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Analysis of Methods for Evaluating the Functional State and Physical Fitness of Men and Women in The Second Period of Adulthood

V. S. Belyaev, A. E. Stradze, I. A. Malygina, Dmitriy Nikolaevich Chernogorov

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ABSTRACT

Methods for evaluating the functional state of the body and physical fitness of men and women in the second period of adulthood have been analyzed in the article. The timely diagnosis of these indicators allows to optimally distribute exercises and adjust them to each trainee. Indicators of the functional state of the body and physical fitness should be analyzed in combination, as it allows to obtain more accurate results.

Materials. Analysis of methods for evaluating the physical and functional state of the body is presented in the article.

Methods. The following research methods have been used in the article: analysis and systematization of scientific and methodological literature, pedagogical experiment, testing, and statistical data processing.

Results. The research has been conducted with the purpose of analyzing the existing methods for evaluating the physical and functional state of the body. The results of a comprehensive research of the indicators of the functional state and physical fitness are more accurate because the human factor is taken into account (the participants could not accurately meet the targets in the calculation). The results have led to a conclusion about the need to use a wide range of methods for diagnosing the functional state and physical fitness.

Conclusion. Conditions for correct performance should be honored in functional tests and physical fitness tests, as this influences the reliability

of the data. The results have led to a conclusion about the need to use a wide range of methods for diagnosing the functional state and physical fitness.

Keywords: functional state of the body, physical fitness, adulthood.

INTRODUCTION

There is a need to preserve and strengthen the health of men and women in the second period of adulthood in the modern society because it contributes to the solution of the economic, social, demographic, and cultural problems of society and is of scientific and practical interest [1].

The WHO experts note that about 60% of the world's population do not comply with the recommended levels of physical activity necessary to maintain health. Physical inertness is a factor of global mortality (1.9 mln deaths in the world) [2-4].

There is an upward trend in the number of adults who require specially selected exercises and individually dosed loads. This requires timely monitoring of the functional state and physical fitness. Given these indicators, the physical load can be optimally selected and adjusted for each trainee [7].

G.L. Apanasenko investigated the problem of assessing human health. D.N. Gavrilov, V.V. Malinin, and M.A. Savenko studied the problem of the motor activity of adult people. O.P. Shchepin described the issues of modern regional peculiarities of public healthcare in Russia. A.I. Kibzun,

E.R. Goryainova, and A.V. Naumov described the theory of probability and mathematical statistics.

METHODS AND ARRANGEMENT OF RESEARCH

A total of 48 people – men aged 35 – 60 and women aged 35 – 55 training at the sports and recreation center Legenda LLC – were involved in the research.

The breath-holding and Ruffier's tests were used on the first day to evaluate the functional state; standard tests of basic physical qualities (endurance, strength, flexibility, speed quality, and speed and power quality) were used to evaluate physical fitness.

A set of tests where values were measured before and after cardio load was used on the second day of testing with the same training group. A 9-minute test on a cycle ergometer was chosen (the load was gradual, 50 – 100 and 150% of body weight with a pulse of up to 150 bpm).

Aside from the traditional indicators of heart rate and blood pressure, the following indicators were also taken into account on the second day: pulse rate, cardiac output, stroke pressure, cardiac and stroke index, left ventricular contraction rate, and stroke volume. The functional state of the cardiovascular system was evaluated before and after the exercises [8].

RESULTS

A comprehensive analysis of the functional state of the body and physical fitness allows to more efficiently control and adjust physical activity during training. This is an important tool for managing the training process. Tables below show the indicators of the functional state and physical fitness of the adult men and women before and after

the experiment. The efficiency of the training process management can be judged by the dynamics of the results.

Table 1 presents the dynamics of indicators of the functional state of the women aged 35 – 55 before and after the experiment. Significant differences are observed in both groups of testees by the breath-holding (sec) and Ruffier's tests (c.u.).

Table 2 presents the dynamics of indicators of the functional state of the men aged 35 – 60 before and after the experiment. Significant differences are observed in both groups of testees by the breath-holding (sec) and Ruffier's tests (c.u.).

Table 3 presents the dynamics of indicators of the physical fitness of the women aged 35 – 55 before and after the experiment. Significant differences are observed in both groups of testees by the tests for evaluating speed qualities, speed and power qualities, strength, endurance, and flexibility. There is a moderately developing impact of the experimental program.

Table 4 presents the dynamics of indicators of the physical fitness of the men aged 35 – 60 before and after the experiment. Significant differences are observed in both groups of testees by the tests for evaluating speed qualities, speed and power qualities, strength, endurance, and flexibility. There is moderately developing impact of the experimental program.

CONCLUSION

The conditions for correct performance should be honored in functional tests and physical fitness tests, as this influences the reliability of the data. The results of the comprehensive research of the indicators of the functional state and physical fitness are more accurate

Table 1. Dynamics of indicators of the functional state of the women aged 35 – 55

Tests	EG (n=12)		P1	CG (n=12)		P2
	Before experiment	After experiment		Before experiment	After experiment	
	M ± m	M ± m		M ± m	M ± m	
breath-holding (expiration, sec)	17 ± 0.5	19.5 ± 0.9	<0.05	17.2 ± 0.6	18.2 ± 0.7	<0.05
breath-holding (inspiration, sec)	29.6 ± 1.3	35.4 ± 1.4	<0.05	28.5 ± 1.3	29.8 ± 1.1	<0.05
Ruffier's (c.u.)	9.8 ± 0.6	8.3 ± 0.4	<0.05	9.8 ± 0.7	9.2 ± 0.6	<0.05

Table 2. Dynamics of indicators of the functional state of the men aged 35 – 60

Tests	EG (n=12)		P1	CG (n=12)		P2
	Before experiment	After experiment		Before experiment	After experiment	
	M ± m	M ± m		M ± m	M ± m	
breath-holding (expiration, sec)	27 ± 0.5	29.5 ± 0.9	<0.05	27.2 ± 0.6	28.2 ± 0.7	<0.05
breath-holding (inspiration, sec)	39.6 ± 1.3	45.4 ± 1.4	<0.05	38.5 ± 1.3	39.8 ± 1.1	<0.05
Ruffier's (c.u.)	14.8 ± 0.6	12.3 ± 0.4	<0.05	14.2 ± 0.7	11.2 ± 0.6	<0.05

Table 3. Dynamics of indicators of the physical fitness of the women aged 35 – 55

Tests	EG (n=24)		P1	KG (n=24)		P2
	Before experiment	After experiment		Before experiment	After experiment	
	M ± m	M ± m		M ± m	M ± m	
Test to evaluate speed qualities. Running 30 m (sec.)	6.1 ± 0.5	5.4 ± 0.3	<0.05	6.2 ± 0.4	5.6 ± 0.7	<0.05
Test to evaluate speed and strength qualities. Long jump (cm)	155.6 ± 1.3	160.4 ± 1.4	<0.05	154.5 ± 1.3	158.8 ± 1.1	<0.05
Test to evaluate strength. Lifting torso forward (count per 60 sec)	30.6 ± 0.6	36.3 ± 0.4	<0.05	29.8 ± 0.7	34.4 ± 0.6	<<0.05
Lifting torso back, bending (count per 60 sec)	13.6 ± 0.6	18.6 ± 0.6		14.6 ± 0.6	17.6 ± 0.6	
Pulling on a high bar (M)	-	-		-	-	
Pulling on a low bar (W)	5.6 ± 0.6	10.6 ± 0.6		6.0 ± 0.6	9.6 ± 0.6	
Test to evaluate endurance. Cooper test (km in 12 min)	1.6 ± 0.4	2.3 ± 0.5	<0.05	1.7 ± 0.4	2.1 ± 0.2	<0.05
Test to evaluate flexibility. Tilt standing forward (cm)	5.7 ± 0.6	10.3 ± 0.4	<0.05	6.8 ± 0.7	7.2 ± 0.6	<0.05

Table 4. Dynamics of indicators of the physical fitness of men aged 35 – 60

Tests	EG (n=24)		P1	CG (n=24)		P2
	Before experiment	After experiment		Before experiment	After experiment	
	M ± m	M ± m		M ± m	M ± m	
Test to evaluate speed qualities. Running 30 m (sec.)	5.6 ± 0.5	5.1 ± 0.3	<0.05	5.7 ± 0.6	5.3 ± 0.4	<0.05
Test to evaluate speed and strength qualities. Long jump (cm)	165.6 ± 1.3	169.4 ± 1.4	<0.05	164.5 ± 1.3	168.8 ± 1.1	<0.05
Test to evaluate strength. Lifting torso forward (count per 60 sec) Lifting torso back, bending (count per 60 sec) Pulling on a high bar (M) Pulling on a low bar (W)	35.6 ± 0.6 17.6 ± 0.6 3.6 ± 0.6 -	40.3 ± 0.4 22.6 ± 0.6 5.6 ± 0.6 -	<0.05	36.8 ± 0.7 18.6 ± 0.6 3.2 ± 0.6 -	39.4 ± 0.6 21.6 ± 0.6 4.6 ± 0.6 -	<0.05
Test to evaluate endurance. Cooper test (km in 12 min)	2.0 ± 0.5	2.5 ± 0.5	<0.05	2.0 ± 0.6	2.2 ± 0.06	<0.05
Test to evaluate flexibility. Tilt standing forward (cm)	4.7 ± 0.6	7.3 ± 0.4	<0.05	4.8 ± 0.7	6.2 ± 0.6	<0.05

because the human factor is taken into account (the participants could not accurately meet the targets in the calculation). The results have led to a conclusion about the need to use a wide range of methods for diagnosing the functional state and physical fitness.

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Impact of the Motor Activity of Men and Women in the Second Period of Adulthood on Physical Fitness and Functional Indicators

V. S. Belyaev, A. E. Stradze, I. A. Malygina, S. Ustinov

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ABSTRACT

The motor activity belongs to controllable factors that influence human health because it ensures disease prevention. Analysis of scientific publications has revealed that motor activity of adult people is insufficient; this leads to the development of hypodynamia and worsens health. The level and nature of motor activity should correspond to the peculiarities of the body (age, gender, functional state, physical fitness, etc.).

This problem requires the study of the relationship between the motor activity of the adult men and women and their indicators of physical fitness and functional state of the body.

The relationship between the motor activity and indicators dependent on it has been reviewed in the article. The impact of the motor activity on the functional state of the body and physical fitness has been determined.

The results have led to a conclusion that the motor activity of adults should be analyzed along with the study of indicators of functional state and physical fitness.

Keywords: *motor activity, functional state of the body, physical fitness, adulthood.*

INTRODUCTION

The issue of motor activity deficit is currently relevant. This also applies to adults [1-4]. It is widely known that this cohort largely has poor health and insufficient level of physical fitness and functional state.

As a result of hypodynamia, problems arise, such as overweight, poor performance, low self-esteem, insuffi-

cient social interaction, and the development of chronic diseases. Numerous studies confirm that these problems are associated with the motor activity, which has an indispensable role in human life [5-9].

The motor activity is needed in adulthood to slow aging and involutional changes in the body [1, 10-13].

The preliminary studies of the authors have confirmed the need for a further thorough study of the motor activity of adults in the modern society.

N.N. Vengerova, G.M. Lavrukhina, O.V. Sapozhnikova, and A.Yu. Fedorova were engaged in the arrangement of the motor activity of adults. A.G. Katanov studied the problems of computer processing of experimental data.

I.A. Arshavsky explored the age physiology problem. A.N. Usatov studied the issues of independent training as a means of increasing motor activity. T.A. Yashina explored the problem of optimizing loads in weight recreational activities.

The purpose of the study is to measure the impact of the motor activity of adults on physical fitness and functional indicators.

Scientific and practical significance of the study is that the obtained results can be used for further scientific research. The identified indicators can be used in the practice of coaches and teachers. Timely control will allow to adjust the load, taking the functional state and physical fitness into account, and more efficiently arrange the training process. Besides, the obtained parameters can be used as a methodological material in training.

MATERIALS AND ORGANIZATION OF THE STUDY

The pedometering method was used to measure the motor activity. The number of movements per day was tracked by a pedometer fixed on the belt. In accordance with this method, the motor activity is measured in the total amount of daily locomotion. The data on the amount of the motor activity of 96 regularly exercising adults (46 of which were men and 50 were women) with a basic average level of fitness have been collected over three months. All the participants in the experiment have attended Atlant and Legenda sports and fitness centers in Sergiev Posad from two months to one year [4, 6, 9]. The sample included only the participants who received full information about the study and gave informed and voluntary consent to participate. The testees were in good health, all the participants were informed of the possible risks and gave their written consent to participate. The study complied with all ethical standards.

A polar group method was used to determine the impact of the motor activity of adults on the level of their functional state and physical fitness. 25% of people with the highest motor activity and 25% of people with the lowest motor activity were selected. As such, two groups 24 people each were formed: the first group with low motor activity and the second with high motor activity [4, 14].

The average daily locomotive activity was 6,123.56 steps in the group with low motor activity and 12,543.54 steps in the group with high motor activity (Table 1).

The level of physical fitness, physical performance, and functional indicators were measured in the participants of the first and second groups simultaneously.

Standard tests were used to measure physical fitness: 30 meters running, long jump from the spot, lifting the body from a prone position, hanging on the crossbar, push-ups in the upright position, and leaning forward (Table 2).

The functional state of the body was measured by the following indicators:

Table 1. Daily motor activity of the men and women in the second period of adulthood by the polar group method

Groups	n	Daily motor activity (steps) (M ± m)
Group with low motor activity	24	6,123.56 ± 176.58
Group with high motor activity	24	12,543.54 ± 502.48

Table 2. Reliability of differences in physical fitness indicators among people in the second period of adulthood (with low and high motor activity)

Groups	n	Physical fitness indicators (M ± m)					
		30 meters running (sec)	lifting the body from a prone position (count per min)	push-ups in the upright position (count)	leaning torso forward, standing on a bench (cm)	hanging on the bar on bent arms (sec)	long jump from the spot (cm)
Group with low motor activity	24	6.02 ± 0.14	30.13 ± 0.83	12.40 ± 1.2	6.00 ± 1.29	9.06 ± 1.3	165.8 ± 6.32
Group with high motor activity	24	5.06 ± 0.13	35.53 ± 1.38	18.73 ± 2.49	6.46 ± 1.82	13.93 ± 1.77	173.13 ± 5.35
P		P < 0.05	P < 0.05	P < 0.05	P > 0.05	P < 0.05	P > 0.05

body weight (kg); body length (cm), Quetelet index (c.u.), vital index (lung capacity/body weight, c.u.), and Robinson index ($HR \cdot SBP/100$, c.u.) (Table 3).

The level of physical performance of the adult men and women was studied with the purpose to determine the state of the cardiovascular system; functional tests involved the recording of the cardiorespiratory system indicators after the exercise (Harvard step test (c.u.) and Ruffier's test (c.u.) (Table 4).

Indices with a change in pulse in the recovery period were calculated to interpret the results. The endurance indicators are higher for the bodies in which recovery processes occur faster [14, 15].

RESULTS AND DISCUSSION

The authors compared the above indicators of the first group (with high mo-

tor activity) and the second group (with low motor activity) in the course of the study. They analyzed the impact of the motor activity on the indicators of physical fitness, physical performance, and functional state of adults.

The statistical data were processed in software SPSS 15.0. The Shapiro-Wilk criterion was used to check for the normal distribution of the measured variables. The parametric methods (Student test) were used for dependent samples in the case of a normal distribution of variables, and the nonparametric methods (Wilcoxon test) were used in the case of nonnormal distribution. The indicators that obey the law of normal distribution are presented as arithmetic mean (M), and standard deviation errors (m), which do not obey the law of normal distribution, are presented as arithmetic mean (Md). Differences were considered statistically significant at $p < 0.05$.

Table 3. Reliability of differences in functional indicators among people in the second period of adulthood with low and high motor activity

Groups	n	Functional indicators (M ± m)						
		weight (kg)	height (cm)	Quetelet index (c.u.)	lung capacity (ml)	vital index (c.u.)	strength index (c.u.)	Robinson index (c.u.)
Group with low motor activity	24	75.5 ± 5.3	175.00 ± 8.55	24.83 ± 1.05	3520.00 ± 88.00	46.93 ± 2.76	0.55 ± 5.85	75.27 ± 6.01
Group with high motor activity	24	72.20 ± 5.65	175.00 ± 5.00	23.59 ± 0.53	3993.00 ± 88.61	55.36 ± 1.73	0.65 ± 0.01	84.43 ± 1.60
P		> 0.05	> 0.05	> 0.05	≤ 0.05	≤ 0.05	≤ 0.05	≤ 0.05

Table 4. Reliability of differences in physical performance indicators among people in the second period of adulthood with low and high motor activity

Groups	n	Physical performance indicators (M ± m)	
		Ruffier's test (c.u.)	Harvard step test (c.u.)
Group with low motor activity	24	8.80 ± 0.83	59.50 ± 1.94
Group with high motor activity	24	5.26 ± 0.57	66.62 ± 1.35
P		< 0.05	< 0.05

Significant differences ($P < 0.05$) were observed in the following: running for 30 meters was 6.02 ± 0.14 (sec) in the group with low motor activity and 5.06 ± 0.13 (sec) in the group with high motor activity. Lifting the body (from a prone position (count per min)) was 30.13 ± 0.83 and 35.53 ± 1.38 , respectively. Push-ups in the upright position (count) was 12.40 ± 1.2 in the group with low motor activity and 18.73 ± 2.49 in the group with high motor activity. Hanging on the crossbar (sec) was 9.06 ± 1.3 and 13.93 ± 1.77 , respectively. No significant differences ($P > 0.05$) were found in leaning forward (cm) (6.00 ± 1.29 and 6.46 ± 1.82) and a long jump from the spot (cm) (165.8 ± 6.32 and 173.13 ± 5.35 , respectively). Speed and strength qualities and flexibility must be developed by special exercises.

Comparison of the functional state of the bodies in the first and second groups indicated that the lung capacity was $3,520.00 \pm 88.00$ (ml) in the group with low motor activity and $3,993.00 \pm 88.61$ (ml) in the group with high motor activity. The vital index was 46.93 ± 2.76 and 55.36 ± 1.73 (c.u.), respectively. The power index (c.u.) was 0.55 ± 5.85 and 0.65 ± 0.01 , respectively. The Robinson index (c.u.) was 75.27 ± 6.01 and 84.43 ± 1.60 , respectively. They all had significant differences ($P < 0.05$). The adults with high motor activity have higher results of the cardiovascular system and respiratory systems activity than the cohort with low motor activity [3, 4, 6, 8].

No significant differences ($P > 0.05$) were found in the body weight/height indicators and Quetelet index – these indicators depended more on genetics than on the motor activity. The group with low motor activity had an average body weight of 75.5 ± 5.3 (kg), while the group with high motor activity had an average body weight of 72.20 ± 5.65 (kg). The group with low motor activity had an average height of 175.00 ± 8.55 (cm), while the group with high

motor activity had an average height of 175.00 ± 5.00 (cm). Quetelet index (c.u.) was 24.83 ± 1.05 in the group with low motor activity and 23.59 ± 0.53 in the group with high motor activity.

Significant differences were observed between the groups with low and high motor activity in the Ruffier's and Harvard step test indices ($P < 0.05$). The Ruffier's index was 8.80 ± 0.83 (c.u.) in the group with low motor activity and 5.26 ± 0.57 (c.u.) in the group with high motor activity. The Harvard step test index was 59.50 ± 1.94 in the group with low motor activity and 66.62 ± 1.35 (c.u.) in the group with high motor activity.

CONCLUSION

The significant differences between groups with high and low motor activity have been identified in almost all the parameters under study, which proves the hypothesis of the study. These indicators were significantly higher in the group with high motor activity than in the group with low motor activity.

The motor activity of adults has direct impact on the indicators of physical fitness, functional state, and performance. The sufficient motor activity of adults contributes to the improvement and maintenance of physical fitness, functional state and working efficiency at a health-safe level.

This study has indicated that the motor activity of adults should be studied along with indicators of physical fitness and functional state.

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Assessment Of The Working And Living Conditions By Participants Of The Zemsky Doctor Program

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ABSTRACT

The purpose of the present work is to study the satisfaction with the working and living conditions as assessed by participants of the Zemsky Doctor program in rural areas. Materials and methods. The study has been carried out by the Tyumen State Medical University of the Ministry of Health of the Russian Federation in association with the Tyumen Public Health Department based on surveying 288 doctors participating in the Zemsky Doctor program in the Tyumen Region (excluding districts). Main results. As a result of the analysis, it has been revealed that one of the main factors of job satisfaction is opportunities of professional and career development. The analysis has shown that on average the program participants give a rather high assessment of the living conditions, although depending on municipal districts the satisfaction considerably differs. Conclusion. The working and living conditions in the rural areas under the study have been grouped according to the respondents' satisfaction. The main factors of dissatisfaction with the working and living conditions in the rural areas included career opportunities, leisure conditions, opportunity for professional growth, and the need for domiciliary duty. The obtained results can be used by the management of both medical organizations and municipal districts to solve the personnel problems in the area of the rural health care when taking relevant management decisions. Substantiation of the study novelty. The Zemsky Doctor program has been in force in the Russian Federation since 2012. Its implementation showed that the program had

only partially solved the personnel problem in the area of the rural health care. Some participants of the Zemsky Doctor program prematurely terminated the concluded contracts. In this regard, it is necessary to carry out studies on the reasons of dissatisfaction with the working and living conditions in the rural areas.

Keywords: rural health care, human resources, medical workers, the Zemsky Doctor program, motivation, satisfaction

INTRODUCTION

The population's life quality largely depends on the state of health care and, above all, on the medical personnel [1–4]. The *Zemsky Doctor* program implemented in the Russian Federation since 2012 aims at solving the problem of providing the rural population with doctors and, as a result, improving the availability and quality of medical care for the population [5]. At the same time, the program implementation has shown that far from all program participants agree to work in rural areas because of one-time payment in the amount of one million rubles [6].

The analysis of the living conditions in rural areas allows stating that the better the living conditions in the locality are organized, the more attractive the jobs for specialists including doctors are [7, 8]. The results of a number of studies confirm the hypothesis that in order to solve the problem of providing the rural population with medical personnel, it is important to create comfortable living conditions in the locality, as well as at the work-

place in the organization [9–13]. It is a problem for the authorities of all levels and branches to retain specialists in rural areas because the medical and demographic characteristics of the population depend on providing rural areas with qualified doctors [14]. It is necessary to solve the problem based on studying the specialists' motivation [15, 16]. Studies of the factors that motivate participants of the *Zemsky Doctor* program in the Tyumen region indicate that there is a need for a deeper study of the doctors' satisfaction with the working and living conditions in rural areas [17, 18].

MATERIALS AND METHODS

The study was carried out to assess the level of satisfaction with the working and living conditions in rural areas. The object of the study was the doctors who worked in medical organizations located in 17 rural districts of the Tyumen Region and who concluded an agreement on the *Zemsky Doctor* program. The method of collecting information was a questionnaire-based survey. Two hundred and eighty-eight people were interviewed. This was about 85 % of all participants in the *Zemsky Doctor* program as on the study date – January 1, 2018. The largest number of participants were in the Tyumen municipal district (111 people – 38.5 %). This was the area with the largest population and number of district hospitals and dispensaries. The share of participants in other areas of the region was on average about four percent of the respondents, while the structure of the sample totality was generally equal to the structure of the general population.

Most of the respondents included women aged 25 to 37 years and having children. To process the results, Excel 2007 was used.

RESULTS

As a part of the study of the level of satisfaction with the living conditions in rural areas, the respondents were asked to assess the relevant working, living and leisure conditions according to the scale from one to seven, where one was entirely dissatisfied, two – mostly dissatisfied, three – dissatisfied rather than satisfied, four – average, five – good, six – mostly satisfied, and seven – absolutely satisfied.

Table 1 shows the results of assessing the labor and socio-psychological conditions. According to the data, the program participants were most concerned about the lack of opportunities for professional and career growth in rural areas (the average score was 3.8 and 3.7, respectively, out of the maximum of seven). Wages, workplace and the need for duty in the hospital and domiciliary duty in the region as a whole were assessed as slightly above the average (3.9 – 4.1). The average values were representative, which was proved by the variation coefficients of less than 33 %.

In terms of the southern areas of the Tyumen Region, the estimates for some criteria varied: by domiciliary duty – from 1.7 to 5.0, by opportunities for professional growth – from 1.6 to 5.1. Salary estimates ranged from 2.1 to 5.3. Estimates for the wages that were below the regional average had been observed in six institutions, including the area with the largest number of specialists who received the one-time payment.

The value above the average was noted for the socio-psychological factors of labor. Relations with colleagues were assessed at the maximum – 6.6. The average score for this criterion was 5.9, while for the relationships with patients – 5.5, and for those with the management – 4.9.

Table 1. Respondents' Assessment of Labor and Socio-Psychological Conditions (one – entirely dissatisfied, seven – absolutely satisfied)

Criteria	Average estimate	Minimum and maximum estimates	Variation coefficient, %
Labor conditions:			
Career opportunities	3.7	1.7 – 4.8	23.4
Opportunities for professional development	3.8	1.6 – 5.1	25.3
Labor intensity	4.1	1.8 – 5.1	21.8
Workplace	4.5	2.4 – 5.7	18.7
Duties in the hospital	4.1	2.8 – 5.5	18.5
Domiciliary duty	3.9	1.7 – 5.0	28.0
Salary	4.0	2.1 – 5.3	19.5
Social and psychological terms and conditions:			
Attitude of executives	4.9	2.9 – 6.0	19.1
Interrelations with colleagues	5.9	4.8 – 6.6	8.5
Interrelations with patients	5.5	4.7 – 6.1	11.5

The results of assessing the satisfaction with the living conditions in the rural area presented in Table 2 showed that among the offered assessment criteria, the highest possible score had been given to such criteria as *Kindergarten* and *School*, 6.0 and 6.1 points of seven possible ones, respectively. The variation range for these characteristics was inconsiderable. The analysis of the data in terms of regions also confirmed the rural residents' satisfaction with the opportunities for pre-school and secondary education of children in the south of the Tyumen Region. Taking into account the fact that the respondents had children and the sample was representative, it was possible to say that the assessment was rather objective. Besides, satisfaction with the provision of accommodation (on average, 5.3), food (on average, 5.8) and conditions for the

development of children and housing and communal services (5.0 points each) was rather high. The range of variation for the last criteria was quite high. Thus, the conditions for the development of children were assessed at 2.1 points in the area that was rather far from the regional center, and the maximum was in the area (6.4) located closest to the regional center. The close location to the regional center turned out to influence human resources in many areas of life and, accordingly, the satisfaction with the living comfort in a village.

In terms of the southern areas of the Tyumen Region, the estimates for some criteria varied sufficiently: the Internet access – from 2.8 to 6.5, provision with fixed communication – from 1.6 to 5.9, and access to transportation – from 1.7 to 6.0.

Table 2. Respondents' Satisfaction with Living and Leisure Conditions, % (one – fully dissatisfied, seven – absolutely satisfied)

Criteria for life and leisure conditions	Average estimate	Minimum and maximum estimates (variation range)	Variation coefficient, %
Accommodation	5.3	3.7 – 6.0	15.0
Internet access	4.8	2.8 – 6.5	30.4
Home phone	3.9	1.6 – 5.9	30.3
Kindergarten	6.0	5.4 – 6.9	9.1
School	6.1	5.1 – 7.0	9.5
Terms and conditions for the development of children	5.0	2.1 – 6.4	19.3
Leisure conditions	3.7	1.5 – 4.2	26.2
Access to transportation	4.8	1.7 – 6.0	22.7
Provision with food	5.8	4.4 – 6.6	11.2
Housing and communal services	5.0	3.3 – 6.5	16.7

Most of the respondents lived in residential premises provided by adminis-

trations of municipalities (64.6 %), 13.9 % had their own accommodation, 5.5 % lived with their close relatives, and 16 % rented accommodation. Municipal housing was provided to specialists under various terms and conditions of rent: 60.2 % – employment-related, 34.4 % – social, and 5.4 % – commercial. Every tenth respondent lived in a private house, and the overwhelming majority lived in apartments.

Almost two thirds of the respondents assessed the accommodation as excellent and good (15.3 % and 51.7 %, respectively), 28.8 % considered it to be satisfactory, and 4.2 % considered it unsatisfactory.

The survey showed that only 19 people out of 288 benefited from social payments for the construction (purchase) of accommodation under the federal targeted program “Sustainable Development of Rural Territories” as a young family or a young specialist, which amounted to 6.6 %. At the same time, less than half of those who did not use it (47.2 %) planned to apply for this type of social guarantee.

To further implement the *Zemsky Doctor* program, the respondents were suggested various measures: accommodation provision (32.3 %), turning accommodation from commercial to service rent to obtain utility benefits (19.6), wages increase (21.4), subsidy increase (7.1), and repeated payment in five years (19.6).

CONCLUSION

The results of surveying doctors who moved to work in rural areas according to the *Zemsky Doctor* program allowed assessing the working and living conditions in rural areas according to the respondents' satisfaction:

The first group where the satisfaction was the lowest included such factors as career opportunities, leisure conditions,

opportunity for professional growth, the need for domiciliary duty, and the home phone,

The second group where the satisfaction was slightly above the average included the following working and living conditions: wages, labor intensity, duty in the hospital, workplace, access to transportation, the Internet access, and management attitude,

The third group that had good satisfaction assessments included such factors as conditions for the development of children, housing and communal services, accommodation, relations with patients and colleagues, provision with food, and

The fourth group included the conditions that were assessed at the maximum; it showed the satisfaction with kindergartens and schools.

The results of the survey confirmed the conclusions made in other studies about the importance of conditions and opportunities for the professional development for doctors [19–20]. Therefore, the management of medical organizations needs to take measures on contributing to the professional and career growth of specialists. To level up the satisfaction with the working conditions, it is necessary to take management decisions on improving the labor organization. As for local governments in some municipalities, they must create conditions for improving the attractiveness of a settlement for specialists: the provision of accommodation under the employment rent with the further transfer to social rent, as well as leisure conditions for the population. And the more distance from large cities is, the more attention should be paid to improving the attractiveness of the settlement for professionals. It is possible to solve the human resources problem of the rural health care with doctors only through joint efforts of health care managers and authorities at various levels.

ETHICAL CLEARANCE

The ethical permission was obtained from the ethical commission at the Department of Public Health and Health Care of the Tyumen State Medical University of the Ministry of Health of the Russian Federation, as well as from the Department of Health Care in the Tyumen Region that agreed to carry out the study.

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Immunological And Morphological Substantiation Of The Use Of Dental Stick With Biopharmaceuticals In The Complex Therapy Of Inflammatory Periodontal Diseases

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ABSTRACT

Aim of the study: clinical, immunological and morphological substantiation of the use of a dental stick with biopharmaceuticals in the complex therapy of inflammatory periodontal diseases. Research methods: leukocyte migration test, cytograms, the study of quantitative and qualitative content of spontaneously released mixed saliva, measurement of the total content of protein, the content of secretory immunoglobulin A (sIgA) and lysozyme in it. Clinical improvement of the periodontal tissues condition after treatment by 77% was registered. OHI-S (hygienic index), PI (periodontal disease index), PMA (papillary-marginal-alveolar index) were 7.5, 3.4, and 8.7 times lower, respectively, compared to the pre-treatment group. The depth of periodontal pockets decreased 2.6-3.4 times, the number of sessions per treatment course was reduced to 3-8 visits to the doctor. The amount of mixed saliva (in comparison with the initial data) increased 2.7 times, normal levels were restored and were 1.2 ml higher than control indicators. Protein levels, lysozyme and sIgA concentrations increased and exceeded the pre-treatment level 1.8 times and by 44.5%, respectively. Cytograms data revealed that the number of red blood cells (in one field of view) in the gingiva specimens in inflammatory periodontal diseases (IPD) patients was 2.3 times lower, count of leukocytes with signs of destruction was 13.4 lower and intact leukocyte count was 3.8 times lower. Lymphocyte count was 2 times lower, indicating that the inflammatory process in periodontal tissues was reduced as a re-

sult of the reduction of the microbial burden: staphylococci and actinomycetes were detected 3 times less often, diplococci – 3.5 times less often, filamentous bacteria and streptococci – 4 times less often, protists – 5 times less often, respectively. The number of cocci microcolonies was 2.7 times higher. The number of fibroblasts (in one field of view) increased threefold, the content of collagen filaments of the normally oriented structure increased 1.4 times, compared to the original data, which indicated the formation of favorable conditions for healing and reparative regeneration processes. The results of the study showed that the use of a dental stick during local IPD therapy is an effective way of correcting changes in clinical and laboratory indicators of local immunity and that dental stick is a promising new dosage form in practical periodontology.

Keywords: periodontitis, immunity, (*Galleria mellonella*), immunoglobulin A, lysozyme.

INTRODUCTION

Inflammatory periodontal diseases (IPD) are socially important issues worldwide, in both developed countries with high living standards and developing countries [14, 15]. IPD in the Russian Federation are wide-spread (55-98%) and have been and remain an important reason for permanent expansion and improvement of various techniques and methods for treatment of periodontal diseases, development of new drugs providing suppression of inflammation

with minimal side effects [1, 2, 8, 9, 13]. In modern conditions of import substitution, the development and practical application of new medicinal products with a broad spectrum of therapeutic effects and high biological activity is highly relevant [6, 7, 12]. We experimentally developed and substantiated a technology that uses a combined composition for the achievement of an effective concentration of biologically active substances in the area of inflammation and its maintenance for a period of time required for treatment. We applied soft dosage form – a dental stick for individual use – in dental practice. The following active substances were used in the dental stick: metronidazole – an antimicrobial substance that has an effect on anaerobic protozoa and bacteria; Bactisubtil – a probiotic for the correction of oral dysbiosis; and, for the first time, an extract of honeycomb moth (*Galleria mellonella*) larvae – a stimulator of metabolic and reparative processes. The dental stick has antiviral, antioxidant, enteroantiseptic, antimicrobial, immunomodulatory, and regenerative properties, and in combination with additional modern excipients – high-molecular compounds – also has a pronounced prolonged effect. This allows to achieve a high concentration of active substances in the gingival fluid in the periodontal complex and directly suppress inflammation and stimulate metabolic and reparative processes in periodontal tissues [3, 10, 11].

Aim of the research:

Immunological and morphological substantiation of the use of a dental stick with biopharmaceuticals in the complex therapy of inflammatory periodontal diseases.

MATERIALS AND METHODS

Studies were conducted on 96 patients with inflammatory periodontal diseases,

aged 20-70 years. Patients signed an informed consent form. Forty-two men (43.7%), and fifty-four women (56.3%) with chronic catarrhal gingivitis (CCG) and chronic generalized periodontitis (CGP), K05.1 and K05.3, respectively, according to ICD-S-3 based on ICD-10. All patients were divided into groups: the control group (n = 25) – practically healthy individuals who did not have dental and somatic pathology at the time of the survey; Group I (n = 96) – IPD patients before treatment; and Group II (n = 96) – IPD patients after treatment with the use of a stick. Assessment of the treatment effectiveness was carried out using clinical and laboratory parameters recorded before and after treatment. The state of periodontal tissues was evaluated using clinical data and indices: hygienic index (OHI-S), periodontal disease index (PI), papillary-marginal-alveolar index (PMA), the depth of periodontal pockets, and radiographs data. Laboratory studies were carried out to obtain cytograms, data on leukocyte migration test indicators, quantitative and qualitative content of spontaneously released mixed saliva, and total content of protein, the content of secretory immunoglobulin A (sIgA) and lysozyme in it [5].

Statistical processing of the results was performed using standard methods. The arithmetic mean (M), the standard error of the arithmetic mean (SE), and the standard deviation values were determined. The assessment of the significance of differences in indicators was performed using Student's t-test. Differences were considered statistically significant at $p < 0.05$ [4].

RESULTS

In practically healthy individuals from the control group, there were no complaints of bleeding gums, and the inspection of the oral cavity did not reveal

a clinical change in the periodontium. IPD patients before treatment had more intense bleeding, hyperemia and swelling of the gums, deeper periodontal pockets, higher abnormal mobility and recession of the teeth, and more severe destructive processes in bone tissue associated with a higher number of removed and filled teeth and worse hygiene. Indicators of dental indices OHI-S, PI, and PMA are shown in Table 1.

The results of the study of local immunity indicators are summarized in Table 2. This data shows that the amount of saliva produced in patients with IPD was initially 2 times lower than in the control group. The protein content exceeded the reference level by 27% and the background number of leukocytes in the oral cavity – by 52%. The migration activity of leukocytes in response to the influence of chemoattractant (egg albumin) was 4 times higher than in the control group. The leukocyte count did not restore to the initial level after the chemoattractant lost its effect. At the same time, the levels of lysozyme (1.9 times) and sIgA (by 43%) were lower in mixed saliva compared to the control group. This data indicated the presence of an inflammatory process in IPD patients, a decrease in antimicrobial protection and intense immunological response.

Results of the use of an experimentally developed dental stick with the original composition showed positive clinical dynamics for the periodontal tissues. Upon completion of the course of treatment, reduction of pain during eating, bleeding, hyperemia and swelling of the gums were recorded in all patients. Reduction of signs of inflammation began on the second day, complete epithelialization occurred after 3–8 days depending on the severity of inflammation. The clinical efficiency of IPD treatment was assessed and assigned one of the following grades: excellent, good,

satisfactory and unsatisfactory. The use of a dental stick contributed to an increase in the number of excellent results in patients to 68.6%. At the same time, periodontal pockets were preserved, reflecting the degree of destruction of the bone of the alveolar processes, their depth decreased 2.6–3.4 times, the mobility of the teeth decreased due to the restoration of dento-gingival attachment. The effectiveness of treatment was also demonstrated by the reduction of periodontal indices after treatment: OHI-S – 7.5 times, PI – by 70%; PMA – 8.7 times (Table 1).

Table 1. Clinical efficiency of treating patients with inflammatory periodontal diseases using a dental stick ($M \pm m$).

Parameters	Patient groups	
	Group I (n = 96)	Group II (n = 96)
1. The disappearance of signs of inflammation, days	0	1.18±0.03
2. The disappearance of pain, days	0	2.13±0.21
3. Complete epithelialization, days	0	4.18±0.13
4. Green-Vermillion index, after 1-3 days	2.32±0.30	0.31±0.02
5. PMA index	46.24±2.11	5.32±0.35*
6. Periodontal index	3.83±0.21	0.41±0.03*

* differences with the original data are significant at $p < 0.05$.

IPD therapy with the use of a dental stick with biopharmaceuticals, due to the original composition of basic and additional substances, had a selective and prolonged effect on microorganisms and pathological (abnormal) focus of inflammation for up to 5.5 hours (experimentally established using thin layer chromatography). This reduced the number of applications to 3 times during the day, and also reduced the number of sessions per treatment course. The number of procedures was determined

based on the rate of disappearance of pathological inflammatory symptoms and was: three sessions for patients with gingivitis and mild CGP, 5.5 sessions for patients with moderate CGP, and 7.5 sessions for patients with severe CGP. Studies of the functional parameters of local immunity showed that the amount of mixed saliva (in comparison with the initial data) increased 2.7 times, normal levels were restored and were 1.2 ml higher than control indicators ($p > 0.05$). Additionally, protein levels in the mixed saliva increased ($p < 0.05$), lysozyme and sIgA concentrations increased 1.8 times and by 44.5%, respectively. This indicated an increase in the bactericidal and antiviral activity of mixed saliva. However, the indicators did not reach the levels recorded in the control, as during inflammation, mixed biofilm flora and microorganism toxins inactivate lysozyme, normal flora loses the ability to synthesize muramidase and is replaced by pathogenic allochthonic flora. Additionally, it was established during the leukocyte migration test that the background number of leukocytes in the lavage fluid did not completely recover. The migration activity of leukocytes in the oral cavity

after stimulation with egg albumin was high, and their number did not recover after the chemoattractant stimulation was stopped. The obtained data showed that the inhibition of leukocyte functional activity in patients with IPD persisted even after treatment, which may be due to the retention of endogenous factors of pathogenesis and biologically active substances in tissues: prostaglandins, peroxidation products, free radicals, endotoxins, exoenzymes, antigenic material. Results of the treatment of IPD patients with the use of dental stick showed a decrease in the severity of the inflammatory process, dysbiosis in the oral cavity, disruption of the general reactivity of the body, and an increase in the activity of local factors of natural protection (Table 2).

The results of the study of cytograms revealed that the number of erythrocytes (in one field of view) in specimens from the gums of patients with IPD after the end of the treatment course decreased 2.3 times, which indicated that the biopharmaceuticals in the stick had a thrombolytic effect. A complex of neutral and alkaline proteinases in its composition leads to a reduction of fibrin deposit in the inflammation area

Table 2. Parameters of local immunity and leukocyte migration test before and after treatment with the use of a dental stick in patients with inflammatory periodontal diseases.

Parameters ($p \pm m$)	Patient groups		
	Control (n = 25)	Group I (n = 96)	Group II (n = 96)
The amount of mixed saliva, ml	3.00±0.05	1.54±0.10	4.22±0.12
Protein, g/l	1.50±0.82	1.90±0.10	3.23±0.21
Lysozyme, g/l	14.30±0.70	7.60±0.50	13.64±0.18*
sIg A, g/l	592.4±24.7	335.0±18.2	484.4±11.2*
Leukocyte count: original, $\times 10^9/l$	0.50±0.02	0.76±0.21	0.53±0.11
10 minutes after stress application (stimulation), $\times 10^9/l$	0.70±0.03	2.78±0.40	1.52±0.10*
20 minutes after stress application (regeneration), $\times 10^9/l$	0.20±0.01	2.70±0.38	0.45±0.12*

* differences with the original data are significant at $p < 0.05$.

and normalization of vascular permeability, improving the microcirculation and rheological properties of blood. The number of leukocytes with signs of destruction (criterion of inflammation intensity) was 13.4 times lower and the number of intact leukocytes was 3.8 times lower, the number of lymphocytes was 2 times lower, indicating that the inflammatory process in periodontal tissues was reduced as a result of reduction of the microbial burden. Staphylococci and actinomycetes were detected 3 times less often, diplococci – 3.5 times less often, filamentous bacteria and streptococci – 4 times less often, protists – 5 times less often, respectively. The number of cocci microcolonies was 2.7 times higher, which indicated the restoration of normal flora. The number of associations of filamentous bacteria and cocci was 2 times higher in case of severe CGP. The epithelium after treatment in 15.8% of patients had signs of increased proliferative activity, “pseudo-key” cells were detected in 6.25% of patients, layers of squamous epithelium were found in 20% of patients, and single epithelial cells were discovered in 40% of patients. In IPD patients, the number (in one field of view) of surface epithelial cells, the number of cells with signs of destruction (vacuolated, naked nuclei) and keratinization, and signs of phagocytic activity (auto-aggressive) in specimens significantly decreased after treatment, which indicated a decrease in the periodontal tissue deterioration. The periodontal pocket cells were not found, the gingival epithelium cells of the gingival sulcus were detected, indicating the regenerative processes that lead to the restoration of the normal organotypic structure of the attachment epithelium – the cells had a polygonal shape, were closely adjoined to each other, the nuclei of cells had an oblong shape. Fibroblast count in one field of view increased threefold and the number of collagen filaments with correct

normally oriented structure was 1.4 times higher compared with the initial data, which indicated the formation of favorable conditions for healing and reparative regeneration processes. Stimulation of fibroblasts and collagen synthesis is one of the likely mechanisms of the reparative effect of biopharmaceuticals in the dental stick composition. It had a stimulating effect on reparative processes in the connective tissue structures and contributes to the reduction of dystrophic processes in them.

DISCUSSION

Combined dental stick composition with biopharmaceuticals with antimicrobial, anti-inflammatory, regenerating effects allows reducing the time period for complete resolution of the inflammatory process by improving the anti-inflammatory therapy in the focus of inflammation and administration of pharmacological substances with a wide spectrum of therapeutic activity. Experimentally developed original composition and production technology of a dental stick have effects on the main pathogenesis stages of IPD, and, due to the consistency and physicochemical properties of the proposed optimal composition of ingredients – foundation and additional surfactants – adheres to the gingival surface. The prolonged effect is experimentally proven to persist for 5.5 hours. The release of the active substance metronidazole within an hour amounted up to 85% and the pharmaceutical accessibility was increased due to the effect of the excipients. All components in the composition of the dental stick have certificates of accordance with quality standards and are officially approved for use in the Russian Federation. All components in the dental stick in combination create and enhance a stable depot of maximum

accumulation of therapeutic concentrations of drug substances and active ingredients in the pathological areas of infection. They have a synergistic and prolonged effect, which allows changing the effect on the cellular mechanisms of inflammation, creates favorable conditions for healing, regeneration, and restoration of tissues of periodontal complex. A comparison of clinical and stomatological data and laboratory tests allows us to conclude that the use of dental stick based on biopharmaceuticals of in complex therapy of IPD improves the clinical efficiency of the IPD treatment and restores disruptions of local immunity. According to cytogram data from the specimens from the patients after treatment, the number of surface epithelial cells, the number of cells with signs of destruction, keratinization, and phagocytic activity decreased; periodontal pocket cells were not found, epithelial cells of the gingival sulcus were discovered, changes in the microbial flora, formation of fibroblasts and collagen, restoration of the normal structure of the gum epithelial cover and functions of epithelial cells were recorded. The obtained results allow us to recommend the use of a dental stick as a new promising dosage form in periodontal practice to control inflammation, preserve teeth and maintain their function for a long period, stabilize the process and increase the duration of remission, accelerate the rehabilitation of patients with periodontal diseases.

CONCLUSION

1) The experimentally developed dental stick has a pronounced prolonged, regenerating, immunomodulatory, antiviral and entero-antiseptic effect, with good adhesion of active substances to the gums and even distribution on the mucosal surface. Stick is convenient to

use, which allows expanding the range of newly created pharmacological forms for treating inflammatory periodontal diseases.

2) The newly developed dental stick affects the main pathogenesis stages of inflammatory periodontal diseases, which allows achieving high clinical efficiency with the subsequent effect of prolonging the therapeutic action, allowing reducing the course of treatment to 7-8 days.

3) The use of a dental stick leads to an improvement in the clinical parameters, dental indices, and indicators of local protection factors (sIgA, lysozyme, leukocyte migration test). The correction of deterioration of local protection factors creates favorable conditions for the surgical phase of treatment and the postoperative period of periodontal tissue repair.

4) The obtained cytogram data indicates that the treatment results in a decrease in the intensity of desquamation of the epithelium, the restoration of the normal structure of the gum epithelial cover and the functions of epithelial cells, the elimination of foci of inflammation, and the restoration of the epithelium structure.

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Specifics Of Psychological And Pedagogic Correction Of Deviant Behavior In Younger Adolescents With Intellectual Disability

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ABSTRACT

Problem and aim. Deviant behavior is not only an alarming phenomenon but also a multitude of social, pedagogic and psychological problems that threaten the society and that became particularly relevant for the young adolescents with intellectual disability. Therefore, the aim of the present article is to reveal the specifics of correctional and developmental work with such children that would provide appropriate interpersonal interaction in the adolescence and the further positive socialization.

Methods. The presented study was conducted in three stages (exploratory-preparatory, experimental and control-generalizing stages) with the use of the Buss-Durkee Hostility Inventory.

Results and discussion. The results showed that the predominant form of the deviant behavior was hostility and violence, as well as a tendency for addictive behavior. Diagnostics of the dominant indices of hostility and aggressiveness demonstrated that the aggressiveness index dominated in the majority of adolescents. The majority of adolescents had a very high or high level of indirect hostility and assault, along with suspicion. The correctional program provides correctional effect for the adolescents with low and medium level of proneness to the deviant behavior.

Keywords: *psychological and pedagogic correction, deviant behavior, younger adolescents, intellectual disability, indices of hostility and aggression*

INTRODUCTION

Psychological and pedagogic correction is a psychological intervention

that targets certain mental structures in order to provide appropriate personality development and functioning [1, 2, 3].

In other words, psychological and pedagogic correction is a type of psychological assistance aimed at correcting personality traits in mental development that fully, or partially, do not meet the age- and social norms of the given society.

Adolescents' behavior is determined by rather high requirements from the society, namely the level of adolescent's independence, self-sufficiency and responsibility has to correspond to the level of adults' social maturity. Social immaturity inevitably leads to the deficits in the interaction between the person and the environment [4, 5, 6].

Adolescence is characterized by anxiety, fears, insecurity and feeling of loneliness. Based on this, adolescents' behavior can take the forms of protest, such as skipping the lessons in school, violence towards animals, aggression towards younger and weaker people, petty theft, alcohol and drugs, vagrancy, etc. [7, 8, 9].

Positive developmental results achieved at the preceding age stages suggest that the child's development during adolescents should not be exceedingly troubled by unfavorable consequences. Therefore, the children with deficient development have more complicated conditions for developing an integral personality. Disability (hereinafter, ID) is a disruption of the normal development rate that causes the child of a certain age to remain within the interests that were typical for the previous age group.

Psychological science defines the concept of behavior as a person's activity in the variety of its manifestations, such as activity, reflection, creation and cognition [10, 11, 12].

External manifestations of activity include various actions, movements and deeds. Internal activity implies the processes of internal regulation, goal-setting, motivation and emotional reactions.

Human behavior is social, which allows addressing it as an action towards the surrounding people and the material world that are regulated by the moral norms and rights.

Evaluating a certain behavior implies comparing it with an established norm. In case of a deviation from this norm, the behavior is considered to be deviant [13, 14, 15].

The concept of deviant behavior includes such characteristics, as criminality, delinquency and immorality.

Delinquent behavioral characteristics include aggression, vagrancy, skipping the lessons in school, extreme disobedience, violence towards the weaker, swearing, hostility towards the adults and extreme intolerance to pedagogic interventions.

Immoral behavior, i.e., behavior that contradicts the general human norms, is related to personality abnormalities. Immoral behavior is a predisposition for criminal and delinquent behavior.

Adolescence is the most difficult and complicated period of children's development, since it is the period of personality establishment. Moreover, it is the most crucial period because it includes the development of the morality bases, social beliefs and attitude towards oneself, the people and the society. Adolescence occurs within the ranges of 10-11 and 15-16 years of age. This interval contains drastic changes in the adolescent's body. It grows intensively, the body mass increases and the skeleton grows faster than the muscles,

cardio-vascular system develops – in general, the body goes through puberty. During this time, substantial imbalance of the development of various organ systems leads to increased fatigue, excitability, irritability and negativism [16, 17, 18].

While addressing behavior, it is necessary to note that, during adolescence, the content and the role of imitation in personality development also change. At the early stages of the ontogenesis, imitation was involuntary and random. In turn, during the adolescence, imitation becomes controlled and voluntary.

In the beginning of this age, adolescents strive to imitate the adults that they find to be an authority for them, and gradually obtain the tendency for imitating older peers. Adolescents often lack critical evaluation of the adulthood attributes that they choose to imitate, which leads to a controversial situation where they do not yet have established capabilities for meeting the requirements of the set example. This often causes various aspect of adolescents' deviant behavior.

Behavior within interpersonal communication becomes the leading activity in the adolescence [19, 20, 21]. It becomes increasingly important for an adolescent to be affiliated to a referent group; an adolescent strives for taking a relevant place within such group. This urge is explained by the fact that it satisfies the adolescent's need in recognition and self-affirmation. Lack of the possibility to feel affinity and relevance in the group often leads the adolescents to social maladaptation and crime. The values are re-evaluated according to the communication with the peers, yet the moral beliefs are situational and do not transform into the worldview, because they are not affected by the relevant group.

As regards the deviant behavior, it is necessary to point out that majority of adolescent felonies and crimes are

committed in the referent group, since the fear of punishment decreases in a group, aggression and violence increase, and criticality of the events and oneself decreases [22, 23, 24].

Personality of an adolescent with deviant behavioral traits is characterized by: decreased general activity and sociability with the urge to dominate; emotional instability and excitability with weak awareness of the negative emotional manifestations (hostility, negativity, etc.); low level of sense of life purpose and ability to control oneself, together with increased self-esteem.

Specifics of the deviant behavior in adolescents with ID are determined by its essence, types and possible reasons.

Instability of the emotional field, being combined with relatively well-developed cognitive activity, leads to rapidly occurring mental fatigue that, in turn, defines frequent mood changes. Such state during the solution of educational problems might become the reason of emotional crashes and deviant behavior [25, 26].

Emotional and volitional immaturity is often combined with undeveloped regulation of behavior; moral immaturity is combined with underdeveloped sense of responsibility and self-sufficiency, weak volitional control and infantile traits in statements and behavior.

Emotional and volitional immaturity is also manifested in the personality specifics of the adolescents with ID, such as increased suggestibility, low awareness and explosive affectivity. Teachers characterize such adolescents as difficult to control, not being aware of the responsibility, passive during the lessons and uncontrollable during the breaks.

These adolescents also demonstrate insufficient level of self-awareness that is presented in largely situational self-esteem and controversial statements about a certain issue. Underdevelopment of internal self-esteem criteria makes

these adolescents highly dependent on the external circumstances, which defines their lack of self-sufficiency, rigid nature of opinions and proneness to conflicts. However, they also have a tendency for overestimating their abilities, having aspirations that are incompatible with their abilities, which might also lead to deviant behavior.

The adolescents' mental instability leads to conflict situations, deficits in self-regulation and self-control. Their interpersonal relationships are based on causality and irresponsibility, they tend to underestimate difficulties and specifics of a given situation. They do not feel long-lasting remorse about educational failures and often forget given promises; they self-validate by the tendency to lie.

Previous studies reported a strong correlation between the deviant behavior and troubled family situation. Many children with ID experience emotional rejection by their parents. Disappointment in one's own child is often followed by shame for her/his incapacity. Parents often reserve to physical punishments that they justify by the fact that the child does not understand verbal instructions. Unfavorable psychological climate in the troubled families is the leading factor of social maladaptation of the adolescents with ID. It therefore defines the deformations in the adolescents' development and socialization, thus facilitating the development of deviant behavior [27, 28, 29].

Therefore, deviant behavior is not only an alarming phenomenon but also a multitude of social, pedagogic and psychological problems that threaten the society and that became particularly relevant for the young adolescents with ID. Therefore, the aim of the present article is to reveal the specifics of correctional and developmental work with such children that would provide appropriate interpersonal interaction in the adolescence and the further positive socialization.

METHODS

The presented study was conducted in three stages (exploratory-preparatory, experimental and control-generalizing stages) with the use of the Buss-Durkee Hostility Inventory.

The group of adolescents that participated in the study presented ID of different genesis: constitutional (13%), somatogenetic (6%), cerebral-organic (33%), and psychogenetic (46%).

The majority of adolescents (12 people) lived in complete families, two were from incomplete families, and one adolescent was living in a foster family. The majority of families belonged to the middle class.

The preliminary interview with school teacher-psychologist revealed that these adolescents had such specific personality traits as anxiety, undeveloped learning motivation and decreased level of the need in achieving high results, along with protest reactions to teachers' demands, proneness to conflicts, verbal and physical aggression and negativity.

RESULTS AND DISCUSSION

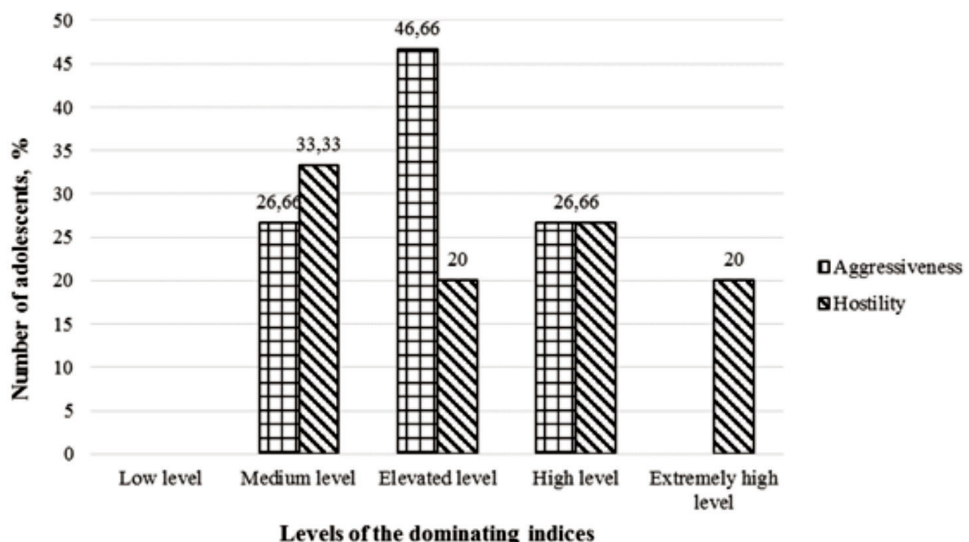
Figure 1 shows the characteristics' distribution upon the five levels of dominating indices of hostility and aggressiveness in younger adolescents.

The hostility index is characterized by the reaction to negative emotions and negative judgments of people and events. The figure shows that the experimental sample did not have the low level of hostility. Five people (33.33%) had the average hostility level, i.e., the environment and educational conditions provided these adolescents with an opportunity to cope with such state on their own.

Three adolescents (20%) presented the elevated hostility level. This means that these adolescents may be impulsive in reacting to the negative emotions and tend to negatively evaluate the events. They can cope with their emotions on their own but, in some cases, might need help from the significant others.

Four participants (26.66%) presented the high level, and three participants (20%) – the extremely high level. These data suggest that these adolescents experience stable hostility towards people,

Figure 1. Distribution of the dominating indices of hostility and aggressiveness in younger adolescents with ID, according to the Buss-Durkee Hostility Inventory



mistrust towards the adults, difficulties in communicating with the peers and the world. Intensive hostility with openly expressed exaggerated feelings has destructive impact on the adolescents themselves.

Adolescents with ID often do not understand what is happening to them, and they are unable to comprehend their feelings, which leads to explosive emotions that are then replaced by isolation and lack of will to communicate.

We would like to note that adolescents with ID experience hostility towards the people near them. These children are constantly ready to openly and actively manifest the negative emotions.

The aggression index is characterized as a tendency for destructive interpersonal relationships. Aggression has different levels of manifestation.

Only four adolescents from the experimental sample (26.66%) demonstrated the medium level of aggression, i.e., within the normal limits. This group of adolescents manifests different types of aggression in emotionally significant and stressful situations, situations of extreme tension; however, in normal conditions, such aggressive behavior is not common in them.

The majority of the participants (seven adolescents, i.e., 46.66%) had elevated level of aggressiveness. They are characterized as being difficult to control and prone to acute negative reactions that become more frequent when the adolescents perceive their environment as hostile.

Four adolescents with ID (26.66%) had high level of aggression that defined a personality that was prone to conflict and incapable of conscious cooperation. Such aggressive adolescents cause a lot of trouble in the educational institution, evoke parental concern and become the reason for conflicts with the peers. The extremely high level of aggressiveness was not revealed in our sample.

The results described above determine the need to conduct the correctional interventions in accordance with a group of general principles [30, 31, 32]: principle of comprehensiveness (psychological and pedagogic correction is an integral system of psychological-pedagogic interventions); principle of confidentiality (all information obtained by a psychologist is not disclosed under any circumstances, unless the client's life is in danger); principle of humanity (kindness and respect towards each participant of the correctional program); principle of unity of diagnostics and correction (diagnostics of certain psychological parameters should be conducted only with the consequent correctional activities, upon the revealed deficits or risk factors); principle of personality approach (an individual approach towards each child as a unique personality that helps the child to self-actualize; personality in general is considered throughout the correction); principle of hierarchy (creation of the zone of proximal development); principle of responsibility (the psychologist is personally responsible for students' well-being); and principle of systematic approach (the psychologist has a clear idea about the ranges of competence and defines them).

Organization of the psychological and pedagogic correction of the deviant behavior in younger adolescents with ID begins with the creation of its model.

Modelling allows describing the main characteristics of the studied process and provides its integral representation.

Modelling the correctional interventions is aimed at changing and developing the communicative skills, conscious regulation of behavior, overcoming selfish motives in interacting with the peers and deceitfulness, along with developing moral norms and values that are shared by the society, the emotional field and empathy.

The correction of the deviant behavior in younger adolescents with ID is conducted in line with psychological-pedagogic approaches, considering the type of personality specifics.

Correctional work is a process that results in revealing the deviations from the expected results of the children's activity and making certain changes in this process, in order to reach a certain outcome. Such type of assistance is the activity that is aimed at developing individual's psychological qualities necessary for improving the adaptation to life conditions and socialization [33, 34, 35].

This assistance is the most successful when the psychological intervention is conducted with special tools. For example, in case of younger adolescents with ID, the most effective forms of assistance are game therapy and psychological gymnastics.

Game therapy within psychological correction helps balancing the personality in the troubled adolescents by developing the skills of self-expression and self-cognition; it also corrects the emotional state. Psychological gymnastics includes the use of motor expression as the main tool of communication in the group. Game therapy and psychological gymnastics, when adapted to the specifics of younger adolescents with ID, help overcoming such phenomena, as tension, anxiety, rigidness and fear of informal contacts in an unfamiliar situation.

Successful correction that does not meet these requirements can lift some barriers in interpersonal relationships and socially accepted behavior, but it cannot guarantee generally successful socialization of the adolescents with ID.

CONCLUSION

Psychological and pedagogic literature lacks a single definition of the deviant behavior. Researchers from different

fields address it in different ways. However, one characteristic is present in the majority of definitions: deviant behavior is characterized by the violation of socially accepted, conventional and well-established moral norms and rules, combined with aggressiveness.

Psychologists characterize adolescence as a particularly uncomfortable age. Adolescents strive to communicate with the peers and belong to referent groups. Their motives change: they want to experience their relevance in the group of peers and to seem like a mature person in front of others. This often becomes the source of the deviant behavior.

The main characteristics of the deviant behavior in the adolescents with ID are insufficient self-control, increased suggestibility, low and imprecise awareness of the moral norms, proneness to conflicts, clear susceptibility to situational factors and aggressive behavior. Factors that affect the development of the deviant behavior include: emotional instability, flaws in the moral behavior and specifics of the interactions within the families of the adolescents with ID.

The suggested psychological and pedagogic correction of the deviant behavior in the adolescents with ID consists of four blocks: diagnostics, correction, analysis and prognosis. Teachers-psychologists need to select the appropriate principles and methods of correcting the conflict behavior, considering the age and individual specifics. It is also necessary to consider that the effectiveness of the psychological and pedagogic correction depends on three components: adequate aims and tasks; correct choice of correctional methods and principles; prediction of the actual results during the modelling stage.

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Antagonistic Activity of Microbial Association of Kefir Grains And The Areas of Its Usage

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ABSTRACT

One of the newest areas of using the potential of a microbial association of kefir grains is obtaining a biodegradable film. The research was aimed at creating a packaging material with new properties of suppressing the development of concomitant microflora in dried berries and fruits.

Keywords: *microbial communities, microbes' survival rate, adhesion, water-soluble biodegradable film, immobilization of microorganisms.*

INTRODUCTION

The main area of practical use of the kefir grains is the dairy industry, where they are used as the basis for obtaining kefir with various fat content. A priority area in using kefir grains in the food industry is obtaining functional food products of high physiological value, with treatment and prevention, dietetic and medicinal properties, i.e. contributing to improving human health. This includes production of not only kefir-based drinks, but also of meat products and sausages subjected to enrichment with microbial cells of kefir grains' association.

Kefir grains have been used for a long time in industrial condition, and have been for many years the object of study of researchers, such as N. I. Khamnaeva, V. D. Olmoeva, Y. A. Zverkova, Rudenko, Kozyreva, E. G. Leonova, D. V. Shalbuev, V. A. Ton, V. A. Alekhina, A. V. Ekhrenova, V. V. Badanov, and others.

Kefir grains are widely used in medicine.

Kefir, being a fermented milk product of combined fermentation that consists of lactic acid bacteria and yeast, and containing immune protein fractions of milk in a highly digestible form, may be used as a therapeutic dietary agent for treating diseases of various kinds associated with anemia, for chronic processes in the respiratory organs, diseases of the digestive system, including disbacteriosis [1].

Consumption of kefir improves protein digestion and reduces the glycemic index; it also stimulates the immune system, has an antibacterial and anticancer effect, and helps improve digestion. Kefir has anti-inflammatory and anti-allergic action, which is a therapeutic potential for treating allergic bronchial asthma [2].

In animal breeding, cultures of strains *Lactobacillus gallinarum* RNCIM B-10131, *Enterococcus hirae* RNCIM B-10091, *Saccharomyces unisporus* RNCIM Y-3416, *Lactobacillus gallinarum* RNCIM B-10134, *Enterococcus hirae* RNCIM B-10088, *Enterococcus durans* RNCIM B-10093 isolated from the microbial association of kefir grains are used for intensifying the growth and development of the experimental young pigs and broiler chickens [3].

The authors also studied the use of whey fermented with kefir grains in the consumer goods industry for processing rawhide [4].

Antibiotic activity of a microbial association of kefir grains is shown in Table 1

Table 1: Antibiotic activity of the microbial association of kefir grains

Name of cultures	Antibiotic activity (dissolution)				
	1:2	1:4	1:8	1:16	1:32
Lactose-fermenting yeast	-	-	+	++	++
Microbial association of kefir grains	-	-	+	++	+++
<i>L. acidophilus</i> 317/402	-	-	-	+	++
Consortium: lactose-fermenting yeast, microflora of the microbial association of kefir grains, <i>L. acidophilus</i> 317/402:					
Variant 1 with the ratios of 0.5:1:1.5	-	-	+	++	++
Variant 2 with the ratios of 1.5:1:0.5	-	-	+	++	++
Variant 2 with the ratios of 1:1:1	-	-	+	+	++

The widely known antibiotic and antagonistic properties of microbial association of kefir grains have been studied. Microorganisms of kefir grains show antagonism to *C. albicans*, to filamentous grains of genera *Aspergillus*, *Penicillium*, *Fusarium*, *Mucor*, *Absidia*, *Rhizopus*, *Cunninghamella*, and the inhibitory effect on the growth of the fungi is observed not only in the kefir microorganisms, but also in their metabolites formed during the cultivation process [5]. Antagonistic properties of microbial association of kefir grains to the microflora of spoilage are widely known. In this regard, searching for ways of using live cells of the microflora of kefir grains in packaging materials is relevant [5].

The latest trend is the use of the potential microbial association of kefir grains in obtaining a biodegradable film based on sodium alginate with live cells of the microbial association of kefir grains.

Based on the specially selected ingredient composition of the film, which includes the microbial association of kefir grains, it is planned to obtain a biodegradable film that would be transparent and have no structural flaws, would feature high plasticity and strength, would have the taste deter-

mined by its purpose, and would feature long shelf life. This is possible because the composition for obtaining an edible homogeneous film with a certain taste that would be degradable in hot water is the following: flavor base, sodium alginate, microbial association of kefir grains, glycerin, water solution of vitamin C. Packing obtained from the described compositions does not react with the products packed in it, does not alter its taste, odor, color, flavor, and does not cause migration of material elements into the product, and does not get destroyed by its effects.

METHODS

The methods used in the research were as follows:

1) Microbiological methods of counting the amount of microflora (i.e. the number of active cells of mesophilic and thermophilic microorganisms, and the number of active cells of the lactose-fermenting yeast, CFU/cm³, electronic microscopy).

2) The antagonistic action of the studied cultures was identified by the method of joint cultivation of the antagonists and the test cultures in milk.

3) Physical methods (pH, titratable acidity, optical density, the rate of base film solidification).

4) Chemical methods, including biochemical one (biochemical analysis of the film).

5) Organoleptic assessment methods (transparency, consistency, taste, color, smell of the films).

6) Bibliographic studies (Analysis of the fundamental literature and publications in the magazines devoted to studying the survival of microorganisms on various media, a patent study of the issue).

RESULTS

The research allows identifying the ability of the microbial communities of the Transbaikalia ecosystem to immobilize themselves, and their survival rate on various media.

The packaging material obtained from the compositions of the studied project will not react with the products packed in it, will not alter its taste, odor, color, flavor, and will not cause migration of the material elements into the product, nor will get destroyed by its effect. Upon reaching the threshold temperature (80 °C) and after wetting with water, the film becomes biodegraded, which is indicated by dissolving in a certain amount of liquid.

An important factor that determines the resistance of the developed polymer to biodegradation is the size of its molecules. Biodegradation of the polymer is initiated by the processes of biological and physical nature.

CONCLUSION

Thus, the microbial association of kefir grains features a high antagonistic activity to the opportunistic microflora. The use of microbial association of ke-

fir grains for obtaining a biodegradable packaging material is of interest.

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Prion Diseases: Actual Clinical and Diagnostic Aspects

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ABSTRACT

Recently, the problem of neurodegenerative diseases in the medical community has become increasingly relevant. This is due to many factors: from insufficiently studied mechanisms of development of some nosological units to low awareness of medical workers. Among neurodegenerative diseases in humans, prions constitute a very specific group, which are infectious protein particles with a unique morphological structure and capable of causing a number of incurable diseases. Despite years of research, no optimal remedy has yet been found to treat them. This review examines the already studied aspects of prion diseases as a class, including small historical background, features of ethiology, pathogenesis, course and outcome of the most common of them, as well as existing research on experimental methods of diagnostics, treatment and prevention of prion infections.

Keywords: prion, Creutzfeldt-Jacob disease, Kuru disease, fatal familial insomnia, Gerstmann-Sträussler-Scheinker Syndrome.

RELEVANCE

A prion is an infectious whole protein particle capable of causing transmissible spongiform neurodegenerative encephalopathy in humans and some animals [1, 2]. In particular, in humans, prions cause Creutzfeldt-Jakob disease (there are several forms: sporadic, variant, familial and, in rare cases, iatrogenic), Kuru (in a number of sources called “kuru”), Gerstmann-Sträussler-Scheinker syndrome and fatal familial insomnia.

The occurrence of these diseases is associated with the transformation of PrPc into pathogenic PrPsc. The initiating pathogenetic factors of infection development, as well as possible methods of its treatment, have still not been found [1].

HISTORY OF PRIONS DISCOVERY

In 1933, Icelandic farmers ordered a large consignment containing sheep from Germany for the development of animal husbandry. Several years later, the outbreak of an unknown disease, later called scrapie, was recorded. That outbreak claimed the lives of a large number of sheep. In order to find out the reason of that outbreak, Dr. W. Sigurdsson conducted research and formulated four signs of a new disease: a considerable incubation period, a slow course, an unusual lesion of tissues and organs, and one-hundred-percent mortality. The above signs formed the basis of a new term “slow infections”. Three years later, a doctor from America (D. C. Gajdusek) studied the Kuru tribes of cannibals in the mountainous regions of New Guinea, and discovered a disease that later was named after them. Kuru disease had all the signs of “slow infections”. Thus the integration of veterinary medicine and human medicine occurred [3-5].

MORPHOLOGICAL FEATURES

The group of transmissible spongiform encephalopathies (TSEs) has a number

of common morphological features: the spongiform changes in the brain, neuronal death, astrogliosis and accumulation of the pathological form of the prion protein (PrP^{Sc}) [4, 6, 7, 8]. Under light microscopy, the vacuolation (hydropic degeneration) of the cytoplasm of neurons including their dendrites and axons is observed. In addition to neurons, the dystrophic changes also affect astrocytes [6, 9].

During the incubation period of TSEs in the brain there can be detected characteristic histopathological signs: increase in the number of astrocytes and activation of microglial cells. These changes often precede vacuolation and neuronal death, as well as the development of the first symptoms [6, 7]. Besides, the number of synapses and dendritic spines decreases in the brain substance before the first clinical manifestations appear [7, 10]. In addition to the general morphological features of transmissible spongiform encephalopathies, each nosological entity has its own characteristics. This is largely due to the selectivity of morphological lesions [6].

CREUTZFELDT-JAKOB DISEASE

During the course of this disease, the cerebral cortex is the typical localization of pathomorphological changes. Besides, the basal ganglia, brain stem and cerebellum structures may be affected [8,9, 11]. If the course of the disease is up to 3 months, spongiform changes prevail in the morphological picture. In the period from 3 months to 1 year, the morphological features typical for TSEs are expressed evenly, and if the course of this disease lasts more than 1 year, the predominance of astrogliosis is noted [12].

In case of **Kuru disease**, amyloid plaques are detected in brain tissues with predominant localization of the

pathological process in the cerebral cortex [6, 13].

Gerstmann-Sträussler-Scheinker syndrome. Histopathological changes are primarily detected in the molecular layer of the cerebellum. The cerebral cortex is less affected [6, 14]. The progression of the disease is accompanied by atrophy of these brain regions [6, 15].

In case of **fatal familial insomnia**, the histopathological changes are localized in the neurons of the thalamus. The typical signs are revealed such as neuron death, astrogliosis and presence of amyloid plaques. Spongiform changes of varying severity are observed [6, 16].

The localization and severity of morphological lesions determine the characteristics of the clinical picture of the disease. In many cases, these diseases are not clinically diagnosed, and the changes are detected only during the morphological examination [9, 17].

ETIOPATHOGENESIS

Located in the 20th chromosome of a human cell, prion protein (PrP^c – cellular prion protein), in its structure, is a sialoglycoprotein with a molecular weight of 30-35 kDa, consisting of four α -helical domains and is encoded by the PRNP gene [18]. It is synthesized mainly in neurons, as well as on the surface of many other cells, for example, in the cells of the spleen, gastrointestinal tract, skin and lymph nodes [19]. Despite the fact that the role of PrP^c in the body is not completely examined, it is already known that the range of its functions is quite wide. In Schwann cells, PrP^c maintains myelin homeostasis interacting with Gpr126 G-protein receptor, provides regulation of synaptic transmission in nerve fibers, and also plays an important role in the functioning of circadian rhythms and a number of metabolic processes. Particular importance in the structure of PrP^c

is given to the N-terminal domain, capable of interacting with various ligands (a4b2 peptide, pathognomonic for Alzheimer's disease, α -synuclein, metal ions, etc.). Under currently unknown mechanisms, the process of changing the conformational form of the protein begins; it includes unwinding in α -helix ending and replacing it with β -sheet. As a result, this section acquires the feature of resistance to protease [20-22].

The formed isoform, called PrP^{sc}, becomes neurotoxic and accumulates as insoluble aggregates, forming highly ordered amyloid fibrils. The result of these processes is cell death and the penetration of the pathological isoform into neighboring cells which forms a vicious cycle. The number of PrP^{sc} proteins prone to aggregation among themselves increases over time and is characterized by exponential growth. From the lesion focus, prions can enter the brain through neuroinvasion or through the blood-brain barrier. Once the brain tissue is infected, the replication process starts. Proteins accumulated in large quantities cause a cascade of degenerative processes including the proliferation of astrocytic neuroglia, microgliosis, as well as tissue atrophy and sclerosis due to amyloid deposition. The so-called spongy changes are formed in the brain, and after this process prions begin to spread along the peripheral nerves as the second stage of the replication [23]. A certain role in the pathogenesis of prion diseases is played by microRNA, a class of small non-coding RNAs. The subject of their activity has recently been thoroughly studied. It is believed that this is a vital and evolutionarily old component of a regulated gene expression system involved in many biological processes including the development of some inherited diseases [24-26]. It was shown experimentally that in the brain infected with prions, the deregulation and an increase in the level of expression of a number of microRNAs (for

example, miR-16 in CA1 hippocampal neurons) are observed possibly potentiating the process of conformational changes in PrP^c [27]. Given the high degree of interaction of the N-terminal domain of PrP^c with various ligands including nucleic acid sequence, it is possible that its connection to certain microRNA genes may occur, so it leads to the catalysis of PrP^{sc} formation from PrP^c [28]. However, the exact mechanisms of conformational changes in prion protein have not yet been fully studied. Along with the sporadic pathway of infection described above, there are two more: hereditary and transmissible. During the first one, a germinative mutation in the 20th chromosome occurs, and the pathogenic isoform PrP^{sc} begins to synthesize in large quantities. The latter one occurs in case of eating infected human brain tissue (Kuru disease) or cattle and thermally unprocessed meat products of animals suffering from prion disease. Besides, it may be observed during the biological origin tissue transplantation, administration of crude immunobiological preparations and blood transfusion procedures (some authors refer to this phenomenon as the "iatrogenic way" [29, 30]. In case of the transmissible pathway, the focus of infection is localized primarily in the intestine from which it penetrates into the lymphoid organs, where it replicates and then spreads to the central nervous system.

CLINICAL PICTURE OF PRION DISEASES

The onset of the classical form of Creutzfeldt-Jakob disease (CKD) occurs in people aged from 17 to 87 years (average - 64 years). The main clinical manifestations that have diagnostic value are: progressive dementia as the main symptom; cerebellar symptoms and visual disturbances, myoclonia,

pyramidal and extrapyramidal manifestations and akinetic mutism [6, 7, 9, 15, 31]. The early signs are often characterized by visual impairment, such as the blurred vision, diplopia, nystagmus, strabismus, visual hallucinations, visual agnosia, scotomas, and narrowing of visual fields. In the case of the massive lesions of the cerebral cortex occipital lobes, the cortical blindness develops in the region of calcarine fissure and due to the cortical-strial changes. [8, 10, 11]. Often, the disease is accompanied by the cerebral symptoms in the form of headaches and dizzy spells. In some rare cases, the progressive dementia is preceded by the neurological symptoms, especially it often happens in the so-called amyotrophic form of the disease. There is the spastic paralysis of the limbs in combination with the disorders of the extrapyramidal system. Tremor, choreoathetoid hyperkinesia, and myoclonic epileptic seizures are observed [8, 12]. The sporadic form of CJD is characterized by the relatively rapid progression; the lethal outcome occurs after 6-8 months from the onset of the disease. The clinical picture includes the behavioral disorders and disorders of the higher cortical functions. Besides, the development of the secondary-generalized myoclonic seizures provoked by bright light and a loud sound is also possible [8, 13]. For the new form of CJD, first described in 1995, there are all the same features as for the classical one, but the disease proceeds with more pronounced personal changes manifested in the form of the apathy abulia syndrome, leading to weight loss and exhaustion [8, 14]. Another distinctive feature of the new form is the absence of changes in EEG [32].

Kuru disease, the peak of which occurred in the middle of the 20th century, was observed mainly among the people of the Fore tribe, living in the highlands of New Guinea and practicing an act of cannibalism. Mostly women and chil-

dren suffered from this disease, and in rare cases men. The average duration of Kuru disease is from 3 months to 3 years. The main symptom is the cerebellar ataxia sometimes occurring with visual disturbances. The later symptoms are the bulbar and pseudobulbar disorders characterized by the so-called "violent laughter". The dementia appears only in the terminal stage. The development of bronchopneumonia and respiratory failure usually leads to death [8]. The onset of Gerstmann-Sträussler-Scheinker syndrome occurs between a person's 30 and 40 years, and its average duration is 5 years. The disease is characterized by the persistent symptoms of the cerebellar lesion, development of progressive dementia and blindness [8].

During the fatal familial insomnia, the dystrophic changes in the thalamus are observed as a result of a point gene mutation of the prion protein located in the 20th chromosome. The type of inheritance is an autosomal dominant [33]. The first signs appear at the age of 25 years and older (usually to 50 years), resulting in death, on average, in 1-4 years. The main symptom is rapidly progressive untreatable insomnia. The lack of sleep for a long time leads to the development of the anxiety-depressive syndrome, following with the hallucinations and growing dementia. Subsequently, a dysfunction of the autonomic nervous system is formed, which occurs due to the violation of circadian rhythms that affect the level of blood pressure, body temperature, heart rate, the concentration of hormones in the blood. The cause of death is the exhaustion and development of intercurrent inflammatory diseases [4, 8].

DIAGNOSTICS OF PRION DISEASES

In all cases of the detection of a rapidly progressive dementia (from several

months to two years) in combination with the multiple neurological manifestations, the prion disease should be suspected and appropriate diagnostic measures performed [8, 14]. In the formulation of likely diagnoses, one should be guided by the following criteria: the progressive dementia, absence of fever, normal ESR, leucoformula, absence of pleocytosis in the cerebrospinal fluid; neurological and morphological symptoms characteristic for this group of diseases; detection of scrapie-associated fibrils and protease-resistant PrPc when carrying out Western blotting; changes in EEG for the sporadic forms of CJD. According to MRI results, the later stages of the disease can be characterized by the changes of the brain in the form of the so-called symptom of "honeycombs" (the bilateral hyperintensive signals on T2-weighted imaging), especially often detected in the region of the caudate nuclei and thalamus. The sporadic form of CDJ is characterized by changes in EEG in the form of the three-phase activity. Depending on the stage of the disease, the focal, bilateral and generalized myoclonic paroxysmal activity is detected. In diagnosing, the assessment of cognitive functions is also important, in particular, using the MMSE with scores below 24. The lumbar puncture and analysis of CSF allows to determine the level of the CJD marker (test specificity is more than 90%). It is possible to conduct an intravital brain biopsy [8, 13]. Nowadays, the most reliable method for diagnosing diseases of the prion group is the detection of PrPS deposits in the biopsy with an immunocytochemical method. The transplanted neuroglial cells are used as a biopsy. With the new variant of CJD, the use of the immunocytochemical method will help to detect the prion protein in the biopsy of the pharyngeal tonsil [8, 16, 34]. A promising method for diagnosing prion diseases is the use of ultrasound spectroscopy of complex

compounds of plasminogen and PrPsc. The method is based on the ability of plasminogen with magnetized particles to form compounds with the pathological prion-protein and precipitate [17, 35-37]. The technique was applied on the cerebellar biopsies of sheep with scrapie [17]. These changes are recorded using the high-resolution ultrasound spectroscopy, which allows one to obtain results in real time. The selective binding of plasminogen to PrPsc can be achieved by using a detergent that accelerates the formation of aggregates [17, 38]. Besides, PrPsc with a tendency to form aggregates binds better to plasminogen than hydrophilic PrPc [17, 35, 36]. The method can be used in the diagnosis of prion diseases to detect PrPsc and differentiate prion protein isoforms.

TREATMENT

Currently, prion diseases are not amenable to therapy by any of the existing methods used in clinical practice, in fact being incurable [1, 7, 40, 41]. Due to the unique features of the morphology and physiology of PrPsc, the immune response to infection is almost completely absent in the host organism, and so it complicates immunotherapy and prevention [1, 4, 42]. The routine use of antibiotics, steroids and antiviral drugs also has no effect [4, 39, 43]. However, some new treatment strategies are being constantly sought. Thus, one of the promising directions in gene therapy is the stabilization of the normal PrPc conformation and prevention of the formation of the pathogenic PrPsc isoform [44, 45]. To do this, it is necessary to exclude the effect of the prion protein gene, for example, by introducing a modified RNA PrPsc or certain genetic mutations. During *in vitro* experiments on animals, it was shown that if Q171R in PrP of a sheep and E219R in PrP of a human are replaced, and these recombi-

nant mutant proteins are introduced to a mouse, the formation of the pathogenic form of PrPsc did not occur [42].

However, given the complexity of the implementation of gene therapy and the lack of a positive effect of existing drugs, at the moment the only method of treatment of the prion diseases is their prevention. In order prevent the eating of infected food products in the Russian Federation, the decree 15 "On Measures to prevent the spread of Creutzfeldt-Jakob disease in the Russian Federation" was signed [32, 46, 47].

Due to the unique morphological features of the prions structure, which give them incredible resistance to any standard methods of disinfection and sterilization, including ultraviolet and ionizing radiation, there is an increased risk of iatrogenic infection, and therefore it requires stricter control over the use and cleaning of medical instruments [32, 42, 48].

In Europe, special importance is attached to limiting the development and distribution of drugs from animal tissues and the use of genetic engineering synthesis for their production [32, 36, 48, 49, 50, 51]. There are reports on the ongoing prohibition of the transplantation and administration of any biological fluids from patients with dementia [8, 37, 48].

CONCLUSION

The first reports of the human prion infections appeared at the beginning of the 20th century. Over the years, the modern medicine has accumulated a lot of information about these infectious agents.

The Nobel Prize was awarded twice: for the first time for the discovery of Kuru in 1976, which the laureate Carlton Haiduzek himself and many scientists of that time considered to be a slow infection. Later, in 1997, Stanley Prusiner was awarded for the discovery of prions.

However, since then no breakthroughs in this area have been marked. High hopes are being placed on new, lifetime diagnostic methods and various techniques of gene therapy, as well as on the widespread dissemination of preventive measures.

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The Use Of Fiberotomy In Patients With Incisor Crowding Before And After Orthodontic Treatment

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ABSTRACT

In the course of the study, histological preparations of 35 patients aged 16–25 years with incisor crowding who underwent orthodontic treatment with the fixed appliances according to the standard technique, had been analyzed. Three groups of patients had been distinguished: the first one was the reference group, the second one was the group of patients with the fiberotomy conducted before treatment with fixed orthodontic appliances, and the third one was the group of patients with the fiberotomy performed after the removal of fixed orthodontic appliances according to a standard technique used in the Department of Maxillofacial Surgery and Dentistry of Samara State Medical University (SamSMU).

Keywords: *incisor crowding, fiberotomy, orthodontic treatment*

INTRODUCTION

The orthodontic movement of teeth affects the intrinsic and gingival fibers of the periodontal ligament, and after the active phase of treatment is completed, time is required for its reorganization. According to A. A. Anikienko, N. V. Pankratova, L. S. Persin [1], the alveolar bone and the intrinsic fibers of the periodontal ligament rather quickly (after 50-80 days of retention) form a stable connection with the aligned teeth [2]. The formation of the gingival fiber network is usually completed within 4-6 months, however, the reconstruction of the gingival fibers located above the alveolar crest continues at an

extremely slow rate [3]. Forces that contribute to the displacement of the tooth, can be maintained even a year after the removal of orthodontic appliance [4, 5].

The dynamic and static functions (note 1) of the individual parts of the chewing apparatus must be balanced (note 2). After orthodontic treatment of incisor crowding, the teeth will move to their original position without balanced pressure exerted on them by the tongue and the lips [6, 7]. Such patients need permanent retention of teeth in order to prevent future recurrence of crowding (note 3).

The issues of morphological (note 4) changes in the mucous membrane of the gingiva occurring after orthodontic treatment and during the retention period have not been sufficiently emphasized in the literature, as well as the issues of morphological changes taking place in the mucous membrane covering the outer surface of the alveolar processes of both jaws in case of using biopsy material have not been properly studied.

This research was aimed at studying the effect of fiberotomy on the duration of both the orthodontic treatment of the incisor crowding and the retention period.

RESEARCH MATERIALS

All patients belonged to the same age group being young people. Diagnostic assessment was carried out using the classification of dentoalveolar anomalies by L. S. Persin in accordance with the algorithm prescribed in the medical card of the patient receiving orthodon-

tic treatment (form 043-1/u approved by the Order of the Ministry of Health of the Russian Federation dated December 15, 2014 No. 834-n).

Thirty-five patients 16-25 years of age with incisor crowding received orthodontic treatment according to the widely accepted technique using fixed appliances (reference group – 1). Patients suffering from similar anomaly were divided into two groups: in the first one (18 cases), fiberotomy was performed before treatment with fixed orthodontic appliances; and in the second one (17 cases), fiberotomy was performed after removal of fixed orthodontic appliances according to the standard technique applied in the Department of Maxillofacial Surgery and Dentistry of SamSMU.

METHODS

Diagnostic assessment of patients was carried out on the basis of clinical examination data, anthropometric analysis of plaster dental casts, dental panoramic X-rays and lateral cephalograms. *Inclusion criteria were as follows:* patients aged 16-25 years with incisor crowding. *Exclusion criteria were as follows:* patients younger than 16 years of age and older than 25 years of age who had previously undergone orthodontic treatment with fixed appliances.

Based on the results of the dissertation research, in 2016, START grant was received for further development of the *Medical vibropneumatic stimulator* project. Patent for invention No. 2624807 Method of treating patients with crowded teeth, state registration dated July 6, 2017 (Fig. 1).

Histological study of the mucous membrane structure of the alveolar process in patients with crowded maxillary and mandibular anterior teeth was performed in accordance with the law “Fundamentals of the legislation of the Russian Federation on the protection

Figure 1. Patent for invention No. 2624807 Method of treating patients with crowded teeth, state registration dated July 6, 2017



of public health” (note 5). Biomedical research was approved after conducting preliminary laboratory experiment (note 6) and after obtaining a written consent of patients. Total information on goals, methods, side effects, possible risks, duration and expected results of treatment was provided to patients to get their consent to it.

As soon as each patient had signed an informed consent, the biopsies of *gingival mucosa* covering the *maxillary and mandibular* alveolar ridges (fiberotomy) were carried out (Fig. 2 and Fig. 3). The tissue was immediately fixed in 40% formalin solution. Histological preparations were prepared through the standard technique of dehydration and compaction of samples with the final embedding in paraffin. Sections were cut 7-8 microns thick with a rotary microtome. After deparaffinization, histological preparations were stained with hematoxylin and eosin. The preparations were analyzed using the light microscopy at 56x, 280x and 500x magnification.

Figure 2. Patient A., 29 years old, (outpatient card No. 00024). Clinical situation before orthodontic treatment of maxillary and mandibular incisor crowding. The area of mucous membrane sampling



Figure 3. Patient D., 28 years old (outpatient card No. 000186). Maxillary and mandibular incisor crowding before orthodontic treatment. Fiberotomy was conducted before the completion of orthodontic treatment and removal of fixed appliances. Mucous membrane biopsy carried out on the (a) maxilla and (b) mandibula



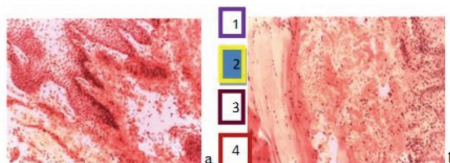
a – maxilla



b – mandibula

While conducting the study, micrographs of clinical samples were obtained at the stage of fiberotomy before and after orthodontic treatment, as well as in 6 months after its completion (Fig. 4).

Figure 4. Patient S., 25 years old (outpatient map No. 000267), with Class II malocclusion and maxillary incisor crowding. Micrographs of the stratified squamous epithelium of the alveolar process mucous membrane consisting of several layers (basal – 1; spinous – 2; granular – 3; keratinized – 4) before orthodontic treatment (a) and at the stage of fiberotomy (b)



RESULTS

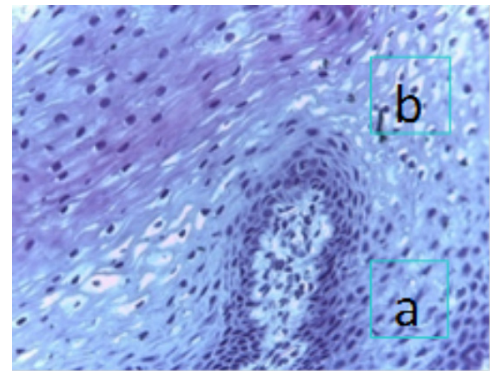
Prior to the **start of orthodontic treatment**, microscopic examination determined that the mucous membrane of the alveolar process in the area of maxillary and mandibular incisor crowding retained its typical structure: it was covered with stratified, squamous, partly keratinized epithelium; the lamina propria was divided into two layers: the papillary one which projected into the epithelium in the form of papillae, and the reticular one formed by dense irregular connective tissue. *The stratified squamous epithelium of the mucous membrane of the alveolar process consisted of several layers: the basal layer (stratum basalis) which was represented by cylindrical cells resting on the basement membrane; the spinous layer (stratum spinosum) where the cells acquired a polygonal shape, increased in size, gradually flattened; the granular layer (stratum granulosum) where the cells became flat, the cytoplasm contained keratohyalin granules; the superficial keratinized layer (stratum corneum) where the nuclei disappeared in the cells and turned into scales, which were exfoliated.*

All four layers – the basal, the spinous, the granular and the superficial keratinized ones – were well expressed. The basal layer rested on the basement

membrane, which separated the epithelium from the lamina propria of the gingival mucous membrane. The cytoplasm of cells of all epithelial layers, except for the stratum corneum, was stained basophilically as, according to classical ideas, it contained a large number of tonofilaments (note 7) – filamentary structures with the thickness of 10 nm, consisting of the prekeratin protein. This protein provided the mechanical properties of the epithelium, determined the gingival turgor, which resisted the mechanical load on the mucous membrane and determined its extensibility. The marginal gingiva was covered by keratinized epithelium, which made it more resistant to mechanical, thermal and chemical effects during meals. The structure of the stratified squamous epithelium of the alveolar process mucous membrane in the area of maxillary and mandibular incisor crowding did not differ from the norm.

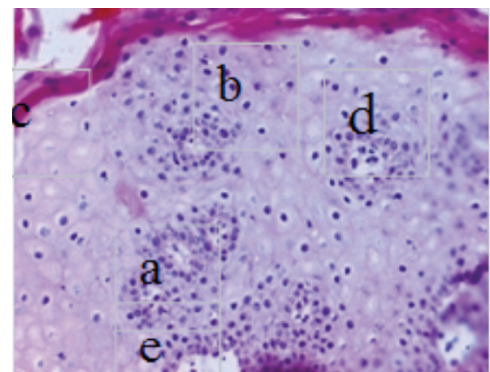
The analysis of micrographs of preparations taken **after orthodontic treatment** has shown that the reactive changes were observed in all layers of the oral mucous membrane. In the epithelium, keratinocytes of the spinous and superficial layers increased in size, the cytoplasm looked pale and didn't react with stains; this pointed to the development of hydropic dystrophy to which epithelium cells were subjected to. Keratinization of the gingival epithelium manifested itself clinically as parakeratosis. However, the number of cells with preserved pycnosis nuclei in the gingival samples taken **after orthodontic treatment** significantly increased, the formed horny scales did not acquire oxyphilic staining, there was no granular layer of epithelium. The cytoplasm of cells of all epithelial layers, except for the stratum corneum, was stained basophilically. Focal leukocyte infiltration was observed in the superficial layers of the epithelium (a), and separation of collagen fiber bundles was induced (b) (Fig.5).

Figure 5. Patient A., 29 years old (outpatient card No. 00053), with Class II malocclusion and maxillary incisor crowding. Micrograph (at 500 nm magnification) of stratified squamous epithelium of the alveolar process mucous membrane before fixed orthodontic appliance removal (reference group – 1)



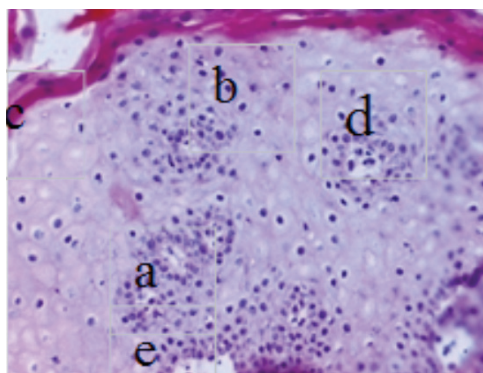
During this period the following conditions came to the fore: a – signs of hydropic dystrophy of the spinous layer emerged; b – focal leukocyte infiltration of the superficial layers of epithelium was observed, c – horny scales acquired oxyphilic staining. Later on (in 6 months after removal of fixed orthodontic appliances), there were no signs of hydropic dystrophy of the spinous layer cells, horny scales were oxyphilically stained, d – parakeratosis persisted, e – there were no cells with keratohyalin granules corresponding to the granular layer (Fig. 6).

Figure 6. Patient A., 29 years old (outpatient card No. 00053). Micrograph (at 280nm magnification) of stratified squamous epithelium of the alveolar process mucous membrane in 6 months after orthodontic treatment (reference group – 1)



Thus, changes in the gingival tissues were restored in 6 months after orthodontic treatment, which evidenced of their adaptive nature aimed at restoring the morphofunctional features of the mucous membrane of the alveolar processes of both jaws.

Figure 7. Patient C., 25 years old (outpatient card No. 000267), with Class II malocclusion and maxillary incisor crowding. Micrograph (at 280nm magnification) of the stratified squamous epithelium of the alveolar process mucous membrane at the stage of fiberotomy before insertion of fixed orthodontic appliance (group 2)



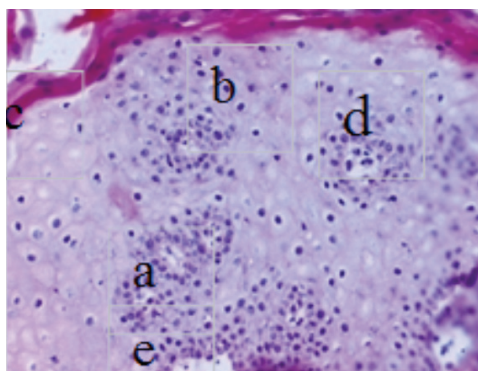
The basal layer rested on the basement membrane (Fig. 7), which separated the epithelium from the lamina propria of the gingival mucosa (a). The cytoplasm of cells of all epithelial layers, except for the stratum corneum, was stained basophilically (b) as, according to classical ideas, it contained a large number of filamentary structures with the thickness of 10 nm, consisting of the prekeratin protein. This protein provided the mechanical properties of the epithelium, determined the gingival turgor, which resisted the mechanical load on the mucous membrane and determined its extensibility. The marginal gingiva (c) was covered by keratinized epithelium, which made it more resistant to mechanical, thermal and chemical effects during meals.

The structure of the stratified squamous epithelium of the alveolar process mucous membrane in the area of max-

illary and mandibular incisor crowding did not differ from the norm.

Microscopic examination of morphological changes in the maxillary and mandibular gingival mucosa after orthodontic treatment has established that the gingival mucosa retained its typical structure: it was covered with stratified, squamous, partially keratinized epithelium; the lamina propria was divided into two layers: the papillary one which projected into the epithelium in the form of papillae, and the reticular one formed by dense irregular connective tissue.

Figure 8. Patient B., 28 years old. Micrograph (at 280nm magnification) of stratified squamous epithelium of alveolar process mucous membrane at the stage of fiberotomy 3.5-4 weeks before removal of fixed orthodontic appliance



The reactive changes were observed in the stratified squamous epithelium of the mucous membrane of both the maxillary and mandibular alveolar processes (Fig. 8). In the epithelium, keratinocytes of the spinous and superficial layers increased in size (a), the cytoplasm looked pale and wasn't stained; this pointed to the hydropic dystrophy development (b) affecting the epithelium cells. Keratinization of the gingival epithelium manifested itself clinically as parakeratosis (c). However, the number of cells with preserved pycnosis nuclei in the gingival mucosa preparations at the fiberotomy stage 3.5-4 weeks before the

completion of orthodontic treatment significantly increased (d), the formed horny scales did not acquire oxyphilic staining (e), there was no granular layer of epithelium (f).

The reactive changes were also observed in the lamina propria of the mucous membrane. The connective tissue outgrowths in the papillary layer were smoothed out, the observed focal lymphocyte infiltration in some areas spread to the reticular layer, and the separation of collagen fiber bundles was noted. The reticular layer looked edematous due to a violation of vascular permeability, most venules were enlarged, they became empty or had a collapsed lumen. In the walls of arterioles, myocytes of the muscular coat showed signs of hydropic dystrophy. The growth of small blood capillaries was observed on the border of the papillary and reticular layers.

During this period, the development of hydropic dystrophy persisted in the spinous layer, focal leukocyte infiltration of the superficial layers of epithelium was observed, and the horny scales acquired oxyphilic staining. Later on, there were no signs of hydropic dystrophy of the spinous layer cells, horny scales were oxyphilically stained, parakeratosis persisted and there were no cells with keratohyalin granules corresponding to the granular layer.

The histological studies of gingival biopsies suggest that **changes in the epithelium at the final stages of orthodontic treatment indicate its damage and reflect the development of regenerative-plastic insufficiency.** The factors that cause the development of regenerative-plastic insufficiency of epithelium of the gingival mucosa include orthodontic treatment (with fixed appliances). When characterizing the lamina propria of the gingival mucosa at the final stages of orthodontic treatment, the presence of multiple intercellular edema should be noted.

Thus, in the examined three groups of patients, the identified structural changes in the gingival mucosa indicate its damage and the presence of chronic productive inflammation as a physiological response to orthodontic treatment with fixed appliances. **The results of the comparison of micrographs of the stratified squamous epithelium of the mucous membrane of the maxillary and mandibular alveolar processes in three groups of patients allowed to reach the aim of study.**

CONCLUSION

1) In patients of the first group (reference), orthodontic treatment of incisor crowding and of Class I-III malocclusion lasted on average 10.9 ± 0.7 months. Patients of the second group, where the orthodontic treatment of incisor crowding was preceded by fiberotomy, achieved successful results in 7.8 ± 0.8 months. In patients of the third group, where fiberotomy was performed after the conclusion of orthodontic treatment, the duration of the whole treatment process was the same as in the reference group (11.0 ± 0.6 months).

2) Structural changes in the gingival mucous membrane, defined during the study, allow making the following assumptions. Based on the terms of the orthodontic treatment of incisor crowding and of Class I-III malocclusion in patients aged 16-25 years, the shortest duration of the active phase of treatment was observed in the group where the fiberotomy was performed immediately before the placement of fixed orthodontic appliances. Similarly, it can be assumed that the duration of the retention period with the use of the retention appliance will be less if the patient undergoes fiberotomy immediately before or after the proposed treatment.

NOTES

Note 1: Plastic (building) **functions** - in physiology, the general functions underlying cellular and tissue processes.

Note 2: To balance - to bring the inter-related sides of any activity into the right ratio.

Note 3: Recurrence (recidive, from lat. recidivus – returning) – the return, the repetition of any phenomenon after its apparent disappearance; med. - remanifestation of the disease after apparent recovery.

Note 4: Morphology (gr. morphe - form + logos - concept, teaching) studies the form and structure of living organisms (anatomy, including embryology, cytology, histology). The term “morphological” refers to the appearance and structure.

Note 5: Approved by the Armed Forces of the Russian Federation on 22.07.1993, No. 5487 (as amended on 07.12.2011), under Article No. 43 on the Procedure of applying new methods for the prevention, diagnosis, treatment, as well as drugs, immunobiological preparations and disinfectants, and carrying out biomedical research.

Note 6: In edition of Federal Laws No. 29-FZ and No. 122-FZ dated 27.02.2003 and 22.08.2004, respectively.

Note 7: (Tonos - (gr.) - tension, stretching and filaments)

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The Effect Of The Lactic Acid Bacteria Culturing Conditions On Their Antagonistic Activity To Pathogens Of Tuberculosis

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ABSTRACT

It has been found that the antagonistic activity of lactic acid bacteria depends on the composition of the nutrient medium and the temperature of culturing. It has been shown that the best antimicrobial effect to mycobacteria is achieved by the cultivation of lactic acid bacteria on the MRS nutrient media and a combined nutrient medium with the use of lactulose or glucose as a source of carbon. The optimum temperature for culturing an association of lactic acid bacteria for achieving high antagonistic activity to mycobacteria is 30°C, and the duration of cultivation is 24 hours.

Keywords: tuberculosis, bacilli, lactic acid bacteria, antagonistic activity, culturing conditions.

INTRODUCTION

Tuberculosis is one of the most important medico-biological and socio-economic problems in many countries [1, 2].

In addition to the social, environmental and economic reasons, the wide spread of tuberculosis is also determined by the emergence of the forms of the disease that are resistant to commonly used medications.

The prolonged nature of antibacterial therapy with high dosages of medications, which causes weakening of the immune system in patients with tuberculosis increases the interest in probiotics as a potential means of reducing the use of antibiotics and their side effects.

Currently, there is more and more evidence that probiotics can not only maintain normal microflora in the gas-

trointestinal tract but also can regulate the immune response outside the gastrointestinal tract, including the mucosa of the respiratory tract, with potential efficacy in modulating the allergic reactions and lungs' infection [3 – 5].

At the RSE “Institute of Microbiology and Virology” of SC MES of Kazakhstan, 10 strains of lactic acid bacteria were selected with high antimicrobial activity against the clinical multiresistant strain *Mycobacterium tuberculosis*, which might be used for creating a probiotic for prevention and comprehensive treatment of tuberculosis [6].

The aim of the research was to identify the factors that determine the antagonistic activity of the selected strains of bacteria.

METHODS

The objects of the study were strains of lactic acid bacteria *L. cellobiosus* 7n₁ and 2/20, *L. fermentum* 27A-4, *L. acidophilus* 27w/60, 27w/84 and 98, *L. brevis* B-3/43, *L. plantarum* 2B/A-6, 22 and 14D/13 with high antagonistic activity to clinical polyresistant strain *Mycobacterium tuberculosis*.

The strains of lactic acid bacteria were grown in the liquid MRS medium for 24 hours at 35°C.

Strain *Mycobacterium* B₅ was used as the test culture for the research. Being very similar to the highly infectious tuberculosis mycobacteria, *Mycobacterium* B₅ has low infectivity and therefore does not require especially safe conditions for experiments. This fact makes it a very

valuable modulator for laboratory studies of tuberculosis.

Antagonistic activity against *Mycobacterium B₅* was determined by the method of diffusion into nutrient agar by the zones of test culture growth inhibition [7].

RESULTS

One of the conditions for improving the antagonistic activity of lactic acid bacteria is identifying the optimum conditions for cultivating microorganisms. With that, important factors are the composition of the nutrient medium and the temperature and duration of cultivation.

To determine the effect of the nutrient medium composition on the antagonistic activity of lactic acid bacteria against *Mycobacterium B₅*, the cultures were cultivated on the MRS nutrient medium, as well as the media combined on the basis of corn extract [8] and skim milk. The results are shown in Table 1.

It has been found that in case of cultivation in milk, the antagonistic activity of the lactic acid bacteria against mycobacteria is less explicitly manifested. With that, it is absent in strains

L. plantarum 14d/13, *L. acidophilus* 27w/60, and *L. acidophilus* 27w/84. The diameter of mycobacteria growth inhibition zones by other strains of lactic acid bacteria did not exceed 9 - 10 mm.

All strains of lactic acid bacteria grown on the MRS and combined nutrient media had antagonism against mycobacteria. With that, the test culture growth inhibition zones in the MRS medium were 16 - 19 mm, and in the combined medium — 18 - 22 mm.

The influence of sucrose, raffinose, and lactulose in the MRS nutrient medium on cells' accumulation and the antagonistic activity of lactic acid bacteria were studied. It has been found that the studied strains of lactic acid bacteria grow on all analyzed carbohydrates. The greatest number of bacterial cells was detected on the medium with lactulose, compared to glucose (Table 2). For example, the number of cells of lactic acid bacteria on a medium with glucose was $n \times 10^8 - n \times 10^{10}$ CFU/ml, and on the medium with lactulose — $n \times 10^{10} - n \times 10^{11}$ CFU/ml. Several strains (*L. fermentum* 27A-4, *Lactobacillus plantarum* 22, and 14d/13, *L. brevis* B-3/43, *L. cellobiosus* 2/20, *L. acidophilus* 27w/60 and 27w/84) show a decrease in their growth on raffinose

Table 1. Antagonistic activity of lactic acid bacteria against *Mycobacterium B₅*

Strains of lactic acid bacteria	The diameter of <i>Mycobacterium B₅</i> growth inhibition zones with growing in various cultural media, mm		
	MRS medium	Combined medium	Skim milk
<i>L. plantarum</i> 14d/13	18.0 ± 0.7	19.0 ± 0.5	0
<i>L. plantarum</i> 22	18.0 ± 0.8	20.0 ± 1.0	10.0 ± 0.3
<i>L. plantarum</i> 2b/A-6	19.0 ± 0.6	22.0 ± 0.6	10.0 ± 0.3
<i>L. fermentum</i> 27A-4	16.0 ± 0.3	18.0 ± 0.0	9.0 ± 0.3
<i>L. brevis</i> B-3/43	17.0 ± 0.3	18.0 ± 0.6	9.0 ± 0.5
<i>L. cellobiosus</i> 2/20	18.0 ± 0.0	18.0 ± 0.3	9.0 ± 0.5
<i>L. cellobiosus</i> 7n ₁	19.0 ± 0.6	19.0 ± 1.0	10.0 ± 0.5
<i>L. acidophilus</i> 27w/60	18.0 ± 0.0	19.0 ± 0.3	0
<i>L. acidophilus</i> 27w/84	19.0 ± 0.3	20.0 ± 0.3	0
<i>L. acidophilus</i> 98	17.0 ± 0.3	19.0 ± 0.6	10.0 ± 0.0

Table 2. Titters of lactic acid bacteria on media containing various carbohydrates

Bacterial strains	Titters of bacteria, CFU/ml, depending on the carbohydrate used			
	glucose	sucrose	raffinose	lactulose
<i>L. plantarum</i> 2b/A-6	3.2 ± 0.3x10 ⁸	5.3 ± 0.3x10 ⁸	3.0 ± 0.3x10 ⁸	2.0 ± 0.3x10 ¹⁰
<i>L. plantarum</i> 22	3.0 ± 0.3x10 ⁹	3.0 ± 0.3x10 ⁹	7.5 ± 0.5x10 ⁸	5.6 ± 0.5x10 ¹⁰
<i>L. plantarum</i> 14d/13	2.6 ± 0.5x10 ¹⁰	3.2 ± 0.3x10 ¹⁰	4.8 ± 0.5x10 ⁹	9.8 ± 0.5x10 ¹¹
<i>L. fermentum</i> 27A-4	8.6 ± 0.4x10 ⁸	6.4 ± 0.3x10 ⁸	5.6 ± 0.5x10 ⁷	3.6 ± 0.4x10 ¹⁰
<i>L. brevis</i> B-3/43	4.5 ± 0.5x10 ⁹	5.1 ± 0.5x10 ⁹	4.2 ± 0.5x10 ⁷	9.9 ± 0.5x10 ¹⁰
<i>L. cellobiosus</i> 2/20	2.6 ± 0.5x10 ¹⁰	3.2 ± 0.3x10 ¹⁰	4.8 ± 0.5x10 ⁹	9.8 ± 0.5x10 ¹¹
<i>L. cellobiosus</i> 7n ₁	1.8 ± 0.4x10 ¹⁰	1.3 ± 0.5x10 ¹⁰	2.0 ± 0.5x10 ¹⁰	9.7 ± 0.5x10 ¹¹
<i>L. acidophilus</i> 27w/60	2.5 ± 0.5x10 ⁹	1.5 ± 0.6x10 ⁹	5.6 ± 0.5x10 ⁶	9.6 ± 0.5x10 ¹⁰
<i>L. acidophilus</i> 27w/84	2.7 ± 0.5x10 ⁹	1.0 ± 0.5x10 ⁷	1.7 ± 0.3x10 ⁷	5.7 ± 0.5x10 ¹⁰
<i>L. acidophilus</i> 98	2.8 ± 0.6x10 ⁹	4.2 ± 0.5x10 ⁹	3.0 ± 0.3x10 ⁹	2.5 ± 0.5x10 ¹⁰

compared to other carbohydrates.

The antagonistic activity of the studied strains of lactic acid bacteria was detected on the media with glucose, lactulose, and sucrose. Strains *Lactobacillus plantarum* 22, 2B/A-6 and 14D/13, *Lactobacillus fermentum* 27 A-4 *L. brevis* B-3/43, *L. cellobiosus* 2/20 and 7n, *L. acidophilus* 27w/60, 27 w/84 and 98 showed high antagonistic activity to *Mycobacterium* B₅ on glucose (17.0; 17.0; 15.5; 20.0; 17.0; 28.0; 21.0; 26.0; 26.5 and 28.5 mm, respectively) and lactulose (22.0; 20.5; 23.0; 26.0; 20.0; 21.0; 29.0; 24.5;

28.0 and 30.0 mm, respectively). With sucrose present in the nutrient medium, antagonism to mycobacteria was not found in culture *L. plantarum* 22, in other media, the antagonistic activity was lower than that on glucose and lactulose. No strain of lactic acid bacteria showed antagonistic activity to mycobacteria when grown on raffinose (Table 3).

To determine the optimal temperature of cultivation, an association of bacteria No. 3 (*L. plantarum* 22 + *L. acidophilus* 98 + *L. cellobiosus* 2/20 + *L. acidophilus* 27w/84) was grown onto nu-

Table 3. Titters of lactic acid bacteria on media containing various carbohydrates

Bacterial strains	The diameter of test cultures' growth inhibition zones, mm, depending on the carbohydrate used			
	glucose	sucrose	raffinose	lactulose
<i>L. plantarum</i> 2B/A-6	17.0 ± 0.2	15.0 ± 0.4	0.0	22.0 ± 0.4
<i>L. plantarum</i> 22	17.0 ± 0.2	0.0	0.0	20.5 ± 0.6
<i>L. plantarum</i> 14d/13	15.5 ± 0.4	14.0 ± 0.3	0.0	23.0 ± 0.4
<i>L. fermentum</i> 27A-4	20.0 ± 0.6	16.5 ± 0.2	0.0	26.0 ± 0.5
<i>L. brevis</i> B-3/43	17.0 ± 0.2	15.0 ± 0.4	0.0	20.0 ± 0.6
<i>L. cellobiosus</i> 2/20	28.0 ± 0.6	10.0 ± 0.2	0.0	21.0 ± 0.4
<i>L. cellobiosus</i> 7n ₁	21.0 ± 0.4	15.0 ± 0.4	0.0	29.0 ± 0.6
<i>L. acidophilus</i> 27w/60	26.0 ± 0.5	17.0 ± 0.2	0.0	24.5 ± 0.5
<i>L. acidophilus</i> 27w/84	26.5 ± 0.5	15.5 ± 0.4	0.0	28.0 ± 0.6
<i>L. acidophilus</i> 98	28.5 ± 0.7	17.5 ± 0.2	0.0	30.0 ± 0.7

trient media: 1 — the MRS medium; 2 — combined medium. Cultivation was performed at 30 and 37°C for 24 and 48 hours.

The results of an accumulation of bacterial cells of the association cultivated on various nutrient media at 30 and 37°C for 24-hours are shown in Table 4.

Table 4. Accumulation of bacterial cells of the association cultivated on various nutrient media at 30 and 37°C for 24 hours.

Variant No.	Nutrient medium	The titer of bacteria, CFU/ml
Cultivation temperature 30°		
1	MRS medium	$2.9 \pm 0.7 \times 10^9$
2	Combined medium	$3.2 \pm 0.3 \times 10^9$
Cultivation temperature 37°C		
1	MRS medium	$3.0 \pm 0.4 \times 10^9$
2	Combined medium	$3.1 \pm 0.3 \times 10^9$

It has been found that titers of bacteria at the temperature cultivation equal to 30°C on the MRS medium were 2.9×10^9 CFU/ml, and on the combined medium — 3.2×10^9 CFU/ml. At the temperature of 37°C on the same media, they were 3.0×10^9 CFU/ml and 3.1×10^9

CFU/ml, respectively. Therefore, the accumulation of bacterial cells on both nutrient media is virtually identical, and their number is the same at the cultivation temperatures of 30 and 37°C.

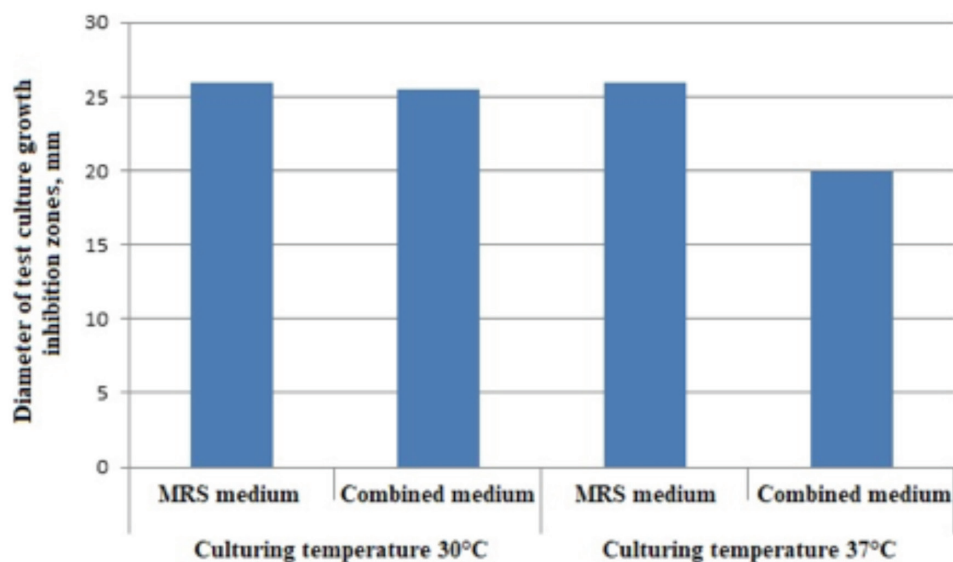
The results of the antagonistic activity of the association of lactic acid bacteria cultivated on various nutrient media at 30 and 37°C for 24 hours are shown in Figure 1.

When grown on both nutrient media at the temperature of 30°C for 24 hours, the association has the same antagonistic activity against mycobacteria.

At the temperature of 37°C, the antagonistic activity of the association grown on the MRS nutrient did not change, and that of the association grown on the combined medium decreased. With that, the growth inhibition zone of the test culture decreased from 25.5 mm to 20.0 mm. This is an evidence of the fact that the temperature of 30°C is more optimal for cultivating the association. Increasing the duration of the association cultivation to 48 hours did not result in increasing the titer of bacteria and their antagonistic activity.

CONCLUSION

Figure 1. Antagonistic activity of the association of lactic acid bacteria cultivated on two (MRS and combined) nutrient media at 30 and 37°C for 24 hours



Thus, the antagonistic activity of lactic acid bacteria depends on the composition of the nutrient medium and the temperature of culturing. The best antimicrobial effect to mycobacteria is achieved by the cultivation of lactic acid bacteria on the MRS nutrient medium and a combined nutrient medium with the use of lactulose or glucose as a source of carbon. The optimum temperature for culturing an association of lactic acid bacteria for achieving high antagonistic activity to mycobacteria is 30°C, and the duration of cultivation is 24 hours.

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Development of A Specialized High Protein Product for Adaptive Nutrition

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ABSTRACT

The article is dedicated to the development of a multicomponent high-protein product for the nutrition of physically active individuals. The possibility to introduce flavoring fillers and a biologically active supplement in the milk and vegetable base of fermented whipped dessert has been established, and the expediency thereof has been justified. Based on a mathematical model, the possibility of preparing dessert systems with the specified optimum parameters has been confirmed. The influence of nondairy protein components on the improvement of functional and technological properties of multicomponent mixtures for desserts has been revealed. It has been demonstrated that the inclusion of desserts with specified optimum parameters in the diet will have a positive effect on increasing the body's adaptive capacity.

Keywords: nutrition, dairy and vegetable dessert, proteins, foam-producing properties, dihydroquercetin, symbiotic starter.

INTRODUCTION

Modern biochemistry, physiology and nutrition science provisions encourage specialists to refine and, in some cases, revise the requirements for newly created products and the principles of their production in accordance with changing working and living conditions of people, as well as deteriorating environmental factors [1, 2, 3, 4].

The World Health Organization developed a global action plan to promote physical activity of the population for

2018–2030 [5]. One of the most important components of the plan is to improve the nutrition structure; the consumption of healthy food helps to prevent many noncommunicable diseases, improving the body's adaptive capacity.

There is an urgent need to develop innovative approaches to the creation of multifunctional ingredients ensuring the leveling of these adverse conditions, on the one hand, and meeting the requirements of food hygiene of the various population groups, on the other hand [6–8].

According to the concept of functional (positive) nutrition, the human body must receive all the beneficial nutrients together with food, and not as a drug formulation.

The deficit of full-fledged protein nutrition of the population (26 % on the average) is a socially significant problem in the Russian Federation. As is well known, among nutrient materials, proteins play a crucial role, and the sustainable combination thereof in the diet is very important. Numerous studies of Russian and foreign scientists have shown that providing full-fledged nutrition is possible based on vegetable proteins. There are developments using proteins from traditional and nontraditional raw materials [9–12]. Soy proteins are widely used.

The research is aimed at further implementing progressive production methods for combined milk and vegetable products, improving and intensifying technological processes, increasing production efficiency, improving the quality and ensuring the safety of products.

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All the above indicates the relevance of the problem considered herein – the development of a specialized high-protein product technology.

MATERIALS AND METHODS

The following materials were selected for the research:

- Protein sources – soy and milk concentrate, SUPRO 760 soy isolate, defatted soy flour (GOST 17109-88);
- The source of biologically active substances – Lavitol (dihydroquercetin) antioxidant (TU 2455-00348375962-04);
- Flavoring fillers – beet puree, carrot puree;
- Symbiotic starter consisting of a consortium of bifidobacteria and lactic acid microorganisms at a 1:1 ratio (DVS starter cultures).

The objects of research were:

- Milk and vegetable mixture in various ratios; and
- Fermented whipped milk and vegetable dessert.

The foam-producing properties of protein solutions were estimated by the following indicators:

- Whipping capacity – the volume of the foam obtained from a certain volume of liquid, referred to a given volume, %;
- Foam stability – time of disappearance of the half the foam volume, min; and
- Foam volume – the volume of foam not destroyed within one hour, %.

The following standard methods were used for the research: the mass fraction of fat was determined as per GOST R ISO 2446-2011, the titrated acidity of the product – as per GOST R 54669-2011, the mass fraction of protein – as per GOST 25179-2014; the total mass fraction of dry skim milk – as per GOST R 54761-2011; and organoleptic evaluation of the product – as per GOST R ISO 22935-2-2011. The following meth-

ods were used to determine carbohydrates: starch – by the Ewers' polarimetric method, sucrose – by the colorimetric method, glucose – by the glucose oxidase method, and dextrans and cellulose – by the enzymatic method [13].

The energy value of the product was calculated based on the chemical composition using the following ratios: 4.1 – for proteins, 9 – for lipids, and 3.75 – for carbohydrates.

All experiments were carried out in five replications; the data were processed using the Excel statistical software package using the Mann-Whitney test. Statistically significant differences at $p < 0.05$ were discussed.

RESULTS AND DISCUSSION

The development of formulations and the industrial production of low-calorie, but biologically full-fledged products, which include combined protein and enriched products, becomes very important [14 – 19].

Given the relevance of the above, studies were conducted to develop a fermented whipped dessert on a milk and soy basis using regional raw resources of the Amur Region, namely soya bean (Lat. *Glycine max*); Larix gmelinii (Lat. *Lárix gmelíni*) or Dahurian larch (Lat. *Lárix dahúrica*); zoned beetroot varieties (Bordeaux 237, Leningradskaya okruglaya 221/17), and garden carrots (Nantskaya 4, Nesravnennaya, Shantene 2461, Moskovskaya Zimnyaya A-515).

As of today, it has been proven that the soy proteins are the most promising vegetable proteins, which is due to the following: first, soybeans are a unique source of protein; soy proteins are characterized by the highest biological value among vegetable sources, they have clinically and experimentally proven hypocholesterolemic effect; secondly, a large-scale production of protein prod-

ucts (isolates, concentrates) has been launched; and thirdly, a wide range of protein products may be produced based on the seeds of this culture [12].

Currently, in the development and production of food products, great attention is paid to their enrichment with natural antioxidants, which reduce the oxidative processes with free radicals, as well as with dietary fibers – as a prebiotic.

During wood harvesting on the territory of the Amur Region, the forest areas of which are represented mainly by coniferous species, the waste remains from the logging industry, the most interesting of which is the root of Dahurian larch. In the process of extraction of the upper layer of the root wood crushed to sawdust, the main product dihydroquercetin is obtained [19, 20], which is manufactured and sold under the Lavitol (dihydroquercetin) trademark at Ametis JSC (Blagoveshchensk, Amur Region).

At the first stage, for the preparation of a whipped dessert on a milk and soy basis, such functional properties of the mix as its foaming ability, reflecting the quality indicators of the finished product, were studied. Moreover, soy proteins have a certain foaming capacity [19 – 22].

During the experiments, the protein concentration in the solution was varied in the range from 5 to 25 %.

Figure 1 presents the results of the studies of the whipping, stability and volume of the foam.

As follows from the data above, of all the studied soy components with increasing protein concentration, the defatted soy flour solutions have the best whipping capacity – from 19 to 97 %. For the solution with the SUPRO 760 soy isolate, slightly smaller values (from 16 to 75 %) were obtained.

The most stable foam was also detected for the soybean flour solution. Thus, half of the foam volume was maintained for (20 – 42) minutes.

The largest foam volume, indestructible within 60 minutes, was observed in the defatted soy flour solution. It should be noted that with an increase in the flour concentration in the solution, the index also tends to increase – 29, 31, 38, 43 and 46 %.

Thus, among the studied soy components, the defatted soy flour is the most preferable one since it meets the requirements of the production technology of whipped dessert to the fullest extent possible, having the best foaming and foam-stabilizing properties of the soy components studied.

The influence of the pH of the medium on the foam-producing properties of the milk and soy mixture was studied taking into account that the reaction of the medium had a significant effect on the foam-producing capacity. The results of the study are shown in Figure 2.

It follows from Figure 2 that with a shift in the pH medium to the acidic side, the foam-producing capacity increases, reaching the maximum value (71.8 %) at a pH of 4.9. This is due to the fact that the fluid flow velocity decreases in the solution, and the adhesion forces between the molecules increase; therefore, foam formation occurs more intensively. Subsequent acidification of the medium is impractical, and the foam-producing process is deteriorating.

For the fermentation of the milk and soy mixture, direct starter cultures were used, namely: YC-180, containing the strains of *Streptococcus thermophilus* and *Lactobacillus delbrueckii* of the bulgaricus subspecies; BB-12 – *Bifidobacterium* type containing *Bifidobacterium lactis*. Fermentation was carried out at a temperature of $(38 \pm 2) ^\circ\text{C}$ for (3 – 5) hours until reaching an acidity of $(80 – 90) ^\circ\text{T}$, then the fermented mixture was cooled to a temperature of $(2 – 6) ^\circ\text{C}$.

Dihydroquercetin is a polyphenol-class bioflavonoid with vitamin P activity, its effect on the body is

Figure 1. The effect of protein concentration in solution on the foaming capacity of the protein mixture: a – whipping capacity; b – foam stability; c – foam volume.

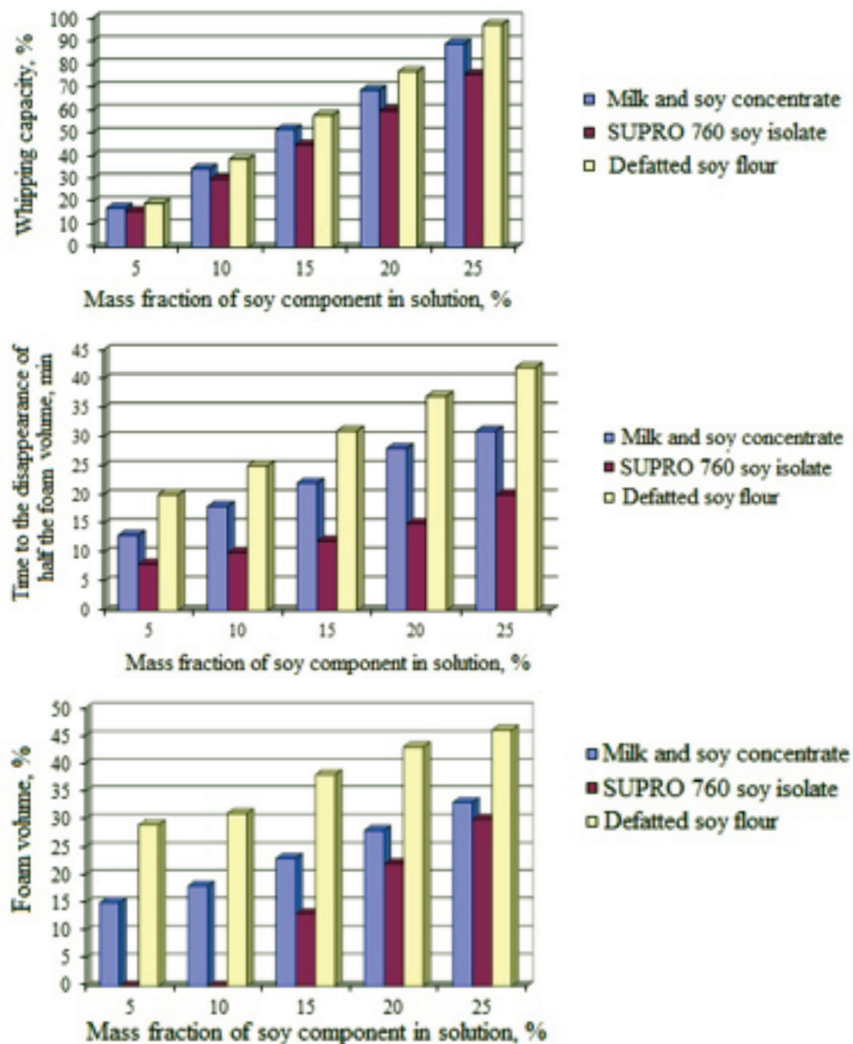
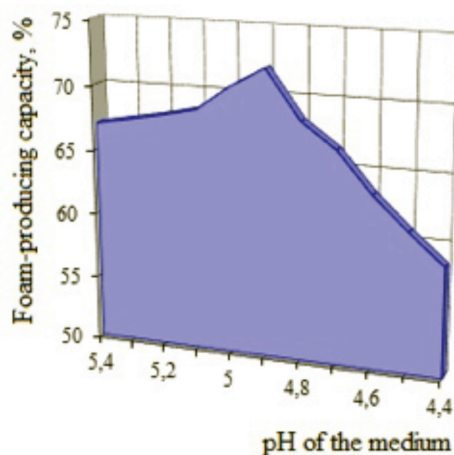


Figure 2. The influence of pH of the medium on the foam-producing capacity of the milk base



expressed in the regulation of metabolic processes, creating protective mechanisms in healthy tissue cells from the pathological effects of hazardous chemicals, radionuclides and magnetic radiation. Dihydroquercetin does not show toxicity, it is active at low concentrations, thermolabile, and resistant to mechanical stress.

At the next stage of the research, significant factors were identified that had the greatest impact on the quality indicators of fermented milk and soy dessert:

- The amount of milk and soy base;
- The amount of flavor components;
- and

– The amount of the Lavitol (dihydroquercetin) food supplement.

As a result of the regression analysis of the experimental data, regression equations were obtained, describing the dependencies of the resulting criteria on the studied factors:

$$\begin{aligned}
 Y_1 &= 4.61 - 0.1188X_1 - 0.2363X_2 - 0.0375X_3 - 0.085X_1X_2 - 0.475X_1^2 - 0.18X_2^2 - 0.4425X_3^2 \\
 Y_2 &= 9.8 + 0.975X_1 + 0.725X_2 + 2.925X_3 - 1.025X_1X_3 + 1.125X_2X_3 - 1.3125X_2^2 - 4.3125X_3^2 \\
 Y_3 &= 109.6667 + 12.8X_2 - 6.3125X_3 + 20.3042X_1^2 + 14.9042X_3^2
 \end{aligned}$$

The adequacy of the equations was tested by the Fisher criterion.

Based on the data obtained, a regressive analysis of the $Y = f(X_1, X_2,$

$X_3)$ dependence was carried out, and mathematical models were constructed reflecting the dependence of the number of probiotic microorganisms on the dose of the Lavitol (dihydroquercetin) supplement (Fig. 3), as well as the effect of the supplement on organoleptic indicators of the finished product (Fig. 4).

The obtained mathematical models made it possible to establish the optimal parameters of the following factors: the amount of the milk and vegetable base – (90.2 – 91.3) %, the content of flavor components in the dessert – (9.7 – 8.6) %; and Lavitol food supplement – 0.056 %.

The novelty of the technological solutions is protected by patent 2477050 “Method for producing a fermented whipped dessert on a milk and soy basis.” The method includes the prepara-

Figure 3. The dependence of the number of bifidobacteria on the amount of the Lavitol (dihydroquercetin) supplement in the milk and vegetable dessert

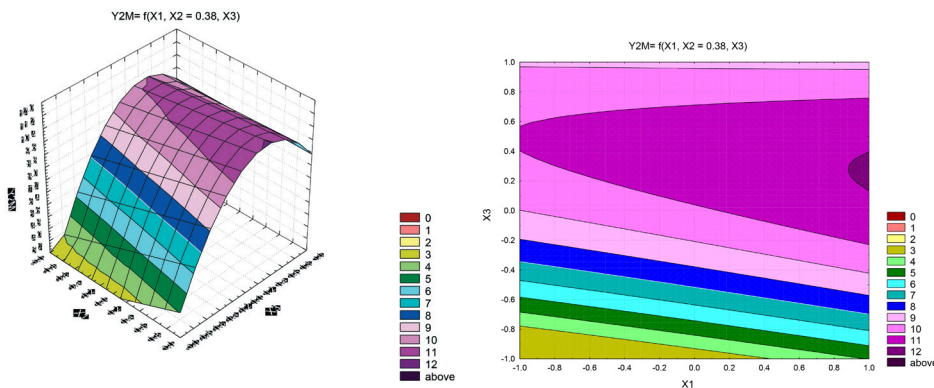
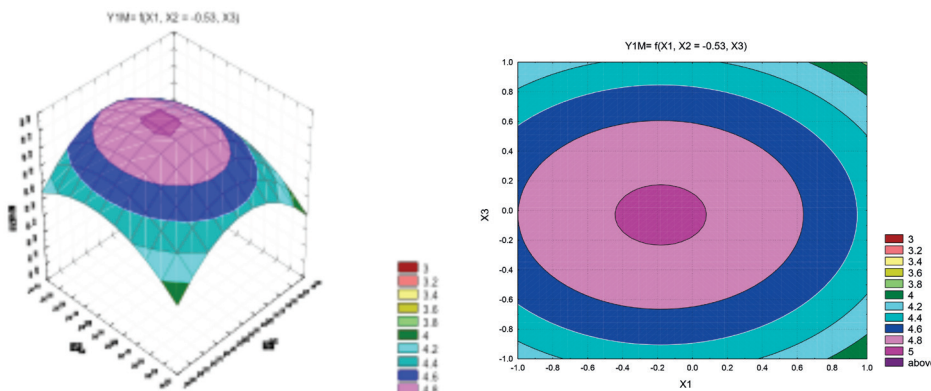


Figure 4. The dependence of the organoleptic assessment on the amount of the Lavitol (dihydroquercetin) supplement in the milk and vegetable dessert



tion of a mixture of milk and soy dispersion and skim milk in the ratio of 85:15, filtering, homogenization, pasteurization at a temperature of $(90 \pm 2)^\circ\text{C}$ with holding for (5 – 10) min, cooling to the fermentation temperature of $(38 \pm 2)^\circ\text{C}$, and introducing the DVS starter. The resulting mixture was fermented at a temperature of $(38 \pm 2)^\circ\text{C}$ for (3 – 5) hours until reaching an acidity of $(80 - 90)^\circ\text{T}$, then the fermented mixture was cooled to a temperature of $(2 - 6)^\circ\text{C}$, and beetroot puree in the amount of 8.6 % or carrot puree in the amount of 9.7 % of the product weight and the Lavitol (dihydroquercetin) food supplement in the amount of 0.056 % of the product weight were added, then the mixture was stirred, cooled to $(0 - 2)^\circ\text{C}$, and whipped for 5 minutes at 1,500 rpm.

Data on the content of basic nutrients are presented in Table 1.

Table 1. Chemical composition and energy value of dessert

Name	Milk and vegetable dessert
Protein, g	6.20
Fat, g	3.2
Carbohydrates, g	28.7
Energy value, kcal/100 g	162

As follows from the table, the fermented whipped milk and vegetable dessert is characterized by a large amount of protein and carbohydrates on the background of a low fat content, which allows recommending the product for the nutrition of physically active people. The comprehensive assessment of the developed milk and vegetable dessert has shown the compliance of its safety and nutritional values with the requirements of regulatory and technical documentation.

The technology for producing the fermented milk ice cream using starter microorganisms, and bee products has also been developed within the chosen

direction (patent of the Russian Federation 2614797).

Thus, the food technologies described are an innovation in the consumer market in the field of functional food, and due to their biological adequacy, they can be recommended as an adaptive nutrition.

CONCLUSION

The possibility of introducing flavoring fillers, biologically active supplements, probiotic microorganisms into the milk and vegetable base of high-protein dessert has been established, and the expediency thereof has been justified. Based on the mathematical model, the possibility of preparing dessert systems with the specified optimum parameters has been confirmed.

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Research of Gnostic Functions in the Elderly People Suffering from Dementia

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ABSTRACT

The study was aimed at investigating the features of gnostic functions in the elderly people suffering from dementia. To implement the objectives of the study and to solve the set tasks, the following methods were used: visual gnosis tests (recognition of images, the selection of three subject pictures, selecting parts of a whole, etc.), the acoustic gnosis tests (score and perception of rhythms, recognition of nonspeech sounds), and tactile gnosis tests (tactile identification, Teuber test, Foerster test). When running the visual gnosis tests, the elderly people with the dementia diseases slowly initiated the tasks, made numerous errors, and sometimes could not cope with the tasks at all. Also, the perception integrity disorders, the presence of fragmentation, lack of accuracy, differentiation, preservation of specific objective images-objects, and the violation in the understanding of the spatial arrangement of things were revealed. When performing the auditory-motor coordination tests, the elderly people suffering from dementia needed more time to listen to, they asked for the repeated sound representation, and there were often errors in the rhythmic structure reproduction. When performing the tactile gnosis tests, the elderly people suffering from dementia had difficulties in identifying the subject by touch, in understanding the right and left-sided spatial relationships, and also made errors in recognizing one of the touches when the experimenter touched their hands. Based on the study results, the recommendations have been developed for the preservation and improvement of the existing gnostic functions' disorders in the elderly people suffering from dementia. The recommendations

are complex, and they can also be useful for the medical staff whose professional activity is directly related to the elderly people suffering from dementia, their relatives and the persons closest to them.

Keywords: *gnostic functions, dementia diseases, the elderly people, neuropsychological diagnostics.*

INTRODUCTION

According to experts of the World Health Organization (WHO), about 19% of the total population in Russia are the elderly people, and by 2050 their number will reach one third. There are 26.5 million of those over 60[1].

Due to the increase in the number of the elderly people, the number of those suffering from dementia in need of psychiatric care is also increasing. According to the WHO, currently, more than 47 million inhabitants of the Earth suffer from dementia, and the number of patients increases by 10 million every year, and by 2050 their number will triple. At the same time, there is no exact information about the number of persons suffering from dementia in Russia. According to the official data, their number is about 1.3 – 1.8 million people, but experts consider such statistics to be understated [2]. It is worth mentioning that in Russia dementia is practically not diagnosed at the initial stages, and the behavioral problems are attributed to the character traits.

It is well known that in the brain of people with dementia the irreversible atrophic process takes place, which di-

rectly affects the mental processes and functions [3], [4]. One of such most vulnerable functions is that of perception, and the gnostic functions' disorders result in deteriorating the quality of life for the elderly people with dementia [5], [6], [7].

Currently, such domestic scientists as S.I. Gavrilova, N.K. Korsakova, I.F. Roshchina et al. are engaged in the study of impaired mental functions in various types of dementia [8], [9], [10]. At the same time, a number of authors proved a significant increase in dementia incidence in the elderly population, associated with high frequency of hospitalizations, costs of public health facilities, a huge burden on the patient's relatives, and medical personnel. With the growing prevalence of dementia diseases among elderly and senile age people, as well as the involvement of a large number of working age people in the medical, psychological, economic problems associated with the dementia disease, it becomes clear that the study of mental processes and functions disturbed as a result of dementia, as well as the development of corrective actions are very topical and important, both in theoretical and in practical terms [11], [12], [13], [14].

MATERIALS AND METHODS

To study the features of gnostic functions in the elderly people suffering from dementia, we used the following methods: analysis of scientific literature in various fields of knowledge (neuropsychology, gerontopsychology and geriatrics, psychiatry), neuropsychological diagnostics, including: visual gnosis tests (recognition of images, the selection of three subject pictures, selecting parts of a whole)[15], the acoustic gnosis tests (evaluation and perception of rhythms, recognition of nonspeech sounds)[6], and the tactile gnosis tests (tactile iden-

tification, Teuber test, Foerster test)[16]. The obtained results were processed by the authors using quantification of various disorders of the higher mental functions proposed by Zh.M. Glozman[16]. Thus, for the performance of the proposed tasks, the subjects could get from zero to three points, where zero points were attributed for the exact execution of the task, and three – in case of inability to perform more than half of the test tasks. The parametric statistical Student's t-test for independent samples was used for mathematical calculations.

The empirical study was organized and conducted on the basis of the Moscow State Budgetary Healthcare Institution Psychiatric Clinical Hospital No. 4 named after P.B. Gannushkin of the Moscow Department of Health. The subjects of the experimental group included 30 people who were hospitalized: 19 of them were the patients with vascular dementia (F01), and 11 – those with Alzheimer's disease (F00). The average age of the subjects was 68.2 years. The control group consisted of 30 people without obvious mental pathologies. The average age of the subjects was 65.4 years.

RESULTS AND DISCUSSION

STUDY OF VISUAL GNOSIS

1. Visual gnosis tests

Three tests were carried out to study the subject gnosis, namely recognition of realistic images; recognition of contour, superimposed and conflict images; and selection of three subject pictures. According to the results obtained for this test, in the elderly people from the two experimental groups, there were significant differences in the performance of tasks, which was also confirmed by statistical significance obtained using the Student's t-test. The subjects from the experimental group

made more errors when performing all three tests. The greatest number of errors was made during the test for recognition of contour, superimposed and conflicting images ($t = 6.8$ with $p \leq 0.01$). The number of errors in such tests as recognition of realistic images ($t = 6.2$ with $p \leq 0.01$) and the selection of three subject pictures ($t = 4.3$ with $p \leq 0.01$) in the elderly people from the experimental group was the same (1.1). It is worth noting that the elderly people without obvious mental pathologies made the lowest number of errors, and they accurately passed the test for recognition of realistic images.

Thus, based on the results of the subject gnosis tests, it can be concluded that the elderly people with dementia are characterized by errors in the perception of realistic images; pronounced defects in the recognition of noisy, superimposed and conflicting images, as well as multiple errors by the type of fragmentary perception.

2. Simultaneous gnosis tests

To study simultaneous gnosis, two tests were carried out, namely the selection of parts of the whole and finishing drawing to the whole. Large differences are observed in the results obtained for the two groups, namely, the experimental group values are very different from the obtained control group values (1.5 and 0.3, respectively), which is also confirmed by statistical significance ($t = 5.5$ with $p \leq 0.01$). Such results may indicate the disorder in the perception differentiation, the process of comparison and the formation of a holistic image – perception of the subject by the elderly people suffering from dementia.

When performing the task, the elderly people suffering from dementia also often resorted to a psychologist, could not find the details on their own, made errors when finishing drawing the objects, thereby obtaining high scores and indicating the impossibility of per-

forming the task independently and multiple errors.

Thus, based on the results of the simultaneous gnosis tests, it can be concluded that the elderly people with dementia are characterized by errors in isolating the essential features of objects; errors of the comparison process; and violations of the perception of the holistic image of the subject.

3. Optical-and-spacial gnosis tests

Three tests were performed to study optical-and-spacial gnosis, namely recognition of time on schematic clocks; setting hands on the clock on the model, and setting the predetermined time. The results obtained in three tests suggest that when performing tasks, both the elderly people from the experimental group and those from the control group made errors. First of all, these errors indicate the quasi-3D disorders, as well as spatial perception disorders.

Thus, when performing a test for time recognition on schematic hours, the elderly people suffering from dementia gave a lot of approximate answers or found it difficult to answer at all ($t = 6.2$ with $p \leq 0.01$). When performing the “setting hands of the clock on the model” test, the painted hands on the clock were set as per the model itself ($t = 6.2$ with $p \leq 0.01$). It should be noted that in the elderly people without obvious mental pathologies, the response period increased in all tests.

Thus, according to the results of optical-and-spacial gnosis tests, it can be concluded that the elderly people with dementia are characterized by a lot of approximate answers; and quasi-3D disorders.

4. Digital gnosis test

A test for recognition and naming of digits was carried out in order to study digital gnosis. The results of this test suggest that the elderly people with dementia made more errors when per-

forming the task (0.8) than those without obvious mental pathologies (0.27), which was also confirmed by statistical significance ($t = 3.3$ at $p \leq 0.01$).

Thus, based on the results of this test, it is safe to say that the digital gnosis in the elderly people suffering from dementia differs from the age norm, leading to errors in the assessment of spatially oriented digits, as well as multiple errors with incomplete correction.

5. Letter gnosis test

A test for recognition and naming of letters was carried out to study letter gnosis. This test indicates that the elderly people with dementia made more errors when performing the task (0.93) than the elderly people of the age norm (0.47), which was also confirmed by statistical significance ($t = 2.9$ at $p \leq 0.01$). It should be noted that several subjects from the experimental group could not cope with the task of naming the spatially-oriented letters presented without drawing the experimenter's attention.

Thus, the results of the letter gnosis tests indicate that the elderly people suffering from dementia are characterized by an increased response period, errors in the assessment of spatially-oriented letters, as well as multiple errors without correction.

6. Colour gnosis test

A color-subject verbal association test was conducted to study color gnosis. The results obtained for this test indicate the errors of the subjects of the two experimental groups (0.6 and 0.23, respectively). The performance of this task by the elderly people suffering from dementia is characterized by the fact that they most often made one mistake in naming the color of a rarely occurring concept, while the elderly people of the age norm named the colors of both concepts – the often and rarely encountered ones. However, it should be noted that some of the elderly people of the age

norm sometimes needed more time to name the color of a rarely encountered concept.

Thus, the results of this test do not allow concluding about any significant differences in the color gnosis between the two experimental groups. In this case, it can only be assumed that the verbal association between the color and the object can be violated both due to the natural aging of the body and due to dementia diseases.

7. Facial gnosis test

A test for the identification of portraits of famous people was performed to study facial gnosis. It is worth mentioning that when performing this test, the elderly people of the two experimental groups almost did not make errors; however, in the elderly people with dementia diseases, the response period was often increased (0.77 and 0.3, respectively). After analyzing the results obtained for this test using mathematical statistics, no statistically significant differences were obtained. Thus, it can be concluded that no significant differences were observed in the facial gnosis of the elderly people, both with dementia diseases and without obvious mental pathologies.

STUDY OF ACOUSTIC GNOSIS

1. Nonverbal hearing tests

Four tests were carried out to study nonverbal hearing, namely paper rustling; clinking spoon on the glass; sounds from audio media; and the melody of a familiar song without words. The results obtained for these tests indicate the differences in the two experimental groups, namely the values in the group of the elderly people suffering from dementia were greater in all four tests for nonspeech hearing than in the elderly people from the group without obvious mental pathologies. This sug-

gests that the subjects from the experimental group made more errors when performing tasks. At the same time, the most difficult tests for them were "Paper rustling" (0.87) and "Sounds from Audio Media" (0.72), which was also confirmed by the statistically significant differences obtained ($t = 3.6$ with $p \leq 0.01$ and $t = 3.2$ with $p \leq 0.01$, respectively).

The smallest number of errors was made when recognizing the sound of a spoon, beating on a glass, and a familiar melody without words (0.53 and 0.5, respectively). At the same time, the indicators for the elderly people from the control group were almost equal in all the tests; however, it should be noted that the most difficult for them were the same tests as for the elderly people from the experimental group ("Paper rustling" (0.25) and "Sounds from Audio Media" (0.3)). These results may indicate that due to natural aging, the auditory attention is deteriorating due to natural aging, resulting in the deterioration of various noises and sounds perception.

Also, when performing these tests, the authors noticed the specifics of the tasks performed by the elderly people suffering from dementia, namely, they needed more time to listen to, they asked for the repeated sound representation, and there was absent-mindedness of auditory attention.

Thus, the results of the nonverbal hearing diagnostic test allow concluding that the elderly people with dementia are characterized by the deterioration of auditory attention; deterioration in the perception of various household noises and sounds; weak differentiation of nonspeech noises; and increase in the response period.

2. Auditory-motor coordination tests

Three tests were carried out to study the auditory-motor coordination, namely rhythm assessment; patterned

execution; by verbal instructions. The obtained results indicate large differences in the two experimental groups in all auditory-motor coordination tests. For example, when performing the tasks, the elderly people from the experimental group had difficulties in understanding the instructions, and in the rhythm assessment test they had extra hits (1.47 and 0.58, respectively), which was confirmed by statistical significance ($t = 5.2$ with $p \leq 0.01$). In the patterned execution test, the subjects of this group showed insufficiency, slowness and perseveration of hits (1.7 and 0.47, respectively), which was also confirmed by statistical significance ($t = 7.2$ with $p \leq 0.01$). Finally, in the "By verbal instructions" tests, the elderly people with dementia quickly forgot the rhythmic structure just presented to them and made numerous requests to repeat the rhythmic series pattern (1.5 and 0.53, respectively). These errors may indicate the auditory arrhythmias. It is worth noting that the number of errors made in the group of the elderly people with dementia has statistically significant differences with the group of the elderly people without obvious mental pathologies ($t = 6.1$ with $p \leq 0.01$).

Thus, the results of this diagnostic test allow to conclude that the elderly people with dementia are characterized by rhythm perception disorders; reproduction errors: extra hits, lack of hits, slowness, perseveration; fast forgetting of the rhythmic structure just presented; and numerous requests to repeat the rhythmic series pattern.

STUDY OF TACTILE GNOSIS

1. Skin-kinesthetic gnosis test

A tactile identification test was conducted to study skin-kinesthetic gnosis. The results obtained in this test suggest that the elderly people with dementia made more errors during the perfor-

mance of the task (1) than those without obvious mental pathologies (0.53). This is confirmed by statistical significance ($t = 2.8$ with $p \leq 0.01$).

It is worth paying attention to the implementation of this task by subjects from the experimental group. For example, the elderly people from this group had difficulties in identifying an object while feeling it, they needed more time, and they named significant features and properties of objects, but could not understand what kind of object it was. It should also be noted that the subjects from the control group quickly and with interest initiated the task and performed it with ease, although sometimes they also needed additional time when feeling the objects.

Thus, according to the results of the skin-kinesthetic gnosis test, it can be concluded that the elderly people with dementia are characterized by difficulties in recognizing objects by skin-kinesthetic sensation; a fault in the analysis of the actively examined subject; and an increased response time.

2. Somato-spatial gnosis tests

Two tests were performed to study somato-spatial gnosis, namely showing the subjects indicated by the psychologist with right (and left) hand; naming the fingers of one's own hand, the hand of a psychologist, and a hand drawn. The results of this test indicate that the elderly people with dementia made more errors when performing two tests (0.8 and 0.83, respectively) than those without obvious mental pathologies (0.53 in each test). Also, when performing this task, sometimes there were difficulties in understanding the right and left-sided spatial relationships in the group of the elderly people with dementia, which may indicate the spacial orientation disorders, as well as a disorder in determining various parameters of space. However, despite this, there were no statistically significant differ-

ences in the two groups, and therefore it can be concluded that difficulties in understanding right and left-sided spatial relationships can arise both from natural aging and due to dementia.

3. Somatosensory gnosis tests

Two tests were performed to study somatosensory gnosis, namely Teuber test and Foerster test.

When performing these tests, the elderly people with dementia made many mistakes. Thus, in the Foerster test, in which the simple shapes, letters or numbers are drawn on the subject hand, and his/her task is to identify and name them, the elderly people with dementia made more errors in the answers than those in the control group (1.13 and 63, respectively), which was confirmed by statistical significance ($t = 3.6$ with $p \leq 0.01$). Approximately the same situation was observed in the Teuber's test, in which the test subject's hand was touched first, then the other and both hands, and after each touch, the subject must answer which particular hand the experimenter touched. In this test, the elderly people with dementia made more errors when localizing the touch than subjects from the control group (1.07 and 0.67, respectively). The elderly people from the experimental group often made requests for a repeated presentation of stimuli, they made errors when recognizing one of the touches when the experimenter touched their hands, and sometimes they needed more time to recognize them. Such errors indicate a somatosensory sensitivity disorder and ignoring of tactile sensations. It should be noted that the elderly without obvious mental disorders coped with the task almost unmistakably, sometimes only resorting to the use of extra time. Finally, after analyzing the test data obtained by mathematical statistics – the Student's t -test – the conclusion was made that the experimental groups had statistically significant differences ($t = 2.7$ with $p \leq 0.01$).

Thus, it can be concluded that the elderly people with dementia are characterized by errors in recognizing one of the touches; errors in localizing the touch, as well as an increase in the response period.

4. Somatognosis tests

A body scheme was made to study somatognosis. When conducting this test, the elderly people with dementia diseases also made more errors when performing tasks (1.03) than those without obvious mental pathologies (0.53, respectively). Thus, for example, in carrying out a task, the elderly people suffering from dementia sometimes had difficulty in displaying body parts at the request of a psychologist, taking into account lateral characteristics. This may indicate a violation of the body scheme preservation, an impaired understanding of the right and left in spatial relationships. When performing these tasks, sometimes only the response period was increased in the elderly people without obvious mental pathologies. Differences in the performance of tasks of the somatognosis test in the groups of subjects were also confirmed by statistical significance ($t = 3.3$ with $p \leq 0.01$).

Thus, based on the results of this diagnostic test, it can be concluded that the elderly people with dementia are characterized by difficulties in showing body parts taking into account lateral characteristics, as well as an impaired understanding of the right and left in spatial relationships.

CONCLUSION

The results of the study have shown that the elderly people suffering from dementia have serious gnostic function disorders, which is most clearly seen when compared with the elderly people without mental pathologies.

For example, the elderly people suffering from dementia have difficulties in recognizing objects, in orientation in place and in time, are characterized by slow mental activity, as well as poor auditory attention. As compared with the elderly people of the age norm, people with dementia made more errors during the test, which also indicated a different degree of the gnostic sphere preservation.

Based on the study results, the recommendations have been developed for the preservation and improvement of the existing gnostic functions' disorders in the elderly people suffering from dementia. The recommendations are comprehensive and are aimed both at correcting gnostic functions that prevent the comfortable flow of sentility, and include measures aimed at preventing disorders of gnostic functions development in the elderly people. Preventive and remedial work includes a diagnostic phase, the purpose of which is to identify abnormalities in the functioning of gnostic functions in the elderly people. The preventive process presupposes the existence of a preventive program, the content of which includes three components, namely the educational, social and cognitive ones. In this case, the content of the educational component is to inform about the consequences that may further affect the person's life. The social component contains help in adapting to the living conditions of the world, orientation in space, and mastering new skills. Cognitive training is aimed at maintaining the cognitive skills of the elderly people to maximize the period of social adaptive functioning. In addition, recommendations have been separately developed for health workers, whose professional activities are directly related to the elderly people with dementia, as well as for relatives and the persons closest to them.

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Biologically Active Dietary Supplement for Correction of Exchange Disorders in Nervous System Diseases

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ABSTRACT

The prescription composition of the biologically active dietary supplement (BADs) Oleopren Neuro has been scientifically substantiated through the pharmacological evaluation of the effective agents, polyphenols being the main of them. The technology of an innovative product has been developed, with the establishment of adjustable production parameters securing high organoleptic advantages and stability of the BADs.

Regulated indicators of quality and nutritional value have been determined. Sanitary toxicological and hygienic safety indicators of the product under development had been studied, which allowed to establish a shelf life of two years taking the safety margin of three months into account. The possible mechanisms of the dolichols effect on the metabolic status of the organism were considered.

Clinical trials of the efficiency and functional focus of a specialized product on a representative group of patients with the dyscirculatory encephalopathy (DE) of vascular genesis stages I – II were conducted. The BADs were included in the diet of patients, along with the basic therapy, one capsule twice a day for 10 days.

The materials obtained in this article allow to recommend the developed product as an efficient means of increasing the body's resistance to adverse effects of the environment, stressful situations, as well as psychoemotional and physical stress.

Keywords: *BADs, prescription composition, production technology, regulated indicators, efficiency, functional focus.*

INTRODUCTION

Specialized products, including the BADs, are increasingly used in the prevention and comprehensive treatment of common diseases [1-7]. Chronic cerebrovascular insufficiency accompanied by headache, noise and dizziness, memory impairment, fatigue, and decreased performance is one of these pathologies [8-14].

The concept of DE, which is the most common neurological disorder and determines the relevance of diagnosis and prevention of the pathology under consideration, is widely used for the clinical description of brain function disorders resulting from vascular disorders [8, 16].

In most economically developed countries, including Russia, there is an increase in cerebrovascular disorders resulting from the above pathologies. According to the WHO, mortality from vascular diseases of the brain is 30 – 50 % of all diseases of the circulatory system, or about 14 % of the total mortality of the population, which substantiates the relevance of the problem and the need to take appropriate measures to solve it.

OBJECTS AND METHODS

Prescription components, experimental and industrial samples of a specialized product were used as objects.

Sixty patients with the DE of vascular genesis stages I – II took part in clinical trials. The DE diagnosis was set by a neurologist after an in-depth ex-

amination of patients based on anamnesis and physical examination results using laboratory and instrumental research methods, as well as psychological testing results for diagnosing the degree of cognitive impairment and assessing the living standards over the course of treatment. 30 patients with the DE stages I – II, along with comprehensive classical treatment (statins, antihypertensives, vascular, nootropic drugs), received the Oleopren Neuro BADS one capsule twice a day for 30 days (Group DE – ON). 30 people with similar pathology who did not receive the specialized product made up a reference group (control group). The difference between the reference parameters was considered statistically different at $p \leq 0.05$. The field studies were carried out in accordance with the principles of the World Medical Association Declaration of Helsinki (as amended in 2000 with the explanations given at the WMA General Assembly, Tokyo, 2004), the rules of the International Conference on Harmonization Good Clinical Practice (ICH GCP), ethical principles set forth in European Union Directive 2001/20/EU, and the requirements of the national Russian legislation. Each patient signed an Informed Consent to participate in the research. The tests were carried out at the Central Research Laboratory of the Kemerovo State Medical Academy and the campus of the city clinical hospital No. 2.

The average age of patients was 59.3 ± 6.8 years. The initial condition of patients with DE of vascular genesis stages I – II was analyzed according to an objective examination based on the registration of subjective complaints and neurological status.

General and special methods of researching the quality, safety and efficacy of BADS are used according to the requirements of regulatory documents [11]. An updated and approved grav-

imetric method for determining the content of acetone-insoluble substances (phospholipids) used to identify the products under development is provided below [15].

The method is based on dispersing the analyzed lecithins in acetone at a temperature 0°C , then filtering the solution, separating the residue and drying it at a temperature of $(105 \pm 2)^{\circ}\text{C}$, followed by weighing. The content of substances insoluble in acetone is an indicator of the content of polar lipids in lecithin.

Conducting a test. The filter is dried in a drying cabinet for one hour at a temperature of $(105 \pm 2)^{\circ}\text{C}$, cooled in the exsiccator for 30 – 40 minutes and weighed. The result is recorded with an accuracy of up to 0.001 g. Subsequent weighing is carried out every 30 minutes after drying until reaching constant weight. The weight is considered constant if the difference between the subsequent weighings does not exceed 0.002 g.

It is allowed to dry the filter to constant weight using the express method with the moisture analyzers HB43-S or Elvis-2, in accordance with the manuals attached to devices.

A lecithin sample is thoroughly mixed. A 100 cm³ glass is weighed together with a glass rod, and the result of weighing is recorded with an accuracy of 0.001 g. 2.000 – 5.000 g of the preparation (depending on the analyzed substance) are placed in a previously weighed glass with a glass rod, 40 cm³ of acetone are added, mixed and heated, without allowing to boil, and then cooled.

Then 30 cm³ of acetone are added, cooled to 0°C , and shaken with a glass rod for two minutes, leaving the glass in an ice bath for 5 – 10 minutes.

After this, the solution is filtered using a pre-dried and weighted filter, a glass with a rod and the filter residue is washed with 20 – 40 cm³ of cooled acetone, if necessary, until the thickened

sample is completely transformed into a fine powder and completely transferred to the filter. After that, the filter with the residue is dried in a drying cabinet or on an Elvis-2 (HB43-S) moisture analyzer at $(105 \pm 2)^{\circ}\text{C}$ to constant weight. At the same time, the glass with a rod and the remaining residue is dried in an exsiccator and weighed. The result is recorded with an accuracy of 0.001 g.

The mass fraction of acetone-insoluble substances (X , %) is found using the following formula:

$$X(\%) = \frac{(m_1 + m_2) \cdot 100}{m} \quad (1)$$

where m is the sample weight, g;

m_1 is the weight of the filter with residue net of the filter weight, g; and

m_2 is the weight of the glass with a rod and residue net of the weight of the glass with a rod, g.

The final result of the determination is found as the arithmetic average of the results of two parallel determinations.

Calculations are made, and the result is recorded to the second decimal place. The final result is rounded to the first decimal place.

Determination of polyprenols using the HPLC method.

The idea of the method lies with the polyprenols extraction from the analyzed object into the solution and subsequent determination by high performance liquid chromatography (HPLC).

Test solution. The exact weighed sample of the analyzed BADS (an amount equivalent to 5 – 10 mg of polyprenols) is put into a 50 ml volumetric flask, 5 ml of 0.1M HCl are added and placed in a boiling water bath for 15 minutes. Then the flask is cooled, 5 ml of methanol and 20 ml of hexane are added and shaken on a vortex shaker for one minute. The contents of the flask are placed in a separatory funnel, the lower phase is drained and discarded, and the upper phase is put into a measuring cylinder. The volume of the solution is recorded.

The solution is filtered through a Blue ribbon filter.

Standard solution. The substance of polyprenols with known content is used as a standard.

30 mg (exact sample) of a standard sample of polyprenols are put into a 50 ml volumetric flask, dissolved in hexane, and brought with it to the mark. The solution is filtered through a Blue ribbon filter.

Preparation of the mobile phase. A mixture of hexane and isopropyl alcohol is 99:1. The mixture of solutions is degassed and filtered through the 0.45 μm filter.

Chromatographic conditions: Devices are any suitable for HPLC; Bolster with length 250 mm, internal diameter 4.0 mm, stationary phase GL EXSIL AMINO, 5 microns (or similar); Eluent feed rate 1.0 ml/min; Bolster temperature 30°C ; Sample volume 20 μl ; Detector UV, 220 nm; Chromatogram recording time – 8 minutes.

Analysis and calculation. After the system suitability is tested, equal volumes (20 μl) of the standard and test solutions are injected alternately into the chromatograph, and chromatograms are recorded. The peak areas of polyprenols in the standard and test sample are identified and measured.

The contents of polyprenols are found using the following formula:

$$X(\%) = \frac{S_o \cdot C_{st} \cdot V_o \cdot 100}{S_{st} \cdot m} \quad X(\%) = \frac{S_o \cdot C_{st} \cdot V_o \cdot 100}{S_{st} \cdot m}$$

where S_o is the sample peak area, S_{st} is the standard peak area, C_{st} is the standard solution concentration (mg/ml), m is the sample weight (mg), and V_o is the sample solution volume (ml).

METHOD OF MATHEMATICAL PROCESSING OF RESEARCH RESULTS

It includes the calculation of the following statistical values:

- arithmetic mean \bar{X} ;
 - standard deviation of a single result $s = \sqrt{s^2}$;
- standard deviation of the arithmetic mean or arithmetic error of all replications x ;
- accuracy of arithmetic mean t ;
 - confidential error of the measured value assessment ξ .

Besides, when a researcher studies the influence of any factors on the technological process parameter, it is also required to establish a correlation and functional relationship between them.

The above statistical values are found using formulas (7.8, 9,10,11,12,14,15,16).

Arithmetic mean \bar{X} is defined as follows:

$$\bar{X} = \frac{\sum_{i=1}^n x_i}{n} \quad (3)$$

where x_i is the value of a single measurement;
 n is the number of repeated measurements.

Standard deviation s is defined as follows:

$$\sigma = \sqrt{\sigma^2} \quad (4)$$

where σ^2 is the deviation equal to

$$\sigma^2 = \frac{1}{n} \sum_{i=1}^n (x_i - \bar{X})^2 \quad (5)$$

hence

$$\sigma = \sqrt{\frac{\sum_{i=1}^n (x_i - \bar{X})^2}{n}} \quad (6)$$

The σ value is always positive. The greater its value is, the greater the variability of the property of the object under study is. The value σ is expressed in the same units of measure as the arithmetic mean.

The value σ is found with an accuracy of one decimal place greater than the accuracy adopted in relation to the arithmetic mean.

Standard deviation or arithmetic mean error X is determined as follows

$$x = \frac{\sigma}{\sqrt{n}} \text{ if } n > 30 \quad (7)$$

$$x = \frac{\sigma}{\sqrt{n-1}} \text{ if } n < 30 \quad (8)$$

Standard deviation (arithmetic mean error) is a named value and is expressed in the same way as the arithmetic mean it is found for. The mean value and its error are usually noted as $\bar{X} \pm x$.

The smaller the error value of the arithmetic mean is, therefore, the smaller is the difference between the parameter values in the sample and the general population.

The arithmetic mean error can be expressed in relative terms – as a percentage (%). In this case, it is called the measure of the arithmetic mean accuracy (m) and is found using formula

$$\Delta_m = \pm \frac{x}{\bar{X}} * 100, \% \quad (9)$$

The smaller is the value Δ_m , the more reliable is the arithmetic mean of the measured indicator value.

The confidence interval is of great importance in assessing the accuracy of the conducted research. Studies are considered reliable if the experiment results *do not exceed the limits of the confidence interval*.

This interval shows the extent to which the exact value of the studied indicator varies in comparison with the general mean, i.e., the true values of the desired value X lie within $(\bar{X} \pm \xi)$.

$$\bar{X} + (\xi) \leq X \leq \bar{X} - (\xi) \quad (10)$$

where \bar{X} is the arithmetic mean;
 ξ is the confidential error; and
 X is the general average value.

These values are found after only reliable results remain in the series of experiments.

The true value of the measured value with a given confidence level (P) must lie within the confidence interval $\bar{X} \pm \xi$.

The Student's t-test is used ($P; f$) to determine the confidence error (ξ) of the result:

$$\xi = t(P; f) \cdot x \quad (11)$$

Criterion $t(P; f)$ is taken from application /14/ depending on the given confidence probability (P) or significance level q ($q=1-P$) and the number of degrees of freedom f .

The rule of thumb can be used to select the confidence probability (P):

$P = 0.99$ in especially important cases;

$P = 0.95$ in processing analytical data;

$P = 0.9$ in processing data of a technological experiment; and

$P = 0.8$ in processing data of a biological experiment.

RESULTS AND DISCUSSION

A description of the effective agents of the initial raw materials determining the functional focus of the product under development is given to substantiate the prescription composition.

Polyprenols are a set of biologically active compounds secreted from coniferous trees. Structurally similar to dolichol, polyprenols replace its deficiency with dysfunction of the dolicholphosphate cycle, which occurs when many pathological states associated with disruption of cell membranes emerge and develop.

Polyprenols participate in regeneration of damaged cell membranes of the liver, secure glycosylation reactions in the dolicholphosphate cycle during the synthesis of glycoproteins; control their biosynthesis, maintaining the immune status of the cell and delivery of immunoglobulins, ensure the induction of interferons, generation of neutrophils, and activation of macrophages of the reticuloendothelial system; regulate the

reduction of cholesterol through activation of dolichol delivery from the endoplasmic reticulum to lysosomes; influence the absorption of peroxide lipids formed in the membrane, improve cell energy metabolism, and participate in the oxidative phosphorylation and activation of mitochondrial function [11-14; 16-23].

Phosphatidylserine (Memree Plus 30L/MemreePlus). A mixture of soybean phosphatidylserine and phosphatidic acid is used to strengthen cognitive health, reduce stress, and improve the efficiency of recovery processes.

Phosphatidylserine is a special type of phospholipids. In turn, phospholipids are the main components of cell membranes that enable cells to retain their structure. They also serve as surfactants controlling various biological processes that occur on the water-air surfaces of lungs and intestines. Phospholipids can interact with enzymes, producing hormones or neurotransmitters.

Phosphatidylserine is found in all cell membranes; its high concentrations are also detected in brain cells.

The level of phosphatidylserine in the brain cells decreases with age. Phosphatidylserine is found in dairy products and meat byproducts. However, these sources are insufficient to satisfy the need for this micronutrient, especially for the elderly and senile people. Intake of an additional amount of phosphatidylserine helps restore its level in brain cells and secure appropriate metabolic processes.

Glycine has a sedative, mild tranquilizing (anti-anxiety) and anti-depressant effect. It reduces anxiety, fear, psychoemotional stress, manifestation of alcohol withdrawal, increases mental performance, sharpens attention, and improves memory and associative processes. This essential amino acid helps improve mood, normalize sleep, survive stress, avoid its aftereffect "blows" (it maintains normal blood pressure

levels), and protect against toxic effects of psychotropic drugs. Glycine helps reduce vegetative-vascular disorders (including during menopause) and severity of cerebral disorders in ischemic stroke and traumatic brain injury.

Glycine belongs to the drugs that improve metabolic processes in the brain. It is part of many biologically active substances, including proteins in human tissues. Glycine is a neurotransmitter involved in the transmission of information along nerve fibers. Glycine receptors are found in many parts of the brain and spinal cord, they inhibit the release of neurotransmitters from neurons that transmit stimulating impulses to the central nervous system.

Tocopherol acetate (Vitamin E) is a fat-soluble vitamin. Its main functions are associated with oxidative processes. As an antioxidant, it inhibits the development of free radical reactions and

prevents the formation of peroxides that damage cellular and subcellular membranes, which is important for the normal operation of the nervous and muscular systems and the body as a whole. In combination with selenium, it prevents the oxidation of unsaturated fatty acids (a component of the microsomal electron transport system), and prevents red blood cell hemolysis. It is a cofactor of enzyme systems that hold key positions in the metabolism, including the childbearing function.

The obtained materials allowed to develop a qualitative and quantitative composition of the formulation of the product under development (Table 1).

The research was conducted to determine the regulated indicators of quality and nutritional value. For this purpose, an organoleptic assessment was given, and safety criteria and nutritional value during production and storage were

Table 1. Prescription of Oleopren Neuro BADS

#	Component	Content, mg/1 capsule not less than	Content, mg/2 capsules not less than	% RDI in 2 capsules*
1	Memree Plus-30L (14.5 %PS, 14.5 % PA)	50	100	N/a
	<i>Phosphatidylserine</i>	<i>7.25</i>	<i>14.5</i>	
	<i>Phosphatidic acid</i>	<i>7.25</i>	<i>14.5</i>	
	<i>Acetone-insoluble substances</i>	<i>27.5</i>	<i>55</i>	
2	Glycine	50	100	
3	Polyprenols mixture 75 %	6.7	13.4	100
	<i>Amount of polyprenols</i>	<i>5</i>	<i>10</i>	
4	Tocopherol acetate 98 %	3.83	7.65	50
	<i>Tocopherol acetate</i>	<i>3.75</i>	<i>7.5</i>	
Filler				
1	Sunflower oil refined	476.87		
2	Aerosil (carrier)	12		
3	Grindox (antioxidant)	0.6		
	Total weight of the capsule contents	600		
Gelcaps				
1	Gelatin (carrier)	113.54		
2	Glycerin (moisture-holding agent)	47.5		
3	Sorbitol (moisture-holding agent)	28.5		
4	Copper complex chlorophyllin (coloring agent)	0.23		
5	Titanium dioxide (coloring agent)	0.23		
	Total weight of gelcaps	190		
	Capsule weight	790		

*RDI – recommended daily intake level according to the EurAsEC standard (introduced by the Resolution of the Commission of the Customs Union No. 622dated 07.04.2014).

studied. Oleopren Neuro BADS was stored in a dry, dark place at a temperature not higher than 25 °C, for 27 months. Safety indicators included the determination of pathogenic microorganisms, including Salmonella, toxic elements: lead, arsenic, cadmium, mercury, iron, copper, pesticides; HCCH (sum of isomers), DDT and its metabolites, heptachlor, aldrin, according to the requirements of TR TC 021/2011 "On safety of food products" (BADS based on vegetable oils, animal and vegetable lipids). The specified group of microorganisms was not found in ten grams of the product. No changes were noted that described other safety indicators upon expiration of the specified storage period. The results obtained allowed to establish a regulated shelf life: two years under the above conditions.

The established nutritional values of a specialized product describe its functional focus, which is confirmed in field tests on a representative group of patients with DE of vascular genesis stages I – II. Based on the results of clinical studies, the BAD is recommended for the prevention and comprehensive treatment of the nervous system disorders, as well as under adverse environmental effects, physical inactivity, increased psychoemotional stress, and stressful situations.

Organoleptic characteristics and nutritional value of the test product are presented in Table 2.

The following areas of polyphenols influence on the correction of metabolic disorders can be suggested, based on the biological role of dolichols:

- participation in the processes of the liver damaged cell membranes regeneration, ensuring the glycosylation reaction in the dolicolphosphate cycle during the glycoprotein synthesis;
- maintenance of the cell immune status, delivery of immunoglobulins, participation in the interferons in-

duction, generation of neutrophils, and activation of macrophages of the reticuloendothelial system;

- decrease in cholesterol level through activation of dolichol delivery from the endoplasmic reticulum to lysosomes; and
- absorption of peroxide lipids formed in the membrane, improvement of the cell energy metabolism, participation in oxidative phosphorylation, and activation of mitochondrial function.

The technological process includes the following main stages (Figure 1):

Preparation of raw materials. Glycine is first grinded in a hammer mill MM10 and sifted through a SGS-30 vibrating screen with a mesh size of 0.4 mm;

Preparation of the mixture for encapsulation. The components of the formulation are metered into the reactor-homogenizer in a specific order: refined sunflower oil; antioxidant Grindox 109; Memree Plus-30h; polyphenols 75 % mixture; tocopherol acetate 98 %; aerosil (stirred and homogenized); glycine (mix and homogenize).

Table 2. Regulated quality indicators of Oleopren Neuro BADS.

Indicator	Description
Appearance	soft gelatin capsules
Capsule color	yellow to orange, residue inside the capsule is allowed
Taste and smell of the capsule contents	specific
Average capsule weight, mg	790 (711 – 869)
Vitamin E content in one capsule, mg	3.75 (2.6 – 4.9)
Polyphenols content in one capsule, mg, not less than	5.0
Content of acetone soluble substances (phosphatidyl serine and phosphatidic acid) in one capsule, mg, not less than	14.5

The compliance of the name, quantity and series of raw materials with a

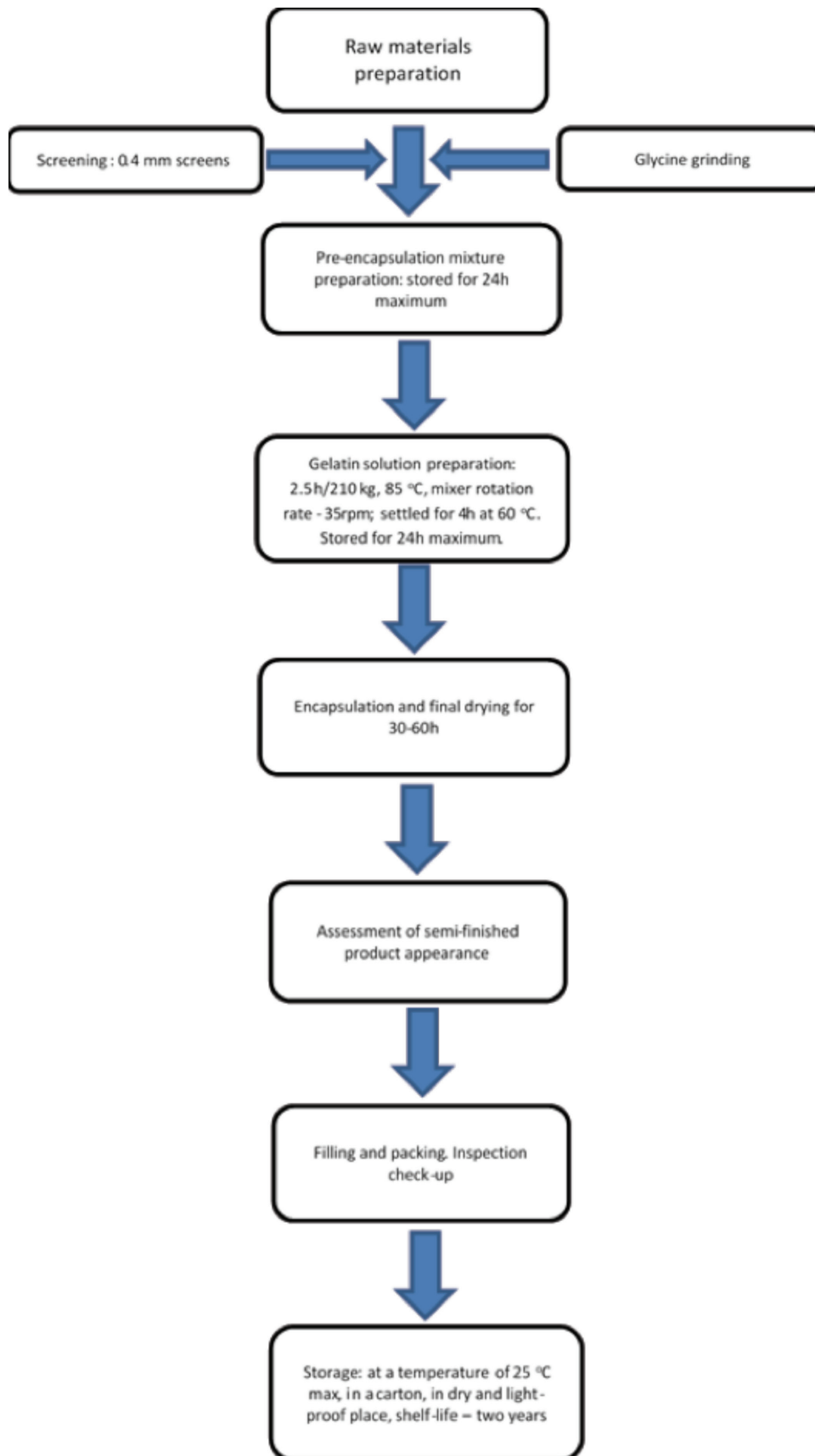


Figure 1. Technological scheme of the Oleopren Neuro BADS production

technological card is checked. There should be no lumps and foreign matter. The shelf life of the mixture is no more than 24 hours in a dark place in a container filled to the top;

Preparation of gelatin solution. The parameters are set in the Melter MGP mixer software: water temperature is 85°C; amount of purified water is according to the boot map; stirrer speed is 35 rpm. The weighted components are loaded in the following sequence: purified water, glycerin, gelatin.

Auxiliary components – preservatives and pigments – are added last. Preparation time is 2.5 hours per 210 kg of ready-made gelatin solution. Upon the completion of the gelatinization process, the solution is discharged through a filter (pore size – 0.2 mm) into a storage tank, settled for four hours at a temperature of 60°C, and fed to the capsule manufacturing site. The shelf life of ready-made gelatin is not more than 24 hours;

Encapsulation and drying. Soft gelatin capsules are made from a gelatin solution and encapsulation mixture in the SGM1010 capsule machine. Capsules are dried for 30 – 60 hours in drying tunnels until the weight of the capsules stops falling;

Evaluation of the intermediate product appearance. It is evaluated visually, an average sample is taken and transferred to the production laboratory for testing for compliance with the withered requirements of technical documentation. The container is marked with a label indicating the name of the intermediate product, quality, batch number, date of manufacture, and the operator's signature;

Packaging. It is evaluated in accordance with the technical documentation for the product. Samples of the finished products (3 packs) are transferred to a collection of arbitration samples.

All stages of the technological process are recorded in the route sheet.

The sparing technological parameters of production are defined, providing high consumer properties and stability of biologically active components of the formulation.

Based on the results of microbiological, sanitary hygienic and sanitary toxicological tests, the hygienic well-being of the product is demonstrated after two months of storage at 25°C in a package, in a dry and dark place, which has allowed to determine shelf life of two years under the above conditions.

The influence of the developed product on the correction of metabolic processes in the DE was studied to prove the efficiency and functional focus.

As a result of treating patients, positive dynamics of both an objective and a subjective state have been demonstrated in both groups. A good tolerability of the BADS has been noted, no side effects on the part of the internal organs, as well as on the nervous, cardiovascular systems, and skin integuments have been observed. A combination of a specialized product with drugs used to treat DE has been tolerated well.

The clear positive dynamics of clinical manifestations of the disease have been established. The overwhelming majority (95 %) improved their general condition, processes of memorizing and reproducing what they read, all patients had less headache, the initiative was activated, 90 % had increased attention and concentration, a decrease in emotional volitional disorders was registered. At the same time, the best indicators have been noted in Group DE – ON. However, the difference has not been statistically significant (Table 3).

As a result of the research carried out using the Nottingham health profile, the positive dynamics of the following living standards have been obtained: energy, pain, emotional state, sleep, social isolation, and physical activity. The living standards during treatment are statistically significantly lower in the

control group in terms of energy, pain, emotional state, physical activity and total points. Better results are shown in the patients taking Oleopren Neuro BADS (Table 4).

The memory, voluntary attention, and exhaustion of patients over the course of treatment were evaluated using the method of learning ten words (by A.R. Luria). Low levels of memory and the absence of a persistent increase in the number of correctly reproduced words were observed in patients with DE prior to its treatment. The memorization curve was described by a zig-zag shape, which indicated the instability and high exhaustion of mnemonic processes. The volume of short-term memory in patients increased significantly at the very first presentation of the stimulating material ($P < 0.05$) after the treatment using a nutritional factor. The number of correctly reproduced words increased with each subsequent presentation; most patients could correctly reproduce all ten words after the third-fourth repetition. The memoriza-

tion curve after the end of the tests was described by a gradual rise, which testified to the sustainability of attention and the absence of the effect of depletion of mental functions. At the same time, these functions improved somewhat earlier in Group DE – ON than in the control group.

Low levels of concentration and its rapid exhaustion were recorded prior to the treatment of patients with DE, i.e., there was a trend to an increase in the time spent by patients on completing the task in each of the following tables. There was a positive change in the concentration of attention after the treatment, the average task completion time was significantly reduced from 61.1 sec before treatment to 43.5 sec in the control group, and 40.6 sec in Group DE – ON by the end of therapy ($P < 0.05$). Attention was described by stability, there were no sharp fluctuations in the level of concentration during the task completion. As such, the results of an experimentally conducted psychological study demonstrate a significant

Table 3. Dynamics of clinical symptoms in patients with DE stages I – II in Group DE – ON and the control group after treatment

Clinical manifestations	Control group No.=30 (100 %)	Group DE – ON No.=30 (100 %)
Improved general health and well-being	30	30
Headache reduction and regression	30	30
Improved process of memorizing and reproducing what they read	28 (93 %)	30
Intensified initiative	27 (90 %)	30
Increased attention and concentration	30	30
Decrease in emotional volitional disorders	28 (93 %)	30
Improved muscle tone	27 (90 %)	30
Reduction of hypertension syndrome	28 (93 %)	30
Positive dynamics on EEG	29 (97 %)	30
Positive dynamics on REG	29 (97 %)	30

Table 4. Living standards for the patients with DE stages I – II in group DE – ON over time against the control group

Indicator	Before treatment, points No.=60	After 30 days, points	
		Control group No.=30	Group DE – ON No.=30
Energy	62.3 ± 0.7	47.4 ± 0.5	33.1 ± 0.6*
Pain	98.4 ± 1.9	69.2 ± 0.7	51.3 ± 0.9*
Emotional condition	52.1 ± 1.1	42.1 ± 1.2	31.5 ± 1.2*
Sleep	73.2 ± 1.3	53.7 ± 0.9	44.7 ± 0.8*
Social isolation	43.2 ± 1.1	31.4 ± 1.1	26.2 ± 0.9*
Physical activity	72.6 ± 0.9	45.8 ± 1.0	37.4 ± 0.8*
Total	401.8 ± 4.1	289.9 ± 3.7	224.4 ± 3.7*

Note: * – differences are significant compared with the results before treatment at $P < 0.05$

improvement in cognitive functions – in particular, memory and attention in patients with DE.

A conclusion has been made that the use of Oleopren Neuro BADS, when added to the comprehensive classical therapy, increases the efficiency of treating DE of vascular genesis stages I – II.

It has been demonstrated that the disturbance of many metabolic processes, the occurrence and development of pathological states, including those with the disorders under consideration, are associated with impaired cell membranes and lead to dysfunction of the dolicholphosphate cycle, which, in turn, increases the output of dolichol from the body, causing its deficiency. In this case, polyprenols that are structurally similar to dolichol replace its deficiency, securing normalization of metabolism [16 – 28].

The following main mechanisms of polyprenols effect on the correction of metabolic disorders can be suggested based on the biological role of dolichols:

– membrane protective: participation in the processes of the damaged liver cell membranes regeneration, securing the glycosylation reaction in the dolicholphosphate cycle during the synthesis of glycoproteins;

– immunomodulatory: participation in the biosynthesis of glycoproteins, maintaining the immune status of the cell, delivery of immunoglobulins, participation in the interferons induction, generation of neutrophils, and activation of macrophages of the reticuloendothelial system;

– hypolipidemic: decrease in cholesterol level through activation of dolichol delivery from the endoplasmic reticulum to lysosomes; and

– antioxidant: absorption of peroxide lipids formed in the membrane, improvement of cell energy metabolism, participation in oxidative phosphorylation, and activation of mitochondrial function.

Advantages of the developed product based on polyprenols are as follows:

- High safety and no side effects;
- Possibility of long-term use, including for the elderly people; and
- Optimum dosages of active ingredients, high efficiency due to their synergism.

CONCLUSION

Comprehensive treatment of patients with DE of vascular genesis stages I – II using Oleopren Neuro BADS favorably influences the clinical manifestations of the disease.

Improvement in health and mood, and therefore in the living standards, is observed during the use of Oleopren Neuro BADS in the comprehensive treatment of patients with DE of vascular genesis stages I – II.

Inclusion of Oleopren Neuro BADS in the comprehensive treatment of patients with DE of vascular genesis stages I – II contributes to the positive dynamics of cephalic and vestibular syndromes, as well as to improving the cognitive functions of patients.

Specialized product Oleopren Neuro BADS is tolerated well by patients and does not cause any side effects.

Recommendations for use are as follows: one capsule twice a day for 30 days for the prevention and comprehensive treatment of DE of vascular genesis stages I – II, as well as against adverse environmental effects, physical inactivity, increased psychoemotional stress, and stressful situations.

The industrial production of Oleopren Neuro BADS is carried out at the enterprises of the Art Life company certified under the international standards ISO 9001, 22000 and GMP rules, which secures the stability of the quality and safety of the products.

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Effective Use of Vitamin D in Mild Cognitive Impairment in Older People

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ABSTRACT

Introduction. *With age, there is a growing risk of vitamin D deficiency and cognitive impairment. Maintaining the older people's health is socially relevant to health systems in the light of the population ageing trend.*

The study was aimed at identifying the relationship of vitamin D levels and symptoms of moderate cognitive impairment in older people.

Methods. *The authors conducted a cross-sectional screening of vitamin D status and cognitive impairment using the memory impairment screen (MIS) questionnaire, as well as the clinical, placebo-controlled study of vitamin D intake at a dose of 2,000 IU/day for 6 months.*

Results. *The frequency of vitamin D deficiency in older patients with signs of cognitive impairment totaled 90.91 %, which was significantly more frequently compared with the group without cognitive impairment, where vitamin D deficiency was found only in 11.36 % of cases. In the dynamics on the background of the vitamin D intake for 6 months, the concentration in the intervention group amounted to 52.34 ± 2.43 ng/ml vs 14.71 ± 1.54 ng/ml in the placebo group. The results of the study of cognitive impairment using MIS for the treatment group were 3.63 ± 0.01 points, which was significantly higher compared with the placebo group – 1.78 ± 0.22 points. A correlation analysis of vitamin D levels and MIS points showed a strong positive relationship, with a correlation coefficient of 0.92.*

Conclusion. *The study identified a positive relationship of increasing vitamin D levels and reducing the symptoms of*

mild cognitive impairment in older people. Achieving vitamin D levels of over 40 ng/ml greatly reduces the symptoms of cognitive impairment identified by the MIS questionnaire, however, the issue of treatment of impaired cognitive functions with vitamin D remains debatable.

Keywords: *older people, mild cognitive impairment, vitamin D, memory impairment screen, MIS*

INTRODUCTION

With the increase in life expectancy and proportion of older people worldwide, widespread computerization and the increasing complexity of technological processes related to the evolution of civilization, the social importance of preserving cognitive abilities is steadily growing [1-4]. It is a fairly well-known fact that with age, a decrease in cognitive functions is observed in many people, which mostly does not go beyond the average age norm and does not cause any violation of the social adaptation of an individual [5]. Only 6 – 8 % of the individuals over 65 develop persistent, pronounced, cognitive deficit that leads to disability and loss of household independence and is defined as dementia [5, 6].

The literature defines a prodromal phase of dementia as “mild cognitive impairment”, the more correct translation of which into Russian, taking into account its meaning will be “умеренное когнитивное расстройство” (umerennoye kognitivnoye rasstroystvo) [7, 8]. Mild cognitive impairment is detected quite often and is prevalent in 15 – 25 %

of older people that is 3 – 4 times higher than the frequency of dementia [9-12].

Modern strategies for prevention of cognitive impairment and dementia include the identification of risk factors and predictors [13, 14]. Since the background and related pathology often cause dementia and these risk factors are modifiable, early detection and treatment thereof provide new opportunities for distancing the onset and preventing the symptoms of cognitive impairment and dementia [15-16].

Vitamin D (25-hydroxyvitamin D or cholecalciferol) is the main substrate from which the bioactive form of calcitriol (1.25-dihydroxycholecalciferol) is synthesized. Limited exposure to sunlight, reduced capacity of the skin to produce vitamin D and reduced intake of vitamin D in the diet can lead to vitamin D deficiency, which affects almost 50 % of the older people worldwide [17]. Animal studies and experimental observations attest to the important role of vitamin D in the functioning of the central nervous system and brain. In large quantities, the vitamin D receptors (VDR) were discovered in the brain tissues [18]. Vitamin D is associated with the synthesis of neurotrophic factors (brain neuropeptide) and neurotransmitters [19], is involved in suppression of the receptors in relevant memory areas, and is associated with phagocytosis and clearance of amyloid produced in Alzheimer's disease [20, 21].

The clinical significance of mild cognitive impairment is determined primarily by an increased risk of dementia. In a year of follow-up, Alzheimer's disease develops in about 10 – 15 % of patients with amnesic mild cognitive impairment (in the general population, the probability of developing Alzheimer's disease is only about 1 – 5 % per year). The probability of transformation into dementia from cerebrovascular moderate cognitive impairment is less well studied and, according to various stud-

ies, ranges from 5 to 10 % per year. Increased mortality of patients is another danger associated with mild cognitive impairment. According to K. Palmer et al. [22], almost 1/3 of patients with mild cognitive impairment died during the 6-year follow-up, most often from concomitant cardiovascular diseases [12].

The study was aimed at identifying the relationship of vitamin D levels and symptoms of moderate cognitive impairment in older people.

MATERIALS AND METHODS

Vitamin D screening

An assessment of the frequency of vitamin D deficiency in the older people (60 to 75 years) with symptoms of mild cognitive impairment and in older people without similar symptoms was made. To compare the frequency of vitamin D deficiency, the patients of the same gender and age with mild cognitive impairments and without them were selected in the ratio 1:2, respectively (66 cases:132 controls).

The immunoelectrochemiluminescent method was used to assess vitamin D which was based on the 25-hydroxyvitamin D light emission (photons of light) measurement. Depending on the light emission intensity, a quantitative level of vitamin D concentration was determined. Vitamin D deficiency was ascertained after determining the level of 25-hydroxyvitamin D by the method below 40 ng/ml.

Cognitive impairment screening

The presence of cognitive impairment was determined by testing using the memory impairment screen (MIS) questionnaire. MIS is a common test for pre-evaluating memory performance. Along with Mini-Cog and GPCOG, MIS is one of three tests recommended in the United States for

assessing the cognitive status of older patients as part of annual health surveys.

A number of studies have shown that MIS is more effective in identifying cognitive impairment and less expensive diagnostic tool than the standard Mini-Mental State Examination (MMSE). The test method using MIS involves the following steps:

Show the patient a sheet of paper with four words to remember, and ask him/her to read these words out loud. (Words are typed in capital letters; the font size of at least 24 points.)

Tell the patient that each word belongs to a separate category. Give an example of a category and ask the patient to indicate which of the words belongs to it (for example, "Which of this is a game?"). Up to 5 attempts are allowed. Failure to perform this task indicates possible cognitive impairments.

When the patient categorizes all four words, remove the demonstration sheet. Tell the patient that he or she will be asked to recall these words in a few minutes.

Engage the patient in distracting tasks for 2 – 3 minutes, such as counting to 20 and back, serial subtraction of seven from one hundred, pronouncing the word GROUND vice versa.

Free recall gives two points for each word. Ask the patient to name as many of these four words as he/she can recall. Give at least 5 sec for the free recall of each word. Go to step 6 if the patient does not name the next word within 10 sec.

Recall with a hint – one point for each word. Read the relevant hint (category) for each word that was not recalled during the free recall (for example, "What was the game?").

The maximum score on the MIS scale is eight points: 5 – 8: cognitive impairments are absent, and ≤ 4 : possible cognitive impairments.

Clinical trial

The relationship between vitamin D status and cognitive ability in a clinical trial of the vitamin D use was studied in patients with a confirmed deficiency compared to placebo. In the empirical part of the work, from the persons with laboratory-proven vitamin D deficiency ($n = 60$), with mild cognitive impairments, 2 groups of 30 people were randomly formed. One group received vitamin D in a high therapeutic dose of 2,000 IU per day for 6 months, another group received placebo with similar organoleptic properties.

Benchmarks

Follow-up measurements of vitamin D levels and MIS testing were conducted prior to entering the study, after 1, 3 and 6 months of testing.

Compliance with medical ethics standards

All stages of this work at the planning stage were analyzed from the standpoint of studying regulatory and legal acts ensuring compliance with ethical principles of research involving human subjects:

Before entry into the study, written informed consent adapted for the purposes of this study was received from each participant. Each of the participants in the cross-section study and randomized controlled clinical trial took part in the research voluntarily and also received guarantees of full anonymity and confidentiality of personal data.

Statistical analysis

Qualitative variables are presented as absolute numbers and their percentages. Quantitative data are expressed as a mean and its standard deviation. Differences between groups based on qualitative data were determined using the Pearson's chi-squared test. The search for differences in groups by quantitative da-

ta was made by the Student's t-test. The correlation was assessed by calculating the Pearson correlation coefficient. The criterion of critical significance was the finding of the probability of first type error of 0.05 %. The statistical analysis was performed in the SPSS 20.0 software.

RESULTS

General characteristics of study participants are shown in Table 1. In the groups with mild cognitive impairments, and without them the ratio of the number of women and men was the same. In the group of persons with cognitive impairments, diabetes was significantly more common than in the group without such impairments – 21.21 % versus 11.36 %, hypertension – 42.42 % versus 19.70 %, and the family history of Alzheimer's disease – 9.09 % versus 3.79 % of cases, respectively.

Table 1. General characteristics of study participants, % (n)

Variables	Mild cognitive impairment, n=66	Persons without cognitive impairment, n=132	Difference test
Men	48.00 (32)	48.00 (64)	>0.05
Women	52.00 (34)	52.00 (68)	>0.05
Diabetes	21.21 (14)	11.36 (15)	<0.05
Hypertonic disease	42.42 (28)	19.70 (26)	<0.05
Family history of Alzheimer's disease	9.09 (6)	3.79 (5)	<0.05

Screening for the frequency of vitamin D deficiency in older people showed that in individuals with signs of cognitive impairment, according to the results of screening tests using the MIS questionnaire (total score < 4), vitamin D levels of less than 40 ng/ml had been found in 90.91 %, which had been significantly more common compared

with the group without cognitive impairments, where vitamin D deficiency had been found only in 11.36 % of cases (Table 2).

Table 2. The frequency of vitamin D deficiency in older people, % (n)

	Mild cognitive impairment, MIS<4	Persons without cognitive impairments, MIS=5 – 8	Difference test
Vitamin D deficiency, < 40 ng/ml	90.91 (60)	11.36 (15)	<0.05
Normal vitamin D content, > 40 ng/ml	9.09 (6)	88.64 (117)	<0.05

In the dynamics on the background of vitamin D intake at an average therapeutic dose of 2,000 IU/day after one month of treatment, the results of testing cognitive impairment as per MIS questionnaire significantly improved, compared to the placebo group, and the study entry point equaled to 2.44 ± 0.43 points against 1.64 ± 0.26 points, respectively, along with higher levels of vitamin D in the blood up to 42.01 ± 1.81 ng/ml vs. placebo group where it was 14.82 ± 0.08 ng/ml. During the subsequent months of follow-up there was an increased vitamin D level and increased number of points in testing using the MIS questionnaire. The best results were achieved with long-term use of vitamin D within 6 months: the concentration in the intervention group amounted to 52.34 ± 2.43 ng/ml vs 14.71 ± 1.54 ng/ml in the placebo group, which was more than 3 times higher than the initial level before the treatment. The results of the cognitive impairment study in the vitamin D group approached the lower limit of the norm and amounted to 3.63 ± 0.01 points that was significantly higher compared with the placebo group, where the result was 1.78 ± 0.22 points (Table 3).

Table 3. The results of testing cognitive impairment and vitamin D concentrations in the blood throughout the study in the intervention and placebo groups, mean \pm standard deviation

Check point	Characteristics	Group of patients with mild cognitive impairments and vitamin D deficiency		Difference test
		Vitamin D group, n=30, 2,000 U/day	Placebo group, n=30	
Before treatment	MIS test	1.71 \pm 0.21	1.83 \pm 0.32	>0.05
	Vitamin D level, ng/ml	14.00 \pm 1.28	14.00 \pm 1.28	>0.05
1 month of treatment	MIS test	2.44 \pm 0.43	1.64 \pm 0.26	<0.05
	Vitamin D level, ng/ml	42.01 \pm 1.81	14.82 \pm 0.08	<0.001
3 months of treatment	MIS test	3.41 \pm 0.11	1.69 \pm 0.48	<0.05
	Vitamin D level, ng/ml	51.67 \pm 0.43	15.43 \pm 2.25	<0.001
6 months of treatment	MIS test	3.63 \pm 0.01	1.78 \pm 0.22	<0.01
	Vitamin D level, ng/ml	52.34 \pm 2.43	14.71 \pm 1.54	<0.001

Also, during the correlation analysis, a strong positive relationship was identified between vitamin D concentrations and number of MIS points – correlation coefficient of 0.92 (Figure 1).

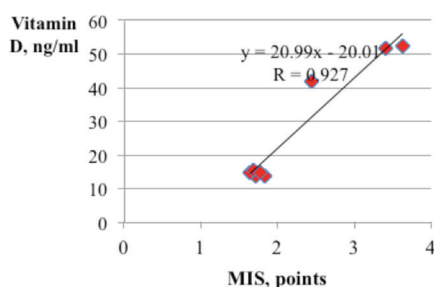


Figure 1. Correlation analysis of the vitamin D level and the number of MIS points, R – correlation coefficient

DISCUSSION

The study has identified the relationship of vitamin D levels and symptoms of moderate cognitive impairment in older people. It has been found that the great-

er the concentration of vitamin D is, the greater the number of MIS points is. These data may be of interest for members of the outpatient unit, where the older patients get for various reasons and where screening can be made of both cognitive impairments, including the latent ones, and the vitamin D level control.

Also, the study has shown that 90.91 % of the older people with mild cognitive impairments had vitamin D deficiency. The result is similar to the previous reports on the high prevalence of vitamin D deficiency in older people [23-25].

This study is limited by the small sample size, as well as by exclusively screening nature of the cognitive function study without a detailed analysis of the status and accounting of somatic impairments.

The greatest benefit of the study is to produce a positive result in the form of higher levels of vitamin D in the blood of older patients to target values above 40 ng/ml and improve the cognitive impairment status. Although in this work, within 6 months of vitamin D intake, the normal value limits were not reached according to the MIS testing, the results were close to this level, which indicated the possibility of using vitamin D as part of complex therapy for mild cognitive impairments in older people.

CONCLUSION

Thus, the study identified a positive relationship of increasing vitamin D levels and reducing the symptoms of mild cognitive impairment in older people. Achieving vitamin D levels of over 40 ng/ml greatly reduces the symptoms of cognitive impairment identified by the MIS questionnaire; however, the issue of treatment of impaired cognitive functions with vitamin D remains debatable.

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Electronic Apps in Assessing Risk and Monitoring of Patients with Arterial Hypertension

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ABSTRACT

The medical social significance of the arterial hypertension (AH) in the world is determined by its high prevalence, which allows to call it a non-infectious pandemic of today. The AH still remains the most common chronic disease that triggers the cardiovascular continuum, significantly reduces the body's adaptive capacity, worsens the living standards for people of socially minded age, and represents the leading global risk of increased cardiovascular mortality.

The purpose of the study was comparison of informative value of various methods for measuring the arterial blood pressure (ABP) (office-based, home-based using electronic apps, and daily) in order to improve the risk assessment of the condition and monitoring the treatment efficiency for the AH patients.

The method of qualitative and quantitative analysis of scientific literature and public online sources was used in the study.

It has been established that the ABP analysis is an important tool to prevent the negative consequences of the AH. The results of the experimental study have revealed that hourly home-based ABP monitoring using a mobile electronic app is more informative than monitoring at long intervals, and provides information which is close to the average daily indicators obtained in the daily ABP monitoring.

Keywords: *arterial hypertension, arterial blood pressure, systolic arterial blood pressure, diastolic arterial blood pressure, antihypertensive therapy, arterial blood pressure monitoring, office-based monitoring, daily monitoring, home-based monitoring, mobile app.*

INTRODUCTION

The AH remains one of the major problems of the modern medicine. Despite the development and introduction of new medical technologies and standards, the incidence rate and mortality from hypertension-related complications in the world grow.

The WHO experts believe that the AH is the most significant cause of death and disability among all cardiovascular diseases [1]. Approximately one-third of adults older than 25 and 90 % of people older than 80 in the world suffer from it, and the total number of hypertensive patients in the world also grows steadily [2]. The AH causes the development of 50 % of cardiovascular disease cases – in particular, coronary heart disease, stroke, chronic kidney disease, and cardiac failure [3]. The high ABP causes about 18 % of deaths in general and more than 40 % of deaths in people with diabetes mellitus [4]. Mortality caused by the high ABP has increased by 8.2 % over the past decade (2006 – 2016) [5]. According to the Framingham Heart Study, the ABP level above 160/90 mm Hg compared to its normal level causes an increase in the risk of cardiovascular events three times in men and six times in women [6].

Despite the undoubted threat posed by the AH and the potential of modern antihypertensive therapy, the recent studies [7] indicate that 50 – 70 % of patients in the general-purpose medical institutions in various European countries have higher levels than target, despite treatment.

The increase in the number of the AH patients who are being treated is accompanied by a paradoxical increase of the proportion of people with uncontrolled ABP among them [8].

56.7 % of patients in the world today are not aware of the AH in them, 28.8 % know about the AH but do not take treatment, and 14.5 % treat the AH but do not control it. The control of the AH at less than 140/90 mm Hg is not achieved in 69 % patients [9]. The level of awareness has direct influence on the number of those being treated and, accordingly, the number of complications of the AH. Therefore, raising awareness of hypertensive patients is an important medical and public task.

The most significant reasons for the low ABP level control in the world are low patient adherence to antihypertensive therapy [10] and significant therapeutic inertia, i.e., a delay in timely enhancement of the drug therapy, appointment of an insufficient number of medications or their incorrect dosing [11]. The problem of implementing the modern treatment standards in real clinical practice, which is largely due to the complexity of applying the therapeutic regimens given in the recommendations, can be solved by the introduction of organizational measures that contribute to increased patient adherence to treatment and increased cooperation with the doctor, including their involvement in patient monitoring of blood pressure at home [12].

Additional information regarding the “out-of-office” ABP level (the so-called “out-of-office ABP”) allows a doctor to adjust medication therapy in time to achieve its optimal value. Due to the relatively large number of measurements in the environment familiar to the patient, the prognostic value of the home-based ABP in regard to predicting the development of fatal and nonfatal cardiovascular events and target organ damage is not inferior to daily

ABP monitoring (DABPM) and better than office-based ABP [13]. However, information on the effect of systematic home-based ABP control on the results of antihypertensive therapy in various populations of patients with the AH is insufficient to recommend its routine use in general practice [14] along with the clinical ABP definition, which remains the traditional basis for clinical decision making. However, office-based data do not provide sufficient information about the efficiency of the AH treatment [15].

D.T. Lackland emphasizes that clinical guidelines and intervention programs focus on the need for the adequate ABP control for primary and secondary prevention of target organ damage [16]. However, studies conducted in recent years in many countries have revealed insufficient coverage and very low efficiency of antihypertensive therapy, despite the advances of the modern medicine [17].

The home-based ABP monitoring, including the use of electronic apps, is a subject of numerous studies of local researchers. At the same time, the ABP self-monitoring takes an important place in the modern guidelines for the AH not only as a method for the ABP assessment, but also as a way to improve the interaction between a patient and a doctor. The ABP self-monitoring allows to clearly demonstrate the success or problems of treating the AH to the patient and contributes to the improvement of the ABP control indicators [18-19]. L.P. Efimova et al. have established (n = 52) that 38 % of the patients independently measure the ABP and record results in the diary; 8 % of patients with the AH do not measure the ABP at home at all; 65 % are examined where they live as planned, annually; 29 % of respondents consider it necessary to take antihypertensive drugs only if they feel unwell. At the same time, 31 % of patients were in in-

patient and outpatient treatment for the AH over the past six months, and 21 % called the emergency because of the ABP increase. Compliance in the group surveyed was 57.5 % of the target, which led to hospitalization and frequent calls to the emergency [20].

The optimal approach to the method and mode of measuring the ABP at home is not yet fully determined. Various modes of the home-based ABP definition have been used in the main studies on its prognostic significance and diagnostic value, despite the recommendations from the European Society of Hypertension and leading cardiac associations [21] on the duration of the period for determining the ABP at home. Besides, most of the scientific works were aimed at studying the value of the home-based ABP for the primary diagnosis of the AH. Information about the possibility of using home-based ABP in patients who have been prescribed antihypertensive therapy as a method of assessing its quality and efficiency is not sufficient, since only a few studies involving a small number of patients are devoted to this issue [22]. That is why the most recent consensus document of the working group of the European Society of Hypertension for monitoring the ABP and cardiovascular variability [23] lists the determination of the optimal mode of measuring the ABP at home among the important issues that should be investigated and would be acceptable for the initial diagnosis of hypertension and control of the treatment efficiency with long-term observation of the patients.

Another advantage of measuring the ABP at home is the ability to assess its variability, which, according to some data, is associated with target organ damage, as well as cardiovascular risk and stroke risk increase, making it a promising therapeutic target for antihypertensive treatment [24].

As such, the complex and multidimensional problem of the ABP control

in the AH patients remains unsolved, despite the powerful capabilities of the modern antihypertensive therapy in the clinical practice, which lays grounds for its further study and developing a set of measures that would significantly increase the efficiency of the AH treatment.

The ABP control in AH patients is considered as an efficient mechanism for preventing the occurrence of such adverse events as myocardial infarction, stroke, chronic renal and heart failure, and peripheral arterial vascular disease, including death. The risk assessment and control of AH patients remains unsatisfactory despite convincing evidence that cardiovascular morbidity and mortality are reduced in the AH treatment.

That is why an important direction in the AH treatment is the implementation of a personalized approach to patients in order to timely identify and prevent the AH among the population. Due to this, there is a task of providing personalized monitoring and control indicators of the health status of each individual for a long time. The modern development of information, computer, mobile, and telecommunication technologies provides new opportunities for solving this relevant problem.

Purpose of the study is the comparison of the information value of various methods for measuring the ABP (office-based, home-based using electronic apps, and daily) in order to improve the risk assessment of the condition and monitor the efficiency of treatment of the AH patients.

METHODS

The efficiency of the doctor's actions in the treatment of each individual patient depends on the quality control of the ABP. Most often, the ABP control is used to determine the level of the office-based ABP, home-based ABP

monitoring (HBABPM) and DABPM. However, each of these methods has its advantages and disadvantages, which requires further research. Compared to office-based ABP, the HBABPM secures measurements over long periods, as well as the ABP variability throughout the day, and it is cheaper and more affordable due to the availability of the existing electronic smartphone apps.

However, unlike the DABPM, the HBABPM does not secure the ABP measurement during normal routine activity and during sleep, as well as quantitative assessment of the short-term ABP variability. Therefore, it is also necessary to conduct the DABPM, especially with increasing ABP, in the evening and in the morning, as well as to determine the degree of the ABP decrease or increase at night.

Sixty patients aged 45 – 59 with the ABP levels above 140/90 mm Hg participated in the study. All patients were measured the office-based ABP for three days using a standard method, and both DABPM and HBABPM were performed. The DABPM was performed using a Meditech ABPM-05 device. The ABP was measured at 15 minutes' intervals throughout the day and every 30 minutes at night. The HBABPM was performed along with ambulatory monitoring of blood pressure for three days after the appointment of antihypertensive therapy.

The patients performed the HBABPM using the OMRON device (Japan) in two ways:

Group 1 (30 patients) measured the ABP regularly every hour during the day with the ability to connect and process information in the Blood Pressure Log – MyDiary electronic app, using the multifunctionality of the app, including the reminder and observation diary functions, etc.;

Group 2 (30 patients) did that randomly three times during the day: in

the morning, in the afternoon, and in the evening.

The average values of systolic arterial blood pressure (SABP) and diastolic arterial blood pressure (DABP) were found for day and night hours. The ABP fluctuations during day and night were estimated according to the SABP and DABP standard deviation. In order to estimate daily fluctuations, the magnitude of its nightly decline was calculated, which was equal to the percentage ratio of the difference between the average day and average night ABP levels to the average daily value. Analysis of the SABP and DABP trends allowed to determine the daily ABP profile (the ratio of the ABP fluctuations during day and night hours). The presence of the night ABP reduction (as normal) allowed to classify the DABPM of a particular patient as a normal profile (dipper), while the absence of a ABP nightly decrease made it in the category “nondipper”, “overdipper”, and “night-peaker”. In the course of the analysis of self-monitoring ABP methods, the patients compared the figures for the average daily ABP level, the difference between the first and last ABP measurement, the average daily values of SABP and DABP, and compared home monitoring data with the DABPM results.

RESULTS

The results of the study have revealed that the average daily ABP levels in the same patient were the lowest when determined using the DABPM and the highest when determined using the office-based ABP measurement (Table 1).

As can be seen from Table 1, the average daily ABP level, which was estimated with DABPM, averaged to as follows: SABP 134.2 ± 1.2 mm Hg and DABP 89.3 ± 2.5 mm Hg. It must be noted that the lower average daily ABP

Table 1. ABP indicators depending on measurement methods ($M \pm m$, mm Hg)

Indicators	ABP measurement methods			
	Office-based ABP	HBABPM, Group 1	HBABPM, Group 2	DABPM (average for two groups)
Daily average ABP: SABP DABP				134.2 \pm 1.2 89.3 \pm 2.5
Average ABP over day: SABP DABP	153.2 \pm 3.3 95.4 \pm 3.6	144.7 \pm 1.8 91.2 \pm 2.1	148.3 \pm 2.6 93.3 \pm 2.9	137.7 \pm 1.5 82.4 \pm 1.8
Average ABP over night: SABP DABP				127.8 \pm 1.9 81.7 \pm 2.1
Daily ABP variability: SABP DABP	4.5 \pm 1.3 2.4 \pm 1.1	11.9 \pm 2.4 9.8 \pm 2.8	13.8 \pm 2.6 10.1 \pm 2.9	12.1 \pm 2.1 9.6 \pm 2.5

figures estimated using this method are explained by the fact that the average ABP levels over night were lower than those measured over day only.

The office-based ABP level was higher than that measured using other methods (SABP 153.2 \pm 3.3 mm Hg and DABP 95.4 \pm 3.6 mm Hg), which was caused by the “white coat” syndrome and other factors, in particular.

The results of the studies indicate that the ABP figures obtained by using the DABPM method every hour (Group 1) were lower than when monitoring the ABP three times a day (Group 2).

The average daily SABP values in Group 1 were 138.2 \pm 1.3 mm Hg for DABPM and 144.7 \pm 1.8 mm Hg for the HBABPM ($P > 0.5$). In Group 2 they were 136.7 \pm 2.1 and 148.3 \pm 2.6 mm Hg, respectively ($P < 0.05$). The average daily DABP values in Group 1 were 82.1 \pm 0.9 mm Hg with DABPM and 91.2 \pm 2.1 mm Hg for the HBABPM ($P > 0.5$). In Group 2 they were 82.7 \pm 2.2 and 93.3 \pm 2.9 mm Hg, respectively ($P > 0.5$). In other words, home-based monitoring with an interval of one hour is almost completely consistent with the average daily SABP level obtained with DABPM, and the method of the ABP measuring only

three times a day provides overestimated indicators of the average daily SABP level. The average daily DABP level was not significantly dependent on the method of measuring pressure, as there were no significant differences between its level in the DABPM or in various methods of home-based monitoring.

Aside from the average ABP level, the ABP variability parameters have been analyzed over several measurements. The smallest variability has been established when measuring the office-based ABP: SABP was 4.5 \pm 1.3 mm Hg and DABP was 2.4 \pm 1.1 mm Hg. In case of the DABPM variability, SABP was 12.1 \pm 2.1 mm Hg and DABP was 9.6 \pm 2.5 mm Hg; with the home-based hourly measurement, SABP was 11.9 \pm 2.4 mm Hg and DABP was 9.8 \pm 2.8 mm Hg in patients of Group 1; SABP was 13.8 \pm 2.6 mm Hg and DABP was 10.1 \pm 2.9 mm Hg in patients of Group 2. In other words, the average daily ABP figures and the ABP variability, which were determined during the hourly HBABPM, were closest to the corresponding indicators of average ABP during daily monitoring, which indicates the greatest informative value of this particular method of home ABP monitoring us-

ing electronic apps compared to daily monitoring. The ABP variability in case of the home-based monitoring was not significantly different from that in outpatient monitoring and was higher than in office-based ABP measurement on average.

The obtained data indicate that the method of home-based monitoring, at which the average ABP values are found in the group, which conducted the measurements every hour using electronic apps, is closest to the average ABP values of daily outpatient monitoring.

As for the determination of sensitivity, it has been found the ABP control during the day is not sufficient, because not all patients revealed an ABP decrease on the first day; in most patients, an ABP decrease was noted on the second or third day, while the ABP should be monitored at home along with the ABP measurement in the office to control the efficiency of antihypertensive therapy (Table 2).

The average values obtained during the HBABPM, especially in Group 1, more accurately determine the level of hypertension in a patient than the level of office-based ABP within three days, because the home-based monitoring using electronic apps allows leveling

the influence of such stress factors as anxious waiting for the doctor and the reaction to examination on the pressure. During the determination of sensitivity to antihypertensive drugs, the level of office-based ABP was usually higher in the same patient as compared to its HBABPM level, especially the one performed every hour using electronic apps.

DISCUSSION

The results of the study demonstrate that the level of office-based ABP is in most cases higher than the average daily ABP level determined using different methods of home-based or daily ABP monitoring. The hourly method of the HBABPM using electronic apps is more informative than monitoring at large intervals and provides information which is close to the average daily indicators obtained during DABPM. As such, the possibility and efficiency of the use of mobile apps by patients for risk assessment and control of the condition of the AH patients have been proven.

Developers offer a large number of medical gadgets and mobile apps for measuring individual physiological and

Table 2. Informative value of various methods in determining sensitivity to antihypertensive drugs in AH patients (M ± m, mm Hg)

Indicator	Before treatment	Day 1	Day 2	Day 3
DABPM (day ABP): SABP DABP		145.5 ± 2.4 96.2 ± 2.8		
Office-based ABP: SABP DABP	167.3 ± 3.2 101.5 ± 2.8	166.4 ± 2.9 101.1 ± 2.3	158.2 ± 2.6 98.5 ± 2.9	154.3 ± 2.1 96.4 ± 2.3
HBABPM (Group 1): SABP DABP		148.3 ± 3.3 89.4 ± 3.1	147.3 ± 3.1 86.2 ± 3.3	142.5 ± 2.9 84.6 ± 2.8
HBABPM (Group 2): SABP DABP		154.6 ± 3.5 92.8 ± 3.1	151.5 ± 2.8 91.3 ± 3.4	146.8 ± 2.2 87.5 ± 2.9

verbal indicators describing the state of human health today: pulse (Instant Heart Rate, Runtastic Heart Rate Monitor), ABP (Blood Pressure Monitor), blood glucose level, quality of hearing and vision, etc. Mobile devices also determine the emotional state and the level of stress (Stress Check), control physical activity and calories burned, sleep phases quality, etc. [25].

The category of m-health apps also includes multiparameter monitoring systems, wearable, textile and implantable sensors of vital health indicators, express analysis systems, apps for monitoring drug use, training systems for stabilizing the emotional state and improving cognitive functions and disability. Remote monitoring and support systems for chronic diseases (Care Innovations, Visi Mobile, hWear (ECG), SugarSenz (diabetes), etc.) are actively developed. It has been proven that medical apps improve well-being, predict the condition of patients and make the prescribed treatment more efficient [26].

Special service platforms are used for collection, transmission and processing of measurement results and the organization of synchronous operation. For example, Apple Health service collects heart rate, glucose, calories, and sleep data through a single interface.

There are medical developments of smartphone manufacturers. For example, Samsung developers offer a private S-Health app with a base of foods and exercises that allows evaluating parameters such as pulse, stress level, sleep, physical activity, and calories burned [26]. The software allows measuring important medical records using sensors and devices, such as blood glucose meters, heart rate monitor, blood pressure monitors, etc. and transfer them to a smartphone via Bluetooth or USB port, where they are presented as tables or charts. They also allow to control body weight, count calories, remind you about the need to take medicines, etc.

The Apple's ResearchKit™ mobile platform (www.apple.com/carekit) is an open source iPhone platform that allows the researchers to directly collect data from patients with future standardization potential and application reuse. Since the platform continues to improve, it can further optimize the data collection process and enable standardized research. Remote monitoring technology also offers similar benefits of speeding up data collection, improving data quality and reducing test costs. GlaxoSmithKline, in collaboration with the McLaren Group and Medidata, is working on a service for receiving real-time data.

The steady increase in the smartphones share opens up opportunities for m-Health. The tasks include a change in the patient-doctor interaction and enabling doctors to have convenient and quick access to the necessary information.

The studies conducted in recent years have shown that m-Health will help save millions of lives, save billions in expenses and democratize access to medical care. Medical apps for cell phones and tablets also include various manuals, drug databases, quick calculations of patient indicators, remote monitoring of vital data and radiological images of patients. Besides, the apps monitor the sleep quality, control the water use, enable patients to communicate with doctors, and even make a cardiogram, which is then transferred to the medical center via GPRS. Many medical apps are used to analyze individual patient data or transform a phone into a medical device to upload individual patient data to medical information databases. The combination of new technologies and the need to be healthy opens up new horizons for both app developers and users.

T.L. Lewis notes that when searching for the term "Cardiology" in the iTunes and Google Play stores, about

400 and 250 medical apps are suggested, respectively. Many of them were developed by the American College of Cardiology (ACC), the American Society of Echocardiography (ASE), and the American Heart Association (AHA) [27].

Website Healthapps (<https://www.healthapps.ru/top/pressure/>) presents the top 5 apps in Russian for the ABP control (Android, iPhone) (Table 3).

However, the analysis has revealed that the existing gadgets and corresponding electronic apps are not comprehensive and do not solve many of the mobile medicine problems. There are no software tools for conducting a comprehensive professional analysis of primary data and questionnaires in such systems.

Therefore, a relevant task is to develop apps that will allow for a comprehensive analysis of the resulting indicators at a higher professional level with the participation of medical professionals.

As such, a multilevel structure with double access can be secured: at the first level, users can independently monitor their health and level of physical activity, as well as make simple calculations using medical calculators; at the second level, when a comprehensive data analysis is required, the access to professional software is provided to doctors to let them more thoroughly study the measurement results, make an express analysis of data and issue corresponding recommendations.

Such approach is also advisable when choosing medications and their dosage, as well as optimizing the time of admission (for example, on the basis of long-term ABP monitoring while taking prescribed medications). The ABP can also be controlled during sleep. Advanced software apps for doctors or their libraries with access to the server part of the mobile kit can be installed directly on mobile devices.

Development of mobile apps for

screening studies using questionnaires (for example, to estimate stress resistance) is also an important task. This will allow to compare subjective assessments of the health state (based on questionnaire results) with objective results of measuring physiological parameters using medical sensors or devices and to optimize the process of treatment or health maintenance.

To implement a multilevel integrated mobile personalized system for long-term monitoring, analysis, risk assessment, and control of the AH patients, the following concept of its creation with a client-server architecture can be suggested.

The structural organization of the client-server part of such a system suggests that the client part ensures user identification procedures; transferring data from medical sensors, devices or input of measurement data from keyboard; creation of a local database, a module for local computing, polls, express analysis and display of results. A global database is formed on the server and a comprehensive analysis is made (for instance, heart rate variability), its results being used for the corrective recommendations. The recommendations part includes several modules for controlling the administration of medications, level of physical activity, diet, etc., as well as adapting to the needs of a specific user. Figure 1 shows the structural organization of such a system.

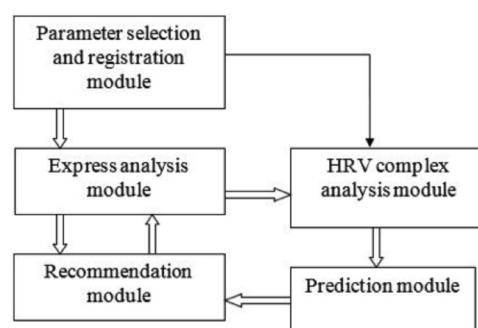


Figure 1. Structure of the mobile personalized system of risk assessment and control of the AH patients

Table 3. Top 5 apps in Russian for the ABP control

Nº.	Name	Functions	Developer
1	Cardio diary	Saving and displaying the input data: blood ABP, pulse; Division into morning or evening readings; Setting alarm reminders; Building charts of pressure changes; and Expert advice and recommendations.	MDHelp
2	Pressure and Pulse Diary	Recording the SABP and DABP readings of the tonometer; Recording health state; Trend tracking; Statistics by different indicators, periods and tags; System of monitoring the drugs taken; Notification system; Data export to mail, to reporting files in various formats; and Backup to SD card.	mEL Studio
3	SmartBP	Recording of SABP and DABP readings; Average ABP is calculated automatically; Adding notes; Storing and viewing records of the ABP measurements at any time; Compatibility with devices for blood pressure measuring; Sending information about the ABP to the doctor, healthcare organization, family members by email or SMS; Creating PDF reports with charts and statistics. Copying files with the ABP information to Google Drive; Data protection; and Setting reminders.	Evolve Medical Systems, LLC
4	Blood Pressure Diary	Saving measurements in the smartphone, including SABP, DABP, measurement location, body position, date, and time; Automatic detection of the AH stage; Calculation of average, maximum and minimum ABP values per month Chart of the ABP dynamics; and Measuring reminder setting.	Siberian Laboratory Applications
5	Blood Pressure	Simple interface; Saving the ABP measurements; Editing and updating; Measurement description; Multiple user support; Interactive charts; Statistics; Data export to report files; and Reminder to measure the ABP.	Klimaszewski Szymon

The data of express analysis describe the current state of the user health and inform them about the changes in the physiological parameters of the body, including blood pressure, that are dangerous for health. The comprehensive analysis is made by professional doctors in order to early detect possible pathologies.

CONCLUSION

The ABP analysis is an important tool to study the functional state of the hu-

man body and prevent the negative consequences of the AH. The development of appropriate software will allow selecting the basic functions optimal from the standpoint of informative value and speed of calculations, and will improve the level of diagnostic and preventive measures.

The results of an experimental study have revealed that the HBABPM carried out hourly using a mobile electronic app is more informative than monitoring at long intervals, and provides information which is close to the average

daily indicators obtained during the DABPM.

In general, the use of mobile electronic apps and service platforms for registering and monitoring physiological and verbal indicators describing the state of human health is a very important part of building the modern information communication systems of the personalized mobile medicine. The next step is to switch from the control and express analysis of particular health indicators to their comprehensive analysis in order to predict the presence and possible development of the disease, determine the risk group, and form special correction programs to stabilize and improve the health of a user.

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Analysis of Efficiency of Sialendoscopy In Patients with Sialolithiasis

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ABSTRACT

The aim of this research was to analyze 106 clinical observations in which sialendoscopy was performed for diagnosis and treatment patients with sialolithiasis. This research showed, that endoscopy of the major salivary gland ductal system allows to obtain information not only on a sialolith, but also on a condition of ductal system. The obtained data define a method of further treatment. Sialendoscopy can be used not only as diagnostic method, but also as an independent method for sialolith removing or as an assistance. The possibility of sialolith removing depends on its mobility, the size of salivary stone, localization and a salivary duct condition.

Key words: *sialolithiasis, sialendoscopy, sialolith, sialoscope, endoscopy, sialolith extraction, stricture, sialendoscopic assistance.*

INTRODUCTION

Currently computer tomography (CT), ultrasound and sialography with contrast agent are used for diagnosis of sialolithiasis besides the main clinical methods. However, despite a wide range of existing methods, diagnostic mistakes reach 46%, as these methods give only indirect signs of that process, which happens inside the salivary gland duct [1].

The implementation of endoscopic equipment in daily practice changed a view on diagnostic and treatment of patients with sialolithiasis. A number of foreign authors consider sialendoscopy the most informative method [2-6], as

it allows to visualize the sialolith and inspect the condition of salivary duct system [7-10].

However, despite advantages of this method, the full-fledged diagnostic sialendoscopy is not always a feasible procedure in obstruction of salivary duct due because of stricture, stenosis or a large sialolith. The possibility of sialolith removing is often limited to size, localization and a condition of duct [2, 3, 7, 11, 12].

On the one hand, the sialendoscopy is a nontraumatic procedure, a performing of unsuccessful procedure is harmless, but from the other hand, it is obvious that the number of inefficient medical procedures has to be minimized. It is necessary to consider that the aggravating factor of a sialendoscopy is the high cost of each procedure, many of which are disposable.

Thus, we consider that opportunities and efficiency of a sialendoscopy are not completely presented in literature. There are few works in literature on this subject, therefore we decided to perform own analysis and to share results of clinical observations.

MATERIAL AND METHODS

This research included 106 clinical observations of patients aged from 18 to 65 years. The study was conducted from 2014 to 2019 at the Center of endoscopic dentistry and maxillofacial surgery "Endostom".

Besides the main clinical examination (survey, examination, palpation and probing), all patients underwent

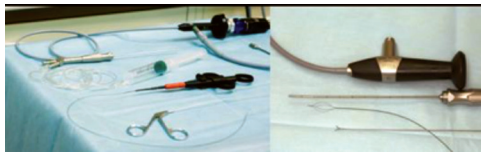
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additional diagnostic procedures: computer tomography (CT), ultrasonography of salivary glands and diagnostic sialendoscopy with using of sialoscope "All-in-one", diameter 1,1 or 1.6 mm (Karl Storz, Germany).

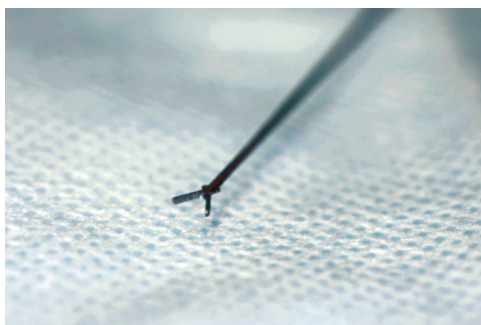
Figure 1. Sialoscopes "All-in-one" Karl Storz, diameter 1,1 or 1.6 mm.



The diagnostic sialendoscopy protocol was similar, all parts of salivary gland duct were inspected. The main purposes of diagnostic sialendoscopy were a detection of sialolith, determination of its sizes, form, structure, localization and mobility, and also the assessment of duct system condition, i.e. the permeability of ducts, presence of stenosis or dilations, inflammatory changes etc. LSD classification (F. Marshall, 2003) was used for systematization of the listed diagnostic data [7].

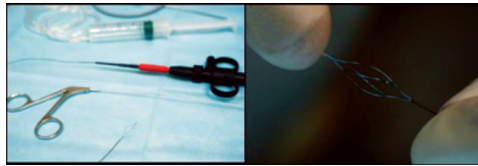
In all clinical cases, after the identification of sialolith, we tried to extract it using sialendoscopic instruments. We used microforceps for stones extraction or its crushing and removing fragments.

Figure 2. Sialendoscopic forceps



Flexible wire basket for grasping and removing sialolith

Figure 3. Sialendoscopic wire baskets



Burr for intraductal fragmentation of sialolith

Figure 4. Sialendoscopic burr



When choosing working tools, we were guided by working channel diameter of sialendoscope. Therefore the working channel of 0.45 mm and sialendoscope diameter of 1.1 mm mean the using only a wire basket on 4 links and a burr (diameter of tools is 0.4 mm). The working channel of 0.8 mm and sialendoscope diameter of 1.6 mm mean the using of several types of wire baskets (on 3,4 and 5 links), burr and special forceps.

RESULTS

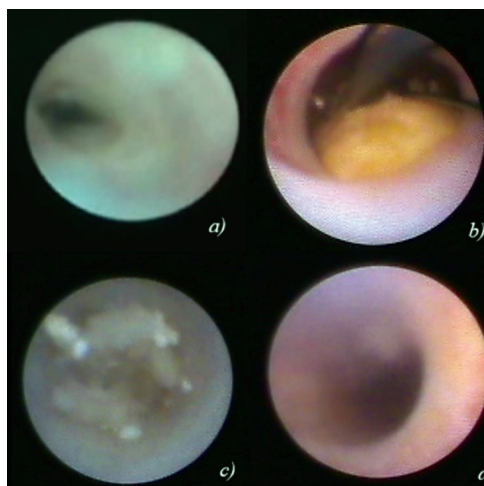
Analyzing and comparing data of additional diagnostic methods, we received following results. According to our data, ultrasonography was the least informative method, because of the highest number of diagnostic mistakes in identification of stones, its dimensions and localization. Stones less than 1.5 mm in diameter was not verified on ultrasonography.

Computer tomography was a high-sensitive and accurate diagnostic method for detection of stones, but didn't reflect the soft tissue condition and salivary gland, respectively.

Results of diagnostic sialendoscopy showed a high sensitivity of this method.

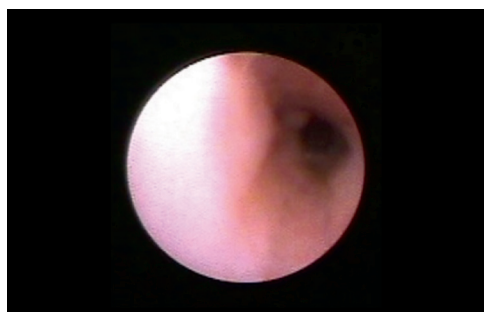
The optics allowed to see stenosis, dilatation of ducts, stricture, mucous plaques, stones and to estimate their characteristics (according to LSD classification Marshall F., 2007).

Figure 5. Endoscopic images: a) stenosis; b) sialolith and dilatation, c) mucous plaque, d) a purulent content in a duct



In total, we investigated 106 salivary glands with sialolithiasis. In 100 (94.4%) clinical cases a diagnostic sialendoscopy of duct was successful. In 6 (5.6%) clinical cases the diagnostic sialendoscopy was difficult due to the stricture in main duct, therefore it was impossible to explore distal parts of salivary gland and estimate the condition of duct system. Consequently, it was difficult to find and extract the sialolith, which was visualized earlier on CT.

Figure 6. A generalized stricture of the initial part of duct

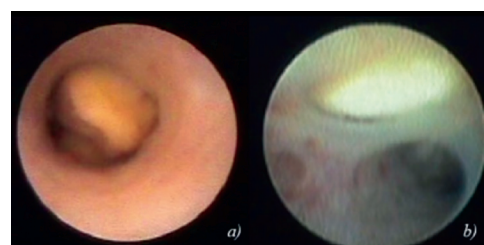


In our study we noticed the difference in practical application of sialendoscopes with different diameter. Sialendoscopes with an external diameter of 1.6 mm belong to semiflexible endoscopes, that promotes a simpler management in a duct. One of disadvantages is difficulties in insertion to the narrow entrance of salivary gland duct or passing of duct areas with stenosis or stricture. Different dilators, bougies and endoscopic guides were used for entrance extension and simple insertion of this endoscope through the entrance of duct.

Semiflexible sialoscope diameter of 1.1 mm is used for ducts with cicatricial changes and expressed stenosis. However, based on our experience, it should be noticed, that it's difficult to maneuver a flexible sialoscope in the channel. In addition, set of tools for sialoscope with small diameter is presented in much smaller volume, thereby the list of indications for application is narrowed significantly at the diagnostic stage.

In 100 (94.4%) clinical cases sialoliths were found during the diagnostic sialendoscopy. In 71 (71%) cases we received a full information about their size, amount, form, structure, localization and mobility. In 29 (29%) cases we received only a partial information as the moving of sialoscope forward was impossible because of large size of the sialolith, expressed bending and channel stricture.

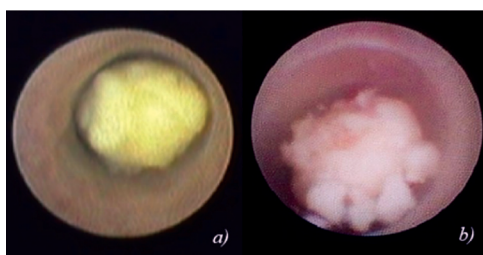
Figure 7. Endoscopic images of sialoliths: a) a mobile sialolith; b) a large sialolith behind the bending of channel



It should be noted, that the evaluation of sialolith's dimensions with using of endoscope, in our view, has a subjective nature, owing to lack of calibration markers on endoscopic tools. In addition, in 29 (29%) cases the sialendoscopy was impossible, when the sialolith was invisible.

During the assessment of stone structure, were interested in its density, i.e. the possibility of its crushing. In our experience smooth stones with round shape have homogeneous and solid structure, therefore there are some difficulties in its crushing. Only friable stones with uneven surface can be crushed with forceps or burr.

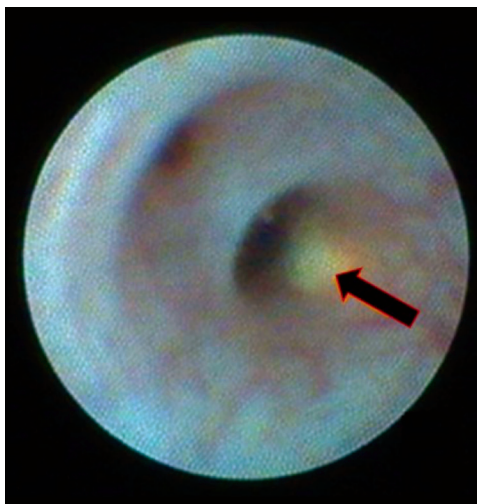
Figure 8. Endoscopic images of sialoliths: a) a solid homogeneous sialolith with round shape; b) a friable sialolith with uneven surface



In 48 (48%) of 100 clinical cases there were mobile sialoliths with a diameter of 5 mm, round shape and solid structure. Sialoliths up to 2.5 mm freely floated along the duct, larger sialoliths had a limit of mobility in extended part of the duct. It should be noted, that in 2 (2%) clinical cases we found small concretions, with a diameter of 1 mm, lying in the thickness of the duct, which were invisible neither on CT nor on ultrasonography. They didn't cause the obstruction of a duct and were easily removed by the tool with a erosive surface of the duct after removing.

In 23 (23%) clinical cases we found immobile sialoliths, from 4 to 8 mm in diameter, with using of sialendo-

Figure 9. Small concretions, lying in the epithelial layer of a duct wall



scope. These sialoliths were localized in the main duct and almost completely blocked this duct. However, we guided the sialoscope behind them and estimated completely the sialolith and distal parts of the duct. A fixation of sialoliths to a duct wall was caused with a big size of sialolith from 6 to 8 mm in diameter in 15 cases and a stricture of the duct – in 8 cases.

In other 29 (29%) clinical cases stones were partially visualized, due to the large size, an irregular shape and also the localization in soft tissue of salivary gland behind sites of stenosis or an expressed bending of the duct. Therefore it was impossible to estimate their characteristics. According to CT data, the size of sialoliths was from 5 to 31 mm. Also, it should be noted that multiple sialolithiasis was in 4 clinical cases. In these cases we could see the stone, using the sialoscope, which completely blocked the salivary duct. So it was impossible to guide the sialoscope for inspection of distal part of duct and other sialoliths, located behind it. In such cases a full diagnosis was possible in case of successful extraction of the sialolith.

Combining all data about sialoliths we structured it according to LSD classification F. Marshall (2003) in table 1.

Table 1. A distribution of removed sialoliths, according to LSD classification F. Marshall (2003).

	Size, mm.	Mobility		Licalization		Visualization		Patients
		yes	no	The main duct	Parenchyma	full	partial	
L1	1-5							48
L2	4-8							23
L3	7-31							20
L3	3-5							9

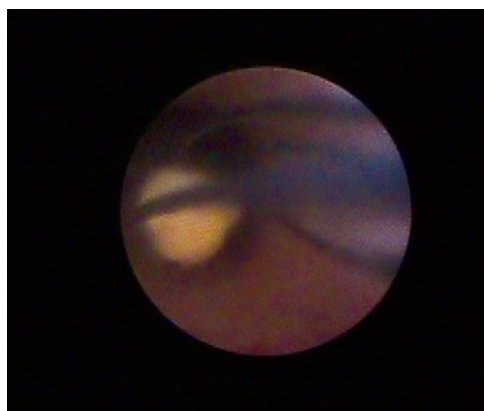
Results of diagnostic sialendoscopy of ductal system showed that in 24 (24%) clinical cases a sialolithiasis was without any changes in ductal system. These features are typical for floating and small stones in parenchymatous tissue of the salivary gland.

Inflammation of the duct at sialolithiasis was in 76 (76%) clinical cases, at the same time in 44 (57.2%) cases – local sialodochitis in location of stone, and in 32 (42.1%) – in form of poured duct inflammation.

In all cases after detection of sialolith we tried to remove it using endoscopic equipment. In total, from 100 clinical cases, 71 (71%) attempts of endoscopic removal of stones were successful.

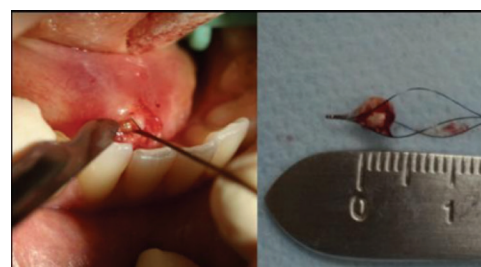
In 29 (29%) clinical cases sialoliths were removed using wire basket or forceps without soft tissue damage. It was mobile stones, up to 2.5 mm in diameter, classified as L1.

Figure 10. Sialolith is trapped using wire basket



In 19 (19%) clinical cases stones were removed the same way, but with additional papillotomy. It was mobile stones, rounded shape, with a smooth surface, from 2.5 to 5 mm in diameter, also classified as L1. They were trapped and carried out through a channel using wire baskets or forceps, but did not pass through the mouth of a channel without incision.

Figure 11. Endoscopic removing of stone with papillotomy



The method of endoscopic crushing and removing of stones was successful only in 3 (10.7%) clinical cases, although the attempt of crushing was in 28 cases. As it was stated above, we used a hand burr or forceps. The burr can slide off a stone surface, damaging a duct wall. Forceps was also ineffective as the force of ramus of forceps was insufficient for crushing solid stones.

In 23 (23%) clinical cases sialoliths were removed by the method of endoscopic-assisted ductotomy. These concretions, 4-8 mm in diameter (L2), had an irregular shape and blocked in the main duct. For extraction such sia-

loliths, the endoscope fixed directly on a stone localization, using a transluminescent in an oral cavity. Then ductotomy and stone removal were performed.

In 29 (29%) clinical cases attempts of endoscopic removal of concretions were unsuccessful. It was the immobile stones, partially visible and located inside the part of salivary gland behind the site of a bending or stenosis (L3a, L3b). The attempt of trapping and removing it with using of endoscopic equipment was unsuccessful. We recommended these patients the operation with using of traditional methods.

CONCLUSION

Summing up the results, we consider that the sialendoscopy provides the unique information, which is inaccessible to any other methods, and plays an important role in choosing a method of treatment. For this reason, we consider that the sialendoscopy has to be used as a standard method of diagnosis of sialolithiasis.

However, the sialendoscopy, as a diagnostic method, is not informative, e.g. in cases of large sialolith, multiple sialolithiasis or stricture of a duct. This method doesn't exclude other diagnostic methods, such as radiology.

Analyzing results of endoscopic extraction of stones, we come to a conclusion that it is effective for mobile sialoliths, up to 5 mm in diameter, classified as L1 (F. Marshall).

In immobile sialoliths, 4-8 mm in diameter, which are localized in the main duct, classified as L2, endoscopy can use only as an assistance during ductotomy. It is not obligatory, but facilitates operation and reduces its injury.

In sialoliths, lying in distal parts behind the bending or strictures (classified as L3a and L3b), use of endoscopy has no essential reasons and does not influence a method and result of treatment.

Thus modern opportunities of a sialendoscopy are not boundless, and, in our opinion, the sialendoscopy is an effective low-invasive method, which is necessary for diagnosis and treatment of patients with sialolithiasis.

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