of the nutritional correction of metabolic processes in the design of the diet.

For the first time, a differentiated approach in the formation of a diet of TB patients is proposed, taking into account the stage of development of the tuberculosis process and the general state of the organism. It seems necessary to enrich the diet of TB patients with appropriate foods of high quality for nutritional correction of immunopathological and metabolic processes, according to the pathogenesis links. Our research has made it possible to identify 4 main pathogenesis links on which we can influence with biologically active substances: reduction of inflammation (activation of immunometabolic processes, reduction of expression of proxy cytokines, increase of phagocytes activity, protection of mucous membranes, activation of cell antibacterial immunity, interleukin synthesis, antioxidant tissue protection, antiseptic, anti-inflammatory, desensitizing, specific bacteriostatic effects); normalization of metabolic disorders caused by inflammation and long-term chemotherapy (increased appetite, enzyme inductors, prevention of negative effects of specific therapy) completion of inflammation and activation of reparative mechanisms (acceleration of epithelisation, restoration of synthetic function of intestinal microflora); correction of psycho-emotional status. According to each of the pathogenesis links, biologically active substances are identified and the group of products with the highest content of these biologically active substances is recommended, and the accessibility of these products to all segments of the population is taken into account[5].

Integrated treatment scheme for NDTB of lung patients was carried out as follows: standard AMBT was combined with the NKPM by enriching patients' diets with appropriate food listed in the diagram of pathogenic nutritional correction for lung NDTB patients. When forming a diet, an individual approach was taken,

5 Процюк Р.Г., Омельчук С.Т., Аністратенко Т.І., Галан І.О. Патогенетичне обґрунтування нутриціологічної корекції порушень процесів обміну при класичній схемі лікування вперше виявленого туберкульозу легень: Інформаційний лист про нововведення в системі охорони здоров'я.Київ: Укрмедпатентінформ МОЗ України. 2016; 20: 8.

taking into account the general state of the organism, the stage of development of the tuberculosis process and food habits. In parallel, a prebiotic based on lactulose was prescribed.

According to a comparative analysis of the clinical efficacy of lactulose-based prebiotics combined with the nutritional correction of exchange processes in the comprehensive treatment of TBT patients, we have found a positive influence on the dynamics of disappearance of intoxicating and respiratory syndrome. It was found that a stable normalization of body temperature, improved appetite, disappearance of night sweats were observed on average after 19.75±3.2 days in patients of the main and 30.55±4.1 days in the control group after treatment ($p<0.05$). The main-group patients' intoxication syndrome faded faster by 10.8±0.97 days. The disappearance of the cough, a significant decrease in shortness of breath from the start of treatment, were observed on average after 37.24±5.12 days in the main group patients and after 46.19±3.44 days in the control group. So the respiratory complaints from the main group patients disappeared more quickly by 8.95±1.68 days.

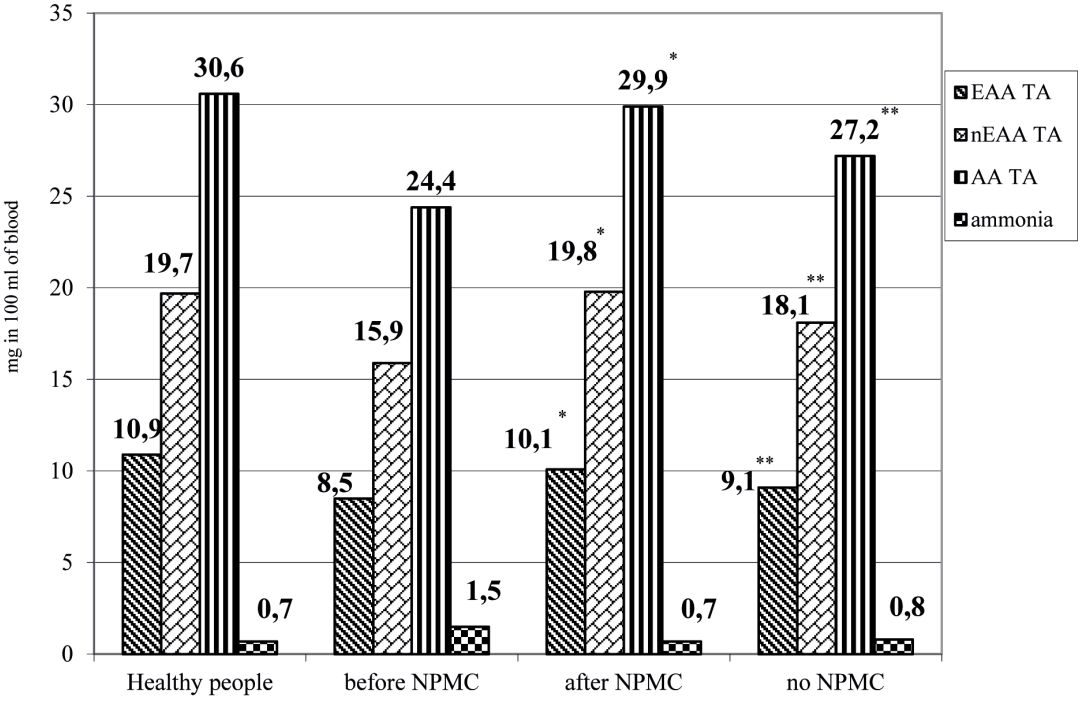
It should be noted that at the end of treatment the disappearance of decay, cavities was observed in 28 patients of the main group (87.0%), which was probably higher ($p<0.05$) than in the control group of patients 16 (53.3%). Increase in the frequency of healing of decay, cavities at the end of treatment by 34.0%. This process is initiated directly during the use period and lasts another 2-3 months, giving a higher percentage of decay cavities healing at the end of the treatment than under the normal AMBT treatment.

An analysis of the duration of the treatment showed that in the main group it was 171.3±4.3 days and in patients of the control group it was 192.4±7.2 days. Thus, the average duration of treatment for patients who in comprehensive treatment received a prebiotic based on lactulose and NPOC ($p<0.05$) was 21.1±2.9 days shorter in the control group.

Analysis of the results obtained on the evolution of PM rates in lung patients with NDTB who took a lactulose-based prebiotic in combination with the NKPM and the group of lung NDTB patients who received a standard AMBT shows that the use of lactulose-based prebiotics in combination with the NKPM in the complex treatment of TB patients contributes to a pronounced normalization of PM, which is manifested significantly ($p<0.05$) higher content of individual EAA (lysine, histidine, arginine, threonine) and, accordingly, higher EAA TA in patients of the main group (almost equal to indicators of healthy individuals)

compared with similar indicators in patients of the control group, after 2 months of treatment. The main patients group have higher levels of individual nEAA (serine, glutamic acid, glycine, glutamine) with certainty (p 0.05) and therefore higher nEAA TA than control group patients.

In the patients of the main group, who in complex treatment applied a correction scheme proposed by us, the level of EAA TA (10.1±0.1 mg in 100 ml of blood serum), nEAA TA (19.8±0.1 mg in 100 ml of blood serum) and AA TA (29.9±0.2 mg in 100 ml of blood serum) compared to the corresponding indicators in the control group (EAA TA (9.1±0.2 mg in 100 ml of blood serum), nEAA TA (18.1±0.2 mg in 100 ml of blood serum) and AA TA (27.2±0.5 mg in 100 ml of blood serum) and it was not distinctly different from those in healthy persons (picture1).



P. 1. Indicators for the total sum of essential, substituted amino acids, their total amount and ammonia in primary and control patients and healthy individuals

*Notes: * - The group value of the indicator accurately differs from that of the treatment, p 0.05; ** - valid differences between the main and control group, p 0.05.*

Patients in the control group after treatment showed only a tendency to increase (p>0.05); EAA TA (9.1±0.2 mg in 100 ml blood serum), nEAA TA (18.1±0.2 mg in 100 ml of blood serum) and AA TA (27.2±0.5 mg in 100 ml of blood serum) compared with the corresponding indicators in healthy individuals.

Analysis of biochemical parameters showed that in patients of the main group there was a significant ($p<0.05$) decrease in ALT by 55.2% (2.2 times) and bilirubin by 33.0%. In the control group, although there is a tendency to reduce ALT and bilirubin, but no statistically significant decrease is observed ($p>0.05$). It should be noted that the common protein level in both groups did not exceed reference values, but in the main group there was a reliable ($p<0.05$) increase in the total protein level to 76.19±0.57 g/l compared to 73.26±0.47/l in the control group. In addition, patients in the main group had a positive ($p<0.05$) increase in the level of urea from 3.3±0.18 to 5.28±0.24 mmol/l. The concentration of urea in the control group patients is definitely lower, indicating low PM intensity. Taking into account the subjectivity of the estimation of symptoms of intoxication, biochemical indicators are an objective factor of improvement of general state of organism, including state of liver.

On the basis of the results of the research, a nutritional protein metabolic correction scheme for lung tuberculosis patients, which includes foodstuffs, has been validated and introduced into the work of specialized institutions, bioactive substances that have a positive influence on the relevant pathogenesis links (reduction of inflammation, normalization of metabolic disorders caused by inflammation, long-term AMBT, activation of reparative mechanisms, correction of psycho-emotional status) and can be used during all stages of treatment. This has contributed to a reduction in the average length of hospitalization, a reduction in the duration of the extinction of intoxicating and respiratory syndrome, and an increase in the rate of healing of cavities at the end of the treatment, insignificant positive effect on biochemical blood and PM. The above-mentioned makes it possible to recommend the use of a prebiotic based on lactulose in combination with nutritional correction of protein exchange in the comprehensive treatment of lung tuberculosis patients as a method of secondary prophylaxis, to improve the treatment and rehabilitation of lung tuberculosis patients by including antimycobacteric drugs in the standard treatment regimen.

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