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Features of microbiota thick to the bowels for patients with hypothyroidism depending on indemnification of disease

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ABSTRACT

Species composition and population level of microflora of the cavity of the large intestine in 44 patients with hypothyroidism have been studied. The dysbiosis of the first degree – in 1 patient, the second degree – in 1 patient, the third degree – in 8 patients and the fourth degree – in 34 patients have been established. Imbalance developed at the expense of eliminations and deficiency of autochthonous anaerobic, obligatory bacteria (*bifid bacteria*, lacto bacteria), contaminations of the large intestine by enterotoxigenic, enteropathogenic and hemolytic *Escherichia*, conventionally pathogenic enterobacteria and an increase of the number of the *bacteriodes, peptococcus, peptostreptococci, clostridia, staphylococci* and yeast-like fungi of the *Candida* type.

Keywords: *microbiota; dysbiosis; hypothyroidism.*

1. INTRODUCTION

Hypothyroidism is one of the most common chronic diseases that develop as a result of a partial or total loss of thyroid function and thyroid hormones [1-4]. Today, the prevalence of manifest hypothyroidism by various data is 0.2-2%, sub-clinical – up to 3% in men and up to 10% in women, and in persons over 70 years old reaches 13-14%. In Ukraine there are about 100 thousand people with this disease on the official account [3,5].

For most patients hypothyroidism is a permanent condition that requires lifelong replacement therapy. Doses of levothyroxine should be adequate for maximum normalization of TTH levels because insufficient hypothyroidism compensation is dangerous due to the negative impact on blood lipid profile and progression of cardiovascular diseases [6-7].

At the same time, according to a number of studies, the presence of gastrointestinal diseases significantly limits the possibility of hypothyroidism compensation or is accompanied by the need for high doses of levothyroxine, and their effective treatment, including eradication therapy, leads to a decrease in the level of Serum TGR in patients with insensitive to high doses of L T4 [8].

Therefore, patients who have an adequate dose of levothyroxine have been significantly higher than expected to take into account the presence of gastrointestinal disorders, including those associated with *Helicobacter pylori* gastritis, atrophy, trophic gastritis, or celiac disease. After treatment it is recommended to re-evaluate this function and, if necessary, dose correction L T4 [7].

It is known that intestinal microbiota is an evolutionary created of microorganisms, which exists as a balanced microecological system, in which the symbiotic microflora is in a dynamic equilibrium, forms the microbial associations that occupy a certain The ecological niche, and refers to the most important factors affecting human health. The use of modern molecular and genetic technologies has allowed obtaining a rather complete representation of the number, genetic heterogeneity and complexity of the bacterial components of the intestinal microbiotas, while clinical studies have shown significance its Interaction with the organism in the formation of various forms of pathology [9].

It is known that normal anaerobic and aerobic microflora of the intestine plays an important role in the formation of colonization resistance. It clearly reacts to changes in the human body as infectious, in non-infectious diseases, including endocrine [1,5,9]. Normal anaerobic and aerobic microbiota of the intestine plays an important role in the formation of colonization resistance. It clearly responds to changes that are taking place in the human body for infectious and a number of no communicable, namely in bronchial asthma, etc. Recent studies have made it apparent that hypothyroidism's most important development accomplices are the intestinal microbiota KM [9], which is referred to as the "micro biaxial organ" or bioreactor due to its plebistropic effect on a wide range of physiological processes in Human body. The numerical volume of intestinal bacteria reaches 100 trillion, which is 10 times greater than the total number of human cells. The biomass of bacteria ranges from 2.5-3 kg, contains about 1000 species of bacteria, most of them are not cultivated *in vitro*, and aggregate the amount of gene KM (methogenic KM) is 150 times greater than the human genome. KM consists of 2000-4000 different species, mainly anaerobic bacteria, 80% of which have not been cultivated to date, and maybe to be determined only. by molecular genetic methods.

The largest and most diverse proportion of microorganisms is localized in the lower part of the small intestine and in the large intestine. Mainly the composition of microbiota is represented by Anaerobes, non-form spores, of which more than 60-80% falls on the type of Firmicutes and about 20-40% belong to *Bacteroides*. In addition to the two mentioned, optional anaerobes are found (e.g. *Escherichia coli*), Gram-positive *enterococcus* and lactic acid

bacteria – representatives of the genus *Lactobacillus*. Intestine on a permanent or temporal basis is a number of bacteria such as *Staphylococcus, Clostridium, Pseudomonas, Proteus, Candida, Enterobacteria*, and many others.

Commonwealth of bacterial intestinal flora generates thousands of biologically active substances, which, in particular, include short-chain fatty acids (SCFA), triethylene (TMA), norepinephrine, serotonin, dopamine, acetylcholine, gamma-aminobutrine Acid, vasoactive intestinal peptide (VIP), histamine, etc. KM is able to remotely control the function of many other organs. For example, it is an effect on the appearance of chronic kidney disease, type 1 and 2, atherosclerosis, cardiovascular diseases, oncopathology, lesions bone tissue.

It is believed that one of the leading properties of the large intestine is the cleavage of food fiberts to SCFA, namely acetate, butyrate and propionate, which are utilized for the synthesis of de novo lipids, glucose and proteins. Acetate and propionate are produced by *Bacteroides* bacteria, and butyrate comes from Firmicutes. Propionate becomes the basis of gluconeogenesis, lithogenesis and protein synthesis, and butyrate is an energy source for epithelial intestinal cells. Butyrate and Propionate are mainly neutralized in the colon, but acetate can get into the systemic circulation and reach certain organs where it is transformed a source of cholesterol synthesis.

Intestinal dysbiosis plays an important role not so much in development as in maintaining the irritable bowel syndrome [1]. It has the value and irritation of the intestinal mucosa with bacterial toxins. Neuroimmunological functions, transport of liquids, blood flow in the thick intestine [7.8] are violated due to activation of cytokines and the direct influence of food antigens. Intestinal microflora disorders Except for pathological changes from the gastrointestinal tract can contribute to malabsorption syndrome, which will lead to the deepening of the unprovoked major diseases of the vitamin deficiency, microelements, disorders Absorption of medicinal agents, etc. All this deepens existing pathological changes in the body, for example, to strengthen the phenomenon of anemia in hypothyroidism [6]. It should also be noted that the intestinal dysbiuse causes a violation of the anti-antioxidant status [5.7], which may cause pathologic changes by almost all organs and systems with hypothyroidism.

According to a number of researchers [8], hypothyroidism is often accompanied syndrome of excessive bacterial growth – a pathological process that occurs due to an increase in the number of bacteria in the lumen of the stomach and thin intestines, which under normal conditions are practically sterile. The last years, there was evidence that therapy with levothyroxine is negatively affected by the intestinal microflora [4].

It is known about disorders of motor activity and transport function in the digestive system as a result of hypothyroidism [10]. The most likely cause of the development of violations Intestine is intestinal edema due to the accumulation of mucopolysaccharides in gastrointestinal tissue, especially hyaluronic acid. Changes in the motor activity of digestive system can cause bloating of the stomach and constipation with hypothyroidism [10].

Data obtained in experimental and some clinical studies, in mainly indicate significant differences in the content of two major bacterial types with hypothyroidism with a prevalence of *Firmicutes* and a decrease in the level *Bacteroides* [7]. However, in some studies, contradictions are obtained relate to the connection of these filotypes with the presence of hypothyroidism. In addition, the literature does not contain data regarding the change in the content of the main filotypes of the KM depending on the state of compensation hypothyroidism [11,12].

At the same time, a number of issues remained beyond the attention of researchers. There are only Individual works that reflect the effect of iodine deficiency on the phenotype of MK. However, the authors of non of them studied the effect of functional disorders thyroid gland on the microekology of the cavity of the colon. Further study requires the question of the dependence of microbiota thick intestine from compensation for hypothyroidism.

The purpose of the work was to study the species composition and population level microflora of the intestinal cavity in patients with primary hypothyroidism depending on from compensation for the disease, as well as the study of the content of the main filotypes of KM in these patients.

2. MATERIALS AND METHODS

44 patients with hypothyroidism (19 men and 25 women) aged 30 to 72 years (average age of 47,3 + 8.9 years) in the compensation stage and decompensation of the disease and 51 practically healthy donor person control group. Depending on the compensation for the disease, 2 was allocated group of patients. The first group (20 patients) consisted of patients in a state of compensation, the second group (24 patients)-in a state of decompensation of the disease. Degree of gravity hypothyroidism was established on the basis of clinical and laboratory data.

Materials of the study were feces, which was taken in sterile penicillin vials (sterilization carried out by autoclaving) from the average portion not less than 2-3 grams. And immediately (after 1-2 hours) were subjected to bacteriological the study.

In sterile conditions, on sterile wax paper, weighed 10 mg vials and placed them in a clean sterile tube, where 0.9 mg sterile isotonic sodium chloride solution and received 1:10 dilution. From this mixture of feces were prepared ten times (1:10-2 to 1:10-10) breeding. From the appropriate dilutions, 0.1 ml was taken and sown with a lawn on Sectors of solid is optimal for each type of microbe environment, where for the corresponding period of thermostat received typical colonies of the corresponding genera or types of microorganisms. Based on the received number of colonies and dilutions determined the population level of each type of microorganism found in excrement.

To detect *Enterobacteria,* the test material was sown on the medium *Endo* and *Ploskirev; Staphylococcus and Enterococci* - on the bloody meat-pumpkin agar (MPA), *Bacteroids, Peptococcus, Peptostreptococci* — on blood agar for bacteroids (CAB), *Clostridia* — on the Wilson-Blair medium, Lactic acid bacteria – on medium MPC-4, *Bifidobacterium* – on the environment Baktofak (Russia), Yeast mushrooms of the genus *Candida* – on a solid Saburo.

Identification of selected cultures was carried out according to morphological, tinctoral, cultural and biochemical properties. Selection and identification of autochtonous obligate anaerobic asporogenic and sporogenic bacteria were carried out in a

stationary anaerostat — "CO_2-incubator T-125" (Swedish firm ASSAB Medicin AB) by known methods [2].

Aerobic autochthonous obligatory and extractive microorganisms were grown on selective media in the thermostat at optimal temperature modes. In some cases, to identify anaerobic bacteria used systems ARI-20A, aerobic-ARI-20 Staph., ARI-20E, Entertet 1.2. Ecological state of microbiocenosis of the cavity of the colon were evaluated by the index of constancy (C%), indicators of the frequency of detection (R and), significance (C), coefficient of quantitative dominance (efficiency). Intestinal dysbiosis was evaluated for [2]. Statistical processing methods variation statistics using Student's trustworthiness criterion for special programs.

3. RESULTS

The first step was to study the species composition of autochthonous bond and facultative anaerobic and aerobic microorganisms of the cavity of thick guts of patients with hypothyroidism, as well as establishing their index of constancy and frequency of occurrence in the cavity of the colon. Study results in the species composition of the microflora of the cavity of the colon and its micro-ecological indicators are given in Table 1.

As can be seen from Table. 1, in patients with hypothyroidism comes the elimination from the cavity the colon of the most physiologically useful anaerobic *bifidobacteria* in parts of the patients eliminate *Enterococci.* On this background comes the contamination cavity of the colon pathogenic *Escherichia* (in 25,0% of patients) and conditionally pathogenic *Enterobacteria* of genera *Citrobacter, Enterobacter, Hafnia*, and also conditionally pathogenic anaerobic asporogenic superiority, *Peptococcus, Peptostreptococci* and aerobic *staphylococci* and yeast mushrooms genus *Candida*.

As a result of such changes, the species composition of the microflora of the cavity is thick gut has changed the role of most microorganisms in microbiocenosis. In the control group (normomicrobiocenosis) according to the index of constancy and frequency occurrence *Bacteroids, Bifid bacteria, Lactobacillus, Peptococcus, Escherichia* and Proteins refer to the constant microorganisms in the cavity of the colon, and *Clostridia, Staphylococci* and *Enterococci* — to those commonly found. Patients with hypothyroidism to constant microorganisms also include *Bacteroids,* Lacto bacteria, *Peptococcus, Escherichia*, Proteins, as well as *Staphylococci,* which often met in the control group. To microorganisms, often found in patients with sub compensated hypothyroidism, are related *bifid bacteria, Prevotella, Peptostreptococci*, pathogenic (hemolytic) *Escherichia* and yeast-like fungi of the genus *Candida*.

Thus, in patients with hypothyroidism a species composition is violated microflora of cavity of the colon at the expense of elimination of *Bifid bacteria*, *Clostridia* and *Enterococci*, as well as contamination in part of the patients cavity colon pathogenic *Escherichia* and conditionally pathogenic predominates, *Peptococcus, Peptostreptococci* and conditionally pathogenic *Enterobacteria* (Citrobakter, Enterbacter, Hafnium), *Staphylococci* and yeast mushrooms of the genus *Candida*.

More informative indicators of change in microbiocenosis of anyone the habitat is the population level of each microbiocenosis associate. Results study of the species composition and population level of the microflora of the cavity of the thick guts in patients with hypothyroidism are given in Table 2. By population level, index of significance (C) and coefficient quantitative dominance (efficiency) basis of microbiocenosis of the colon cavity. In practically healthy persons, *bifid bacteria*, *Bacteroids, Lactobacillus* and autochthonous bonded *Escherichia*. A certain role played by the *Peptococcus.* Insignificant, minor the role in microbiocenosis play *Peptostreptococci, Clostridia, Proteis, Enterococci, Staphylococci.*

In patients with hypothyroidism, the leading role in microbiocenosis plays *Bacteroids, Peptococcus, Escherichia* and other microorganisms. At the same time in this group. Patients have significantly reduced the role of Bifid bacteria and Lactobacilli, but the role of conditionally pathogenic Staphylococci, yeast-like fungi of the genus *Candida, Enterobacteria (Citrobacter, Enterobacter, Hafnium*) and pathogenic Escherichia, conditionally pathogenic *Prevotel, Peptococci, Peptostreptococci* and normal *Escherichia.*

Consequently, in patients with hypothyroidism, population level, index decreases the significance and the coefficient of quantitative dominance in *bifid bacteria*, *Lactobacillus, Enterococci* - the main representatives of autochthonous obligatory intestinal microflora; which forms the colonization resistance of the intestinal mucosa. Against this backdrop, the population level is increasing microecological parameters in conditionally pathogenic *Bacteroids, Peptococcus, Peptostreptococci, Escherichia, Staphylococci* and yeast-like fungi of the genus *Candida.* Such changes contribute to the contamination of the cavity of the colon pathogenic Escherichia's, conditionally pathogenic predominant, *Enterobacteria (Citrobacter, Enterobacter, Hafnium), Staphylococci* and yeast mushrooms of the genus *Candida*, which in the cavity of the colon reach high population level.

Table 1. Species composition of the microflora of the cavity of the colon in patients with hypothyroidism.

Microorganisms	Environmental indicators		The main group (n=44)	Control group (n=51)
Anaerobic bacteria				
Bifid bacteria	n C% Pi		6 30, 00 0, 04	48 94, 12 0, 16
Lactobacillus	n C% Pi		18 90, 00 0, 13	49 96, 08 0, 16

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Microorganisms	Environmental indicators		The main group (n=44)	Control group (n=51)
Bacteroids	n C% Pi		20 100, 00 0, 15	51 100, 00 0, 17
Prevotes	n C% Pi		4 20, 00 0, 03	0 0 0
Peptococcus	n C% Pi		18 90, 00 0, 13	36 70, 59 0, 12
Peptostreptococcus	n C% Pi		4 20, 00 0, 03	2 3, 92 0, 01
Clostridia	n C% Pi		2 10, 00 0, 01	16 31, 37 0, 05
Aerobic microorganisms				
E. coli	n C% Pi		20 100, 00 0, 15	51 100, 00 0, 17
E. coli (Hly+)	n C% Pi		5 25, 00 0, 04	0 0 0
Proteas	n C% Pi		12 60, 00 0, 09	26 50, 98 0, 08
Citrobacter	n C% Pi		3 15, 00 0, 02	0 0 0
Enterobacter	n C% Pi		3 15, 00 0, 02	0 0 0
Hafnium	n C% Pi		2 10, 00 0, 01	0 0 0
Enterococcus	n C% Pi		1 5, 00 0, 01	9 17, 65 0, 03
Staphylococcus	n C% Pi		12 60, 00 0, 09	17 33, 33 0, 06
Yeast mushrooms of the genus *Candida*	n C% Pi		6 30, 00 0, 04	1 1, 96 0, 01

Established that the relative content of the main microbial filotypes differed from healthy subjects compared with patients with hypothyroidism. Thus, the content *Firmicutes* in patients with hypothyroidism was significantly higher and the content of *Bacteroides* - significantly lower in relation to healthy individuals (Table. 3). Analyzing the content of the main microbial filotypes depending on the state of compensation, Hypothyroidism has been found that in patients in the state of compensation and decompensation hypothyroidism content *Firmicutes* was significantly higher, and the content of *Bacteroides* –Relatively lower in patients with compensations and healthy persons.

Analysis of changes in the species composition and population level of the microflora the cavity of the colon gave the opportunity to establish that at all Inspected patients with hypothyroidism revealed intestinal dysbiosis. So, the dysbiosis of the IV degree was established in 34 (77%) patients, the third degree — at 8 (18%) patients, II degree — in 1 patient, I degree — in 1 patient. So, with Hypothyroidism is a prerequisite for the violation of intestinal microbiota, as well namely: a violation of the morph-functional state of the gastrointestinal tract; changes from the hepato-biliary system; dysfunction of the pancreas; hemitichypoxia, due to violation of tissue respiration, changes from the side respiratory, cardiovascular systems, anemia; hypothyroidism obesity; violation of lipoperoxidation; changes in the immune system etc. In your own queue, disturbed microbiocenosis of the above-mentioned processes, but also the emergence of a whole series new pathological changes that can affect the course of this disease.

Table 2. Population level of microflora of the cavity of the colon in patients with hypothyroidism.

Microorganisms	Environmental indicators	The main group (n=44)	Control group (n=51)	P
Anaerobic bacteria				
Bifid bacteria	M ± m C ККД	4, 76 ± 0, 59 2, 40 18, 01	9, 38 ± 0, 09 21, 34 125, 54	< 0, 001

Microorganisms	Environmental indicators	The main group (n=44)	Control group (n=51)	P
Lactobacillus	M ± m C ККД	7, 24 ± 0, 37 11, 87 82, 17	8, 76 ± 0, 06 18, 73 112, 45	< 0, 001
Bactericides	M ± m C ККД	9, 55 ± 0, 01 18, 06 120, 43	8, 54 ± 0, 02 19, 21 113, 02	< 0, 001
Prevotes	M ± m C ККД	9, 12 ± 0, 07 3, 45 23, 00	0 0 0	0 0 0
Peptococcus	M ± m C ККД	9, 20 ± 0, 04 15, 08 104, 41	8, 10 ± 0, 06 12, 81 75, 38	< 0, 001
Peptostreptoco-ccus	M ± m C ККД	8, 97 ± 0, 06 3, 39 22, 62	8, 04 ± 0, 02 1, 12 4, 39	< 0, 001
Clostridia	M ± m C ККД	8, 84 ± 0, 06 1, 11 11, 07	8, 02 ± 0, 08 5, 40 33, 89	< 0, 01
Aerobic microorganisms				
E. coli	M ± m C ККД	9, 50 ± 0, 02 17, 97 119, 80	8, 52 ± 0, 02 18, 88 111, 08	< 0, 001
E. coli (Hly+)	M ± m C ККД	8, 86 ± 0, 08 4, 47 27, 93	0 0 0	0 0 0
Proteas	M ± m C ККД	3, 58 ± 0, 10 4, 06 27, 09	3, 44 ± 0, 07 3, 78 24, 08	< 0, 05
Citrobacter	M ± m C ККД	8, 90 ± 0, 12 2, 24 16, 83	0 0 0	0 0 0
Enterobacter	M ± m C ККД	8, 85 ± 0, 07 2, 23 16, 74	0 0 0	0 0 0
Hafnium	M ± m C ККД	8, 95 ± 0, 05 1, 13 11, 35	0 0 0	0 0 0
Enterococcus	M ± m C ККД	9, 00 1, 13 5, 67	10, 26 ± 0, 10 4, 40 25, 86	0 0 0
Staphylococcus	M ± m C ККД	5, 89 ± 0, 05 6, 68 44, 56	3, 90 ± 0, 12 2, 98 16, 53	< 0, 001
Yeast mushrooms of the genus *Candida*	M ± m C ККД	5, 65 ± 0, 09 2, 85 21, 37	4, 00 0, 55 1, 09	0 0 0

Table 3. Content of main microorganism filotypes, depending on compensation of hypothyroidism, %.

Microbial filotype	Healthy	Patients with hypothyroidism		P
		Compensation (TTG 4.2 μM / ml)	Compensation (TTG greater than 4.2 μM / ml)	
Firmicutes	35 (22-37)	37 (31-44)	58 (40-63)	**0,012**
Bacteroides	47 (35-54)	42 (32-46)	30 (22-35)	**0,024**
Correlation F/B	**0,7 (0,6-0,7)**	**0,9 (0,7-1,1)**	**1,9 (1,1-2,3)**	**0,005**

4. CONCLUSIONS

Hypothyroidism is accompanied by the formation of intestinal dysbiosis IV degree in 77% of patients.

Intestinal disbiosis in patients with hypothyroidism is formed at the expense of elimination of the cavity of the colon *Bifid bacteria, Enterococci, Clostridium* and contamination with her pathogenic *Escherichia* and conditionally pathogenic *Enterobacteria* (*Citrobacter, Enterbacter Hafnia's*), *Staphylococci, Peptococcus, Peptostrecocci* and yeast mushrooms of the genus *Candida*.

In patients with hypothyroidism, the population level, index decreases the significance and the coefficient of quantitative dominance in *Bifid bacteria, Lactobacillus* and *Enterococci*, as well as these indicators, increase in pathogens Escherichia and conditionally pathogenic *Enterobacteria, Staphylococci, Peptococci, Peptostrecocci, Prevotel* and yeast mushrooms of the genus *Candida*.

Detected violations of the KM, namely, decrease in the amount *Bacteroides*, increasing *Firmicutes* and F/B ratios can not

only play a pathogenic role in the development of hypothyroidism, but also contribute deterioration of its course and compensation.

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