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USE OF ALGORITHM OF THE PREVENTION COMPLEX OF INFLAMMATORY PROCESSES IN THE ORAL CAVITY IN METABOLIC SYNDROME

Lyudmila Kravchenko, Olena Appelhans, Anatoliy Poliakov, Liana Unhurian, Oleksandr Pasechnyk, Mariya Rozumenko, Yana Ivanova, Vladislav Rozumenko

The aim *of the work was to evaluate in the experiment the effectiveness of the developed treatment-and-prophylactic complex for the prevention of periodontal tissue disorders under metabolic syndrome simulation.*
Materials and methods. *The study of biochemical and immunological changes in the blood serum, liver and gingival tissue was performed during simulation on the metabolic syndrome of alimentary genesis on Wistar rats, all animals were divided into 5 groups: 1) intact; 2) with simulated metabolic syndrome; 3) in a week after the start of MS simulation 5 times a week in the morning perorally administered a "Capillaroprotect" aqueous solution (bioflavonoid, antioxidant) produced by "Ekosvit Oil" (Ukraine) at a rate of 135 mg/kg; 4) under similar conditions receiving the preparation based on the dihydroquercetin were locally applied on gums a new dental elixir based on bee products and adaptogens of plant origin by 0,5 ml/rat with a tampon, which has held for 5–7 minutes; 5) during MS simulation from the second week were used the preparation based on the dihydroquercetin, the dental elixir topically on gums and physiotherapy.*
Results. *Under conditions of experimental MS simulation with a diet rich in saturated fats and carbohydrate there are systemic disorders in the body: reduced nonspecific antimicrobial protection, increased microbial contamination, intensification of lipid peroxidation, the development of inflammation and hepatotoxicity. Prophylactic administration of the proposed dihydroquercetin preparation to animals in the process of simulation of MS significantly inhibits the established disorders, positively affecting the biochemical parameters of the blood serum, liver tissue, periodontium, reducing triglycerides, total cholesterol, glucose level, restoring the state of non-specific resistance, lipid metabolism, preventing inflammation and hepatosis, as well as contamination with pathogenic microflora.*
Conclusion. *The proposed treatment-and-prophylactic complex, which includes the dihydroquercetin preparation, used per os in combination with local therapy of periodontal tissues with a tooth elixir based on propolis and biologically active substances of plant origin adaptogens with ultraphonophoresis under induced metabolic syndrome significantly removed the negative effects of its most important components*
Keywords*: metabolic syndrome, treatment-and-prophylactic complex, inflammation, cytokine status, periodontal tissues*

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1. Introduction

The work is a fragment of the scientific work "Development of new therapeutic and prophylactic agents and pathogenetic justification of their use in inflammatory periodontal diseases against a background of metabolic syndrome" the state registration number 0120U002197.

The clinical course and prognosis in patients with metabolic syndrome (MS) to a great extent depend on the presence of comorbid pathological conditions that have a negative impact on the development of complications. The high prevalence of comorbid diseases in the set of symptoms structure over the past 10 years in Ukraine necessitates a comprehensive approach to the assessment of patients with MS, considering the accompanying pathological conditions to prevent complications and implement optimal strategies for treatment and prevention. The interaction of diseases changes the clinical picture of their course, impairs the quality of life of patients, which limits or complicates the treatment and diagnostic process [1, 2]. There are many questions about the mechanisms of development and progression. The researchers are rather careless about the connection of carbohydrate and fat metabolism disorders with mechanisms of endothelium function regulation, oral tissue microcirculation based on insulin resistance in MS, which is the reason of inflammatory and dystrophic inflammatory processes. MS and concomitant pathologies have not been studied. Considering the treatment of early detection of MS and associated disorders and diseases is of great medical and social importance. So, there is a need to develop methods for the prevention and treatment of comorbid pathological conditions on the background of metabolic syndrome.

The oral tissues are also involved in the pathological process in MS [3, 4]. So, it is advisable to study the links in the pathological chain of set of symptoms that

provoke inflammatory diseases in the oral cavity, and the development of preventive and curative measures aimed at eliminating the whole set of factors that determine the total risk of chronification of concomitant comorbidities manifestations.

The prevalence of the metabolic syndrome (MS) and its complicated course have identified it as an important medical and social problem for society. In patients with MS, the periodontal disease is detected with a rapid development course with a significant decrease of regenerative and reparative processes. At the same time, dentists have no recommendations for treatment and prevention measures, including cavity hygiene. Existing standards of rendering dental care to patients with MS still do not provide additional general somatic approaches to the pathogenetic treatment of periodontal diseases associated with MS [5, 6].

The aim of the work was to evaluate in the experiment the effectiveness of the developed treatment-and-prophylactic complex for the prevention of periodontal tissue disorders under metabolic syndrome simulation.

2. Planning (methodology) of research

Methodology of research was performed using rats as a universal test system in the study effect of drugs including in this treatment and prophylactic complex (Fig. 1).

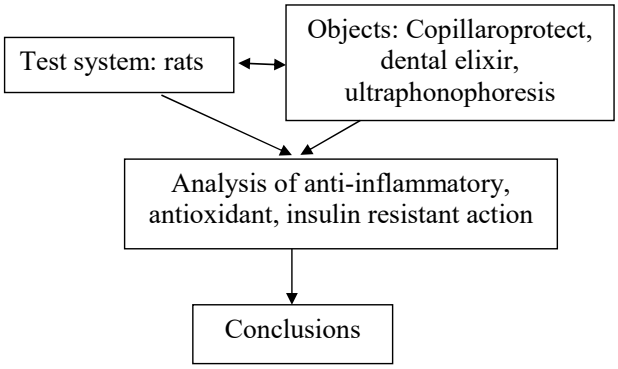

Fig. 1. Algorithm of the research

3. Materials and methods

Experimental studies were carried out according to the program in 2021, is a fragment of the scientific work "Development of new therapeutic and prophylactic agents and apathogenetic justification of their inflammatory periodontal disease against a background of metabolic syndrome", state registration No. 0120U002197.

The experiment was performed on 48 white Wistar rat males, aged 2–3 months, with appropriate standard condition of the oral cavity, weighing (238±10) g, obtained in the vivarium of the Odessa National Medical University. The animals were studied in accordance with the requirements presented in the international guidelines for biomedical research with experimental animals, as well as in accordance with standards the Council of Europe Bioethics Convention 1997, the European Convention for the Protection of Vertebrate Animals. Minutes of the meeting of the commission on bioethics Odesa National Medical University No. 3 dated 12/11/2021.

All animals were divided into 5 groups: I – an intact group consisted of 8 rats. The animals in this group received a standard vivarium diet and had free access to drinking water. The rats of group II were simulated MS by introducing 20 % internal lard into the diet, and 10 % fructose solution was used instead of drinking water. The duration of MS simulation was 70 days [7–9]. The introduction of these substances into the diet were explained by a possibility of creating disorders of metabolism of carbohydrates and lipids of an alimentary nature in the body of animals typical for MS manifestations. The rats of group III on the background of MS simulation, in a week after the start, 5 times a week in the morning were per-orally administered a "Capillaroprotect" aqueous solution (bioflavonoid, antioxidant) produced by "Ekosvit Oil" (Ukraine) at a rate of 135 mg/kg. Rats of group IV, which under similar conditions received a drug based on dihydroquercetin, were locally applied to the gum with a new dental elixir based on beekeeping products and adaptogens of plant origin at 0.5 ml/rat with a tampon, which was washed for 5–7 min [10].

The rats of group V during MS simulation from the second week were used the preparation based on the dihydroquercetin, the dental elixir topically on gums and physiotherapy. In 70 days after the beginning of the experiment, the animals were removed under the thiopental narcosis (40 mg/kg) by dissection of the major vessels, the blood from which the blood serum was obtained was collected, the gums were cut off, the liver was removed after its preliminary perfusion with chilled saline. Insulin resistance was evaluated by the level of triglycerides, HDL, cholesterol. The blood serum level of triglycerides (TG) was determined using the enzymatic colorimetric test [11], general cholesterol (Ch) [11], Ch in high-density lipoproteins (HDL) [11], glucose [11], alanine aminotransferase (ALT), aspartate aminotransferase (AST) activity [11].

In the liver and gums tissues, the level of lipid peroxidation (LPO) was determined by the level of malonic dialdehyde (MDA) using the thiobarbituric method [11] and the state of the antioxidant system – by catalase activity [11], the level of antioxidant-prooxidant index (API), which was calculated by the ratio of catalase activity to MDA level. Biochemical markers of inflammation were revealed: elastase activity [12], urease activity [12], acid phosphatase [12], insulin resistance – triglycerides level [11], non-specific immunity – lysozyme activity [12].

Statistical processing of digital data was performed using the software STATISTICA 6.0. The values of the arithmetic mean (M) and the mean error (m) were calculated for all indicators. The significance of the difference in values was determined using t-Student test. The changes were considered statistically significant at $p<0.05$.

4. Results

Experimental studies of the treatment-and-prophylactic complex effect on the condition of liver tissues, gums of rats under MS simulation demonstrated a positive effect of biochemical processes of animals. In the serum of animals of the experimental group during MS simulation in 10 weeks, there was a significantly higher concentration of total cholesterol (6.24±0.05) mmol/l and triglycerides (2.18±0.02) mmol/l compared with the intact group (respectively (4.86±0.04) mmol/l and (1.38±0.02) mmol/l) (p<0.001)). At the same time, the level of cholesterol in high-density lipoproteins during MS simulation decreased 3 times. Serum glucose in animals with MS was 2.4 times (p<0.001) higher than in intact rats. The functional disorders in the liver of rats during MS simulation was proved by a significant increase in the serum transaminases activity. So, ALT activity increased 2.2 imes (p=0.001), ACT activity – 1.7 times (p=0.001) relative to the data in the intact group. Under the action of the dihydroquercetin preparation the main blood serum parameters of rats decreased, which characterize the manifestations of experimental MS – triglycerides level – by 24.8 % and total cholesterol – by 14 %. The level of HDL cholesterol was determined to be 2 times increased but did not reach the level of the intact group. The level of glucose in the blood serum of rats under the influence of the drug was reduced 2 times, reaching the values of the intact group. The dihydroquercetin preparation improved the functional state of the rats' liver – the activity of ALT in the blood serum was reduced 1.5 times, AST – 1.3 times as compared to rats with MS model.

In the conditions of MS modelling, LPO processes were activated – the MDA level in blood serum increased on average from (2.87±0.70) mmol/l to (4.20±0.50 mmol/l), i.e., 2 times, in tissues liver from (3.86±0.11) mmol/kg to (7.12±0.60) mmol/kg – 1.8 times, the mucous membrane of the oral cavity from (4.64±0.50) mmol/kg to (6.16±0.50) mmol/kg – 1.3 times (p=0.001). At the same time, there was a decrease in the activity of antioxidant protection due to the functional activity of the catalase enzyme with a tendency to decrease by an average of 8–11 % (p<0.05). Oral administration of the drug dihydroquercetin against the background of MS modelling inhibited the increase in MDA, the level of triglycerides in the liver, and prevented the decrease in the activity of lysozyme and catalase.

A more pronounced positive effect on the studied parameters in the tissues of the gums of rats with MS simulation had a combined usage with per os the dihydroquercetin preparation of the new dental elixir with ultraphonophoresis (Table 1).

Table 1

The effect of the prophylactic complex on the indicators of microbiocenosis, nonspecific resistance, antioxidant-prooxidant system, insulin resistance, inflammation in the gums of rats during the development of metabolic syndrome (M±m)

Indicators	Investigation groups				
	Intact group n=8	MS model, n=10	MS model+the dihydroquercetin preparation, n=10	MS model+the dihydroquercetin preparation+dental elixir, n=10	MS model+the dihydroquercetin preparation +dental elixir +physiotherapeutic procedure, n=10
Urease activity, μ-cat/kg	0.82± ±0.06	1.78± ±0.10	1.18± ±0.12	1.06±0.10	0.92±0.08
p	–	–	<0.05	<0.05	>0.05
p_1	–	<0.05	<0.05	<0.05	<0.05
Lysozyme activity, units/kg	386± ±19	168±12	296±15	330±12	342±14
p	–	<0.05	<0.05	<0.05	>0.05
p_1	–	–	<0.05	<0.05	<0.05
Elastase activity, μ-cat/kg	28.3± ±1.3	39.6± ±1.8	30.6± ±1.4	28.8±1.2	27.9±1.5
p	–	<0.05	<0.05	>0.05	>0.05
p_1	–	–	<0.05	<0.05	<0.05
Acid phosphatase activity, ncat/g	14.8± ±0.40	24.6± ±0.60	20.2± ±0.50	16.8±0.49	15.2±0.58
p	–	<0.05	<0.05	<0.05	>0.05
p_1	–	–	<0.05	<0.05	<0.05
Catalase activity, μ-cat/kg	9.12± ±0.10	7.70± ±0.40	8.42± ±0.11	8.82±0.12	8.99±0.10
p	–	–	<0.05	>0.05	>0.05
p_1	–	<0.05	>0.05	<0.05	<0.05
MDA level, mmol/kg	8.64± ±0.40	12.60± ±0.90	10.12± ±0.70	8.97±0.80	8.88±0.60
p	–	–	>0.05	>0.05	>0.05
p_1	–	<0.05	<0.05	<0.05	<0.05

Note: p – the probability of difference relative to the intact group; p_1 – the probability of difference relative to the group with metabolic syndrome

According to the obtained data, the simulation of MS resulted in metabolic processes disorders in the tissues of rats' gums: an increase in elastase activity by

63.5 % (p=0.001), an increase in MDA by 45.8 % (p=0.001), an increase in urease activity by 65.8 % (p=0.001), triglyceride level by 133.4 % (p=0.001) with a decrease in catalase activity by 15.6 % (p=0.001) and lysozyme activity by 57.0 % (p=0.001). The conducted biochemical analysis determined an increase in contamination of the opportunistic pathogen, LPO activation and inflammation against a background of reduced nonspecific and antioxidant protection of gums tissues during the development of metabolic syndrome.

The use of the prophylactic complex effectively prevented the MS simulated disorders. The use of per os the dihydroquercetin preparation in the morning with local application to the tissues of the periodontal mucosa of the dental elixir by applying a wet swab in the amount of 0.5 ml with simultaneous exposure to ultraphonophoresis at a frequency 830 kHz, intensity 0.4 W/cm^2 in a pulse mode for 5 minutes, once a day, five times a week inhibited the occurrence of periodontal complications during the period of MS simulation. Pathogenic microflora reduction was determined in the gum's tissues (almost 2 times reduction of urease activity) (p<0.05), the inflammatory process (1.4 times decrease in elastase activity (p=0.001), 1.4 times – MDA level (p<0.05), 1.6 times – acid phosphatase activity (p<0.05). Under conditions of MS simulation, the treatment-and-prophylactic complex led to 1.8 times decrease in triglycerides, had antioxidant properties, keeping on a high level of non-specific protection – catalase activity, API index and lysozyme activity. The activity of lysozyme in the gums of rats with the prophylactic use of the complex 2 times exceeded the value in rats with MS, the activity of catalase, API in the gums were near those in intact animals.

Changes in the level of pro- and anti-inflammatory cytokines in animals with simulation of MS and the comparative effect of the prophylactic complex on them were studied (Table 2).

The level of interleukin IL-2 in animals of the intact group was 4.10 pg/ml, while this figure in rats with a simulated MS increased 1.4 times to 5.86 pg/ml. When using the prophylactic complex on the background of MS simulation, the level of IL-2 decreased by 28.9 % to 4.52 pg/ml, slightly exceeding the level of the intact group.

The level of pro-inflammatory interleukin IL-6 in the blood serum of rats with MS increased 4.4 times. The prophylactic complex caused 2.4 times decrease in IL-6 level (p<0.05).

The average level of anti-inflammatory IL-4 in rats with MS simulation decreased 2.1 times as compared with intact animals. During preventive measures against the background of MS simulation, the studied indicator in rats increased on average 1.9 times and did not differ significantly from intact animals.

Anti-inflammatory IL-10 in rats with MS decreased 2.8 times as compared with intact animals (p<0.05). When using the prophylactic complex, its level with MS simulation in rats increased 2.3 times.

Table 2

Influence of the prophylactic complex on indicators of the cytokine status of animals at induced metabolic syndrome (M±m)

Indicators	Groups of animals		
	Intact, n=10	Metabolic syndrome, n=10	Metabolic syndrome+preventive complex, n=10
IL-2, pg/ml	4.10±0.10	5.86±0.20	4.52±0.20
P	–	=0.001	>0.05
p_1	–	–	=0.001
IL-6, pg/ml	0.30±0.08	1.42±0.30	0.58±0.10
P	–	=0.001	>0.05
p_1	–	–	=0.005
IL-4, pg/ml	0.38±0.07	0.18±0.06	0.34±0.08
P	–	<0.05	>0.05
p_1	–	–	<0.05
IL-10, pg/ml	1.20±0.24	0.42±0.06	0.98±0.08
P	–	=0.005	>0.05
p_1	–	–	=0.001

Note: p – the probability of difference relative to the intact group; p_1 – the probability of difference relative to the group with metabolic syndrome

5. Discussion

Thus, with the development of MS in the blood serum of animals, the level of pro-inflammatory increased and the level of anti-inflammatory interleukins decreased. The literature data gives contradictory data on the dynamics of changes in the level of pro- and anti-inflammatory cytokines [13–15]. The introduction of the components of the prophylactic complex in the scheme of MS simulation gives a positive effect confirmed by improvement of indicators.

The obtained data indicate that in animals against a background of MS simulation, cellular mechanisms of cytokine regulation are disrupted, which can be both a consequence and a cause of metabolic, humoral, and structural disorders. The use of the treatment-and-prophylactic complex gave a positive effect in general. The difference with untreated animals in increasing the level of anti-inflammatory interleukins and decreasing the level of pro-inflammatory interleukins when using the treatment and prophylactic complex was significant.

The obtained results prove that under conditions of experimental MS simulation with a diet rich in saturated fats and simple carbohydrates there are systemic disorders in the body: reduced nonspecific antimicrobial protection (lysozyme activity), increased microbial contamination (urease activity), intensification of lipid peroxidation (MDA level), the development of inflammation (elastase activity) and hepatotoxicity (ALT activity). In the liver of rats, simulation of pathology caused activation of LPO, excessive accumulation of fat (triglycerides) and a decrease in nonspecific resistance

(lysozyme activity). These data confirm the results of other authors regarding the development of metabolic syndrome with a high-calorie diet and a significant share of LPO processes in the damage of lysosomes with the release of lysosomal enzymes [11, 12, 16]. It is known that lysosomes accumulating LPO products are damaged by the release of enzymes, causing the destruction of subcellular structures [9, 17]. At the same time, there is an increase in pathogenic microflora in the gums, the development of inflammation against the background of a decrease in non-specific immunity and the activity of antioxidant protection. Our data is confirmed by the research of scientists [3, 8, 18].

Prophylactic administration of the proposed dihydroquercetin preparation to animals in the process of simulation of MS significantly inhibits the established disorders, positively affecting the biochemical parameters of the blood serum, liver tissue, periodontium, reducing triglycerides, total cholesterol, glucose level, restoring the state of non-specific resistance, lipid metabolism, preventing inflammation and hepatosis, as well as contamination with pathogenic microflora.

The capillary-protective action of the applied drug is realized in 2 directions: indirectly and directly. The indirect way is associated with the prevention of atherosclerotic plaques formation in the arteries by reducing the level of cholesterol and triglycerides in the blood, as well as inhibiting the inflammatory reaction in the vascular wall. The direct mechanism is related to the protection of the most important chain of the vascular system – capillaries, through which there is an exchange of oxygen and nutrients between blood and cells. The drug which contains dihydroquercetin protects cell membranes, normalizes their permeability and elasticity, improves capillary function, restores blood microcirculation, normalizes metabolism at the cellular level. It is known that by improving microcirculation with increasing reserve capacity of the capillary bed, the agent reduces trophic disorders [3, 19, 20]. The experiment revealed an increase in cell sensitivity to insulin under the dihydroquercetin preparation action. Biologically active components of the drug have vasodilatory, antihypoxic, anti-edematous properties that contributes to the mechanism of its anti-inflammatory action, improves cellular metabolism, stimulates the immune system, activates regenerative processes.

A combined topical application of the new dental elixir based on propolis and biologically active substances of plant origin adaptogens with ultraphonophoresis on the oral mucosa areas in combination with the dihydroquercetin preparation provides rapid arrest of inflammation, anti-edema effect, correction, and improvement of structural and functional condition of periodontal tissues.

Disadvantages of case-control studies:

1. Systematic errors in determining the representativeness of the “control” group.

2. The probability of errors in the reproduction of the model.

3. The impossibility of studying rare factors of influence.

4. Difficulty in studying time-varying risk factors.

5. Possibility of “biasing” the results if not confounders will be considered (factors, both related with the studied risk factor, and affecting outcome development).

This version of the study was conducted within the framework of an existing cohort study, which allows levelling several shortcomings and increasing its evidence value.

Study limitations. The experimental study is limited to testing in a great number of animals in accordance with the Recommendations for the Use of Laboratory Animals and the Directives of the European Council (2010/63/EU). A minimum sample of animals was used to study the effects of the constituent preparations of the treatment-and-prophylactic complex at the systemic and local levels. These studies should be continued for a more complete examination of the properties of the proposed complex, which can increase its medical significance of implementation.

Prospects for further research. Further studies of metabolic and immunological changes in periodontal tissues, alveolar bone in the experiment under the conditions of metabolic syndrome simulation and testing the new oral hygiene product are perspective, which will inhibit risk factors for comorbid pathology manifestation and expand the complex of treatment and prevention measures.

6. Conclusions

1. The research have shown that the proposed treatment-and-prophylactic complex, which includes the dihydroquercetin preparation, used per os in combination with local therapy of periodontal tissues with a tooth elixir based on propolis and biologically active substances of plant origin adaptogens with ultraphonophoresis under induced metabolic syndrome significantly removed the negative effects of its most important components in the form of normalization of glucose level, triglycerides, total cholesterol, anti-inflammatory interleukins in the blood serum, improving the functional state of the liver and periodontal tissues.

2. A regular administration of the dihydroquercetin preparation against a background of MS simulation prevented the nonspecific immunity decrease in the liver of rats (lysozyme activity), antioxidant protection (catalase activity) and inhibited the increase in triglycerides, MDA level.

3. A topical application of the treatment-and-prophylactic complex in the process of MS simulation in rats led to a positive effect on the biochemical parameters of periodontal tissues, significantly reducing triglycerides level, providing anti-inflammatory and antioxidant effects, activating local functional activity of antioxidant enzymes, nonspecific resistance.

4. The created treatment-and-prophylactic complex at MS simulation improved metabolism, reduced signs of oral cavity inflammation, demonstrating periodontal-protective properties, that allows to offer it for clinical approbation in patients with MS for the purpose of prevention of periodontal diseases.

Conflict of interest

The authors declare that they have no conflict of interest in relation to this research, whether financial, personal, authorship or otherwise, that could affect the research and its results presented in this paper.

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Kravchenko Lyudmila, Doctor of Medical Science, Professor**,** Department of Therapeutic Dentistry**,** Odessa National Medical University**,** Valikhovsky lane, 2, Odessa, Ukraine, 65082

Olena Appelhans, Doctor of Medical Science, Professor**,** Department of Normal and Pathological Clinical Anatomy**,** Odessa National Medical University**,** Valikhovsky lane, 2, Odessa, Ukraine, 65082

Anatoliy Poliakov, Doctor of Medical Science, Professor, Head of Department, Department of Internal Medicine No. 3, Odessa National Medical University, Valikhovsky lane, 2, Odessa, Ukraine, 65082

Liana Unhurian*, Doctor of Pharmacy Sciences, Professor**,** Department of Organization and Economics of Phar-macy, Odessa National Medical University, Valikhovsky lane, 2, Odessa, Ukraine, 65082

Oleksandr Pasechnyk, PhD, Associate professor, Department of Surgical dentistry, Odessa National Medical University, Valikhovsky lane, 2, Odessa, Ukraine, 65082

Mariya Rozumenko, PhD, Department of Orthopedic Dentistry, Odessa National Medical University, Valikhovsky lane, 2, Odessa, Ukraine, 65082

Yana Ivanova, Assistant, Department of Internal Medicine No. 3, Odessa National Medical University, Valikhovsky lane, 2, Odessa, Ukraine, 65082

Vladislav Rozumenko, PhD, Department of Orthopedic Dentistry**,** Department of Therapeutic Dentistry, Odessa National Medical University, Valikhovsky lane, 2, Odessa, Ukraine, 65082

***Corresponding author:** Liana Unhurian, e-mail: lianau@ukr.net*