MINISTRY OF EDUCATION AND RESEARCH
OF THE REPUBLIC OF MOLDOVA
MOLDOVA STATE UNIVERSITY
INSTITUTE OF PHYSIOLOGY AND SANOCREATOLOGY

As a manuscript
C.Z.U.: 614.2:616-008.9(478)(043.3)

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STRENGTHENING THE HEALTH OF THE POPULATION WITH INCREASED METABOLIC RISKS

331.04 – HEALTHY LIFESTYLE AND HEALTH EDUCATION

Summary of the thesis of habilitated doctor in medical sciences

CHISINAU, 2022

The thesis was developed within the Scientific-Methodological Center in Health and Biomedicine of the Institute of Physiology and Sanocratology.

The doctoral habilitation thesis is part of the project approved and financed by the National Agency for Research and Development, number 20.00208.1908.01 from 03.01.2020.

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(*approved by the decision of the MSU Scientific Council, minutes no. 14 of 31.10.2022***)**

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Defense of the thesis will take place on January 12, 2:00 p.m., in the Meeting of the Public Defense Commission, Academy str., 1, floor 3, conference room No. 352, Chisinau, Republic of Moldova.

The habilitated doctor thesis and the scientific summary can be consulted at the Andrei Lupan Central Scientific Library (Chisinau, Academy str., 5A) and on the website of NAQAER.

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CONTENT

CONCEPTUAL MILESTONES OF THE RESEARCH

Actuality and importance of the topic addressed. Statistical data indicate an alarming increase in the risks of metabolic syndrome (MS), which argues for the increase in the incidence of hypertension, type II diabetes and obesity both globally and nationally. Namely, these pathologies have a pandemic character with a continuous growth trend. Obesity affects about 4 billion inhabitants, type II diabetes about 1 billion, and cardiovascular diseases, arterial hypertension, ischemic and heart diseases (IHD) occupy the first place in the structure of the general morbidity of the population on the globe and the first place in the structure of mortality. Some research shows that the risk factors of MS are multiple, which requires both fundamental and applied research [3, 4, 26].

Major metabolic risk factors – hypertension, obesity and type II diabetes are determinants that directly influence human and public health in all countries of the world. Each of them represents true non-infectious pandemics, and the situation is aggravated when these factors often act together with interdependent associated pathologies, with cumulative actions and which further increase the danger of complications with disastrous consequences. Thus, 25% of the global population is affected by these risks with isolated or associated action in comorbidities of various combinations. By 2040, MS morbidity and mortality are expected to rise by up to 50%. These conditions are characteristic of the entire population regardless of age, sex, geographic region and social status [14, 26, 33].

Modern society with its alert lifestyle, accompanied by permanent stresses, with present overloads, a diet based on over-processed products and in increased quantities, sedentary lifestyle and physical hypoactivity, has caused the share of non-infectious (non-communicable) diseases to increase extremely rapidly in the structure of morbidity and population mortality [68]. The last half century was marked by a 10-fold increase in the number of patients with type II diabetes. The same rhythm characterizes hypertension and cardiovascular diseases. The most serious problem that has come to the fore is the significant decrease in the age of onset of metabolic diseases and the risks of disease. More and more teenagers and even children are affected by such conditions with manifestations of type II diabetes, obesity and incipient borderline hypertension. In the last 50 years, the number of young people (5-19 years) with overweight and obesity has increased 10 times in the world, and their growth trend remains on the rise [14, 25].

Since these risks have an increasingly pronounced tendency to be associated in interdependent comorbidities and with common mechanisms of occurrence, it is necessary to develop and approach some strategic measures to combat their early, premorbid states. In almost

90% of cases, diabetes is associated with obesity or excess weight, which are ultimately the cause and lead to the appearance of hypertension, chronic liver and pancreas disease, some forms of cancer, etc. This directs us towards concrete and effective preventive measures through lifestyle changes and its optimization. The food factor, physiological and rational nutrition, combating sedentarism, physical activity and mobility are essential measures that should be taken to delay and stop pre-morbid, pre-clinical processes until the onset of actual pathologies [1, 2, 23,33].

The concept regarding the elaboration of the theory and practice of strengthening and maintaining health [52]. The concept of metabolic health and the approach to adipose tissue and as an organ of internal secretion [69] have triggered confrontations, views and opinions that are sometimes diametrically opposed. New paradigms have been established in the approach and analysis of metabolic conditions with major risks and severe complications. The phenomenon of obesity is the basis of the appearance of several premorbid conditions, which then evolve and turn into serious pathologies with severe irreversible complications, with high costs of treatment and recovery of invalidations [60, 66]. According to WHO globally, the number of overweight people is approaching an impressive figure, which varies between 3.5-4 billion people with a constant trend of growth globally [53].

In the last two decades, opinions and concepts about obesity have also changed radically. Thus, it was found after extensive research, that adipose tissue is not a simple deposit responsible for energy, thermal insulation and protection of internal organs. It is a complex tissue, producer of metabolites, adipokines, sphingolipids and many other bioactive factors whose number reaches 600 [73, 75]. Adipose tissue has also been assigned the function of internal secretion. It is not homogeneous as it was thought until a few years ago, actually dividing into three distinct forms: white, brown and beige and affecting health differently [40, 57].

The scientific-theoretical study carried out at this research stage revealed a close correlation between obesity and type II diabetes, which also represents a major medico-social problem with a pandemic character. The danger is determined by the complications and consequences of this type of diabetes primarily on the cardiovascular system, where the risks of ischemic heart disease increase almost 4 times, of myocardial infarction 6-10 times, of cerebral stroke 7 times. The old approaches to type II diabetes, where insulin resistance and hyperglycemia are presented as central factors of the pathogenesis, cannot fully explain the mechanisms of its appearance and evolution. The association of these pathologies in comorbidities causes a synergistic increase in blood glucose and lipidemias, which have been called glucose-lipotoxicity with synergistic effects and clinical manifestations and negative

consequences [76, 83]. Thus a vicious circle appears between these two processes, which stimulate each other initially caused by the chronic hyperlipidemia characteristic of obesity and which leads to dysfunctions of the β-pancreatic cells at the molecular level, manifesting through endoplasmic reticulum stress and mitochondrial oxidative stress. The analyzed bibliography shows that more and more researchers talk about chronic inflammatory processes present in the association between type II diabetes and obesity. Pre-inflammation is caused by insulin resistance, which in turn depends on the increased content of visceral fat, producing pro-inflammatory cytokines: interleukin-6 (IL-6), IL-1β, IL-8, TNFα, etc. initiators of vascular inflammation and installation of insulin resistance and hyperinsulinemia [61, 63]. At the same time, leptin resistance appears with a negative effect on the energy balance, caused by adipokines. But adipose tissue also produces a series of anti-inflammatory substances, among which adiponectin stands out. Lipidogenesis mediators activate some enzymes (IKKβ) in adipocytes and hepatocytes with impaired insulin receptor conjugation. Simultaneously, there is a decrease in GLUT4 that ensures the penetration of glucose into the cell and the occurrence of hyperglycemia. The intracellular glucose deficit stimulates the transition to the use of another alternative energy substrate – free fatty acids, which in turn induce insulin resistance and trigger gluconeogenesis with the onset of type II diabetes. Most of the time, the cascade transformations at the cellular level listed above lead to the appearance of another metabolic risk factor - metabolic HTA (hypertension) where hyperinsulinemia plays a decisive role by blocking the transmembrane mechanisms of ion exchange (Na^+, K^+, Ca^{2+}) ATPase-dependent and increase in intracellular Na^+ and Ca^{2+} content accompanied by decrease in K^+ ions with pressor action, increase in Na^+ reabsorption in distal and proximal tubules of the nephron, with H_2O retention and appearance of hypervolemia; stimulation of proliferation of vascular smooth muscle tissue, contraction of arterioles and increased vascular resistance; stimulation of the sympathetic nervous system and the activity of the renin-angiotensin-aldosterone system. All these changes gradually lead to the development and increase of blood pressure [78].

The metabolic syndrome gathers a group of associated disorders that evolve latently over a period of up to 15 years, when clinical manifestations and the establishment of a stable diagnosis begin to appear, and it remains one of the controversial problems of modern medicine. The existence of divergences and contradictions in the MS approach is due to the complexity of its pathogenic mechanisms. In our opinion, a point of reference could be the role of obesity and its place in this syndrome. Opinions are divided, but numerous studies show that abdominal obesity plays a primary role in the appearance of MS components: insulin resistance, hyperinsulinemia, hypertension, etc. [11]. There is still no clarity in the identification of a basic

pathophysiological mechanism, which could give this phenomenon an identity, which could place it among the nosological entities, but numerous studies and researches prove exactly this - its presence increases the morbidity by 2 times and mortality in cardiovascular diseases and 5 times in DM type II [43]. All of the above determined the need for a complex study of health and increased metabolic risks.

The purpose of the work: Studying the complex of measures necessary to strengthen the health of the population with increased metabolic risks by developing original methods of prevention and new approaches to therapeutic management.

Research objectives:

1. Statistical-demographic analysis of the population with increased metabolic and circulatory risks during the years 2015-2020 (hypertension, type II diabetes/insulin resistance, obesity/dyslipidemias.

2. The detection, highlighting and influence of major risk factors in the occurrence of essential metabolic and circulatory disorders on the health of the population.

3. Evaluation of some methods of preclinical diagnosis of metabolic and circulatory disorders in people with increased metabolic risks.

4. Scientific argumentation of new approaches in the application of rehabilitation and recovery methods to strengthen health.

5. Development of recommendations for health education and healthy lifestyle with biotyped and personalized functional nutrition of subjects with increased metabolic risks.

6. The development of new products with a metabolic-protective effect and the study of their curative-prophylactic properties.

Research hypothesis: The concept of metabolic risks, of the metabolic syndrome, was argued by the existence and action of frequent risk factors on human health. It includes in itself both the functional and physiological disorders of the body, as well as the usual environment, climatic conditions, drinking water quality, air quality, way of life, the multitude of exogenous, ecological factors, etc. Endogenous, genetic, premorbid factors, metabolic disorders and concurrent nosologies also play a significant role in health risk. In this context, the metabolic risks determined by hypertension, type II diabetes and dyslipidemias, obesity cause increased risks for the health of the population. The concept of metabolic risks, of the metabolic syndrome, was argued by the existence and action of frequent risk factors on human health. It includes in itself both the functional and physiological disorders of the body, as well as the usual environment, climatic conditions, drinking water quality, air quality, way of life, the multitude of exogenous, ecological factors, etc. Endogenous, genetic, premorbid factors, metabolic disorders

and concurrent nosologies also play a significant role in health risk. In this context, the metabolic risks determined by hypertension, type II diabetes and dyslipidemias, obesity cause increased risks for the health of the population.

Despite the encouraging research, additional research is opportune and necessary in determining the mechanisms for reducing the increased risks to human health and highlighting the methods of strengthening it. As a result, minimization through prophylaxis, their early diagnosis, nutrition and stimulation of the intestinal microbiota, administration of biologically active remedies and prebiotics, through the implementation of the biotyped and personalized way of life, can ensure the strengthening of the health of the population.

Synthesis of research methodology and justification of chosen research methods. A complex case-control study with an analytical character was carried out through various research-investigation methods, objective clinical examination, biochemical, electrocardiographic explorations, blood pressure dynamics, body mass index for each participant in the study based on WHO criteria. The research included 1380 eligible cases of research subjects, special study questionnaires of lifestyle, anthropogenic and anthropometric parameters; risk reduction - hypertension - 356, type II diabetes - 526 cases and obesity - 526 cases. The healthy lifestyle study included 687 subjects divided into 3 risk groups: hypertension – 201, type II diabetes – 252 cases and obesity – 234 cases aged between 30-70 years.

Each research subject had the study inclusion form, positive informed consent, clinical, paraclinical and laboratory examination data (hematological indices assessed according to the Abacus method, ESR - the Werstergren method, biochemicals according to the standard DIA Sys test, blood glucose - the "CHOD" tests -PAP", Creatinine - CREAP test, bilirubin - DCA, AST and AST - UV, triglycerides - GPO, etc.). Research methods were also used in the development and research of products with specific biotechnological metabolic-protective action of toxicity in accordance with the international recommendations of ICH M3 (R2) and the Kerber method, the method for determining free amino acids - with the help of the AAA-339 analyzer (Prague) and so on Data processing was performed using MS Excel capabilities, Student's significance and $p<0.05$, standard deviation and correlation indicator.

Summary of the sections of the thesis: The work includes: annotation presented in the languages: Romanian, Russian and English, list of tables, list of figures, list of abbreviations, introduction, four chapters, general conclusions and practical recommendations, bibliographic sources including 466 titles, 16 appendices, statement regarding the assumption of responsibility and CV the The doctoral habilitation thesis is presented on 292 pages, its content being supplemented with 51 tables and 24 figures.

THESIS CONTENT

1. INCREASED METABOLIC RISKS AND POPULATION HEALTH (LITERATURE REVIEW)

The chapter includes a deep analysis of the latest data from the specialized literature at the national and international bibliographic level. Scientific data are presented on the determinants of metabolic syndrome, which summarily and selectively distort the health of the population as a whole. The major risk factors of metabolic syndrome are described, namely hypertension, type II diabetes, obesity, chronic systemic inflammation, oxidative stress, and synergistic metabolic disorders. The chapter ends with conclusions.

2. MATERIAL AND RESEARCH METHODS

The study was approved by the Scientific Research Ethics Committee of the Institute of Physiology and Sanocratology (opinion No. 1 of 04/12/2019 and No. 14 of 02/22/2021). In order to achieve the proposed goal, the case-control study was carried out, with an analytical character, which was carried out during the years 2015-2020 in accordance with the Principles of the Declaration of Helsinki - WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. The following research methods were used: investigation, objective clinical examination, biochemical explorations, electrocardiography, echocardiography, dosed physical exercise test ECG. Data from the Bureau of Statistics and the Health Management Center of the Ministry of Health were used. The study design was developed and was carried out in three stages.

The fundamental study was focused on the development of products with metabolic protection, antihypertensive, hypoglycemic and lipid-lowering effects. The preclinical stage, the logical experimental training was carried out in the Vivarium of the Institute of Physiology and Sanocratology on 3 groups of rats, 20 in each group and 20 in the control groups, with the administration of product compositions 1, 2, 3 with the study of acute, chronic toxicity and the biological effects on the body and protein, carbohydrate and lipid metabolism. The research was based on the principles of Good Practices and the Agreement of the Scientific Research Ethics Commission of the Institute of Physiology and Sanocreatology.

Criteria for inclusion in the study: age 30-70 years; voluntary informed consent to participate in the study with metabolic disorders and hypertension, type II diabetes, obesity. **Criteria for exclusion from the study:** Negative informed consent; major surgical intervention in the last month (intervention with major risk of bleeding); liver cirrhosis; renal failure with estimated glomerular filtration rate < 60 ml/min/1.73 m2; age ≥75.

Characteristics of the research groups. The study samples were determined by the finalization formula for each study – according to the inclusion and exclusion criteria. Characteristics of research groups of subjects with metabolic risk – HTN – 356 (100%). Archive documents were studied and surveys of 356 people, subjects with HTN, men – 156 (43.8%), women – 200 (56.2%) divided into age groups 30-40 (42%), 41 -50 (62%), 51-60 (118%), 61-70 (134%). Baseline assessments were performed of the general study group with distribution into 3 groups according to the presence of criteria for MS: the HTN group, the type II DM group, and the obesity group. The diagnosis of MS in the patients included in the study was established according to the presence of ≥ 3 of the IDF, AHA/NHLBI (2009) criteria. Anthropometric diagnostic criteria: 1. Abdominal obesity (abdominal circumference ≥ 94 cm for men and ≥ 80 cm for women); 2. Triglycerides > 1.7 mmol/l (or specific lipid-lowering treatment); 3. HDL cholesterol: men < 1mmol/l (40 mg/dL), women < 1.3 mmol/l (50 mg/dL) (or specific treatment); 4. BP s ≥ 130 mmHg or BP d ≥ 85 mmHg or antihypertensive therapy; 5. Basal blood glucose ≥ 5.6 mmol/l.

General characteristic of the group of participants. The research was carried out in several stages (the work steps were followed, graphically systematized in diagrams, which reflect the research design, from Figure 2.1.) – *stage 1*.

At *stage 2*, applying the inclusion/exclusion criteria, 1384 were selected, who constituted the general research group, respecting the following criteria: age 30-65 years; with abdominal obesity (CA ≥ 90th); citizens of the Republic of Moldova; the ability to communicate well with the researcher; understanding and complying with the study requirements and signing the informed consent and written assent.

Subjects with the following characteristics were excluded from the research: secondary obesity of endocrine, genetic, neurological origin, having a suggestive clinical examination, confirmed by specialized studies; Secondary hypertension: renal, endocrine, neurogenic, drug-induced, etc., having a suggestive clinical examination, confirmed by specialized examinations; acute conditions, accompanied or not by fever, under treatment or not; chronic respiratory, cardiovascular, gastrointestinal, renal, neurological, endocrine, etc. diseases, under treatment or not.

The selected participants were subjected to a complex examination, which included: completion of a specially developed questionnaire, clinical examination on the systems, laboratory tests with the evaluation of some indices of the lipid spectrum (total cholesterol, triglycerides, HDL-cholesterol), of the carbohydrate spectrum (glycemia basal, TTGO (oral glucose tolerance test – selective) and uric acid level analysis.

At *stage 3,* after obtaining the clinical and paraclinical data evaluation results, the respondents were divided into three research groups: 1, 2, 3.

At *stage 4,* comparisons were made between the groups, according to the criteria: some elements of the lifestyle, symptoms, demographic profile, anamnestic, anthropometric, hemodynamic, biochemical indexes, cardiac function and morphology, values of the intimate complex - average at the level of the carotid artery joint and epicardial adipose tissue, MS severity score, etc., with statistical analysis of the obtained results.

At *stage 5*, based on the results obtained, conclusions were issued and practical recommendations were developed. The subjects were not remunerated and incurred no financial costs related to participation.

Ethical considerations. The study took into account the international norms of medical ethics, established by the Declaration of Helsinki, regarding the preservation of the confidentiality of the participants' data. The research protocol was approved by the Research Ethics Committee of the Institute of Physiology and Sanocratology (minutes no. 1 of 04/12/2019 and no. 14 of 02/22/2021). The data of the results were communicated only to the respective participant, the personal data of each subject was not used and will not be used for other purposes.

During the research, I used the following research methods: historical (anamnesis), comparative, biostatistical, etc.

Research methods. The research carried out represents a study in which a series of investigation methods were used: standardized interviewing of subjects, comprehensive and selective research, data collection from the medical documentation of the Bureau of Statistics, the Health Management Center of the Ministry of Health of the Republic of Moldova, the plan and methods for assessing certain anthropometric, biochemical, imaging parameters. The paraclinical investigations were taken from the medical records. Clinical methods, anthropometric status, hemodynamic status, paraclinical methods (biochemical, hematological methods, determination of free amino acid content), research methods in the development of products with metabolic-protective action and statistical data analysis were used.

3. THE IMPACT OF MAJOR METABOLIC RISK FACTORS ON THE HEALTH OF THE POPULATION OF THE REPUBLIC OF MOLDOVA (2015-2020)

The study covered the period 2015-2020 and was based on the analysis of the data of the National Bureau of Statistics and CMSMSRM with the analysis of the prevalence, incidence and

mortality of hypertension, diabetes and obesity as determining factors of metabolic-circulatory syndrome disorders with a major impact on the health and mortality of the population.

3.1. Prevalence of hypertension, diabetes, dyslipidemia and obesity in the population of the Republic of Moldova

3.1.1. Prevalence of diseases of the circulatory system per 10 thousand population in the period 2015-2020

Circulatory system diseases during the research period had a trend and an increase from 1639.1 in 2015 to 2136.8 in 2019 and a small decreasing curve in 2020 to 2005.6. Hypertensive disease also had a positive dynamic from 996.6 in 2015 to 1365.1 in 2019 with a small decrease in 2020 to 1267.5.

Compared to diseases of the circulatory system and hypertensive diseases, cerebrovascular diseases had relatively uniform indices 198.4 in 2015, 2020.0 in 2018, 219.3 in 2020.

Prevalence of ischemic heart diseases in the Republic of Moldova for the years 2015-2020 per 10 thousand population. Ischemic diseases with hypertension increased from 241.0 in 2015 to 279.5 in 2020. Ischemic diseases without hypertension kept a relatively stable prevalence 70.9 in 2015, 66.9 in 2020, and angina pectoris increased from 119.4 in 2015 to 122.2 in 2020.

Myocardial infarction had a downward trend, with the prevalence reaching figures of 4.8 per 10 thousand population in 2015 to 4.2 per 10 thousand population in 2020. Hypertension had the highest index in 2019 – 1365.1 with a stability in 2020 at 1267.5 vs. 966.6 in 2015.

The prevalence of cerebrovascular diseases showed an increasing trend during the investigation period from 138.1 in 2015 to 169.5 in 2020. These data refer to cerebrovascular diseases without hypertension. Cerebrovascular diseases with high blood pressure had a downward trend – from 60.3 in 2015 to 49.8 in 2020.

Intracerebral hemorrhages decreased from 1.5 in 2015 to 0.9 in 2020. Cerebral infarction – 6.9 in 2015 to 4.0 in 2020, and subarachnoid hemorrhage remained at 0.6-0.5 indices per during the 2015-2020 period.

3.1.2. Prevalence of endocrine diseases and obesity in the Republic of Modova per 10 thousand population in 2015-2020

In that period, endocrine-metabolic diseases had an ascent from 605.6 in 2015 to 731.5 in 2020. The peak of prevalence in this period was detected in 2019 – 782.3. Diabetes mellitus and obesity have had an increasing trend. So, the prevalence of diabetes increased from 254.3 in 2015 to 335.2 in 2020, and insulin-dependent diabetes had a straight-line prevalence of 50.0

throughout the research period. There is a significant increase in type II diabetes from 200.3 in 2015 to 285.2 in 2020. This denotes metabolic disorders and metabolic risks for the health of the population in general in the Republic of Moldova [82].

Our research also focused on the study of the prevalence of diseases of the circulatory system for the period 2015-2020 per 10 thousand descriptive population, on the municipalities and areas, but also the districts of the Republic of Moldova. Diseases of the circulatory system, in the DDR Chisinau had absolute values on the rise - 136500 (1681.3) in 2015 and a value of 201735 (2432.6) in 2019, with a small decrease 170941 (2061.1) in 2020 [20, 22].

3.2. The incidence of hypertension, diabetes, dyslipidemia and obesity as major risk factors for population health

3.2.1. The incidence of diseases of the circulatory system in the population of the Republic of Moldova per 10 thousand inhabitants for 2015-2020

The study focused on the incidence of 4 nosologies - diseases of the circulatory system, hypertensive disease, acute myocardial infarction, cerebrovascular diseases. Research has shown that diseases of the circulatory system per 10 thousand inhabitants during the study period had a decreasing trend from 181.3 in 2015 to 108.4 in 2020. This decreasing trend in incidence was also demonstrated in hypertensive disease - from 92.8 in 2015 to 51.0 in 2020. Cerebrovascular diseases decreased insignificantly from 29.4 in 2015 to 15.6 in 2020 and acute myocardial infarction from 4.8 – 2015 to 4, 2 in 2020 [35].

The incidence of cerebrovascular diseases in the Republic of Moldova in the period 2015-2020 per 10 thousand inhabitants had a decreasing trend [9].

Cerebral infarction – 2015 – 29.4, in 2020 – 15.6. Sequelae of cerebrovascular diseases – 3.4 in 2015 and 2.7 in 2020. Intracerebral hemorrhage 2.1 in 2015 and 1.3 in 2020. The incidence of ischemic heart disease in the Republic of Moldova during the research period – ischemic diseases – 17.3 in 2015 and 13.0 in 2020, hypertension – 9.5 in 2015 and 5.4 in 2020, and angina decreased from 7.4 in 2015 to 5.0 in 2020. The incidence of hypertension in the Republic of Moldova in the period 2015-2020 per 10 thousand inhabitants had two periods of increase and decrease. In 2015 – 92.8, and in 2017 – 13.9 and significantly 51.0 in 2020.

We carried out descriptive research on the incidence of diseases of the circulatory system in the period 2015-2020. In 2015 – 64446 (181.3) and in 2020 – 38420 (108.4), which denotes a significant decrease. The incidence of hypertensive disease in 2015 – 32988 (92.8), and in 2020 – 18086 (51.0). The incidence of ischemic disease accompanied by hypertensive disease in 215 – 6159 (17.3), in 220 – 4604 (13.0). Incidence of ischemic heart disease not accompanied by hypertensive disease, in 2015 – 3367 (9.1), in 2020 – 1900 (5.4). The incidence of

cerebrovascular diseases with hypertensive disease – 2015 – 6422 (18.1), in 2020 – 3785 (10.7). The incidence of cerebrovascular diseases without hypertensive disease, in 2015 – 4021 (11.3), in 2020 – 1738 (4.9).

The incidence of subarachnoid hemorrhage, from the total number of cerebrovascular diseases 2015 – 214 (0.6) in 2020, 156 (0.4), with a decrease of 0.2. The incidence of intracranial hemorrhage from the total number of cerebrovascular diseases in 215 – 534 (1.5) and in 2020 – 314 (0.9), with a decrease of 0.6. The incidence of cerebral infarction, from the total number of cerebrovascular diseases in 2015 – 2451 (6.9) in 2020 – 1412 (4.0) with a decrease of 2.9. Incidence of sequelae of cerebrovascular diseases in 2015 – 1205 (3.5) and in 2020 – 940 (2.7) a decrease of 0.5.

3.2.2. The incidence of endocrine-metabolic diseases as a major risk factor for health in the period 2015-2020

The incidence of endocrine-metabolic diseases had a significant decreasing trend towards 2020. So, the incidence in 2015 was 91.3, and in 2020 – 65.6, a significant decrease of 25.7. Diabetes in 2015 – 29.2, in 2020 – 20.9. Type II diabetes had a stable incidence of 3.2 in 2015 and 31 in 2020. Obesity was 24.8 in 2015 and 17.2 in 2020.

We carried out incidence research through endocrine diseases, nutrition and metabolism under a general and selective aspect. The total incidence in the Republic in 2015 – 32457 (913), and in 2020 – 23261 (65.6), which demonstrates a significant decrease in the period 2015-2020. This refers to the RDD of the municipality of Chisinau - from 9694 (119.4) in 2015 to 6219 (75.0) in 2020.

In the Northern RDD – 8442 (85.3) in 2015 and 5591 (57.2) in 2020. This trend is also demonstrated in the Central RDD, the Southern RDD, the UTA Gagauzia RDD, in the municipality and districts with 17.6±0.9 %, $p<0.05$.

The incidence of diabetes in the period 2015-2020 had a significant descent - from 10387 (29.2) in 2015 to 7400 (20.9) in 2020. In the RDD of Chisinau municipality - 2547 (31.4) in 2015 and 1661 (20.0) in 2020.

In Northern DRR – 3046 (30.8) in 2015 and 1926 (19.7) in 2020. This trend is also observed in districts and municipalities. In districts 7736 (28.3) in 2015 and 5499 (21.4) in 2020, in municipalities – 2960 (30.8) in 2015 and 1849 (18.8) in 2020.

We also researched the incidence in this period 2015-2020 of insulin-dependent diabetes. Total per republic 1136 (3.2) in 2015 and 1111 (3.1) in 2020. It is significant and conclusive that type I diabetes has a continuity throughout the entire period of constant research.

3.2.3. Obesity incidence as a major health risk factor 2015-2020

Obesity, like hypertension and diabetes, is a major risk factor for the health of the population, being a component of metabolic-circulatory syndrome disorders.

The obesity incidence study, which was carried out with some analytical and descriptive features for the first time, demonstrated that the obesity incidence in the Republic of Moldova during the study period in 2015 was 8829 (24.8) and in 2020 – 6106 (17.2). By district 6519 (25.2) in 2015 and 4606 (18.0) in 2020.

On the municipalities – 2188 (22.7) in 2015 and 1445 (14.7) until 2020. In the Chisinau DRR municipality – 2051 (25.3) in 2015 and 1583 (16.7) in 2020. Northern DRR – 2551 (25.8) in 2015 and respectively 1494 (15.3) in 2020; RDD Centru – 3015 (28.5) in 2015 and 2273 (21.7) in 2020. RDD Sud – 886 (16.6) in 2015 and 837 (15.6) in 2020. RDD UTA Gagauzia – 203 (12, 5) in 2015 and 64 (4.0) in 2020.

3.3. General mortality and through increased metabolic risks of the population of the Republic of Moldova for 2015-2020

3.3.1. General mortality of the population of the Republic of Moldova per 100 thousand inhabitants in the period 2015-2020

The mortality of the population of the Republic of Moldova during the study period had an upward trend. In 2015 – 1122.8 with a decrease in 2017 – 1036.0 and with a significant increase in 2020 – 1141.2 [5, 12].

3.3.2. Mortality of the population due to diseases of the circulatory system

The mortality of the population from diseases of the circulatory system had a similar expression 648.2 in 2015, 605.4 in 2017 and an increase in 2020 of 645.2 per 100 thousand inhabitants. Mortality from ischemic heart diseases also had a decrease from 348.6 to 312.9 in 2019 and an increase in 2020 of 354.5. Mortality from myocardial infarction during the study period had different rates. The peak period of mortality was in 2016 – 56.3, and in 2020 it decreased to 49.3. The study of the mortality of the population of the Republic of Moldova due to cerebrovascular diseases had a continuous decrease - 164.3 - 2015, 159.2 - 2016, 151.8 - 2017, 147.4 - 2018, 145.7 - 2019 and 141.2 in the year 2020.

The study of mortality due to cerebro-vascular accidents in the Republic of Moldova during the study period had different trends. Cerebral coma has decreased from 53.6 in 2015 with a stabilization in 2020 at the index of 41.9. Ischemic stroke had stable indices during this period – 47.2, 47.2, 45.1, 45.6, 49.5, 48.1. Hemorrhagic stroke had an increasing trend – 34.4 in 2015 and 28.4 in 2020. Mortality due to arterial hypertension had an upward growth aspect – 53.8 in 2015; 59.3 – 2016; 59.3 – 2017; 60.0 – 2018; 67.0 – 2019; 75.8 – 2020.

3.3.3. Mortality from endocrine diseases and diabetes

The study of mortality from endocrine-metabolic diseases in the period 2015-2020 had a stabilization with an insignificant increase: 11.7 in 2015; 11.9 – 2016; 12.0 – 2017; 12.2 – 2018; 10.7 – 2019 and 13.4 in 2020.

We also studied diabetes mortality during this period. The mortality index of the nosology had an increase from 11.5 in 2015 to 13.2 in 2020. We studied the mortality of the population both descriptively and analytically. So, the general mortality of the population in the period 2015-2020 in the Republic of Moldova per 100 thousand inhabitants, in 2015 – 1122.8, 2016 – 9083.5, 2017 – 1036.0, 2018 – 1049.0, 2019 – 1037.0 , 2020 – 1141.5 RDD Chisinau municipality – 792.8 – 2015, 772.2 – 2016, 740.9 – 2017, 764.5 – 2018, 733.1 – 2019, 935.3 – 2020.

In the RDD "North" a small decrease in mortality is observed - 1312.9 - 2015, 1262.6 - 2016, 1228.7 - 2017, 1222.1 - 2018, 1205.4 - 2019 and 1309.3 - 2020. RDD "Center" in 2015 – 1197.1, 2016 – 1152.1, 2017 – 1072.1, 2018 – 1104.4, 2019 – 1101.1 and 2020 – 1149.1.

The general mortality of the population due to diseases of the total circulatory system in the Republic had a stability – 648.2 – 2015, 617.3 – 2016, 605.4 – 2017, 609.4 – 2018, 606.8 – 2019 and 645.2 – 2020. Chisinau municipality RDD – 432.3 – 2015 and 483.0 in 2020. “North” RDD – 817 – 2015 and 801.2 – 2020. “Center” RDD – 667.0 – 2015 and 645.2 – 2020 RDD "South" - 643.0 - 2015 and 630.0 - 2020. RDD "UTA Găgăuzia" - 580.0 - 2015 and 568.1 - 2020.

The study of the general mortality of the population due to endocrine-metabolic diseases demonstrated a decrease from 7.4 in 2015 to 6.4 in 2020, and in the DDR "North" an increase from 16.0 - 2015 to 19.2 in 2020; in RDD "Center" from 9.0 in 2015 to 9.6 in 2020; RDD "South" from 13.9 in 2015 to 18.0 in 2020. In RDD "UTA Găgăuzia" the index of 17.3 was characteristic for the year 2015 as well as for 2020. Overall in the Republic during this period there is an increase from 11.7 in 2015 to 13.4 in 2020.

Mortality due to diabetes decreased - 7.3 in 2015 and 6.0 in 2020 in the RDD of Chisinau municipality, and in the "North" RDD an increase from 15.7 in 2015 to 19.0 in 2020. In the RDD "Centre" the increase from 8.9 in 2015 to 9.5 in 2020, RDD "South" from 13.5 in 2015 to 18.0 in 2020, RDD "UTA Găgăuzia" from 17.3 in 2015 to 22.3 in 2020 and total for the Republic – 11.5 in 2015 and 13.2 in 2020.

4. BIOTYPED AND PERSONALIZED LIFESTYLE FOR SUBJECTS WITH INCREASED METABOLIC RISK

4.1. Scientific argumentation of the biotyped and personalized lifestyle of subjects with increased metabolic risks

Multiple scientific and health education papers have been written about healthy lifestyle (HSV), generalizing various beneficial methods and actions to achieve this major goal. Some recommendations have been described, mainly for the general public, regarding maintaining a healthy lifestyle in some patients with certain diseases [13, 16, 21, 24, 28, 30]. Until now there is no clear vision in the argumentation of MSV for subjects with metabolic risk factors – arterial hypertension, type II diabetes, obesity. Each individual has its own physiological, metabolic peculiarities of the intestinal biota. To a large extent, metabolism also depends on psychophysiological aspects, psychosomatic correlation, healthy nutrition, activity regime, sleep, motor skills, professional activities, etc. Both the genetic components that determine the type of metabolism, fermentopathies, but also everyday activities, traditions and eating habits etc. are specific [2, 42, 46].

There is a close interrelationship between health systems and healthy lifestyles. The multitude of existing concepts each have their own and carry within them the positive element aimed at maintaining the physiological balance of each individual. But not all of them have a clear and accessible message that convinces us and guides us in our everyday life. We are trying to propose and realize a concept that is based on two fundamental elements: simplicity and accessibility on the one hand, and the factor of individuality that implies the principle of personalizing the lifestyle, on the other hand.

We set out to argue a new lifestyle approach (SV) specific to subjects with increased risks, and especially with hypertension, type II diabetes, obesity, i.e. the pathologies that make up part of the metabolic syndrome, which largely determines the condition of health, longevity, life risk and even mortality of the population. In the scientific deductions we argue the biotyped and personified lifestyle concept for subjects with increased metabolic risks:

1. Determination of the psychophysiological state, based on the indicators: the type of reaction to visual and auditory stimuli, psychomotor coordination, concentration of attention, short-, medium- and long-term memory, the performance of higher nervous processes – analysis, synthesis, logical thinking, spatial representation, of psycho-behavioral indicators – psycho-effective, neurovegetative, sensory-sensory, sleep disorders, but also anxiety, hypoactivity as well as hyperactivity, changes in the dynamics and structure of the personality, of the visual and

auditory analyzer.

2. Determination of the constitutional biotype. Each individual is a biotype, it has its individual peculiarities, which are characterized by functional similarities including physical constitution, which largely determines the functional aspect of metabolism. This external manifestation of the individual is due to the physiological and psychological properties of the personality, based on the human genome. The constitutional nature determines the nature of the metabolism. This somatotype, or the physical component of the individual has changes in the process of ontogenesis, but also of epigenetic factors. The constitution somatotype must be determined based on anthropometric measures, which is of three constitution types: asthenic (weak), normosthenic (normal), hypersthenic (thorough).

3. Determination of the type of metabolism. Metabolism is the main function of the body, which depends on enzymes and enzymopathies. Metabolism is genetically determined and correlates directly with body type. If the metabolism deteriorates, then the general homeostasis of the body is distorted. In subjects with metabolic risks – circulation disorders with arterial hypertension, type II diabetes, obesity quite severe metabolic changes occur.

4. Determination of cardiovascular and circulatory bioenergetics. Arterial hypertension is a disease with major risks, which due to its evolution and severe complications (strokes and heart attacks) is the main cause of mortality in the population. Recent WHO 2020 data shows that 1.3 billion people suffer from this disease, and 2/5 of them suffer from it in a latent form, it being a component of the metabolic syndrome, and largely determined by the psycho-emotional state as an element of basis, which disrupts the regulation of the vasomotor system and hormonal control mechanisms [59].

It should be taken into account that different psychosomatic types respond differently to emotional factors depending on their reactivity and have a different incidence of HTN.

5. Determination of the glycemic profile. The glycemic profile, as well as the dynamic observation of blood glucose, is intended to monitor the body's carbohydrate metabolism over a certain period of time. The determination methods are varied and based on the glucose-oxidizing method. The determination is made fasting by the glucose tolerance test (TGTO). Physiological levels are 3.3-5.5 mmol/l of blood sugar. A prediabetes is considered to start from a glucose level ≥6.1 mmol/l.

6. Determining the intestinal microbiota and combating dysbiosis. The intestinal microbiota is represented by a huge number of microorganisms, which exceeds the number of somatic cells, and directly influences the health status of the macroorganism. It is mostly represented by 99% anaerobic bacteria, most of which belong to 30 types. They are present in

anaerobic digestion, having an important role in the formation and maintenance of immunity.

7. Sanogenic nutrition depending on the constitutional type, type of metabolism and metabolic risks. A healthy diet depends not only on the quality of products and nutrients, but also on its correlation with constitutional biotypes, which ensure a stable metabolism and morphophysiological functioning of the body of individuals of each biological type. It is necessary to take into account their characteristics for the overall optimization of the body's nutrition, because the ratio of carbohydrates, lipids and proteins differs from one type to another, and the metabolism is also different through the speed of biochemical reactions, especially of the enzymes of the digestive system, as well as individual pH.

8. Combating oxidative stress. Remedies for combating oxidative stress are represented by different groups of substances of an enzymatic and non-enzymatic nature. The most important are SOD (superoxide dismutase, catalase and peroxidases). The second group is represented by ascorbic acid, tocopherol, β carotene, lycopene as well as polyphenols – flavin and flavonoids, tannins and anthocyanins. Antioxidants are mostly contained in medicinal plants that are widely used in phytotherapy and the production of widespread natural remedies.

9. Combating chronic systemic inflammation. Chronic systemic inflammation is one of the main causes of several metabolic diseases with an increased incidence and prevalence. The causes of chronic systemic inflammation are different, but they are mainly due to adipocytokines represented by a whole class of substances: leptin, resistin, angiotensinogen, interleukin 6 (IL-6), adipsin, etc., which are synthesized in white adipose tissue. The combat methods would be substances with anti-inflammatory effect, which are contained in brown and beige adipose tissue by converting white tissue and transforming it into muscle tissue.

10. Combating sedentarism and activating motor skills. Motricity or physical effort is one of the basic factors in maintaining metabolism at physiological levels, by lowering blood sugar. Maintaining its normal values is achieved by the rapid release of muscle and liver glycogen, and after their exhaustion by the synthesis of glucose (gluconeogenesis) from glycerol and amino acids. The sympathetic nervous system is activated with the release of catecholamines that influence vasoconstriction but also the suppression of insulin secretion.

4.2. Scientific approach to lifestyle and glycemic control in subjects with increased metabolic risks

Hyperglycemic syndrome includes a whole group of conditions whose main symptom is high blood glucose. Diabetes mellitus type 2, which is included in the hyperglycemic syndrome group, was selected as a model for the complex correction of hyperglycemia. It is known that this disease is characterized by affecting the sensitivity to insulin, which is synthesized by the

cells of the pancreas.

The disease is accompanied by disturbances of all types of metabolism, including carbohydrate, lipid, protein and hydrosaline. This situation leads to serious damage to the internal organs and vital systems of the body, significantly reduces the quality of life and has a negative effect on the ability to work and the length of life. The main danger of the disease is the development of hyperglycemic coma, which can lead to irreversible damage to the body or even death [28, 30].

According to modern theories, the following factors play an essential role in the development of diabetes: hereditary predisposition, abuse of easily assimilable carbohydrates, hypodynamia, obesity, physical and mental trauma, some infections and intoxications, atherosclerosis, hypertension, acute and chronic pancreatitis, cholecystitis and hepatitis, endocrine disorders, pregnancy.

Statistical data show that in the last 30 years the number of patients with diabetes has increased dramatically. In the list of the most common diseases, diabetes occupies the third place, second only to diseases of the cardiovascular, circulatory and oncological systems.

One of the reasons for the rather modest successes in the treatment of diabetes lies in the fact that the tactic of eliminating the symptoms of a dysfunction of the body dominates - to restore the metabolism of carbohydrates and the function of the pancreas. At the same time, we do not pay attention to the fact that the named dysfunctions have caused general disturbances in the whole body and, in order to achieve the expected effect, we must restore the activity of the whole organism in a complex. To reveal the causes of metabolic disorders, it is necessary to identify the factors that cause them. If we exclude viral, bacterial and parasitic diseases, it becomes obvious that the main causes of metabolic imbalance and chronic pathologies represent a complex of interconnected factors - the nutritional system, the lifestyle and the psychological state of man. Since these factors are determined by man, through his actions and will, we can say that all chronic diseases, including diabetes, are caused by ourselves. Everything we eat, drink, what way of life we lead and how we think, all this reflects on the whole organism and the state of health depending on their quality [50, 51].

Despite the fact that these identified causal factors are quite well known, the situation has not changed regarding the stable consolidation of health, the prevention of metabolic syndrome and chronic pathologies.

The modern approach to the prevention and treatment of diabetes is a fragmented or too one-sided approach, which mainly considers the glycemic index of the diet, the use of hypoglycemic products and insulin [79]. Very little or almost no consideration is given to such

important factors as the lifestyle and the human psychosomatic state, which are the main causes of diabetes [2].

The negative influence of the mentioned factors, which manifests a chronic character, triggers a chain of future pathology, which begins with metabolic disorders, suppression of the immune system, and the suppressed immune system is not able to prevent mutagenic processes. Mutagenic processes occurring in the genetic code of the cell are not able to maintain the metabolism within sanogenic limits. This is where the vicious circle ends. If the indicated processes are not prevented, then the pathogenic processes are triggered, which acquire a general character. Here the well-known truth must be noted, that any disease is an accumulation in the body of enormous amounts of foreign substances (toxins, free radicals and all kinds of metabolites).

Lifestyle factors. Among the lifestyle factors, the manifestation of diabetes and its prevention, the most significant role is played by physical activity, sleep and the optimal alternation of active activity and rest. Excessively comfortable living conditions lead to a decrease in physical activity, especially that of a dynamic nature. Hypodynamia, as is known, leads to hypofunction of organs and the body as a whole, to a total disruption of microcirculation and, in turn, to hypofunction of organs and physiological systems [81].

Sleep is very important for maintaining an active immune system. Sleep and immunity are almost synonymous. With the reduction of sleep, immunity drops sharply, and the probability of any disease increases. If a person sleeps less than five hours, the activity of the immune system is reduced more than 2 times, compared to those who sleep more than seven hours. To maintain our health at a good level, we must live in accordance with the energy rhythms of nature and give sleep the right time and duration (from 10-11 pm to 6-7 hours). Sleep plays an important role in the production of melatonin, a hormone that plays an important role in maintaining circadian rhythms and ensuring metabolic processes.

A reasonable alternation between work and rest is necessary, so that the body has time and possibilities to restore its body and ensure its reparative processes.

Psychosomatics. Despite the fact that most specialists analyze chronic diseases only from the standpoint of food factors, such an attitude towards this problem is somewhat one-sided, because it only highlights the influence of the nutritional aspect on the physiological mechanisms of disease manifestation. Man is not just a physical body. Each of us possesses an individual psyche with a personal worldview and a typical way of thinking.

To defeat the disease, it is necessary to eliminate its source - to change the worldview. The inner world, the conception of the world, must be corrected by man himself. The mechanism

of disease manifestation begins with informational-energetic disturbances, i.e. with the conception of the world and with psychosomatics. Then, somatization processes intervene: biochemical disturbances, structural changes, followed by organ disturbances and clinical manifestations (symptoms). The formula of the mechanism of occurrence of chronic diseases, including diabetes, is reduced to the following. The body responds to our thoughts, and the brain forces the body to release a set of hormones that correspond to our thoughts. The moment a thought appears in the brain, a chain of biochemical reactions takes place there. The body processes them and launches another chain of reactions appropriate to the thought we generated. If we permanently (or in most cases) have a negative mood, then our body gets used to and becomes dependent on a certain hormonal and biochemical background of homeostasis, which is formed during disappointment, frustration, fear, depression and other negative emotions. Every situation, every emotion and thought forms neural connections in the brain, and the more frequently a situation is repeated, the more durable the neural connections become. Later this fact is established in the subconscious in the form of appropriate programs, then they become a habit and work automatically. We cannot even realize that they are destroying our body and health. This is how the mechanism of dependencies is formed. The brain is constantly connected to the body, that's why we have the sensations we think about. We become dependent on the chemicals and hormones produced by our own body in response to the situation that has become ordinary for us. We want this fact to be permanent and stable. If the negative is not a reality, then we look for it in our past, we create it in our brains in the form of virtual variants and internal dialogues. The body reacts equally whether the emotions are caused by real or virtual events.

Each metabolic disease, including hyperglycemia and, in particular, type 2 diabetes, in addition to general approaches, is distinguished by its specificity with the manifestation of psychosomatics. Analysis of the works of psychosomatic specialists allows us to conclude that the cause of negative thoughts and emotions that cause diabetes lies in excessive attachment to material things. The predominance of thoughts of a material nature with a negative accompaniment leads to the blocking of the central energy center, which controls the endocrine regime of the pancreas. The stronger and systemic the blockage of the central energy center, the more the functional activity of the pancreas is disturbed, which leads to the appearance of hyperglycemia and diabetes [60].

The healthy lifestyle for subjects with metabolic risks can be materialized by them, it has an epigenetic character, which is acquired depending on the conditions of the habitat or its change, on the socio-economic situations; is aimed at maintaining and strengthening the state of health representing a set of habits and behaviors influenced and directed both by one's own

intelligence and general and sanitary culture as well as, to a large extent, by the environment - nature, health, communication - all interrelated with each other.

Lifestyle components for these subjects can be both positive and negative. Positive habits and attitudes actively and consistently promote a healthy lifestyle, and skills depend more on the person and their capabilities. The educational factor represents taking useful information and good examples from doctors, health specialists, teachers, educators-pedagogues. In this context, the formation of SSV for subjects with metabolic risks is a process that manifests itself in dependence on the variability of the environment and the needs of adaptability and the knowledge of the individual. The goal of SSV is ultimately to know, avoid or counter metabolic factors – HTN, DM type II, obesity, awareness and perception of these diseases as harmful and threatening factors for health, for the quality of life and its duration. The motivation must be personalized-individual but also social by understanding the benefits of a SSV, minimizing increased metabolic risks.

Scientific data confirms that lifestyle has a weight of 50% on health, compared to the influence of the environment 20% and medicine only 10%. Precisely this fact comes to argue for its customized implementation.

The purpose of accepting and installing a personified and biotyped SSV is to maintain physical and mental health by avoiding risk factors, which can be excluded from our lives.

Depending on their nature, the risk factors are divided into variable and invariable factors, and the component elements that influence SSV are very different, including: food, mobility, habits and harmful habits - smoking (tobacco consumption), alcoholism (alcohol consumption), the use of drugs/medications, daily stress, measures and personal hygiene, work and rest (wake-sleep state), health monitoring at a certain frequency, other daily habits that can affect our health (interpersonal relationships, driving behavior – seat belt, compliance with road and speed rules, promotion of sports and hobbies of general culture – dance, dramaturgy, painting, etc.) [71].

There is a close interrelationship and interdependence between valences and health status. Balanced nutrition helps us maintain the optimal level of energy and the plasticity of organs and tissues; ensures growth and development in early ontogeny, but also throughout life; contributing to the regeneration process (anti-aging); - adequate and complete nutrition leads to increased life expectancy, because the presence of antioxidant substances and fermented dairy products (microbiotic products) can stop inflammation and thus inhibit the aging processes related to it; strengthens the immune system by ingesting macro- and micronutrients, and increasing resistance to metabolic (oxidative) stress, to inflammation; balances the emotional and state of

mind.

Motility (physical exercise) is another important element that directly influences health. Both aerobic and anaerobic exercises stimulate metabolism, reduce degenerative processes and strengthen immunity.

High blood pressure can be monitored and kept under control by simple measurement methods, even at home. High blood pressure occurs when blood pressure rises above certain physiological (normal) values. BP ≤ 140/80 mm Hg.

In order to avoid these diseases and risks, it is necessary for the subjects to lead a lifestyle by: maintaining weight within normal limits; reducing salt consumption; avoiding alcohol and tobacco consumption; light exercise practice; avoiding emotional overloads; antihypertensive medication.

These are the recommendations that allow subjects to lead a decent to healthy lifestyle, respecting food regimes, work-rest (wake-sleep), physical exercise, avoiding harmful habits and habits, monitoring body mass, blood pressure, cholesterol and blood sugar. These tips are included in the individual breviary of each subject with increased metabolic risks. It is important to create a favorable communication environment with positive emotions both in the family and at work or with the people with whom we are constantly in contact.

4.3. Minimizing metabolic risks in subjects with metabolic disorders through biotyped and personalized lifestyle enhancement

The biotyped and personalized lifestyle study was conducted with the inclusion of 100 subjects with metabolic disorders – 50 men (50%) and 50 women (50%) aged 30-70 years. For objectivity and conclusiveness, the subjects who had other factors were excluded: hereditary diseases - hypothyroidism, Cusing's disease, hypothalamic tumors, intoxication with drugs (antidepressants, contraceptives, hormones), those who consume alcohol in excess, with occupational forced sedentarism. The main objective of the implementation of the biotyped and personified lifestyle was the etiopathogenetic determination, the decrease in blood pressure, the decrease in body mass and blood glucose, through physical activity and motor skills [54, 65], behavioral therapy, through sanogenic, hypocaloric nutrition depending on age, constitution type [36], metabolism type, in accordance with the conceptual provisions of the biotyped and personalized lifestyle [45, 64].

The research was carried out in accordance with the methodology and Decision of the Research Ethics Committee and the informed consent of the subjects included in the research.

Various indicators were analyzed on the following groups - psychophysiological (type of reaction, adequate psychomotor coordination, concentration of attention, yield of nervous

processes - analysis, synthesis, logical thinking, spatial representation, psychobehavioral indicators - psychoaffective, neurovegetative, sensitive, short memory, dyssomnias, depressions , anxiety, hypoactivity and hyperactivity); nutrition correlated with the type of constitution and metabolism – normosthenic (normometabolic), asthenic (hypermetabolic), hypersthenic (hypometabolic) and caloric value of food, obesity indicators – body mass, overweight, obesity (abdominal and gluteofemoral), BMI, CA, diet ; motor skills (physical activity); administration of probiotics and antioxidants; adaptogenic training, the dynamics of blood sugar, glycosylated hemoglobin, blood sugar profile, hemodynamics - TAS, TAD and other determinants of lifestyle (Table 4.1.).

Table 4.1. Dynamics of psychosomatic, anthropometric, hemodynamic, glycemic, lipid, obesity indicators: motor, adaptogenic and risk minimization after the implementation of biotyped and personalized lifestyle (BPLS) in subjects with increased metabolic risks

Indicator	Until the implementation of BPLS	After BPLS implementation
The type of appropriate reaction (%)	67 (67%)	89 (89%)
Adequate psychomotor coordination (%)	71 (71%)	88 (88%)
Concentration of attention (%)	82 (82%)	91 (91%)
The yield of nervous processes: analyze synthesis logical thinking spatial representation	 79 (79%) 74 (74%) 91 (91%) 100 (100%)	 87 (87%) 85 (85%) 94 (94%) 100 (100%)
Psychobehavioral indicators (accusations): psycho autonomic sensitive-sensory	 63 (63%) 18 (18%) 32 (32%)	 21 (21%) 11 (11%) 15 (15%)
Short term memory	87 (87%)	92 (92%)
Dyssomnias: difficulty falling asleep frequent awakening tiredness on waking bad dreams	 28 (28%) 62 (62%) 86 (86%) 18 (18%)	 13 (13%) 38 (38%) 39 (39%) 11 (11%)
Depression	22 (22%)	8 (8%)
Anxiety	24 (24%)	9 (9%)
Hypoactivity	7 (7%)	3 (3%)
Hyperactivity	4 (4%)	2 (2%)
Caloric value (24 hours kcal): normosthenic (normometabolic) asthenic (hypermetabolic) hypersthenic (hypometabolic)	 uncontrolled regime uncontrolled regime uncontrolled regime	 2000 kcal/24 hours 2200 kcal/24 hours 1800 kcal/24 hours
Lean body mass (kg)	87.4±1.92	76.3±1.11
Overweight (%)	62 (62%)	70 (70%)
Obesity (%):	38 (38%)	30 (30%)

abdominal (%) gluteo-temporal (%)	28 (28%) 10 (10%)	21 (21%) 9 (9%)
BMI kg/m^2	32.1±0.7	28.2±0.4
Motricity (physical activity)	mild 22 (22%) average 20 (20%) sedentary lifestyle 58 (58%)	9 (9%) 91 (91%) 0 (100%)
Probiotics (a.c., %)	absent	absent
Antioxidants (a.c., %)	absent	products 1, 2 and 3 after recommendation
Adaptogenic training (%)	absent	100% applied
Basal glucose (mmol/l)	6.9±0.5	5.6±10.2
Glycosylated hemoglobin (mmol/l)	7.4±0.3	6.2±0.2
Glycemic profile (mmol/l)	7.5±0.4	6.8±0.5
HTN >130/85 mmHg TAS DBP	 158.8±1.4 91.1±1.4	 147.2±1.2 87.2±1.1
Excessive consumption of: liquids (l) salt (g) coffee and teas (l)	 2.1±0.3 5.0±0.1 Yes	 1.5±0.1 4.0±0.1 No
Nocturnal feeding	14 (14%)	Nou
Alcohol consumption	26 (26%)	No
Smoking	35 (35%)	31 (31%)

We conducted a selective study in the assessment of lifestyle knowledge in subjects with metabolic-circulatory disorders. The assessment of the level of knowledge regarding metabolic risks – hypertension, type II diabetes and obesity was carried out on a sample of 100 subjects with metabolic syndrome (men – 48 (48%) and women – 52%) with an average age of 59±1.6 years).

The subjects who knew about metabolic disorders were 20 (20%), about HTN – 96 (96%), about DM type II – 42(42%), and obesity – 100(100%). Information regarding HTN symptoms – 52 (52%), DM type II – 31 (31%), obesity – 100(100%), overweight 26 (26%). Information on prophylaxis – HTN – 61 (61%), DM type II – 57 (57%), obesity – 63 (63%). Information on metabolic risk factors: HTN – 26 (26%), DM type II – 23 (23%), obesity – 59 (59%). Information about the harm of abuse of harmful habits: alcohol – 100 (10%), smoking (tobacco) – 100 (100%), sedentary lifestyle – 87 (87%).

A special role in informing and educating the population for health, a decent lifestyle and its practice takes place through the main information sources, namely: TV, radio, doctors, public lectures, medical staff, hygienists, relatives, other sick people, films etc. (Table 4.2.).

Table 4.2. Popularizing sources of information on increased metabolic risks and lifestyle to strengthen human health

Source	They got information	I want more information
Radio broadcasts	31 (31%)	49
Conversations with doctors	92 (92%)	100
TV shows	42	62
Publications in the press	26	36
Conversations with other patients	23	24
Conversations with relatives	46	51
Popular medical literature	19	63
Movie	7	74
Public lessons in the fields of health and lifestyle	8	16

5. REDUCTION OF METABOLIC RISKS AND IMPROVEMENT OF HOMEOSTASIS THROUGH THE ADMINISTRATION OF REMEDIES BIOLOGICALLY ACTIVE

5.1. Development of products with metabolic-protective effects

Given the systemic metabolic disorders in patients with metabolic disorders: hypertension, hyperglycemia, hyperlipidemia, chronic systemic inflammation, as a result of the theoretical-bibliographic and phytotherapeutic studies, we determined the phytoprotective formulas from native medicinal plants with metabolic-protective action and selectively targeted etiopathogenetic action. Following the testing of different plant materials, 4 new recipes were developed to improve the homeostasis of subjects with metabolic risks. The main elements of the new recipes are plant-based components:

Phytotherapeutic composition no. 1 (Short Term Patent No. 1500) (P-1)

The invention relates to preventive medicine, namely to a phytotherapeutic composition for obtaining aqueous infusion with antihypertensive effect.

The result of the invention consists in widening the range of phytotherapeutic products for lowering blood pressure, improving the organoleptic properties, due to the synergistic effect of the qualitative and quantitative ratio of the components.

The obtained infusion has a specific taste of medicinal plants and is brown in color.

The advantages of the claimed invention compared to the closest solution: it can also be used by people who do not tolerate alcohol and ensures a decrease in blood pressure by 20-40 mm Hg; possesses enhanced organoleptic properties; improves the function of the cardiovascular system; can replace drug treatment in the case of HTN of gr. II.

The phytotherapeutic drink exhibits a pronounced hypotensive and tonic action, improves the function of the cardiovascular system.

The successful selection of the components of the proposed composition gives the finished product their properties, more than that - it ensures a specific synergistic effect in this composition and in this quantitative ratio, i.e. the biological activity of the set of ingredients exceeds the sum of the effects of the action of each of them taken separately, which which provides the composition with pronounced curative-prophylactic properties.

How to administer the infusion – 100 ml 3 times a day.

This phytotherapeutic composition was used on a group of 60 people, of which 49 were women and 11 were men, the average age of the people being 48 years, all of them suffered from high blood pressure. II and 90% of the patients returned to borderline physiological indices.

The obtained infusion is used daily 100 ml, 3 times a day 30-40 minutes before meals for 21 days, with the possibility of repeating the cure.

According to the Medicines and Pharmaceutical Activity Law, the doctor has the right to prescribe the master prescription with phytotherapeutic compositions, having previously consulted the antagonistic and synergistic effects of the medicinal plants and the single administration doses. According to the master recipe in the pharmacy, the product P-1 was prepared.

Given the fact that the components of the indicated recipe have a traditional use in the treatment of patients with metabolic disorders, they do not require additional studies of adverse effects and their incompatibility, which are described in the specialized literature.

Phytotherapeutic composition no. 2 (Short Term Patent No. 1499) (P-2)

The invention relates to preventive medicine, namely to a composition for obtaining the aqueous infusion with the effect of reducing low-density lipoproteins (LDL).

The successful selection of the components of the phytotherapeutic composition gives the finished product their properties, more than that, it ensures a specific synergistic effect in this composition and in this quantitative ratio, i.e. the biological activity of the set of ingredients exceeds the sum of the effects of the action of each of them taken separately, which which provides the composition with pronounced curative-prophylactic properties.

The obtained infusion has a bitter taste and a greenish color.

Cholesterol cannot dissolve in the blood. It must be transported from and to the cells by means of molecules called lipoproteins. On the one hand, low-density lipoproteins (LDL) are also known as "bad" cholesterol. On the other hand, there is also the so-called "good" cholesterol or high-density lipoproteins (HDL).

These two types of lipids, together with triglycerides, make up the total level of cholesterol in the blood.

The advantages of the claimed invention compared to the closest solution: the significant reduction of the amount of low-density cholesterol (LDL), in the medium by 71mg/dl; enhanced organoleptic properties due to the ingredients it contains.

To prepare the infusion, all the phytotherapeutic components are procured, weighed according to the required amount and ground together until a homogeneous mass is obtained. Then add boiling water until a liter of infusion is obtained, let it cool in the dark, to room temperature.

The infusion is used daily 100 ml, 3 times a day 30-40 minutes before meals for 40 days, with the possibility of repeating the cure.

According to the Medicines and Pharmaceutical Activity Law, the doctor has the right to prescribe the master prescription with phytotherapeutic compositions, having previously consulted the antagonistic and synergistic effects of the medicinal plants and the single administration doses. According to the master recipe in the pharmacy, the product P-2 was prepared.

Given the fact that the components of the indicated recipe have a traditional use in the treatment of patients with metabolic disorders, no additional studies of adverse effects and their incompatibility, which are described in the specialized literature, are required.

Phytotherapeutic composition no. 3 (Short Term Patent No. 1498) (P-3)

The invention refers to preventive medicine, namely to a phytotherapeutic composition for obtaining the aqueous infusion with the effect of reducing body mass.

The obtained infusion exhibits a hypoglycemic action, improves glucose tolerance, and possesses high organoleptic qualities, it has a greenish-brown color, the taste is bitter, a fact that contributes to weight loss.

The successful selection of the components of the phytotherapeutic composition gives the finished product their properties, more than that - it ensures a specific synergistic effect in this composition and in this quantitative ratio, i.e. the biological activity of the set of ingredients exceeds the sum of the effects of the action of each of them taken separately, which which provides the product with pronounced curative-prophylactic properties.

The advantages of the claimed invention compared to the closest solution: the more effective reduction of the average weight by 2.0-2.5 times; it has enhanced organoleptic properties due to the ingredients it contains.

The following degrees of obesity are known, related to the body mass index (BMI): I – 30.0-34.9; II – 35.0 – 39.9; III – 40.0 – 44.9; IV – greater than 45.

If the BMI is up to 25, it is considered within physiological limits, and if it is 25-30, it is considered a slight increase in body mass, that is, it represents an overweight stage.

The body mass index is calculated according to the formula: BMI = Body mass/height.

For example, if the body mass is 100 kg, and the height is 1.60 meters, then the BMI is 39.0.

The claimed composition was used on a batch of 99 people, of which 92 women and 7 men, all people were selected in 3 groups. The first group used the phytoceai according to the analogous solution, the second group the phytoceai according to the closest solution, and the third group used the infusion according to the claimed composition. All tested persons were diagnosed with obesity of degree I-II. During 60 days, a significant decrease in body weight was observed daily, for example when using the reference solution the body mass decreased on average by 1.4 kg, according to the reference solution which represents the closest solution, the body mass decreased in on average by 2.6 kg, and according to the claimed composition the body mass decreased on average by 5.1 kg in 60 days.

The obtained infusion is used daily 100 ml, 3 times a day 30-40 min before meals for 60 days, with the possibility of repeating the cure.

According to the Medicines and Pharmaceutical Activity Law, the doctor has the right to prescribe the master prescription with phytotherapeutic compositions, having previously consulted the antagonistic and synergistic effects of the medicinal plants and the single administration doses. According to the master recipe in the pharmacy, the product P-3 was prepared.

Given the fact that the components of the indicated recipe have a traditional use in the treatment of patients with metabolic disorders, there is no need for additional studies of the adverse effects and their incompatibility that are described in the specialized literature.

Phytotherapeutic composition No. 4 (Application submitted to AGEPI on 28.12.2021 and AGEPI Decision No. 10102 of 28.07.2022) (P-4)

The invention refers to the food industry, sanocratology and medicine, in particular to a phytotherapeutic, biologically active food supplement, which has the activity of stimulating the growth and development of the intestinal microflora.

Dysbacteriosis is a condition in which the composition and ratio of the microorganisms that populate the intestine change (the useful bacteria become fewer and the harmful ones, respectively, more), which leads to the disruption of the activity of the gastrointestinal tract.

In the case of dysbacteriosis, harmful bacteria and fungi appear in the intestine (for example, fungi from the Candida family), and the number of useful microorganisms decreases, which leads to digestive disorders. Long-term dysbacteriosis is characterized by dysregulation of the absorption of vitamins, fats, other food components, which leads to weight loss and anemia [72]. The basic components of the treatment are: compliance with the diet and the mandatory introduction of lactic acid products enriched with live bifidobacteria into the diet. Antibiotics or bifidobacteria are prescribed in some cases to inhibit harmful bacteria in the gut; the special products, which normalize the composition of the intestinal microflora (bifi-form, bifidumbacterin, bificol, hilac, linex and others). The treatment, as a rule, allows the restoration of a normal digestion within two months.

The result of the claimed invention consists in obtaining the widening of the range of phytotherapeutic food supplements, biologically active, which activate the stimulation of the growth and development of the intestinal microflora with an immunostimulatory effect at the same time, due to the successful selection of the quantitative and qualitative components and which show an eloquent synergism.

The phytotherapeutic, biologically active food supplement has the following advantages: the claimed supplement, in addition to the effect of stimulating the growth and development of the intestinal microbiota, has an immunostimulatory effect at the same time; it is simple in preparation technology; it does not require a prescription, as it is not a medicine; the treatment period for dysbacteriosis is reduced from 2 months in the environment to 21 days.

The claimed biologically active food supplement (SABA), with the composition named above, was administered to the patient for 21 days (1 capsule 3 times a day before meals) complementary to the basic therapy of the nosologies diagnosed by the family doctor and confirmed by to the Medical Council of the institution where he was hospitalized. After the administration of SABA, complementary to the basic treatment, the patient's condition improved. Objective: hemodynamic indices – blood pressure decreased, from 170/100 mmHg to 140/80 mmHg, blood sugar decreased from 8.2 mmol/l to 5.9 mmol/l, body mass decreased by 4.5 kg , triglycerides decreased from 0.49 to 0.36 mM/l, AST decreased from 146 to 74 mM/l, ALAT from 128 to 72.6 mM/l. The intestinal microbial balance was restored, for *Bifidobacterium lactis* and *Lactobacillus acidophiphilus* 109 and 108 respectively, the immune system was strengthened by the fact that immunoglobulins M, G, A had an increasing tendency from 1.09 to 1.39, from 6, 22 to 6.71, from 0.81 to 1.13 respectively, T lymphocytes (CD^+) from 66.89 to 72.14, T helpers ($CD3^+CD4$) from 0.68 to 0.29.

Significantly improved lipid peroxidation. Ceruloplasmin decreased from 244 to 235

mg/dL, glutathione catalase and peroxidase increased from 10.7 to 13.8 and from 6.6 to 7.9 mM/L respectively. Superoxide dismutase remained at the same level 1096 uc/l. Malonic dialdehyde decreased from 39.6 to 37.1 mjM/l.

At the same time, the patient's hematological indices improved: Hb increased from 109 to 117 g/l, erythrocytes from 2.9 to 3.2 x1012, leukocytes had constant indices. Platelets, eosinophils, lymphocytes did not change significantly.

Biochemical indices had a tendency to improve – total bilirubin decreased from 22.9 to 17.6 mM/l, urea from 8.9 to 7.6 mM/l, creatinine from 126 to 117 mM/l, and total protein increased from 72.1 to 76.2 g/l. Total cholesterol decreased insignificantly from 4.51 to 4.48 mM/l.

The low values of *Bifidobacterium lactis* and *Lactobacillus acidophiphilus* returned to the physiological norm of 109 and 108 CFU/ml respectively.

In the end, we can conclude that the claimed SABA has an action of stimulating the intestinal microbial flora (biota), immunostimulatory, minimizing the metabolic risk and post-COVID-19 immunoinflammation processes.

According to the Medicines and Pharmaceutical Activity Law, the doctor has the right to prescribe the master prescription with phytotherapeutic compositions, having previously consulted the antagonistic and synergistic effects of the medicinal plants and the single administration doses. According to the master recipe in the pharmacy, the product P-4 was prepared.

5.2. The study of elaborated remedies with biologically active effects

5.2.1. Toxicity of biologically active products in the experiment in rats

The acute toxicity studies of those three products were performed on rats according to international ICH M3(R2) recommendations and included physiological, hematological, biochemical parameters, etc. It was also estimated based on the LD50 in rats at increasing doses according to the research methodology. The control groups included intact animals that received regular food rations, maintained in identical vivarium conditions, t – 18-20°C, humidity – 55-60%. Animal behavior was studied and estimated.

The research carried out on the action of Preparation P-1 on the control and experimental groups demonstrated both the hypoglycemic effect and weight gain. After feeding the laboratory animals according to the food rations and the research methodology, we demonstrated that the hypoglycemic effect depended both on the numbers of the feeding rate of administration of the preparation P-1 and on the duration of the experiment – at the beginning of the research, in the middle of the experiment, at the beginning period, as well as at its end - 60 days after the

initiation of research. In table 5.4. the dynamics of the indices can be observed depending on the number of food rations and the experimental period, both in the control group and in the experimental one. In the control group, the indices and their dynamics were not significant ($p>0.05$). In the experimental group, a decrease in blood glucose indices is observed from 5.96±0.03 to 4.7±0.06, $p<0.05$.

Research on the effects of the preparation P2 demonstrated the lipid-lowering effect (Table 5.5.). Body mass indices at both feeding rates and study periods did not change significantly. The hypolipidemic and body mass effect was demonstrated in the experimental group both at feeding rates 1-5 and during the research periods. In the environment, body mass indices 358.0±0.28 at the beginning of the period decreased to 333.0±0.26 towards the end of the experiment (Figure 5.1.).

The chronic toxicity of the products was tested in rats. The following indicators were studied: survival, dynamics of changes in body mass and body temperature, general condition of animals. The study was performed on three batches of 20 rats each. No animals died during the tests. We also studied body mass, including in comparison groups. The duration of the chronic toxicity study was 6 months from LD50.

Selectively for the preparation P-1 with hypoglycemic action we obtained conclusive results (Table 5.1.).

Table 5.1. Dynamics of glucose indices under the influence of P-1 in rats

The control group			
No. Ord.	At the beginning of the experiment	In the middle of the experiment	At the end of the experiment (60 days)
1	4.2±0.01	4.2±0.01	5.8±0.01
2	3.8±0.02	6.3±0.02	5.6±0.01
3	4.4±0.04	7.0±0.02	5.9±0.02
4	3.1±0.05	4.4±0.03	5.5±0.02
5	4.0±0.02	6.0±0.01	5.5±0.04
M±m	3.9±0.02	5.58±0.01	5.66±0.03
The experimental group			
1	4.8±0.02	4.7±0.01	4.3±0.02
2	5.6±0.01	5.2±0.01	4.9±0.02
3	5.8±0.03	4.6±0.02*	5.4±0.03
4	5.2±0.02	3.8±0.03*	5.4±0.04*
5	5.8±0.02	5.2±0.05	4.6±0.02*
M±m	5.96±0.03	4.7±0.06*	4.92±0.04

Note: * - significant comparative differences ($p<0.05$)

We also conducted a targeted selective study for the P-2 preparation on body mass (Table 5.2.).

Table 5.2. Effect of P-2 preparation on body weight in rats

The control group			
No. Ord.	At the beginning of the experiment	In the middle of the experiment	At the end of the experiment (60 days)
1	321±0.39	324±0.12	327±0.45
2	231±0.35	239±0.24	241±0.36
3	270±0.15	304±0.25	313±0.25
4	251±0.24	279±0.13	299±0.21
5	342±0.31	359±0.28	359±0.23
M±m	389.4±0.25	395.8±0.26	398.8±0.16
The experimental group			
1	301±0.25	285±0.34	279±0.24
2	267±0.23	257±0.31	245±0.22
3	242±0.22	239±0.24	235±0.23
4	235±0.35	231±0.36	228±0.25
5	285±0.26	278±0.25	270±0.36
M±m	358.0±0.28	340.6±0.43	333.0±0.26

The effects of products P-1, P-2, P-3 on the hematological indices (Table 5.3.) in the experimental and control groups were also studied. The research showed that with all 3 products, the indices of erythrocytes, hemoglobin, ESR and leukocytes had a non-significant increasing trend ($p>0.05$). In the experimental group of preparation P-2, erythrocytes increased from 9.4 to 11.9±0.9 ($p<0.05$).

Table 5.3. Effects of P-1, P-2 and P-3 products on hematological indices in rats

Groups	Preparation	Erythrocytes million/μl	Content of hemoglobin g%	VSH mm/h	The number of leukocytes
Control group	1	9.2±0.4	10.5±0.2	2.5±0.3	9.3±0.4
Experimental group		9.3±0.7	11.8±0.8	2.3±0.7	9.4±0.8
Control group	2	9.2±0.7	10.4±0.8	2.5±0.4	9.3±0.5
Experimental group		9.4±0,	11.9±0.9	2.4±0.9	9.5±0.9
Control group	3	9.2±0.4	11.7±0.8	2.4±0.7	9.3±0.4
Experimental group		9.4±0.9	11.8±0.7	2.4±0.9	9.5±0.8

5.3. Clinical-biological study of products in subjects with increased metabolic risks

The clinical study of the elaborated products P-1, P-2 and P-3 included a wide range of selective indicators for each researched preparation. Hematological parameters (hemoglobin, erythrocytes, leukocytes, platelets (unsegmented and segmented), eosinophils, lymphocytes were studied at different stages of the research (at the beginning of administration of the preparation P1, P2 and P3, at the end of administration, relative to the experimental group and the control group) [10, 31, 41, 48, 56].

Biochemical parameters (ALT, AST, FA, GGTP, total bilirubin, unconjugated bilirubin,

albumin, urea, creatinine, total protein, cholesterol, β-lipoproteins, triglycerides, α-fetoproteins) were studied for each preparation and at the two stages of research – at the beginning and at the end of the administration of the preparation, both in the control group and in the research group.

Immunological indicators (IgM, IgG, IgA), T-lymphocytes, T-helpers, cytotoxic lymphocytes, $CD3^+$, CD8, immunoregulatory index ($CD3^+$, $CD4^+$, $CD3^+$, CD8), Interleukins were also investigated. The research also included lipid peroxidation research (ceruloplasmin, catalase, glutathione peroxidase, superoxide dismutase, Mg, K, Zn, Cu, malonic dialdehyde, hydroperoxides, HPLM isopr, HPLT isopr, HPLI hexane, HPLM hexane, HPLT hexane, total antioxidant activity, which fully characterized the body's metabolism on the background of P-1 administration.

In Table 5.4. the biological effects and dynamics of some parameters of metabolism in the dynamic research group are presented - until the start of administration of the preparation and at the end of its administration.

Table 5.4. Biological effects of P-1 preparation on metabolism in subjects with increased metabolic risks

Parameter	The investigated group	
	Until the start of administration of the preparation	End of administration of the preparation
Hematological parameters		
Hemoglobin, g/l	111±0.68	117.1±1.29*
Erythrocytes, $*10^{12}$	3.81±0.06	3.87±0.15
Leukocytes, $*10^{9}$	3.9±0.21	4.8±1.04
Platelets, $*10^{3}$/mL	181±0.0002	182±0.0003*
Unsegmented neutrophils, $*10^9$/l	0.04 (2%)	0.08 (3%)
Segmented neutrophils, $*10^9$/l	2018 (46%)	5180 (57%)*
Eosinophils, %	0.6	2.3*
Lymphocytes, $*10^{9}$/mL	1250 (21%)	2880 (29%)*
Biochemical parameters		
ALT, u/L	66±11.8	52.3±4.3*
AST, u/L	69±9.4	53.6±5.3*
FA, u/L	29.5±1.7	34.5±1.6*
GGTP, u/L	22.17±1.5	19.1±2.4*
Total bilirubin, mM/L	21.81±3.3	17.6±2.3*
Unconjugated bilirubin, mM/L	12.9±0.7	12.4±0.3
Albumin, g/L	34.3±2.1	36.8 ±3.4
Urea, mM/L	8.7±0.4	7.6±0.3*
Creatinine, mM/L	126±2.9	116±2.4*
Total protein, g/L	72.33±1.6	75.4±8.9*
α-fetoprotein, u/ml	4.83±0.2	7.4±0.2*
Immunological parameters		
IgM, mg/dL	1.08±0.03	0.81±0.007*
IgG	6.24±0.68	7.9±0.6*

IgA	0.94±0.13	1.8±0.2*
T-lymphocytes ($CD3^+$)	68.54±0.69	72.65±1.34
T-helpers ($CD3^+$, $CD4^+$)	0.4±0.03(38%)	0.83±0.03(31%)*
Cytotoxic lymphocytes ($CD3^+$, CD8)	0.3±0.03	0.6±0.03*
Immunoregulatory index ($CD3^+$, $CD4^+/CD3^+$, CD8)	1.5±0.04	2.4±0.13*
Interleukins (IL) IL 1, pg/Ml[5] IL 6, pg/Ml[4] IL 8, pg/Ml[1] IL 10, pg/Ml[1]	 5.1±0.2 9.6±0.3 16±0.2 9.4±0.2	 5.3±0.2 9.8±0.3 17.06±0.4 9.38±0.2

Note: * - significant comparative differences ($p<0.05$)

A positive dynamic of the P-1 preparation on the body and some parameters studied - hematological, biochemical, immunological and lipid peroxidation system was demonstrated.

Both hemoglobin, erythrocytes, leukocytes, platelets, neutrophils had an increasing trend, and segmental neutrophils, eusinophils and lymphocytes had a dynamic with significance $p<0.05$. Unsegmented neutrophils increased from 2 to 3%, segmented neutrophils from 46% to 57%, and eosinophils from 21% to 29%. ALT, AST, FA, GGTP, total bilirubin, albumin, urea, creatinine, total protein had a trend with veridical significance ($p<0.05$).

Immunological parameters significantly increased IgM from 1.08±0.03 to 0.81±0.007; Ig G from 6.24±0.68 to 7.9±0.06; Ig A from 0.94±0.13 to 1.8±0.02; T lymphocytes (CD3+) from 68.54±0.69 to 72.65±1.34; T helper (CD3+CD4+) from 0.4±0.03 (38%) to 0.83±0.83 (31%), Cytotoxic lymphocytes (CD3+CD8) from 0.3±0.03 to 0.6±0.03; the immunoregulation index – 1.5±0.04 to 2.4±0.13. This trend can also be seen with interleukins ($p<0.05$).

The study of the biological effects of the P2 preparation on metabolism is presented in table 5.5.

Table 5.5. Biological effects of P-2 preparation on metabolism in subjects with increased metabolic risks

Parameter	The investigated group	
	Until the start of administration of the preparation	End of administration of the preparation
Hematological parameters		
Hemoglobin, g/l	109±0.82	118.1±1.29*
Erythrocytes, $*10^{12}$	3.81±0.09	3.9±0.18*
Leukocytes, $*10^9$	3.9±0.21	4.8±1.13*
Platelets, $*10^3$/mL	182±0.0002	184±0.0008*
Unsegmented neutrophils, $*10^9$/l	0.043 (2%)	0.09 (3%)*
Segmented neutrophils, $*10^9$/l	2009 (48%)	5159 (57%)*
Eosinophils, $*10^3$/mL	0.9%	2.3%*

Lymphocytes, *10^9/mL	1219 (21%)	2878 (30%)*
Biochemical parameters		
ALT, u/L	69±10.9	52.6±4.7*
AST, u/L	69±9.8	54.3±6.8*
FA, u/L	38.4±1.9	33.4±1.3*
GGTP, u/L	22.19±1.8	17.2±2.9*
Total bilirubin, mM/L	22.84±3.9	18.9±2.8*
Unconjugated bilirubin	12.9±0.87	12.5±0.3
Albumin, g/L	35.8±1.9	37.9 ±2.8
Urea, mM/L	8.7±0.6	7.4±0.8*
Creatinine, mM/L	128±2.3	117±2.2*
Total protein, g/L	68.3±2.1	76.2±2.2*
α-fetoprotein, u/ml	4.87±0.2	7.4±0.2*
Immunological parameters		
IgM, mg/dL	1.01±0.03	0.84±0.003*
IgG	6.31±0.94	7.7±0.6*
IgA	0.91±0.16	1.7±0.2*
T-lymphocytes ($CD3^+$)	68.46±0.72	72.84±1.24*
T-helpers ($CD3^+$, $CD4^+$)	0.4±0.04(37%)	0.89±0.08(32%)*
Cytotoxic lymphocytes ($CB3^+$, CD8)	0.4±0.01	0.6±0.01*
Immunoregulatory index ($CD3^+$, $CD4^+/CD3^+$, CD8)	1.6±0.03	2.4±0.14*
Interleukins (IL) IL 1, pg/Ml[5] IL 6, pg/Ml[4] IL 8, pg/Ml[1] IL 10, pg/Ml[1]	 5.1±0.3 9.6±0.4 16±0.5 9.2±0.3	 5.3±0.2 9.8±0.4 17.09±0.2 9.89±0.2

Note: * - significant comparative differences ($p<0.05$)

Hematological, biochemical and immunological parameters were studied. The research demonstrated that the P-2 preparation had a beneficial effect on the metabolism, including the indices of hemoglobin, erythrocytes, leukocytes, platelets, neutrophils, eosinophils with significance ($p<0.05$). The most truthful action was demonstrated on the increase of lymphocytes from 21% to 30% ($p<0.05$). Some biochemical indices had a tendency to improve liver function. The indices of ALT, AST, FA, GGTP, bilirubin decreased on average by 1.8 ($p<0.05$). Other indicators, albumin, total protein increased by 0.8 ($p<0.05$). Immunoglobulins had a different dynamic: IgM decreased from 1.01±0.3 to 0.84±0.003 ($p>0.05$), IgG and IgA had a tendency to increase non-eloquently ($p>0$, 05), T-lymphocytes, T-helpers, lymphocytes, Immunoregulatory Index increased veridically ($p<0.05$). Interleukins had an insignificant dynamic ($p>0.05$).

The research results of the biological effects of the P3 preparation on metabolism are presented in Table 5.6. According to the study methodology, hematological, biochemical and immunological parameters were investigated. Hematological indices – hemoglobin, erythrocytes, leukocytes, platelets, neutrophils, eosinophils, lymphocytes had a significant increase ($p<0.05$). Likewise, leukocytes increased from 3.8±0.19 to 4.9±1.19; neutrophils from 47% to 56%;

eosinophils from 0.7% to 2.2% and lymphocytes from 20% to 29%. Biochemical indicators of metabolism had positive dynamics. The indices of ALT, AST, FA, GGTP, total bilirubin, urea had a significant decrease ($p<0.05$), while albumin, total protein, α-fetoproteins increased significantly ($p<0.05$).

Table 5.6. Biological effects of P-3 preparation on metabolism in subjects with increased metabolic risks

Parameter	The investigated group	
	Until the start of administration of the preparation	End of administration of the preparation
Hematological parameters		
Hemoglobin, g/l	111±0.82	119.0±1.39*
Erythrocytes, $*10^{12}$	3.91±0.08	4.2±0.16*
Leukocytes, $*10^{9}$	3.8±0.19	4.9±1.19*
Platelets, $*10^{3}$/mL	181±0.0007	184±0.0008*
Unsegmented neutrophils, $*10^{9}$/l	0.040 (2%)	0.09 (3%)*
Segmented neutrophils, $*10^{9}$/l	2000 (47%)	5150 (56%)*
Eosinophils, $*10^{3}$/mL	0.7%	2.2%*
Lymphocytes, $*10^{9}$/mL	1200 (20%)	2800 (29%)*
Biochemical parameters		
ALT, u/L	68±11.4	51.2±3.9*
AST, u/L	69±9.9	54.6±6.1*
FA, u/L	31.8±1.9	30.9±1.1**
GGTP, u/L	21.24±1.9	19.1±3.8*
Total bilirubin, mM/L	22.19±1.8	19.7±3.6
Unconjugated bilirubin, mM/L	13.1±0.7	11.0±0.4*
Albumin, g/L	32.3±2.1	36.2 ±3.1*
Urea, mM/L	9.3±0.4	7.2±0.1*
Creatinine, mM/L	129±2.9	112±3.4*
Total protein, g/L	69.3±1.1	73.8±2.9*
α-fetoprotein, u/ml	5.73±0.2	7.9±0.4*
Immunological parameters		
IgM, mg/dL	1.06±0.05	0.91±0.009*
IgG	6.18±0.78	7.9±0.6*
IgA	0.94±0.19	1.8±0.4*
T-lymphocytes ($CD3^+$)	68.54±0.71	72.89±1.61*
T-helpers ($CD3^+$,$CD4^+$)	0.5±0.01(37%)	0.91±0.09(33%)*
Cytotoxic lymphocytes ($CB3^+$, CD8)	0.3±0.06	0.5±0.09*
Immunoregulatory index ($CD3^+$, $CD4^+/CD3^+$, CD8)	1.6±0.04	2.4±0.19*
Interleukins (IL) IL 1, pg/Ml^5 IL 6, pg/Ml^4 IL 8, pg/Ml^1 IL 10, pg/Ml^1	 5.1±0.2 9.6±0.4 15±0.6 9.2±0.2	 5.3±0.9 9.9±0.8 18.02±0.3* 9.81±0.4*

Note: * - significant comparative differences ($p<0.05$)

5.3.1. Biological effects of P-1, P-2, and P-3 products on protein metabolism (free amino acids) in subjects with increased metabolic risks

The effects of the three patented products on blood amino acids in research subjects were studied. 100 subjects with increased metabolic risks (HT, DM type II and obesity) were included. All three products had a direct metabolic-protective action (Figure 5.1 and 5.2.).

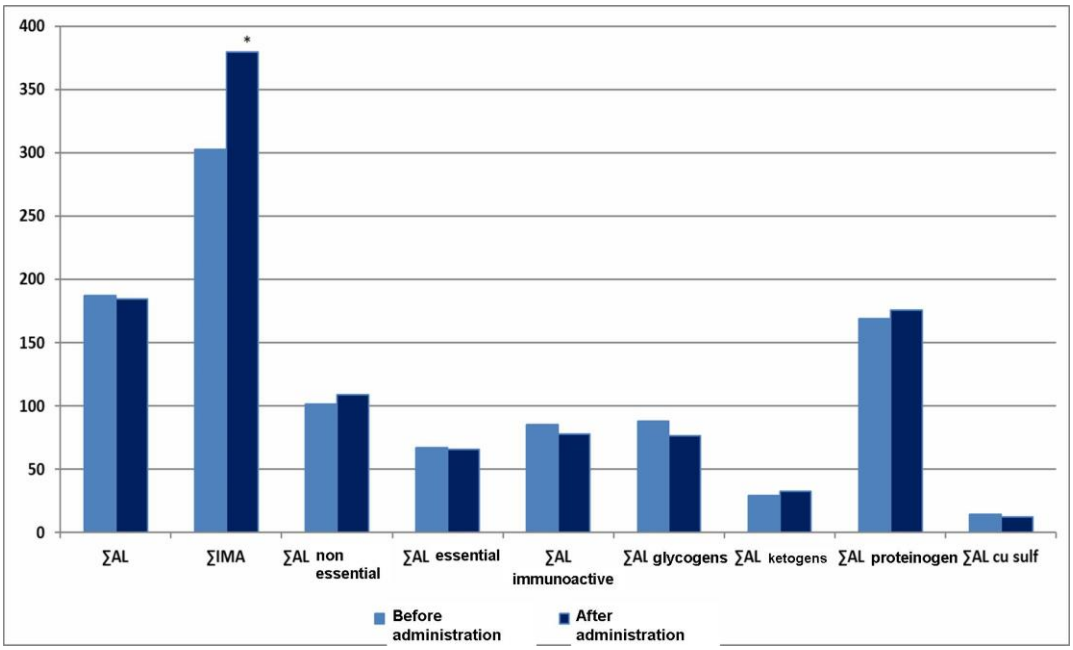

Figure 5.1. The content of free amino acids and end products of nitrogen metabolism in plasma (µmol/100 ml) after administration of the P-1 preparation in subjects with increased metabolic risks (* - significant comparative differences (p<0.05))

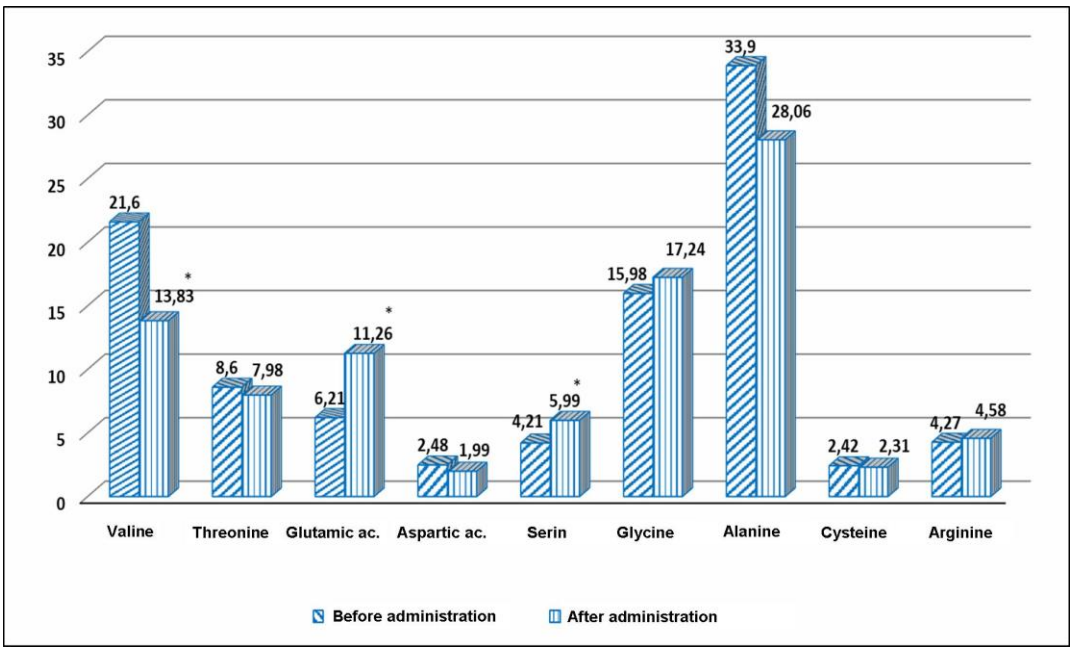

Figure 5.2. The content of immunoactive amino acids in plasma (µmol/100 ml) after administration of the preparation P-1 in subjects with increased metabolic risks (* - significant comparative differences (p<0.05))

In Figure 5.3. and 5.4. the dynamics of the amino acid indices of the preparation P-2 (Patent no. 1499) are presented [47].

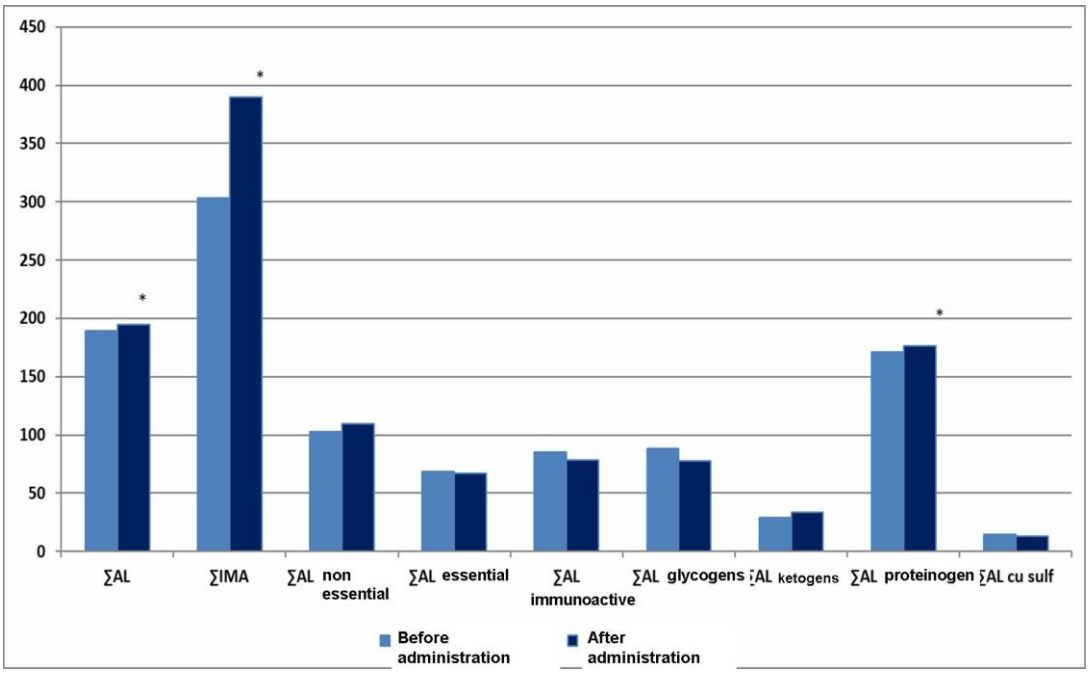

Figure 5.3. The content of free amino acids and end products of nitrogen metabolism in plasma (µmol/100 ml) after administration of the P-2 preparation in subjects with increased metabolic risks (* - significant comparative differences (p<0.05))

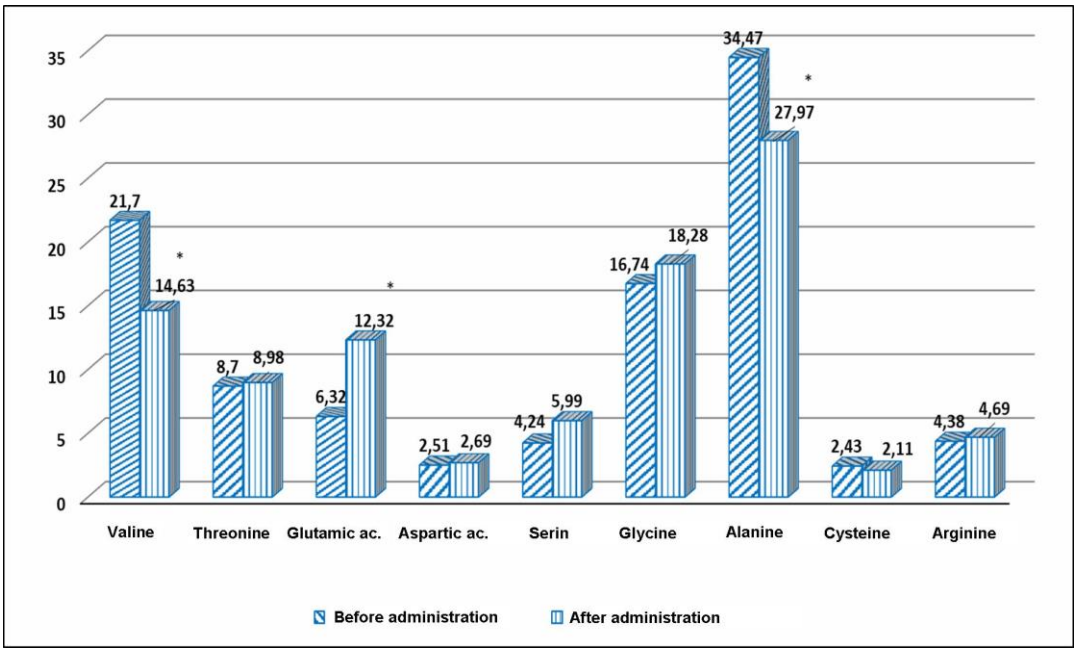

Figure 5.4. The content of immunoactive amino acids in plasma (µmol/100 ml) after administration of the preparation P-2 in subjects with increased metabolic risks (* - significant comparative differences (p<0.05))

In Figure 5.5. and 5.6. the dynamics of the amino acid indices of the preparation P-3 (Patent no. 1500) are presented

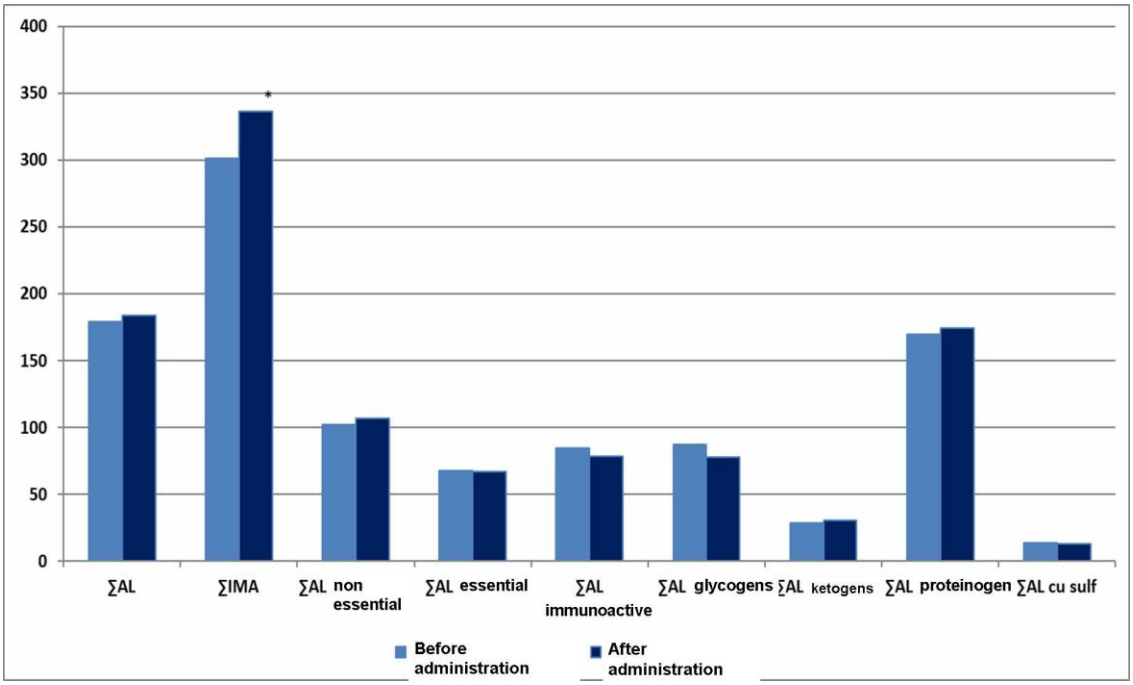

Figure 5.5. The content of free amino acids and end products of nitrogen metabolism in plasma (µmol/100 ml) after administration of the P-3 preparation in subjects with increased metabolic risks (* - significant comparative differences (p<0.05))

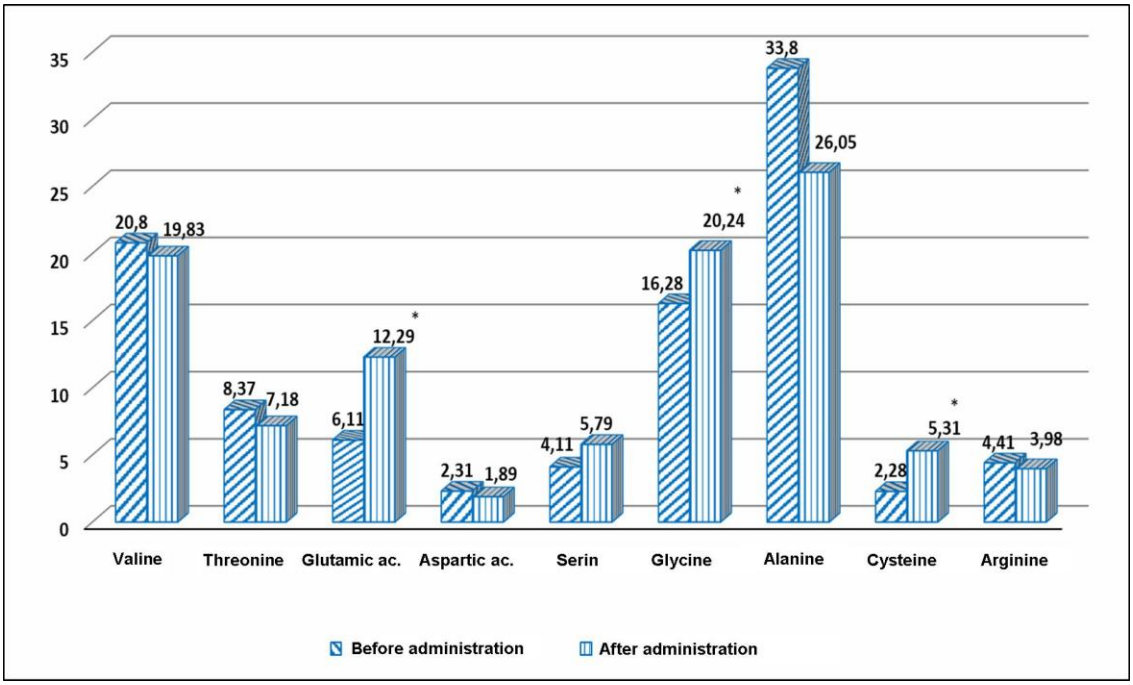

Figure 5.6. The content of immunoactive amino acids in plasma (µmol/100 ml) after administration of the preparation P-3 in subjects with increased metabolic risks (* - significant comparative differences (p<0.05))

5.3.2. Biological effects of P-1, P-2 and P-3 products on lipid metabolism in subjects with increased metabolic risks

The preparation P-1 has a pronounced effect of normalizing lipid metabolism by reducing the level of triglycerides and decreasing total lipids associated with the intensity of metabolic processes (Table 5.7.). Some biochemical parameters had an insignificant change ($p>0.05$), cholesterol, α-fetoproteins had a veridical trend and significance ($p<0.05$). The lipid peroxidation system - ceruloplasmin, catalase, glutathione peroxidase, superoxide dismutase had significant changes ($p<0.05$). The improvement of Mg, K, Zn, Cu and other indices was also observed insignificantly ($p>0.05$). Total antioxidant activity increased from 1.33±0.17 to 1.56±1.08 ($p<0.05$) [6, 17, 58, 67, 70, 74, 80].

Table 5.7. Biological effects of P-1 product on lipid metabolism in subjects with increased metabolic risks

Parameter	The investigated group	
	Until the start of administration of the preparation	End of administration of the preparation
Cholesterol, mM/L	4.49±0.11	3.9±0.12*
β-lipoprotein, mmol/l	3.59±0.3	3.6±0.2
Triglycerides, mM/L	0.47±0.04	0.39±0.06*
Lipid peroxidation system		
Ceruloplasmin, mg/dL	243.00±17.00	335±12.8*
Catalase, mM/L	10.70±1.200	13.80±1.09*
Glutathione peroxidase, mM/L	6.60±0.60	7.90±0.40*
Superoxidismutase, uc/l	1096.00±22.8	1209.00±29.10*
Mg, mM/L	0.79±0.002	0.81±0.007*
K, mM/L	4.25±0.50	4.40±0.30*
Zn, mM/L	29.70±0.89	30.20±0.37*
Cu, mM/L	17.24±0.33	18.20±0.26*
Malonic Dialdehyde, mM/L	39.60±1.27	37.10±1.04
Lipid hydroperoxides I isopr, uc/ml	378.40±1.16	381.20±0.97*
HPL-M isopr	443.80±1.14	446.80±1.14
HPL-T isopr	442.09±1.32	443.10±1.29
HPL-I hexane	71.10±1.15	72.30±1.42
HPL-M hexane	72.40±0.12	75.10±0.18*
HPL-T hexane	72.30±0.18	74.20±0.32*
Total antioxidant activity isopr, mM/L	1.33±0.17	1.56±1.08

Note: * - significant comparative differences ($p<0.05$)

Research has shown that the P-2 preparation had a beneficial effect on lipid metabolism. Cholesterol, β-lipoprotein and triglyceride indices decreased, but insignificantly ($p>0.05$) (Table 5.8.). Lipid peroxidation system – ceruloplasmin increased from 245±2.1 to 338±12.9, catalase from 10.9±1.4 to 13.6±1.09, glutathione peroxidase from 6.6±0 .4 to 7.9±0.6; superoxide dismutase from 1098±21.9 to 1212±29.2 ($p<0.05$) [55]. Mg, K, Zn, Cu, malonic dialdehyde

increased significantly ($p<0.05$). Total antioxidant activity increased from 1.38±0.16 to 1.57±0.21 ($p<0.05$).

Table 5.8. Biological effects of P-2 preparation on lipid metabolism in subjects with increased metabolic risks

Parameter	The investigated group	
	Until the start of administration of the preparation	End of administration of the preparation
Cholesterol, mM/L	4.86±0.12	3.7±0.16*
β-lipoprotein, mmol/l	3.87±0.30	3.7±0.80
Triglycerides, mM/L	0.37±0.04	0.39±0.08
Lipid peroxidation system		
Ceruloplasmin, mg/dL	249.00±2.10	338.00±12.90*
Catalase, mM/L	10.9±1.40	13.60±1.09*
Glutathione peroxidase, mM/L	6.6±0.40	7.90±0.60*
Superoxidismutase, uc/l	1098±21.90	1212±29.20*
Mg, mM/L	0.74±0.002	0.81±0.003*
K, mM/L	4.14±0.40	4.20±0.20
Zn, mM/L	29.7±0.81	30.90±0.27*
Cu, mM/L	17.24±0.32	18.40±0.19*
Malonic dialdehyde, mM/L	39.80±1.21	38.30±1.09
Lipidic hydroperoxides isopr, uc/ml	378.80±1.11	382.30±0.98*
HPL-M isopr	443.80±1.14	446.40±1.16*
HPL-T isopr	444.01±1.30	446.09±1.11*
HPL-I hexane	71.30±1.12	72.40±1.49
HPL-M hexane	72.90±0.12	76.10±0.26*
HPL-T hexane	72.40±0.18	74.30±0.28*
Total antioxidant activity isopr, mM/L	1.38±0.16	1.57±1.21*

Note: * - significant comparative differences ($p<0.05$)

The results of research on the biological effects of the P-3 preparation on metabolism are presented in Table 5.9. Biochemical indicators of metabolism had a positive dynamic. Cholesterol indices, β-lipoproteins had a significant decrease ($p<0.05$). And the lipid peroxidation system had a beneficial activity. It significantly increased the activity of enzymes - ceruloplasmin, catalase, glutathione peroxidase, superoxide dismutase. K, Mg, Zn, Cu had insignificant changes ($p>0.05$). Total antioxidant activity increased from 1.34±0.19 to 1.58±1.11 ($p<0.05$).

Table 5.9. Biological effects of P-3 preparation on lipid metabolism in subjects with increased metabolic risks

Parameter	The investigated group	
	Until the start of administration of the preparation	End of administration of the preparation
Cholesterol, mM/L	4.97±0.18	3.60±0.14*
β-lipoprotein, mmol/l	3.59±0.40	3.70±0.40*
Triglycerides, mM/L	0.39±0.07	0.40±0.11

Lipid peroxidation system		
Ceruloplasmin, mg/dL	246.00±18.00	339.00±11.8*
Catalase, mM/L	11.70±1.1	13.70±1.09
Glutathione peroxidase, mM/L	6.70±0.40	7.90±0.60
Superoxidismutase, uc/l	1098.00±22.70	1212.00±28.90*
Mg, mM/L	0.79±0.004	0.81±0.007
K, mM/L	4.20±0.5	4.30±0.30
Zn, mM/L	29.50±0.87	30.20±0.39
Cu, mM/L	17.23±0.21	18.20±0.27*
Malonic dialdehyde, mM/L	39.40±1.26	36.20±1.13*
Lipid hydroperoxides I isopr, uc/ml	379.60±1.16	380.40±0.96
HPL-M isopr	443.80±1.17	446.90±1.07*
HPL-T isopr	441.08±1.29	444.08±1.09*
HPL-I hexane	70.80±1.16	72.30±1.94
HPL-M hexane	72.70±0.19	74.90±0.18*
HPL-T hexane	72.80±0.19	73.90±0.39
Total antioxidant activity isopr, mM/L	1.34±0.19	1.58±1.11

Note: * - significant comparative differences ($p<0.05$)

5.3.3. Effects of P1, P2 and P3 products on carbohydrate metabolism in subjects with increased metabolic risks

The effects of P-1, P-2 and P-3 products on carbohydrate metabolism were studied (Table 5.10.)

Table 5.10. Dynamics of glycemic indices (mmol/l) as a result of administration of P-1, P-2 and P-3 products in subjects with increased metabolic risks

Preparation	Until administration	After administration
P-1	7.4±1.08	6.8±1.13
P-2	7.2±1.11	6.1±1.02
P-3	7.3±1.14	6.6±1.11

Research has shown that after taking P1, P2 and P3 products, blood sugar levels decreased. The effect of the product with hypoglycemic action was demonstrated by the product P-2, blood sugar decreased from 7.2±1.11 to 6.1±1.02 mmol/l ($p<0.05$).

5.4. Gut microbiota and its influence on the metabolic syndrome in subjects with increased metabolic risks

The hematological, biochemical, immunological parameters of the lipid peroxidation system, including the total antioxidant activity, were studied. At the same time, T/A, TAS, TAD and blood glucose indices were monitored, even after the administration of the products developed by us (Table 5.11 and 5.12.). Given the fact that metabolic disorders are associated pathologies from several nosological components, we conducted research on the synergistic effect of the products on the subjects' metabolism (n=100).

Table 5.11. Synergistic effect of P-1, P-2 and P-3 products on hematological, biochemical, immunological parameters and lipid peroxidation system in subjects with increased metabolic risks

Parameter	The investigated group	
	Until the start of administration of the preparation	End of administration of the preparation
Hematological parameters		
Hemoglobin, g/l	112.00±1.08	120.70±1.72*
Erythrocytes, $*10^{12}$	3.87±0.09	4.30±0.24
Leukocyte, $*10^{9}$	3.70±0.29	4.90±1.29
Platelets, $*10^{3}$ /mL	181.00±0.0005	186.00±0.0009*
Unsegmented neutrophils, $*10^{9}$/l	0.04 (2.1%)	0.09 (3%)*
Segmented neutrophils, $*10^{9}$/l	2000 (47%)	5184 (57%)*
Eosinophils, $*10^{3}$/mL	0.7%	2.3%*
Lymphocytes, $*10^{9}$/mL	1280 (21%)	2897 (30%)*
Biochemical parameters		
ALT, u/L	69.00±2.40	50.10±1.80*
AST, u/L	71.00±8.70	53.70±3.90*
FA, u/L	31.90	30.10*
GGTP, u/L	21.14±1.40	18.20±2.60
Total bilirubin, mM/L	23.90±2.20	18.60±4.10
Unconjugated bilirubin	13.10±0.50	10.10±0.70*
Albumin, g/L	32.80±2.40	38.40±2.90*
Urea, mM/L	9.70±0.30	7.40±0.10*
Creatinine, mM/L	127.00±2.90	111.00±1.80*
Total protein, g/L	68.40±3.10	74.90±1.80
Cholesterol, mM/L	4.51±0.12	3.90±0.11
β-lipoprotein, mmol/l	3.51±0.20	3.50±0.10
Triglycerides, mM/L	0.45±0.04	0.39±0.03
α-fetoprotein, u/ml	4.81±0.30	5.30±0.40
Immunological parameters		
IgM, mg/dL	1.09±0.02	1.09±0.008
IgG	6.28±0.71	7.90±0.80
IgA	0.91±0.14	1.90±0.40*
T-lymphocytes ($CD3^+$)	68.59±0.78	73.71±1.54*
T-helpers ($CD3^+$, $CD4^+$)	0.40±0.03 (38%)	0.91±0.04 (49%)*
Cytotoxic lymphocytes ($CB3^+$, CD8)	0.30±0.02	0.60±0.04**
Immunoregulatory index ($CD3^+$, $CD4^+/CD3^+$, CD8)	1.50±0.06	2.50±0.15
Interleukins (IL) IL 1, pg/Ml[5] IL 6, pg/Ml[4] IL 8, pg/Ml[1] IL 10, pg/Ml[1]	 5.10±0.2 9.60±0.30 17.00±0.200 9.30±0.10	 5.40±0.20 9.80±0.40 17.10±0.30 9.39±0.30
Lipid peroxidation system		
Ceruloplasmin, mg/dL	243.00±17.00	336.00±11.90*
Catalase, mM/L	10.70±1.20	13.90±0.10*
Glutathione peroxidase, mM/L	6.60±0.70	7.90±0.30

Superoxidismutase, uc/l	1097.00±21.60	1209.00±29.7*
Mg, mM/L	0.79±0.001	0.84±0.008
K, mM/L	4.26±0.40	4.40±0.60
Zn, mM/L	29.80±0.87	29.80±0.71
Cu, mM/L	17.26±0.38	17.28±0.41
Malonic dialdehyde, mM/L	39.90±1.20	39.80±1.34
Lipid hydroperoxides I isopr, uc/ml	378.70±1.11	378.80±1.41
HPL-M isopr	444.70±1.11	445.80±1.09
HPL-T isopr	444.02±1.29	449.70±1.12*
HPL-I hexane	71.60±1.11	72.60±1.18
HPL-M hexane	72.90±0.12	72.80±0.31
HPL-T hexane	72.60±0.19	72.80±0.42
Total antioxidant activity isopr, mM/L	1.39±0.18	1.39±0.21

Note: * - significant comparative differences (p<0.05)

Table 5.12. Synergistic effect of P-1, P-2 and P-3 products on blood pressure and blood glucose in subjects with increased metabolic risks

Parameter	The investigated group (n=15)			
	Until the start of administration of the products		End of product administration	
	BPS	BPD	BPS	BPD
Blood pressure, mm Hg	158.20±1.10	94.3±0.70	147.50±1.09*	91.10±0.60*
Glucose, mmol/l	7.90±1.30		6.70±0.80	

Note: * - significant comparative differences (p<0.05)

At the same time, free amino acid indices were studied, including the immunoactive ones (Figure 5.7. and 5.8.)

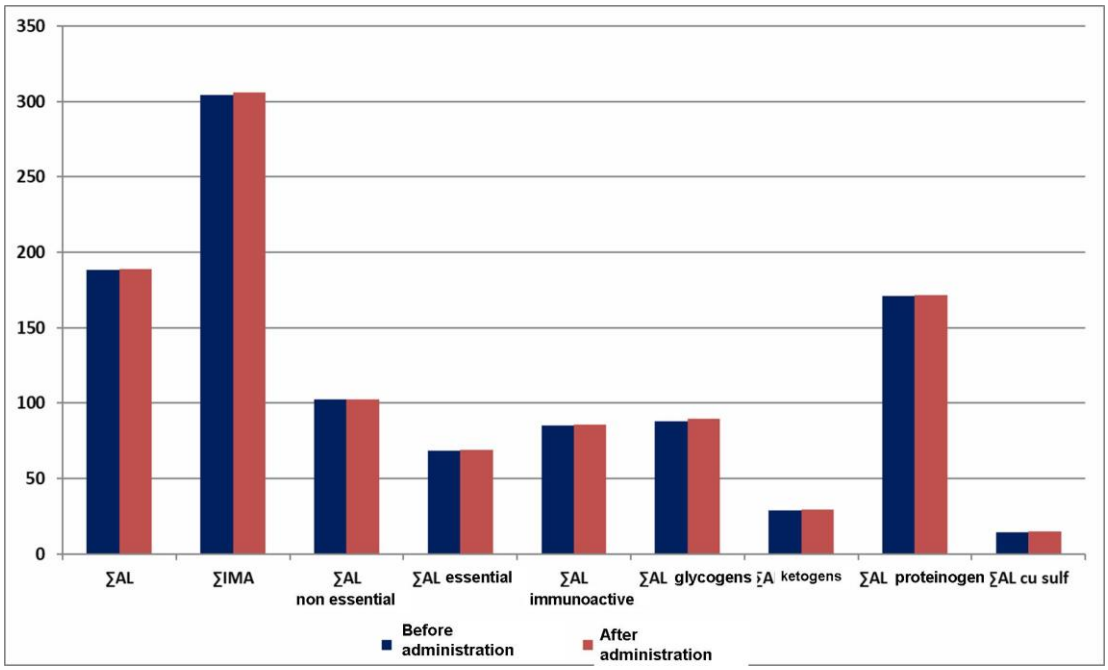

Figure 5.7. The synergistic effect of P-1, P-2 and P-3 products on the content of free amino acids and end products of nitrogen metabolism in plasma (µmol/100 ml) in subjects with increased metabolic risks (* - significant comparative differences (p<0 ,05))

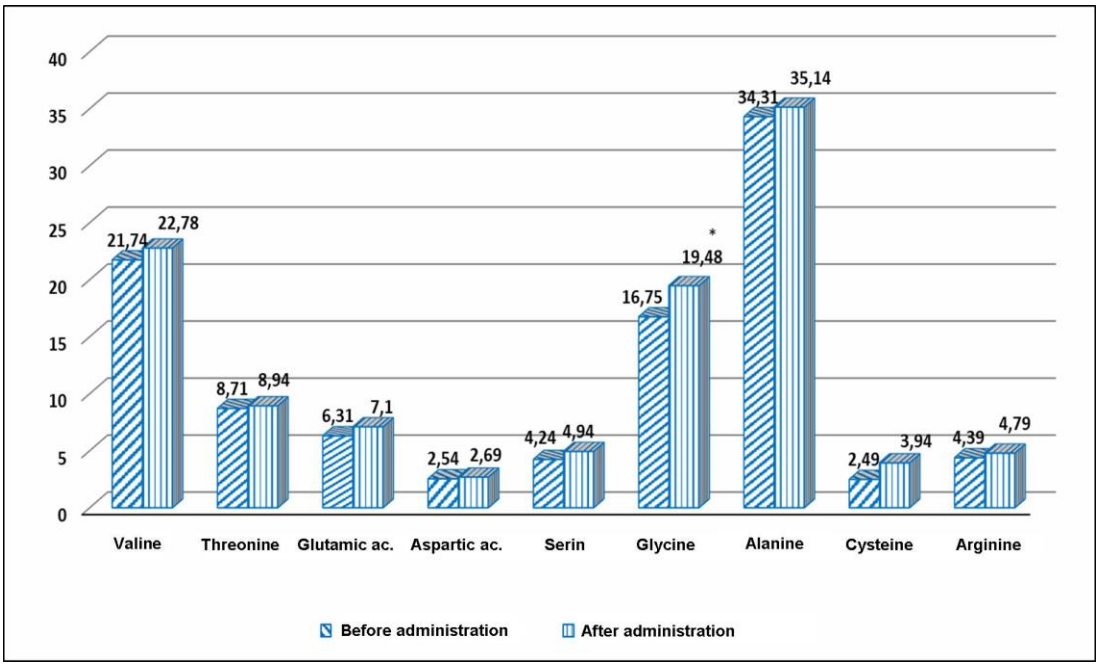

Figure 5.8. Synergistic effect of P-1, P-2 and P-3 products on the dynamics of immunoactive amino acids in subjects with increased metabolic risks (* - significant comparative differences ($p<0.05$))

5.4.1. Methods of preclinical diagnosis of metabolic disorders in subjects with increased metabolic risks

The metabolic syndrome is an integrative notion, which encompasses several pathologies and major risks with an ever-increasing incidence and prevalence and which substantially determines the state of health. It is accompanied in its evolution by changes in the intestinal microbiota and the functionality of the neuro-humoral and immune systems. Without underestimating the role of genetic and epigenetic (environmental) factors, the intestinal biota is a defining factor in the establishment and progression of non-communicable pandemic metabolic diseases (obesity, type II diabetes and hypertension, etc.).

The microbiotic phenomenon is a relatively new, interdisciplinary problem, which is the subject of an increasingly in-depth study, given its importance in the occurrence of psychosomatic diseases with increased incidence and which largely determines population morbidity and mortality globally. The increased interest of researchers in different fields of biomedicine is demonstrated by the appearance in the last 2-3 decades of the impact publications Scopus and Pubmed. In 1997, 51 articles with the generic "microbiota" were published, in 2007 - 389, and in 2017, 5851 were already published [34, 37, 38, 39, 49].

More and more research tends to approach this phenomenon as a symbiotic factor of somatic-psychic partnership in maintaining metabolic homeostasis and health in general. The

perspectives of studying the microbiota presuppose new approaches and visions in the strategy of prevention and therapies of somatic and somato-psychic disorders.

It is very important that many of the discoveries in the field are made in the preclinical (premorbid) period [62].

18 subjects with metabolic disorders (HT, DM type II, obesity) and 22 subjects in the post-COVID-19 period were examined for the microorganism index compartment Bifidobacterium bifidum, Lactobacillus acidophilus, Escherichia coli and Enterococci. The indices are compared with those determined scientifically, physiologically by the scientists B.A. Senderov et al., 1996 (Table 5.13.).

Table 5.13. Indices of microorganisms in investigated subjects

Species of microorganisms	*Healthy subjects		[1]Subjects with MS	[2]Subjects in the post-COVID-19 period	P
	25≥70	>70			
Bifidobacterium bifidum	10^9-10^{10}	10^9-10^{10}	10^7-10^8	10^8-10^9	<0,05
Lactobacillus acidophilus	10^7-10^9	10^7-10^8	10^6-10^8	10^7-10^8	<0,05
Escherichia coli	10^7-10^8	10^8-10^9	10^9-10^{10}	10^9-10^{10}	<0,05
Enterococci	10^6-10^7	10^7-10^9	10^8-10^{10}	10^8-10^{10}	<0,05

*- Indices of healthy subjects (B.A. Senderov, 1996)
1 – Subjects with MS (N=18, - patients with hypertension, type II diabetes, obesity)
2 – Subjects in the post-COVID-19 period (N=22)

The quantitative level of intestinal bacteriocenosis had a tendency to increase *Escherichia coli* both in subjects with MS - from 109-1010 (N- 107-108) and in those with COVID-19 - 109-1010 (N- 107- 108). *Bifidobacterium bifidum* indices tended to decrease in subjects with MS - 107-108 (N- 109-1010), and 108-109 (N- 109-1010) in subjects in the post-COVID-19 period.

The downward trend was also observed in *Lactobacillus acidophilus* – to 106-108 (N-107-109) for MS subjects and 107-108 in post-COVID-19 syndrome subjects.

It is opportune to continue research in order to determine the development of selective prebiotics for metabolic disorders and post-COVID-19 syndrome. The preclinical diagnosis methods of MS must be implemented in the practice of family doctors, which can lead to the determination of the state of health, but also its fortification [43, 49, 58, 72, 77].

Table 5.14. Microorganism indices in investigated subjects with diabetes mellitus (DM)

Species of microorganisms	Healthy subjects (25≥70 years)	Subjects with type II diabetes	P
Bifidobacterium bifidum	10^9-10^{10}	10^7-10^8	<0,05
Lactobacillus acidophilus	10^7-10^9	10^5-10^6	<0,05
Escherichia coli	10^7-10^8	10^8-10^9	<0,05
Enterococci	10^6-10^7	10^6-10^7	<0,05

Table 5.15. Microorganism indices in investigated subjects with hypertension

Species of microorganisms	Healthy subjects (25≥70 years)	Subjects with hypertension	P
Bifidobacterium bifidum	10^9-10^{10}	10^8-10^9	<0,05
Lactobacillus acidophilus	10^7-10^9	10^7-10^9	<0,05
Escherichia coli	10^7-10^8	10^7-10^8	<0,05
Enterococci	10^6-10^7	10^6-10^7	<0,05

Table 5.16. Microbial indices in obese investigated subjects

Species of microorganisms	Healthy subjects (25≥70 years)	Obese subjects	P
Bifidobacterium bifidum	10^9-10^{10}	10^7-10^8	<0,05
Lactobacillus acidophilus	10^7-10^9	10^6-10^7	<0,05
Escherichia coli	10^7-10^8	10^8-10^9	<0,05
Enterococci	10^6-10^7	10^6-10^7	<0,05

Table 5.17. Microorganism indices in research subjects with metabolic syndrome

Species of microorganisms	Healthy subjects (25≥70 years)	Subjects with metabolic syndrome	P
Bifidobacterium bifidum	10^8-10^{10}	10^6-10^7	<0,05
Lactobacillus acidophilus	10^7-10^9	10^5-10^6	<0,05
Escherichia coli	10^7-10^8	10^8-10^9	<0,05
Enterococci	10^6-10^7	10^7-10^8	<0,05

5.4.2. Development of the P-4 preparation with symbiotic, regulatory, antioxidant and adaptogenic action

The invention refers to the food industry and health care, namely to a biologically active food supplement with antioxidant and adaptogenic activity. The formation of a stable and sustainable antioxidant potential of the body is one of the priority tasks of modern physiology and biomedicine, because it addresses health and longevity issues.

It is known that all chronic diseases are accompanied by metabolic disorders caused by the acidification of the body and the high concentration of free oxidizing radicals. As medical practice shows, solving this problem by means of food rations requires a long period of time and strict adherence to the diet, which does not always lead to positive results. This is a significant disadvantage of this approach.

The problem that the invention solves consists in widening the range of food supplements

with increased antioxidant activity, by obtaining a biologically active supplement that would act not only by inhibiting free radicals with their subsequent reduction, but that would also act at the level of their production , thus increasing the antioxidant effect, at the same time it would also possess an adaptogenic effect.

The essence of the invention consists in the fact that the biologically active food supplement with antioxidant and adaptogenic activity contains, in % mass: dry extract of Amaranth seeds, dry extract of Wormwood leaves, dry extract of Dihydroquercetin, dry extract of Walnut shells, extract dry Dandelion root, dry Griffonia seed extract, dry Watercress root extract, dry Rhodiola root extract, dry Basil grass extract, dry Sage leaf extract, dry Rosemary extract.

Rezultatul tehnic constă în obţinerea lărgirii unei game de suplimente alimentare cu activitate antioxidantă sporită, care are acţiune dublă – eficient inhibă radicalii liberi cu ulterioara lor reducere şi totodată mai eficient inhibă producerea acestora, la fel posedă și o activitate adaptogenă. Rezultatul tehnic se datorează selectării reuşite a raportului cantitativ şi calitativ al componentelor, care manifestă un sinergism şi produc un efect antioxidant mai pronunţat și totodată posedă un efect adaptogen [8].

The food supplement has the following advantages: it has a greater antioxidant effect compared to the closest solution, which can be seen in the table below, which has a double action - it effectively inhibits free radicals with their subsequent reduction and also more effectively inhibits their production; at the same time it also possesses adaptogenic qualities.

The influence of the supplement on the formation of the body's antioxidant potential was studied in experimental investigations, carried out on white rats, Wistar line, selected according to the principle of analogy, according to weight, age and sex. The experimental animals were divided into three groups: group 1 (control) received only basic balanced ration (RB) without food supplement; group 2 (control) received a similar ration (RB) + food supplement (SA) from the nearest solution; group 3 (experimental) received a similar ration (RB) + the biologically active food supplement (SA) according to the claimed invention.

The animals in groups 2 and 3 received the corresponding food supplements based on the calculation of 1g/10kg body weight. In animals from control groups 1 and 2 and experimental group 3, the content of oxidized glutathione and carnosine was determined in the blood, the obtained experimental data being included in Table 5.18.

Table 5.18. Antioxidant activity of P-4 supplementation in rats

Animal groups	The particularities of food	Indices of antioxidant activity	
		Oxidized glutathione, μmol/100mg	Carnitine, μmol/100mg
1 (control)	Basic Ration (BR)	37.08 ± 0.01	30.01±0.01
2 (control)	BR+SA according to the nearest solution	32.05 ± 0.01	35.70±0.01
3 (experimental)	BR+SA according to the claimed invention	24.02±0.01	45.06±0.01

Oxidized glutathione was taken as a criterion for evaluating the antioxidant potential.

The lower the level of oxidized glutathione, the higher the level of reduced glutathione and the higher the body's antioxidant potential, because it has a greater potential to neutralize free radicals. Thus, the lower the level of oxidized glutathione, the higher the antioxidant potential.

Glutathione has a special role in the body's antioxidant protection. The high detoxification potential of glutathione is determined by the content of sulfhydric groups (□SH), which absorb not only free radicals, but also metabolic toxins and heavy metals. Enzymes of the body's antioxidant system neutralize about 70% of oxidants and toxic substances. The increased content of carnosine in the animals of the experimental group, which were administered the claimed supplement, indicates that cell damage by free radicals is prevented, so the proposed supplement possesses antioxidant properties by inhibiting the production of free radicals.

The method of preparation of the biologically active food supplement with antioxidant effect is as follows: the components of the supplement are procured, weighed and taken in the following ratio, in mass %: dry extract of amaranth seeds 12, dry extract of wormwood leaves 10, dry extract of dihydroquercetin 8, walnut shell dry extract 9, dandelion root dry extract 7, griffonia seed dry extract 7, burdock root dry extract 11, rhodiola root dry extract 15, basil grass dry extract 10, dry extract of sage leaves 6, dry extract of rosemary 5, and mix well for 3-5 min, until a homogeneous mass is obtained. The homogeneous mass obtained is yellow to greenish in color with a bitter smell and taste, specific to the plants used, later it is conditioned and encapsulated in hard gelatinous forms of different sizes, starting with sizes 00; 0; 1. The supplement is packed in plastic bottles of 90 or 100 capsules, accompanied by the leaflet for use. Take 2 capsules 3 times a day, 15 minutes before meals.

The obtained experimental data demonstrate that the proposed dietary supplement increases the body's antioxidant and adaptive potential. The supplement can be recommended as a prophylactic remedy or it can be included in the composition of functional food products

predestined to increase the body's adaptive and antioxidant potential. The composition of the biologically active food supplement is accessible and inexpensive.

5.4.3. The biological effect of the P-4 preparation on the intestinal microbiota

This biologically active food supplement has a stimulating effect on the intestinal microbiota, minimizing metabolic risks with an immunostimulating effect.

Dysbacteriosis - is a condition in which the composition of the microorganisms that populate the intestine changes (useful bacteria become less and less, and harmful ones, respectively, more), which leads to the disruption of the activity of the gastrointestinal tube.

The human intestine is populated by huge colonies of microbes - "harmful", "beneficial" and "neutral". Beneficial microbes - *Bifidobacteria* and *Bacteroides* are saprophytic and beneficial. They stimulate digestion, are anti-allergic, maintain the immune system and even reduce the possibility of developing oncological diseases. But it also shows an antibiotic effect targeting: staphylococci, proteia, streptococci, fungi from the Candida family. Sometimes, under the influence of external factors, this balance is disturbed - the number of "useful" bacteria decreases, and harmful microbes begin to dominate the intestine - a condition called "dysbacteriosis" develops. Dysbacteriosis - it is not an independent disease, but a manifestation of other diseases in the body. This condition can accompany gastritis, pancreatitis and other diseases of the digestive organs, it can also be a consequence of an intestinal infection sustained, or it can develop following the long-term administration of antibiotics [15, 17, 18, 19, 77].

In the case of dysbacteriosis, harmful bacteria and fungi (for example, those from the Candida family) appear in the intestine, and the number of saprophytic microorganisms decreases, which sets up the dysregulation of digestion. Long-term dysbacteriosis is characterized by dysregulation of the absorption of vitamins, fats, other food components, which leads to weight loss and anemia. The basic components of the treatment are: compliance with the diet. Lactic acid products, enriched with live bifidobacteria, must be included in the diet. Antibiotics or bifidobacteria are prescribed in some cases to inhibit harmful bacteria in the gut; the special products, which normalize the composition of the intestinal microflora (bifi-form, bifidumbacterin, bificol, hilac, linex and others). The treatment, as a rule, allows the restoration of a normal digestion within two months.

The result of the claimed invention consists in obtaining the widening of the range of phytotherapeutic food supplements, biologically active, which activates the stimulation of the growth and development of the intestinal microflora during the post-COVID-19 rehabilitation

period and immunostimulatory effect at the same time, due to the successful selection of the quantitative and qualitative components and which shows a synergism.

The phytotherapeutic, biologically active food supplement has the following advantages: the claimed supplement in addition to the effect of stimulating the growth and development of the intestinal microflora (during the post-COVID-19 rehabilitation period) and immunostimulatory effect at the same time; it is simple in preparation technology; it does not require a prescription, as it is not a medicine; the treatment period for dysbacteriosis is reduced from 2 months in the environment to 21 days.

Clinical case: Patient "X", 56 years old, in the records of the family doctor for 12 years with the diagnosis of high blood pressure (HT), diabetes type II (DM type II), obesity gr. I, post-COVID-19 syndrome in 2020, over 10 months, was hospitalized in the IMSP medical institution, the Clinical Hospital of the Ministry of Health, in the gastroenterology department with the listed nosologies, in a state of undercompensation with a negative PCR test, vaccinated with both doses Sinopharm. The conclusion of the family doctor and the Medical Council is that the patient has been suffering from metabolic syndrome for about 15 years. On admission: blood pressure – 170/100 mmHg, blood sugar – 8.2 mmol/l, body weight – 105 kg, triglycerides – 0.49 mM/l, AST – 146 U/L, ALAT – 128 U/L, IgM – 1.09 mg/dl, IgG – 6.22 mg/dl, IgA – 0.81 mg/dl, T-lymphocytes (CD^+) - 66.89, T helpers ($CD3^+$, CD4) - 0.68. The microbial sample of the faecal masses was taken from the patient according to the usual microbiological method. It was determined that *Bifidobacterium lactis* and *Lactobacillus acidophiphilus* had low values compared to the physiological norm [method B.A. Senderov, 1996], - 10^7-10^8 (norm 10^9-10^{10}) and 10^6-10^8 (norm 10^7-10^8) CFU/ml respectively.

Escherichia coli and *Enterococci* had elevated values – 10^9-10^{10} (norm 10^7-10^8) and 10^8-10^{10} (norm 10^6-10^7) CFU/ml respectively.

The claimed biologically active food supplement (SABA), with the composition named above, was administered to the patient for 21 days complementary to the basic therapy of the nosologies diagnosed by the family doctor and confirmed by the Medical Council of the institution where he was hospitalized. After administration of SABA, the patient's condition improved. Objective: hemodynamic indices – blood pressure decreased, from 170/100 mmHg to 140/80 mmHg, blood glucose decreased from 8.2 mmol/l to 5.9 mmol/l, body mass decreased by 4.5 kg, triglycerides decreased from 0.49 to 0.36 mM/l, AST decreased from 146 to 74 mM/l, ALAT from 128 to 72.6 mM/l. The intestinal microbial balance was restored, for *Bifidobacterium lactis* and *Lactobacillus acidophiphilus* 10^9 and 10^8, respectively, the immune system was strengthened by the fact that immunoglobulins M, G, A had a tendency to increase

from 1.09 to 1.39, from 6, 22 to 6.71, from 0.81 to 1.13 correspondingly, T-lymphocytes (CD^+) from 66.89 to 72.14, T-helpers ($CD3^+$, CD4) from 0.68 to 0.29.

Significantly improved lipid peroxidation. Ceruloplasmin decreased from 244 to 235 mg/dL, catalase and glutathione, peroxidase increased from 10.7 to 13.8 and from 6.6 to 7.9 mM/L respectively. Superoxide dismutase remained at the same level 1096 uc/l. Malonic dialdehyde decreased from 39.6 to 37.1 mjM/l. At the same time, the patient's hematological indices improved: Hb increased from 109 to 117 g/l, erythrocytes from 2.9 to $3.2x10^{12}$, leukocytes had constant indices. Platelets, eosinophils, lymphocytes did not change significantly. Biochemical indices had a tendency to improve – total bilirubin decreased from 22.9 to 17.6 mM/l, urea from 8.9 to 7.6 mM/l, creatinine from 126 to 117 mM/l, and total protein increased from 72.1 to 76.2 g/l. Total cholesterol decreased insignificantly from 4.51 to 4.48 mM/l. The low values of *Bifidobacterium lactis* and *Lactobacillus acidophiphilus* returned to the physiological norm 10^9 and 10^8 CFU/ml respectively.

Finally, we can conclude that the claimed SABA has an action of stimulating the intestinal microbial flora (biota), immunostimulatory, minimizing metabolic risk and immunoinflammation processes.

GENERAL CONCLUSIONS

1. In order to identify high metabolic and circulatory risks for the health of the population, the occurrence of hypertension, type II diabetes, obesity and dyslipidemias, as well as chronic systemic inflammation and oxidative stress, were highlighted and argued. Cumulative metabolic and circulatory risks have been found to substantially determine population health and subsequent exacerbation of cardio-metabolic stress [33].

2. The prevalence of diseases of the circulatory system in the Republic of Moldova has an increasing trend: diseases of the circulatory system from 1639.1 in 2015 to 2005.6 in 2020 per 10,000 inhabitants; hypertensive disease from 966.6 in 2015 to 1267.5 in 2020 and cerebrovascular diseases from 198.4 in 2015 to 2019.3 in 2020. The prevalence of endocrine-metabolic diseases increased in the period 2015-2020 from 605.6 in 2015 to 731.5 in 2020, selectively by diabetes from 254.3 in 2015 to 335.0 in 2020, and insulin-dependent diabetes had a stability over the research period of 50.0 with a prevalence of obesity of 163.5 in 2015 and 186.3 in 2020 per 10,000 inhabitants [32].

3. The incidence of diseases of the circulatory system in the Republic of Moldova in the period 2015-2020 had a decrease - diseases of the circulatory system - 181.3 in 2015 and 108.4 in 2020, including hypertensive disease - 92.8 in 2015, 51.0 - in 2020. Myocardial infarction had

a decrease in incidence from 4.8 to 4.2 in 2020 per 10,000 inhabitants. Cerebrovascular diseases had values between 29.4 in 2015 and 15.6 in 2020. The incidence of endocrine diseases had a decreasing trend – 91.3 (2015) and 65.6 (2020). Diabetes in 2015 – 29.2, in 2020 – 20.9 and shows an increase in type II diabetes, and obesity – 24.8 (2015) and 17.2 (2020) per 10,000 inhabitants [32].

4. The general mortality of the population of the Republic of Moldova in the period 2015-2020 had an upward trend - 1128.8 in 2015, with a decrease in 2017 to 1036.0 and with a significant increase in 2020 of 1141.2. Mortality due to diseases of the circulatory system from 648.2 in 2015 and 645.2 in 2020 per 10,000 inhabitants. Mortality from endocrine-metabolic diseases increased – 11.7 (2015) to 13.4 (2020). Diabetes mortality increased from 11.5 (2015) to 13.2 (2020) per 10,000 inhabitants.

5. The lifestyle of subjects with metabolic syndrome must be biotyped and personalized by constitution type, metabolism type, sanogenic nutrition, motility, intestinal biota activation, consumption of, be it by daily regimen, weekly, monthly, quarterly and annual schedule with monitoring psychophysiological, clinical-biochemical indicators, blood sugar, blood pressure, obesity indicators according to surveys developed by us.

6. Carbohydrate metabolism in people with increased body mass and decreased from 6.9±0.5 to 5.6±0.2 ($p<0.05$), glycosylated hemoglobin from 7.4±0.3 to 6, 2±0.2 ($p<0.05$), and the glycemic profile from 7.5±0.4 to 6.8±0.5 ($p<0.05$). Hemodynamic indices – TAS with a decrease from 91.1±1.4 to 87.2±1.1 ($p<0.05$), which denotes the expression of the influence of insulin resistance for the subsequent prognosis of metabolic and circulatory disorders.

7. The administered products have some detoxification properties accompanied by a decrease in total bilirubin for P1 from 218±3.9 to 17.6±2.3 ($p<0.05$), for P2, from 22.8±3.9 to 18.9±2.8 ($p<0.05$), for P3 from 22.19±1.8 to 19.7±3.6 ($p<0.05$), at the same time the albumin increase for P1 from 34.3±2.1 to 36.8±3.4, $p<0.05$, for P2 from 35.8±1.9 to 37.9±2.8, for P3 from 32.3± 2.1 to 36.2±3.1 ($p<0.05$), total protein increase for P1 from 72.3±1.6 to 75.4±2.9, for P2 from 68.8± 2.1 to 76.2±2.2 ($p<0.05$). Decreased urea indices on average by 1.2±0.6 ($p<0.05$) and transaminases by 12.2±0.4 ($p<0.05$).

8. The developed and administered products had an action including immunostimulatory which is the basis of health fortification veridically manifested by increasing the indices of immunoglobulins – P1 – IgG 6.24±0.68 to 7.2±0.6 mg/dL ($p< 0.05$) and the reduction of IgM and IgA by 0.12±0.06 mg/dL ($p<0.05$), which denotes the decrease of chronic systemic immunoinflammation in these patients and of $CD3^+$ cellular immunity by 3.8±1, 21 ($p<0.05$), of $CD3^+$ by 3.9±1.46 ($p<0.05$), of T-helpers ($CD3^+$, $CD4^+$) by 0.42±0.02 (3.8%).

9. Oxidative stress in people with metabolic and circulatory risks was manifested by a significant increase in the total antioxidant activity in the isopropanolic phase, which increased by 0.23±0.09 ($p<0.05$), which also correlates with the activity of the peroxidation system lipids, the increase of catalase activity by 0.3±0.09 ($p<0.05$), of glutathione peroxidase by 0.9±0.2 ($p<0.05$), of lipid hydroxyperoxides by 0.3±0.28.

10. Lipid metabolism in subjects with metabolic and circulatory risk denotes a predisposition to the atherosclerotic process. The research showed that for all products administered, cholesterol decreased by 0.6±0.12 ($p<0.05$), β-lipoproteins by 0.01 ($p<0.05$), triglycerides by 0.9±0, 2 ($p<0.05$) indicating the improvement of lipid metabolism.

11. Strengthening the health of the population of the Republic of Moldova must be achieved by minimizing the increased metabolic risks - arterial hypertension, type II diabetes, chronic systemic inflammation, oxidative stress, through a biotyped and personified way of life and the administration of metabolic-protective products, the activation of the intestinal biota [16] , the development and implementation of the National Program to combat the metabolic syndrome in the Republic of Moldova.

12. The development and administration of products 1, 2 and 3 demonstrated in the subjects included in the study beneficial effects on metabolism – the general condition improved, the appetite normalized, the body mass decreased by 1.9±0.3 kg ($p<0.05$) and psychoemotional status normalized.

13. The implementation of the biotyped and personalized lifestyle according to the surveys developed by us strengthens the health of subjects with increased metabolic and circulatory risks: of the indicators, the improvement of the appropriate reaction by 22%, of the psychomotor coordination by 17%, of the concentration of attention by 9%, of the nervous processes (synthesis, analysis, logical thinking) in the environment by 7.6%, reduction of psychobehavioral indicators by 21.3%, improvement of short-term memory by 5%, reduction of sleep disturbances by 58%, reduction of depressive states by 14%, of anxiety by 15 %.

14. The anthropometric indices of people with increased body mass and abdominal circumference tended to decrease – body mass decreased from 87.4±1.92 kg to 76.3±1.11 kg, and overweight increased by 8%, correlatively with a decrease in obesity by 8%, BMI decreased from 32.1±0.7 to 28.0±0.7, in men from 102.8±1.7 to 95.4±1.3 ($p< 0.05$).

PRACTICAL RECOMMENDATIONS

1. Development and implementation of the National Program to combat increased metabolic risks and strengthen the health of the population of the Republic of Moldova.

2. Ensuring measures to minimize increased metabolic risks through the medical and personal activities of the EPS of the population.

3. Implementation of early diagnosis of metabolic risks by biotyping of individual types and gut microbiota.

4. Improvement of metabolic disorders through the administration of developed biologically active nutraceutical remedies.

5. Conjugation of medical and individual efforts to ensure the implementation of the biotyped and personalized style of subjects with increased metabolic risks.

6. The involvement of media resources in the promotion of the biotyped and personalized lifestyle of subjects with metabolic syndrome in the work of family doctors, medical centers, in communities, in families, the EMC of medical workers and public lessons in health.

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LIST OF PUBLISHED WORKS ON THE THEME OF THE THESIS

1. Specialized books

1.2. collective specialty books

1. KHALANGOT, M., GURIANOV, V., VAISERMAN, A., STRELE, I. **FEDASH, V.**, KRAVCHENKO V. Diabetes in Eastern Europe. In: *Diabetes Mellitus in Developing Countries and Underserved Communities*. Cham, Switzerland: Springer, 2017, p. 191-223, 294 p. Doi: 10.1007/978-3-319-41559-8. ISBN 978-3-319-41557-4. ISBN 978-3-319-41559-8 (eBook).
2. NĂSTASE, C., OJOVAN, V., **FEDAȘ, V.** *Sindromul metabolic și sănătatea orală.* Chișinău: Tipografia „Poliviz-Design", 2021, 136 p. ISBN 978-9975-3434-6-6.
3. MEREUȚĂ, I., BACIU, A., **FEDAȘ, V.** *Fortificarea sănătății: plasticitatea și diminuarea riscurilor metabolice.* Chișinău: Tipografia „Poliviz-Design", 2022, 206 p. ISBN 978-9975-3434-8-0.
4. MEREUȚĂ, I., OJOVAN, V., **FEDAȘ, V.** *Diabetul zaharat: Sistemul integral de corecție a stării funcționale în hiperglicemie.* Chișinău: Tipografia „Poliviz-Design", 2022, 48 p. ISBN 978-9975-3434-9-7.
5. **FEDAȘ, V.,** BOLOCAN N., MARGA S., NĂSTASE C. *Fortificarea sănătății. Ghid practic.* Chișinău: Tipografia „Poliviz-Design", 2021, 122 p. ISBN 978-9975-3434-7-3.

2. Articles in scientific journals

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6. LISTOPADOVA, L., BACIU, A., MEREUTA, I., IONESCU-TIRGOVISTE, C., CARNICIU, S., **FEDAS, V**. Prevention of eating behavior disorders by indirect balancing of activating and reward systems. *Proceedings of The Romanian Academy. Series B: Chemistry, Life Sciences and Geosciences.* 2020, 22(2), p. 105–109. ISSN: 1454-8267.
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9. MEREUȚĂ, I., **FEDAȘ, V.,** TOMȘA, A., CEBOTARI, A. Sindromul metabolic și alte comorbidități în structura mortalității prin COVID-19 în Republica Moldova (martie-decembrie 2020). *Buletinul Academiei de Științe a Moldovei. Științe medicale.* 2021, nr. 2 (70), 40-45. Doi: https://doi.org/10.52692/1857-0011.2021.2-70.05. ISSN 1857-0011.
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3. Articles in conference proceedings and other scientific events

3.3. in the works of scientific events included in *Register of materials published on the basis of scientific events organized in the Republic of Moldova*

12. MEREUȚĂ, I., POLEACOVA, L., **FEDAŞ, V.** Sindromul metabolic – o provocare sau o dilemă a secolului XXI? În: *Culegerea de lucrări ale Conferinței științifice internaționale „Sănătatea, medicina și bioetica în societatea contemporană: studii inter și pluridisciplinare",* ediția a III-a. Chişinău: Print Caro, 2020, p. 308-313. ISBN 978-9975-56-805-0.
13. **FEDAŞ, V.** Sindromul metabolic și microbiota intestinală – interrelații și interdependențe. *Materialele Conferinței Științifice Internaționale: „Sănătatea, medicina și bioetica în societatea contemporană: studii inter și pluridisciplinare"* Ediția a III-a, Chișinău: Centrul Editorial-Poligrafic „Print Caro", 2020, p. 359-364. ISBN: 978-9975-56-805-0.

14. BACIU, A., **FEDAŞ, V.**, MEREUŢĂ, I., LISTOPADOVA L. Aplicarea metodelor avansate de cercetare într-un program de prevenire a disabilităţilor prin colaborarea dintre cercetători şi diagnosticieni. În: Materialele Conferinței Științifice Internaționale „*Sănătatea, medicina și bioetica în societatea contemporană: studii inter și pluridisciplinare*”, 29-30 octombrie 2021, ediția a IV-a. Chișinău: Print Caro, 2021, p. 312-316. ISBN 978-9975-56-935-4.
15. **FEDAŞ, V.** Semnificația calității grăsimilor consumate și a stimulării hipotermale în mecanisme antiinflamatoare și în prevenția obezității. În: Materialele Conferinței Științifice Internaționale „*Sănătatea, medicina și bioetica în societatea contemporană: studii inter și pluridisciplinare*”, 7-8 octombrie 2022, ediția a V-a. Chișinău: Print Caro, 2022, p. 279-285. ISBN 978-9975-165-12-9.

4. Patents and other intellectual property objects (IPO)

4.2. issued by the State Agency for Intellectual Property

16. MEREUŢĂ, I., **FEDAŞ, V.**, CARAUŞ, V., BACIU, A. Compoziție fitoterapeutică pentru obținerea infuziei apoase cu efect de reducere a masei corporale. Brevet de invenție de scurtă durată 1498 MD. Nr. depozit: s20200104, data depozit: 2020.08.26. BOPI, 2, 2021, p. 47-48. ISSN 2345-1815.
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18. **FEDAŞ, V.**, MEREUŢĂ, I., CARAUŞ, V., BACIU, A. Compoziție fitoterapeutică pentru obținerea infuziei apoase cu efect antihipertesiv. Brevet de invenție de scurtă durată 1500 MD. Nr. depozit: s20200106, data depozit: 2020.08.26. BOPI, 2, 2021, p. 48-49. ISSN 2345-1815.

5. Theses at scientific events published in scientific magazines / collections of papers

5.1. in journals from the Web of Science and SCOPUS databases

19. BACIU, A, **FEDAŞ, V.,** MEREUŢĂ, I., IONESCU-TÎRGOVIŞTE, C. CARNICIU, S. Prevention of disability by early and timely diagnosis of neurodegeneration using biomedical engineering method. *Balneo and PRM Research Journal*. 2021, 3(12), L22. ISSN 2734-844X.
20. BACIU, A. **FEDAS, V.,** MEREUTA, I., IONESCU-TÎRGOVIŞTE, C., CARNICIU, S. LISTOPADOVA, L. Environmental and lifestyle factors in neuromodulation of central monoaminergic neurotransmitter systems. *Balneo and PRM Research Journa*l (Congress Abstracts, National Congress of Physical and Rehabilitation Medicine & Balneology with

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21. BACIU, A**., FEDAŞ, V**., MEREUŢĂ, I., IONESCU-TÎRGOVIŞTE, C., CARNICIU, S. The revival of the traditions of health creative tourism in the Dniester-Prut-Danube region. *Balneo Research Journal*. 2020, 11(3), P10. ISSN: 2069-7597, eISSN: 2069-7619.
22. MEREUȚĂ, I., BACIU, A., CREȚU, F., POLEACOVA, L., **FEDAȘ, V.** Stilul de viață, sănătatea psihică și longevitatea. *Sănătate Publică, Economie și Management în Medicină* (I-ul Congres Național de Geriatrie și Gerontologie din Republica Moldova, cu participare internațională, 23-24 septembrie 2021), 2021, Supliment la nr. 3(90), 26-27. ISSN 1729-8687. E-ISSN 2587-3873.
23. BACIU, A., MEREUTA, I., **FEDAS, V.** Psychosomatic and psychovegetative vulnerability in dependence on gas exchange function in aged sport veterans and non-trained individuals. *Sănătate Publică, Economie și Management în Medicină* (I-ul Congres Național de Geriatrie și Gerontologie din Republica Moldova, cu participare internațională, 23-24 septembrie 2021), 2021, Supliment la nr. 3(90), 39-40. ISSN 1729-8687. E-ISSN 2587-3873.
24. **FEDAS, V.**, MEREUTA, I., POLEACOVA, L., LISTOPADOVA, L, BACIU, A. The balance of metabolic supply of adipose, bone and muscle tissues plasticity in aged sport veterans. *Sănătate Publică, Economie și Management în Medicină* (I-ul Congres Național de Geriatrie și Gerontologie din Republica Moldova, cu participare internațională, 23-24 septembrie 2021), 2021, Supliment la nr. 3(90), 40-41. ISSN 1729-8687. E-ISSN 2587-3873.

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25. BACIU, A.Ja., **FEDAS, V.V.**, MEREUTA, I.E., CECAN, M., LISTOPADOVA, L.A. Biomedical engineering and occupational therapy approach in technologies for enhancement human labor and defense abilities. *In: The 5th International Conference on Nanotechnologies and Biomedical Engineering*: Abstract Book, November 3-5, 2021, Chisinau, p. 124. ISBN 978-9975-72-592-7.
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36. **FEDAȘ, V.** Obezitatea – noi abordări, paradigme și oportunități. În: *Integrare prin cercetare și inovare:* Rezumatele comunicărilor Conferinței științifice naționale cu participare internațională, 10-11 noiembrie, 2020, Chișinău. Chișinău: CEP USM, p. 110-113. ISBN 978-9975-152-48-8. ISBN 978-9975-152-50-1.
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38. BACIU, A., LISTOPADOVA, L., FEDAS, V. The necessity for modernization of the adaptogenic concept on the basis of combining the application of adaptogens with the optimization of the lifestyle. În: *Integrare prin cercetare și inovare:* Materialele lucrărilor Conferinței științifice naționale cu participare internațională dedicată aniversării a 75-a a Universității de Stat din Moldova, 10-11 noiembrie, 2021, Chișinău. Chișinău: CEP USM, 2021, p. 18-20. ISBN 978-9975-152-48-8. ISBN 978-9975-158-60-2.

ANNOTATION (Romanian)

Fedaș Vasile, „Fortificarea sănătății populației cu riscuri metabolice crescute”. Teză de doctor habilitat în științe medicale, Chișinău, 2022.

Structura tezei: introducere, șase capitole, concluzii generale şi recomandări practice, bibliografie din 466 de titluri, 16 anexe, 190 pagini de text de bază, 24 figuri, 51 tabele. Rezultatele obţinute sunt publicate în 38 de lucrări ştiinţifice.

Cuvinte-cheie: sănătate, riscuri metabolice, metabolism, tulburări metabolice, hipertensiune arterială, diabet zaharat tip II, dislipidemie, obezitate, inflamație cronică sistemică, mod de viață biotipizat și personalizat.

Scopul lucrării: Studierea complexului de măsuri necesare pentru fortificarea sănătății populației cu riscuri metabolice crescute prin elaborarea unor metode noi de prevenție și abordărilor originale de management terapeutic.

Obiectivele cercetării: 1) Analiza statistico-demografică a populației cu riscuri metabolice și circulatorii crescute în perioada anilor 2015-2020 (hipertensiunea arterială, diabetul zaharat tip II, obezitatea și dislipidemiile. 2) Relevarea și evidențierea rolului și impactului factorilor de risc major în apariția tulburărilor metabolice și circulatorii esențiale asupra sănătății populației. 3) Evaluarea unor metode de diagnostic preclinic al tulburărilor metabolice și circulatorii la persoanele cu riscuri metabolice crescute. 4) Argumentarea științifică a abordărilor originale în aplicarea metodelor noi de readaptare și recuperare pentru fortificarea sănătății. 5) Elaborarea recomandărilor pentru educația în sănătate și a modului sănătos de viață cu alimentație funcțională biotipizată și personalizată a subiecților cu riscuri metabolice crescute. 6) Elaborarea noilor produse cu efect metabolico-protectiv și studierea proprietăților curativ-profilactice ale acestora.

Noutatea şi originalitatea ştiinţifică: În premieră este argumentat inpactul factorilor esențiali de risc metabolic în populație, inclusiv inflamația cronică sistemică, rolul microbiotei; fiind analizată statistic și demografic, populația cu hipertensiune arterială, diabet zaharat tip II, dislipidemie și obezitate, analitic și discriptiv; este argumentată științific readaptarea și reabilitarea metabolică; sunt elaborate noi produse cu efect metabolico-protectiv; fiind elaborate recomandări ale modului de viață biotipizat și personalizat la subiecții cu tuburări metabolice.

Rezultatul obținut, care contribuie la soluționarea unei probleme științifice importante constă în dezvoltarea conceptului despre impactul factorilor de risc metabolic în populație, inclusiv inflamația sistemică cronică, a criteriilor depistării precoce a denaturării metabolismului, a posibilităților readaptării și reabilitării metabolice, a eliminării stresului oxidativ, a argumentării noii viziuni a stulului de viață biotipizat și personalizat cu scopul educației și fortificării sănătății populației.

Semnificaţia teoretică constă în dezvoltarea concepției declanșării denaturărilor metabolice, cu implicarea inflamației cronice sistemice, a diminuării stresului oxidativ prin administrarea produselor bioprotectoare metabolice cu biotipizarea și individualizarea stilului sănătos de viață.

Valoarea aplicativă a lucrării constă în elaborarea metodei de diagnostic preclinic al dereglărilor metabolice și a prebioticului de corecție a biotei intestinale; în aplicarea alimentației sanogene, a modului de viață biotipizat și individualizat, prin educația medicală a populației, menținerea și fortificarea sănătății populației cu riscuri metabolice crescute.

Implementarea rezultatelor ştiinţifice: Rezultatele cercetărilor au fost implementate în procesul de cercetare a Institutului de Fiziologie și Sanocreatologie, institutele similare din România, Ucraina, Rusia, în procesul didactic al Universității de Stat din Moldova, a Universității de Stat de Medicină și Farmacie „N. Testemițanu”, Universitatea din Tiraspol, în programele de EMC în readaptare și reabilitare, în activitatea medicilor de familie, a specialiștilor din instituțiile medicale publice și private, în centrele de reabilitare, de educație pentru sănătate.

ANNOTATION (English)

Fedas Vasile "Strengthening the health of the population with high metabolic risks", Thesis of Doctor habilitated in Medical Sciences, Chisinau, 2022.

Thesis structure: introduction, six chapters, general conclusions and practical recommendations, bibliography of 466 titles, 16 appendices, 190 pages of basic text, 24 figures, 51 tables. The results are published in 38 scientific papers.

Keywords: health, metabolic risks, metabolism, metabolic disorders, hypertension, type II diabetes, dyslipidaemia, obesity, chronic systemic inflammation, biotyped and personalised lifestyle.

Aim: To study the complex of measures needed to strengthen the health of the population at increased metabolic risk by developing new prevention methods and novel therapeutic management approaches.

Research objectives: 1) Statistical-demographic analysis of the population with increased metabolic and circulatory risks during 2015-2020 (hypertension, type II diabetes mellitus, obesity and dyslipidemias. 2) To identify and highlight the role and impact of major risk factors in the occurrence of key metabolic and circulatory disorders on population health. 3) To evaluate preclinical diagnostic methods for metabolic and circulatory disorders in people with increased metabolic risks. 4) Scientific argumentation of novel approaches in the application of new methods of rehabilitation and recovery for health fortification. 5) Development of recommendations for health education and healthy lifestyle with biotyped and personalized functional nutrition for subjects with increased metabolic risks. 6) Development of new products with metabolic-protective effect and study of their curative-prophylactic properties.

Scientific novelty and originality: For the first time, the impact of essential metabolic risk factors in the population, including chronic systemic inflammation and the role of microbiota, is argued; the population with hypertension, type II diabetes, dyslipidemia and obesity is analysed statistically and demographically, analytically and discriminately; metabolic readaptation and rehabilitation is scientifically argued; new products with a metabolic-protective effect are developed; biotyped and personalised lifestyle recommendations in subjects with metabolic tuburification are developed.

The result obtained, which contributes to the solution of an important scientific problem, is the development of the concept of the impact of metabolic risk factors in the population, including chronic systemic inflammation, the criteria of early detection of metabolic distortion, the possibilities of metabolic readaptation and rehabilitation, the elimination of oxidative stress, the argumentation of the new vision of biotyped and personalized lifestyle with the aim of education and strengthening the health of the population.

The theoretical significance lies in the development of the concept of triggering metabolic derangements involving chronic systemic inflammation, decreasing oxidative stress by administering metabolic bioprotective products with biotyping and individualization of healthy lifestyle.

The application value of the work lies in the development of the preclinical diagnostic method of metabolic disorders and prebiotic correction of intestinal biota; in the application of healthful nutrition, biotyped and individualized lifestyle, through medical education of the population, maintaining and strengthening the health of the population with increased metabolic risks.

Implementation of scientific results: the results of the research were implemented in the research process of the Institute of Physiology and Sanocreatology, similar institutes in Romania, Ukraine, Russia, in the educational process at the State University of Moldova, Nicolae Testemitanu State University of Medicine and Pharmacy, State University of Tiraspol, in CME programs in recovery and rehabilitation, in the work of family doctors, specialists in public and private medical institutions, in rehabilitation, health education centers.

FEDAȘ VASILE

STRENGTHENING THE HEALTH OF THE POPULATION WITH INCREASED METABOLIC RISKS

331.04 – HEALTHY LIFESTYLE AND HEALTH EDUCATION

Summary of the thesis of habilitated doctor in medical sciences

Approved for printing: 23.11.2022	Paper format 60×84 1/16
Offset paper. Offset printing.	Printing 50 copies
Pattern sheets:	Order No. ...

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