KHRYSTYNA MOSKVA

ENDOCRINOPATHIES AND THEIR CONNECTION WITH THE GUT MICROBIOTA

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CONTENT

ENTRY

Relevance of the topic. According to an analysis by the World Health Organization (WHO) and the International Diabetes Federation (IDF), the number of diabetic patients (DM) in the world among the adult population aged 20–79 years in 1985 was 30 million, and in 2040 642 million patients are projected, covering 10% of the world's population [**109**, **258**].

According to the Center for Medical Statistics of the Ministry of Health of Ukraine, as of January 1, 2017, 1,237,270 patients with diabetes mellitus were officially registered in Ukraine, excluding the Autonomous Republic of Crimea, the city of Sevastopol and the territories of Donetsk and Luhansk regions that are not controlled by Ukraine, and is about 3% of the total population. At the same time, there is an annual increase of 5–7 % [257].

Thyroid diseases are considered comorbid to DM. In particular, one of the observational crossover studies determined that the prevalence of thyroid dysfunction in the presence of type 2 diabetes mellitus (T2DM) was 48% (n=92), and among the 40% (n=37) of those who were diagnosed for the first time, 45% (n=15) had subclinical hypothyroidism [38]. At the same time, thyroid dysfunction is directly related to the content of iodine, and both its excess and deficiency cause changes in carbohydrate metabolism and damage to internal organs [209]. Until recently, it was believed that the common pathogenetic mechanisms of DM and thyroid dysfunction are insulin resistance (IR), defects in the immune response, and chronic inflammation. However, in recent decades, it has been possible to find out that behind the manifestation of many endocrinopathies, functional and structural changes in the gut microbiota (GM) are hidden. What's more, the GM can remotely monitor the function of many other organs [246]. For example, its connection and influence on the appearance of type 1 diabetes [96], CD-2 [179], diffuse toxic goiter [**7**, **51**], hypothyroidism, autoimmune thyroiditis (AIT) [247], atherosclerosis, cardiovascular diseases in general [**112**, **241**],

oncopathology [179], chronic kidney disease [**22**, **150**], non-alcoholic fatty liver disease [233], bone damage [222], depression [6].

GM is called a "microbial organ", or "bioreactor", because it has a pleiotropic effect on a wide range of physiological processes in the human body [**12**, **112**]. The number of gut bacteria reaches 100 trillion, which is ten times the total number of all human cells [128]. The biomass of bacteria ranges from 2.5–3 kg [6], contains about 1000 species of bacteria, most of which are not cultivated *in vitro* [214], and the total number of GM genes, i.e. its metagenome, is 150 times greater than the human genome [**121**, 222].

The commonwealth of the bacterial flora of the gut generates thousands of biologically active substances, which include short-chain fatty acids (SCFA), trimethylamine (TMA), norepinephrine, serotonin, dopamine, acetylcholine, γ-aminobutyric acid, vasoactive intestinal peptide, histamine, etc. It was found that in the gut, as well as in the liver, due to a number of complex transformations, the FXR receptor is expressed, which regulates fibroblast growth factor 15, which enters the liver through the portal system and controls the synthesis of fatty acids (FA) that bind to membrane receptors of bile acids TGR5, which are expressed in brown adipose tissue and in skeletal muscles and increase the intracellular content of cyclic adenosine monophosphate (cAMP). After that, the iodothyronine-deiodinase activity of type 2 is enhanced, an enzyme that promotes the conversion of thyroxine (T4) to triiodothyronine (T3) [128]. Studies have also found that almost 20% of serum T3 is of direct intestinal origin [246]. Since the synthesis of thyroid hormones is impossible without a sufficient amount of trace elements such as iodine and selenium, their successful assimilation of GM is especially relevant in living conditions in areas with iodine deficiency.

At the same time, the gut has a complex nervous system containing more than 600 million neurons and glial cells. The enteric nervous system (CSS), also called the second brain, is responsible for barrier, transport, secretory functions, local blood circulation, peristalsis, which directly affect the absorption of trace elements, glucose, as well as autoimmune, allergic reactions, inflammatory processes, etc. [**15**, 173].

1. FOUNDATION A TENDENCY TO METABOLIC DISORDERS, STARTING FROM THE INTRAUTERINE PERIOD OF THE FORMATION OF THE INTESTINAL MICROBIOTA AND AT THE STAGES OF THE LIFE OF A HUMAN HOST

1.1. The condition of the mother and the intrauterine period of the child's development

The state of the mother's GM forms the microbiota of the unborn child with all the advantages and disadvantages. The statement regarding GM that the first colonization of the body occurs during the swallowing of amniotic fluid or the passage through the birth canal of a woman in labor has been refuted today, because the first bowel movement of the child, meconium, contains microorganisms. Even before childbirth, microorganisms populate the placenta, amniotic fluid and umbilical cord of the fetus [**31**, **47**]. In particular, it was found that the decisive basis for the development of necrotizing enterocolitis in a child was the state of the mother's GM suffering from endocrinological diseases - DM, obesity, various variants of goiter, etc. [11]. Despite this, the mother's unfavorably altered GM in the form of dysbiosis (more harmful bacteria and fewer beneficial ones) causes a number of complications during pregnancy, such as preeclampsia, prematurity and metabolic dysfunction [41]. Therefore, an imbalance of intestinal microflora not only indicates the presence or expected metabolic diseases of the mother, but also signals the future problems of the child, since the laying of GM begins with intrauterine development.

As you know, DM is associated with metabolic disorders based on multifactorial and complex pathogenesis. The three main dangers of type 2 diabetes, such as hyperglycemia, insulin resistance (IR) and hyperinsulinemia, subsequently lead to chronic diseases, diabetic complications, including hyperlipidemia, inflammation in the form of damage to the tissues of the kidneys, eyeballs, heart, blood vessels, etc. [48]. DM is one of the most common pathologies that, under conditions of pregnancy,

certainly affects the GM of the fetus. According to a study by the Diabetes Alliance, in 2019, the incidence of diabetes among adults in the world was 8.3%, by 2045 this proportion will increase to 9.6% [107]. It follows that the formation of abnormal and persistent changes in the GM of the unborn child, and then of an adult, due to the mother's illness, occur more often, and therefore each time require more and more attention of scientists.

One study showed that children of mothers with gestational diabetes were more likely to develop neonatal complications, among which jaundice was leading [**70**]. It is assumed that undesirable consequences in children occur when the mother's gestational diabetes manifests itself during the first and second trimesters of pregnancy. During this period, less microbial diversity of the intestine is recorded, as well as a decrease in the relative amount *Coprococcus* and *Streptococcus* [272]. Bacteria *Coprococcus* and *Streptococcus* produce a number of metabolites, including butyrate and lactate, which are necessary for maintaining gut health and immune regulation during pregnancy.

It is also known that the method, regimen and composition of nutrition certainly affect human GM. This postulate also applies to pregnant women, as the effect of GM not only on the human host, but also on the fetus. As it turned out, the configuration of GM is laid not only by the mother, it is also dictated by the eating behavior of the ancestors of the proband. Experimental studies in mice confirmed that repeated reintroduction of fiber into the diet of animals (from lines where previous generations were fed junk food), gut microbiotic diversity was only partially restored and was accompanied by a constant loss of bacterial strains over many subsequent generations [**156**, **224**].

Nevertheless, a premature baby is at the highest risk of developing diseases. Absent or insufficient colonization of the child's intestines, as an independent factor, can lead, for example, to the appearance of necrotizing enterocolitis and a number of other diseases [170]. It is noteworthy that the meconium of premature infants differs because, as mentioned above, under normal conditions, colonization of the intestine occurs throughout the entire period of intrauterine development [170].

1.2. The factor of childbirth

During childbirth, newborns are exposed to a wide range of microorganisms involved in colonizing the intestine. In particular, it was found that the structure of the intestinal microbiota of women after childbirth and their babies was similar [**70**]. The method of childbirth is crucial. As a result of a cesarean section, the baby first receives the microbiota of the mother's skin, unlike vaginal delivery [**46**, 66]. The microbiota of babies after cesarean section contains more *Firmicutes*, while after physiological childbirth – *Bacteroidetes* [111]. At the initial stages of colonization, aerobic microflora in the form of enterobacteria, staphylococci and streptococci prepares the child's intestines for further colonization by anaerobic microflora. Many microorganisms can be pathogenic. Obviously, after childbirth, the colonization of the baby's intestines is chaotic. The components of this early process include environmental influences, the method of feeding, medicines (for example, antibiotics). During the first year, the infant's intestines gradually prepare for colonization of a more pronounced anaerobic community of microbes [191].

As already mentioned, maternal diseases play a significant role in the formation of the baby's GM. In the presence of gestational diabetes, the number of microorganisms of the type *Actinobacteria* and childbirth *Collinsella*, *Rothia, Desulfovibrio,* which can persist for up to eight months after childbirth [221], modulating the baby's GM during subsequent breastfeeding.

1.3. Breastfeeding

Breastfeeding is a natural way to eat optimally, as it provides the appropriate physiological need of the baby due to the content of certain proteins, fats, carbohydrates, immunoglobulins, endocannabinoids and many other essential substances. Breast milk contains about 600 different types of bacteria, including *Bifidobacterium adolescentis, Bifidobacterium breve, Bifidobacterium bifidum, Bifidobacterium dentium, Bifidobacterium longum*, as well as prebiotics in the form of oligosaccharides - non-digestible polymers that are growth stimulants for *Bifidobacterium* [161]. Bifidobacteria are responsible for strengthening the protective

properties of the intestinal mucosa, increasing the production of immunoglobulin A, which correlates with the modulation of the intestinal immune system.

Breastfeeding, as well as the duration of weaning and the consistent introduction of different types of food, affects the infant's GM and immune system in some way [55]. The microbiome of breastfed infants, which is more enriched with virulence-related genes, demonstrates a multifactorial correlation between gut flora genes with bacterial pathogenicity and host gene expression associated with immune and defense mechanisms.

The composition of the operational taxonomic unit (OTU) of the microbiota was different between breastfed and formula-fed infants. It has been stated that breast milk promotes the relationship between the immune system of the mucous membrane and the microbiome, provides support for intestinal homeostasis [213]. Aerobic microorganisms are more likely to occur in the feces of breastfed infants, while anaerobic and facultative anaerobic microorganisms, which predominantly use anaerobic glycolysis, are more commonly detected in the feces of formula-fed infants.

1.4. Further stages from childhood to senile age

In the early stages of human development, as it turned out in the process of involving metagenomic analysis, it is diet that affects the formation and composition of GM [**29**, **225**]. The formation of the GI microbiota in childhood affects the development of the immune system and the induction of oral tolerance. Disturbances in the microbiome during this period provoke the development of immune-mediated diseases. Most bacteria type *Bacteroidetes* and *Proteobacteria* fixed in the GM as early as five weeks after birth, *Firmicutes* – a little later; at school age appear *Actinobacteria, Firmicutes and Bacteroidetes* [84]. Even so, early childhood problems, such as teething, salivation, digestion, and bowel passage time, can also affect GM during aging and old age. Therefore, in a 3-year-old child, the bacterial composition resembles that of an adult and remains stable until old age, except for the appearance of disturbances such as prolonged changes in diet or repeated use of antibiotics [114].

Despite the similarities, there are still marked differences in the microbiota in the elderly compared to young adults. In general, in the elderly, there is a decrease in microbial diversity with a reduced composition of lactobacilli, bacteroides *Prevotella* and *Faecalibacterium prausnitzii*, as well as an increase in the proportions of *Ruminococcus*, *Atopobium* and *Enterobacteriaceae*.

With the help of metagenomic analysis, it was found that the composition of GM changes in the early stages of human development and is directly influenced by diet [**130**]. Since the infant's diet consists of breast milk and formula, such a microbiome has minimal diversity and is enriched mainly with genes to facilitate the use of lactate [205]. A shift in the functional ability of the predominant use of plant-based glycans occurs before the introduction of solid foods. In terms of ecological succession, the infant microbiota, dominated by *Bifidobacterium*, changes over time to the adult microbiota, which is dominated by *Bacteroidetes* and *Firmicutes*.

There are marked differences in the microbiota of older adults compared to younger adults, with relative proportions *Bacteroidetes* predominate in the elderly compared to a larger proportion of *Firmicutes* in young people. In the elderly, in addition to a decrease *Bifidobacteria* note a significant decrease *Bacteroides* and *Clostridium cluster IV*. At the same time, variability between individuals is characterized by distinct fluctuations from 3 to 92 % for *Bacteroidetes* and from 7 to 94 % for *Firmicutes* [114]. The mentioned feature of variability makes it difficult to study the features of changes in the GM of various diseases and under the influence of drugs.

Changes in GM in the elderly are associated, in particular, with a complaint of weakness. A significant decrease in microbial diversity with a reduced composition of lactobacilli, *Bacteroides/Prevotella* and *Faecalibacterium prausnitzii,* as well as an increase in the share *Ruminococcus, Atopobium* and *Enterobacteriaceae* observed in people with high rates of weakness. Claesson and co-authors [45] and other authors [1], investigated the associations between diet, environment, health and microbiota in 178 older adults (>65 years) and found an association between GM diversity and individual functional independence. A decrease in microbial diversity was recorded in

people living in short- or long-term inpatient facilities compared to those living in a community. The differences were characterized by the presence of weakness, a decrease in dietary diversity, as well as an increase in inflammatory markers (serum TNF-α, IL-6, IL-8, C-reactive protein). Patterns of eating behavior correlated with the composition of GM, and the most influential types of food were vegetables, fruits, and meat. Full clustering of associations made it possible to identify four food groups: low-fat/high-fiber, moderate-fat/high-fiber (98% of community members and day hospitals); moderate fat content / low fiber content and high fat content / low fiber content (83 % of subjects in long-stay locations). Among community residents, the association between several health indicators (including weakness) was characterized by low levels of variability, while for subjects in long-stay locations, the most significant correlations were associated with functional independence, Barthel index (functional score), nutrition, blood pressure, and calf contour. It has been suggested that this may be due to the effects of diet and/or microbiota on muscle mass and sarcopenia, and therefore weakness.

2. DETERMINING AXES OF INFLUENCE OF THE GUT MICROBIOTA

2.1. Intestines - brain

GM metabolites can be absorbed into the bloodstream and transported across the blood-brain barrier to regulate brain function. Thus, neuroendocrine hormones and neuroactive substances synthesized by certain types of intestinal bacteria are involved in neurotransmission. The connection between the two is called the enteric-cerebral axis, where the brain and intestines interact reciprocally [52].

Autism, Parkinson's disease, neurodegenerative diseases and mental disorders are pathologies that often arise as a result of changes in the functioning of the intestine and brain, in particular, it can be associated with the following infectious agents as *Clostridium difficile* [**3**, 85].

Autism is a disorder that alters social interaction and perception of information. Disorders in the composition of intestinal microorganisms can affect brain activity and neurological development. The role of the "gut-brain" pair, or "mouth-brain" in neurodevelopmental disorders relative to the autism spectrum, has been clarified, but its participation in neurodegenerative and psychiatric disorders has been determined quite recently. Studies have highlighted the effects of GM on brain activity and human behavior; It has been suggested that microbial imbalances can cause the appearance of many pathological conditions, including behavioral [**57**, **89**, **180**].

Neurodegenerative diseases are a class of diseases that lead to the destruction of nervous tissue. Studies reveal that through the intestines, a number of microorganisms can influence the increasing severity of Parkinson's disease and Alzheimer's disease. It is believed that about 30% of the GM in people with Parkinson's disease differs from the GM of healthy people, according to the higher content Bacteria *Escherichia coli, Klebsiella pneumoniae* and *Klebsiella quasipneumoniae*. The

destruction of the intestinal barrier can also provoke neurodegenerative diseases and inflammation of the brain [30].

The GM axis – the brain is involved in the pathophysiology of neuropsychiatric disorders, for example, depression and anxiety, confirming dependence on the level of neurotransmitters. It refers to the modulation of changes in systems such as serotonergic, dopaminergic and noradrenergic, which directly affect mood and feelings of anxiety [105]. For example, gamma-aminobutyric acid (GABA), the main inhibitory neurotransmitter of mammals in the central nervous system (CNS), is produced by lines *Lactobacilli* and *Bifidobacteria*, especially *Lactobacillus brevis*, *Bifidobacterium dentium*, *Bifidobacterium adolescentis*, and *Bifidobacterium infantis*. Despite this, it is known that *Lactobacillus rhamnosus* demonstrates its therapeutic potential in modulating the expression of central GABA receptors, influencing depression and anxiety [231].

Another important mediator of the enteric-cerebral axis is serotonin (5-hydroxytryptamine 5-HT), which is produced by enterochromaffin cells of the gastrointestinal tract. As a metabolite of the amino acid tryptophan, it plays a key role in mood regulation [173]. 95% of serotonin is stored in enterochromaffin cells and intestinal neurons, while only 5% is found in the central nervous system. It was found that in bacteria-free mice, the level of serotonin in the blood is halved compared to normal mice [158].

In the literature, we will look at contradictory conclusions about certain bacterial strains that cause mental illness and how to treat them using prebiotics, probiotics or symbiotics. At the same time, the potential benefits of using probiotics and prebiotics to improve mental health in clinical trials are also not denied [210].

Individual variability of the GM is also involved in the processes mentioned above. The GM axis – the brain and individual variability of GM – are serious challenges that await serious study in order to find out their contribution and interdependence [2, 105].

In general, GM affects brain function through neuronal, endocrine, and immune pathways [196].

Understanding the connection between the gut and the brain will help to look deeper into the pathogenesis of many diseases and develop more effective methods of diagnosis and treatment.

2.2. Intestines - skin

The intestine-skin axis includes diseases such as psoriasis, acne vulgaris and even skin cancer [85]. Psoriasis is a chronic autoimmune disease characterized by red, scaly patches on the skin and is increasingly diagnosed. Acne vulgaris (acne) is a common disease that not only affects the skin (often due to growth *Cutibacterium acnes*) in the form of blockage and inflammation of hair follicles and sebaceous glands, but also has a significant impact that can be compared with chronic systemic diseases such as diabetes mellitus and epilepsy. It was found, in particular, that the imbalance of GM plays the role of a trigger for a further increase in markers of the inflammatory process [59]. We also note that if earlier acne occurred more often during puberty, then modern studies indicate its maturation and occurrence in middle-aged people. The influence of a number of hormones on the occurrence of acne should also not be overlooked, as, for example, an increase in androgen levels. A number of observations have confirmed that most patients with acne vulgaris suffer from constipation, have bad breath, and complain of gastro-duodenal Reflux. And in the presence of seborrheic dermatitis, a syndrome of bacterial overgrowth develops in the small intestine.

With regard to skin cancer, a pronounced increase in this pathology among the population is also recorded. And while the number of scientific papers on psoriasis and skin cancer has increased, there have been fewer publications on acne, despite the greater prevalence and psychosocial burden [43]. Stress is recognized as a common and determining etiological factor in the occurrence and exacerbation of many skin diseases, which indicates a powerful influence of the psychophysiological component with the obvious involvement of the mechanisms of the central nervous system, which was mentioned in the previous part, which concerned the intestine-brain axis [90].

2.3. Intestines - heart

GM disorders that are accompanied by the appearance and increase in severity of CVDs, such as atherosclerosis, hypertension and heart failure, may be associated with dysbiosis [19]. First of all, as you know, this applies to dyslipidemia (in particular, hypercholesterolemia), which, as a connecting link, unites problems of the intestine and cardiovascular system. Despite this, the component of many bacterial strains is endotoxin - lipopolysaccharide, which, growing, provokes the formation of atherosclerotic plaques - atherogenesis, followed by the launch of a cascade of inflammatory reactions of a local and systemic nature. The interaction between GM and the cardiovascular system is also mediated by microbial metabolites such as trimethylamine N-oxide (TMA-N-oxide), short-chain fatty acids (SCFAs), which can have both harmful and protective effects on cardiovascular health [28]. Therefore, nutritional characteristics play a key role in the formation of the composition of GM, thereby affecting the health of the cardiovascular system. For example, Mediterranean and vegetarian diets are associated with a favorable GM profile in terms of reducing the risk of CVDs, complications of type 2 diabetes, as well as its occurrence and course, overweight and obesity, hypertriglyceridemia [79]. It logically follows that therapeutic measures such as probiotics, prebiotics and fecal microbiota transplantation, which affect GM, indirectly modulate the appearance and course of CVDs and associated DM, autoimmune diseases, etc. [85, **218**]. This can also include autoimmune thyroiditis.

2.4. Intestines - lungs

The lung microbiota contains a significantly smaller number of microflora units than in the intestine. Its composition depends on many factors: pH, oxygen content, mucociliary clearance, etc. As in the intestines, strains predominate in the lungs *Firmicutes, Bacteroidetes*, *Proteobacteria* and *Actinobacteria.* From birth to throughout human life, both biotopes closely interact with each other. For example, in newborns with cystic fibrosis, it was found that despite the fact that different genera dominated the intestines and in the respiratory tract, some of them overlapped, like

here *Veillonella* and *Streptococcus*. The increase in diversity in the GI was duplicated over time by diversity in the airways. A high degree of consistency was observed between bacteria, whose number increased or decreased in both compartments; In particular, a significant proportion (14/16 genera) that grew in the intestines increased in the respiratory tract. At the same time, the respiratory microbiome was characterized by greater similarity between patients with the same disease than GM [157].

The gut-lung axis is believed to encompass pathologies such as lung cancer, pneumonia, chronic obstructive pulmonary disease, asthma [85]. In particular, after the outbreak of the epidemic of coronavirus infection, M.M. Mishin and co-authors [5] drew attention to the fact that there is an interaction between the GI and the lungs through GM and its metabolites. Analyzing the literature data for almost two years of the spread of COVID-19, the presence of bilateral interaction during the disease was found. On the one hand, impaired intestinal barrier function is accompanied by the translocation of bacteria, as well as products of resident microflora or its metabolites from the intestinal lumen through the portal vein system to the liver and/or through the lymphatic pathway to the lung tissue. On the other hand, the virus directly reduces the number of nACh-receptor in the GI, which leads to an imbalance of the GM. Because of such phenomena, multiple organ failure occurs. The development of an infectious process in the lungs provokes excessive family growth *Enterobacteriacae* in the intestines and dysbiosis. It is striking that patients with a positive (PCR) test for coronavirus infection will isolate the virus from the intestine for a long time, and tests performed simultaneously with this process from the oral and nasal cavities do not confirm the presence of the disease.

In the article of other domestic authors [10] describes in detail the role of the vagus nerve, which, as the longest cranial nerve in the human body, engages sensitive fibers and transmits information not only from the heart, pancreas, liver, stomach and intestines, but also from the lungs to the brain. The vagal afferent endings of the vagus nerve are located under the intestinal epithelium, and therefore, through certain strains of bacteria, they directly or indirectly receive signals from the intestinal microbiota and even affect human behavior.

2.5. Intestine - metabolism

Pathological conditions centered on the gut-metabolism axis include DM, metabolic syndrome, obesity, mitochondrial dysfunctions, and oncopathology in general [85]. S. M. Tkach believes that the main function of GM is its metabolic activity in the colon. Due to the microbial fermentation of carbohydrates in the colon, the human body receives 10% of the necessary energy reserves. It has also been found that under the influence of modern Western European eating habits, this process proceeds mainly in the proximal regions, not reaching the distal, and therefore, due to the lack of complex carbohydrates, available proteins and amino acids are used during further movement through the intestines. Such a switch in the work of the microbiota leads (according to the data *in vitro*) to the appearance of such harmful products as ammonia, phenols, p-cresol, hydrogen sulfide that provoke inflammatory bowel disease, including the occurrence of cancer [9].

In addition to metabolic, GM performs two more important functions: protective - through strengthening intercellular connections in the intestinal mucosa and increasing mucin production with increased epithelial regeneration, as well as immune - based on the secretion of pro-inflammatory cytokines and the formation of immunological tolerance. Violation of the above three areas of work of the GM entails the appearance of metabolic disorders, in particular, the so-called metabolic syndrome. Metabolic syndrome, as a nosological unit, was once debunked [117], however, in the literature sources the habit of referring to this term as a set of metabolic abnormalities remained. The latter include central obesity, IR, hypertension, atherogenic dyslipidemia, fatty liver disease, hyperuricemia, heart failure with preserved ejection fraction, impaired renal function, polycystic ovary syndrome, sleep apnea, symptomatic activation with tachycardia, chronic inflammation [64]. The listed components in one way or another echo the three main directions of the GM's work. The gut-metabolism axis has found its new extended reading at the stage of studying and searching for new criteria for metabolic syndrome.

2.6. Intestine - thyroid gland

In the scientific literature, we look at single sources describing a new GM axis – the thyroid gland [35]. Jiamin Cao and co-authors included in their study 1560 instrumental variables of GM and found that the classes *Deltaproteobacteria* and *Mollicutes*, as well as groups of genera *Ruminococcus torques*, *Oxalobacter* and *Ruminococcaceae* acted as markers and/or risk factors for the development of Graves-Basedow disease. Family *Peptococcaceae* and genus *Anaerostipes* turned out to be protective markers against the disease. An important role was assigned *Clostridium innocuum* and *Anaerofilum.* The onset of the disease was characterized by the growth of the genus *Anaerofilum* and a decrease in the relative number of the genus *Clostridium innocuum*, which, according to the authors of the publication, testifies to the causal effect of GM on Graves-Basedow disease.

2.7. Intestine - immune system

The ability of GM to regulate the human immune system is noteworthy (microbial symbionts encourage plasma cells to proliferate with increased phagocytic activity of macrophages, monocytes, growth of specific IgA, synthesis of cytokines, etc.). In particular, SCFAs, as end products of fermentation in the colon, directly affect the systemic immune response.

Enough evidence has been collected that early disorders of the formation and formation of GM, and this applies to the period of intrauterine development, newborn (up to 10 days), infancy (up to 1 year), nursery (up to 3 years) and less preschool age, lay the foundation for allergic and autoimmune diseases. In particular, the leaky gut syndrome is a component of the pathogenetic development of such autoimmune diseases as systemic lupus erythematosus, type 1 diabetes, multiple sclerosis [44]. On the part of endocrinology, autoimmune diseases of the thyroid gland can also be added here. For a group of ailments, the pathogenesis of which is an autoimmune process, a decrease in the number and activity of suppressor Treg lymphocytes is also characteristic [4].

Since the middle of the twentieth century, studies of the immune system of sterile or almost sterile animals have become widespread. It was found that birth,

feeding and living in almost sterile conditions deprives experimental animals not just of a number of advantages, but of the ability to live normally and fight infections. A key disorder to which others were added was an inferior immune system. For example, in animals, the absence or underdevelopment of lymphoid follicles in the small and especially in the large intestine, lack of Peyer's plaques was recorded [125]. In the intestines of experimental mice and rats, almost no regulatory Treg (special T-lymphocytes), previously called suppressor, was found. Treg directly affects the immune system, modulates it, maintains tolerance to its own antigens and ultimately prevents the onset of autoimmune diseases. The concentration of protective antibodies, namely Ig A, was also very low.

It has been found that a sufficient number of *Clostridium* suppresses the excessive immune response due to the induction of Treg cells, in part due to the metabolite butyrate. And the colonization of some commensals, for example, *Bacteroides* and *Bifidobacterium,* strengthens the intestinal barrier by stimulating the expression of antibacterial substances and intercellular adhesion molecules, and to suppress inflammation by modulating the transduction of inflammatory signals or induction of regulatory T-cells (Treg cells) [122].

3. GUT MICROBIOTA IN DIABETES MELLITUS AND CONCOMITANT CONDITIONS, TAKING INTO ACCOUNT THE IODINE DEFICIENCY REGION

3.1. Fundamental discoveries as a basis and a guide for further scientific research

Over the past decades, interest in the issue of GM has increased tenfold. Searching for terms such as "gut microbiota" or "gut microbiome" on the World Wide Web yields millions of results. And not only doctors and researchers are interested in this topic. Even an average citizen knows that feces reflect the state of health (not just the presence or absence of worms), and therefore you need to pay attention to their consistency, color, inclusions, smell, etc. [230]. The mass media through journalists, doctors, scientists, through popular science television programs and films, famous bloggers and other means of communication actively influence the opinion of listeners and viewers. And although disgust still exists, fecal transplantation is talked about and written more frankly and more often. Food manufacturers and pharmaceutical companies of various types, due to the growing popularity of the topic, are bringing more and more products to the market, the purpose of which is to influence GM. And although the declaration of a positive impact on the GM does not always come true in practice, the number of intermediaries is growing like an avalanche. That is why it is so important to apply all available levers of influence of evidence-based medicine, to continue to increase the number of high-quality experimental and clinical studies. Only in this way will science distinguish true facts from fiction.

The history of the study of GM dates back to the last century, when in 1903 Ukrainian scientist, one of the founders of comparative pathology, evolutionary embryology, immunology and microbiology Ilya Mechnikov drew attention to the discovery of the Bulgarian student Stamen Grigorov and suggested that the longevity

of Bulgarian peasants is associated with the consumption of fermented milk products [168]. The Nobel Prize laureate in physiology or medicine for his work on immunity believed that lactic acid bacteria, which he named *Lactobacillus bulgaricus*, contribute to the rejuvenation of the body, despite the harsh living conditions of the peasants of that time. Mechnikov was convinced that by replacing harmful gut bacteria with useful ones, it is possible to influence the course of the disease and life expectancy. Actually, since then, thanks to Mechnikov, it is believed that the use of fermented milk products is useful. The collapse of the antibiotic era seen today, the emergence of resistant strains and other problems [142] additionally focused on finding new ways to fight infections due to the impact on gut health and immunity.

A tectonic shift in the field of microbiology, affecting all compartments of the body without exception, and as a result, a wide range of medical disciplines, including pathophysiology, as a link between them, was the international project "Human Microbiome". The project involved 80 US research institutions. Since 2008, over the next five years, it has been discovered that only a tenth of the body's cells belong to the human body, and the other nine belong to the cells of microorganisms. The total number of the latter is several hundred trillion microorganisms and is 1-3.5% of the human body weight. Therefore, the microbiome was recognized as a separate organ of the human body [108].

Scientists identified more than 1300 reference strains and reported on the structure of the microbiome using the example of 300 healthy individuals in 18 locations of the human body. The discovery that two healthy people can have different microbiota, and that this depends on the mode of birth (physiological or caesarean), the method of feeding (breastfeeding or formula), where they live, the presence of stress, diseases, education, gender, and many other factors, as we mentioned earlier

At the same time, it was possible to single out the typical characteristics of each section of the intestine. To do this, a sample clustering approach based on their taxonomic similarity was used. The types of oral and intestinal microbiome communities were expected for each other, even though their taxonomic composition

differed, and their stability was lowest in the oral cavity and highest in the vagina and intestines. Thus, it was concluded that, despite significant intra- and interpersonal variations in human GM, the types of communities of microorganisms could be predictable because they corresponded to certain characteristics of the individual's life history [108, **63**]. In addition, as part of the previously mentioned Human Gut Microbiome project, a number of archaea, fungi, and viruses that inhabit the GI ecosystem were discovered.

To get an idea of the commonalities and differences between gut microbiomes in different populations, Arumugam M. and colleagues sequenced 22 fecal European metagenomes from Danish, French, Italian, and Spanish individuals that had been selected to establish diversity and combined them with previous sequencing results from Japanese and Americans to obtain 39 individuals as samples for comparison [23]. Scientists have found that despite the huge number of species living in the gut and their interindividual variability, the composition of the microbiota can be divided into at least three distinct clusters. The resulting clusters were called enterotypes. Enterotypes contain functional markers that correlate with individual characteristics such as age and BMI and are not specific to a nation or continent.

Twelve genes were likely correlated with age and three functional modules with BMI. Starch degradation enzymes, such as glycosidases and glucan phosphorylases, increased, indicating a decrease in the efficiency of the breakdown of dietary carbohydrates in the host with age. that such functional markers can be used for diagnosis, as well as a tool for the prognosis of many pathologies, for example, regarding colorectal cancer and other conditions or diseases related to obesity, namely metabolic syndrome, DM and cardiovascular pathology, etc.

The distal intestine deserves special attention, since the most diverse and largest number of bacteria live in it. As research in recent years has found out, [25] The colon microbiota and its collective genomes (microbiome) endow the human body with genetic and metabolic characteristics, including the ability to accumulate nutrients that

are not otherwise available. These capabilities are provided by a huge population of strains and subspecies of bacteria, which is actually dominated by a relatively small number of divisions (types). As a result of the discussion on the topic of the functional parts of the intestine, the authors of the publication rightly call the human large intestine an "anaerobic bioreactor", bringing this term to the first page of the abstract of their scientific work.

3.2. General view of the gut microbiota

The gut microbiota is often referred to as the gut microbiota or gut microbiome, however, these terms have different meanings [230]. The microbiome (from Latin. *micro* – "small", *bios* – "Life") refers to the set of genomes of all microorganisms of the environment as a whole (including bacteria, viruses, fungi, archaebacteria) or environments of a certain localization (for example, skin, intestines, etc.), while the term "microbiota" is a collection of only microorganisms without taking into account genes for a particular environment.

Up to 1 billion people enter the intestine through the oral cavity, as through the gate. microorganisms per day. A significant part of them is washed from the inner surfaces of the oral cavity to the stomach. In passing, we note that there are more anaerobes in saliva than aerobes. The aggressive environment of the stomach also does not allow more microorganisms to linger in it, while the final sections of the small intestine and large intestine are characterized by the greatest degree of colonization of microflora.

The gut microbiome is characterized by a complex hierarchical structure and symbiotic interactions that provide the host body with biologically active substances (vitamins, amino acids, hormone-like and antibacterial substances, etc.). Human GM has trillions of microorganisms, including about 200 of the most common and almost 1000 rare strains, the number of genes of which exceeds the human genome by 100 or even 150 times [95]. It is believed that the permanent (main, resident) microflora

accounts for 90%, the additional (optional, concomitant) – 10% and the occasional (transient, residual) – 0.01%. The life of microorganisms that have entered the gastrointestinal tract takes place in the epithelial film - a phenomenal phenomenon of nature that lines the intestinal mucosa, protecting the body from penetration and colonization by pathogenic microorganisms. For this purpose, a variety of microflora produces bacteriocins, lysozyme and other specific antibiotic-like compounds.

Starting from the domain, the sequence of the main taxonomic ranks of the GM looks like this: kingdom – division (sometimes the term "type") – class – series – family – genus – species. For example, the domain *Bacteria*, the kingdom *Eubacteria*, the division (phylum) *Proteobacteria*, the class *Gamma-proteobacteria*, the order *Enterobacteriales*, the family *Enterobacteriaceae*, the genus *Escherichia*, the species *Escherichia coli*.

The microbiota of the human colon is individual and can differ both in species and in strains of microorganisms, but the presence of common features allows it to be studied and analyzed [230]. Basically, GM contains the following four categories: *Firmicutes*, *Bacteroides*, *Actinomycetes* and *Proteus* [42]. It has been established that the ratio of anaerobes to aerobes of the intestinal biocenosis of a healthy person is a constant value and is 10:1, and on the basis of jointly identified *Bacteroides, Prevotella, Ruminococcus* The human microbiome is divided into three enterotypes.

The microflora of the colon is represented mainly by anaerobic gram-negative bacteria of the department *Bacteroidetes* (about 20 genera) and gram-positive – *Firmicutes* (more than 200 genera) [197]. Concomitant aerobes include aerobes in the form of Escherichia coli, lactobacilli, enterococci, etc., and residual aerobes include staphylococci, clostridia, proteas, fungi. This rather simplified classification does not take into account a number of other microorganisms, which is usually diagnosed in human GM. We are talking about the following genera: *Succinomonas, Wolinella, Roseburia, Propionobacterium, Spirochetes, Ruminococcus, Selenomonas, Fusobacterium, Campylobacter, Disulfomonas, Acetovibrio, Butyrovibrio, Peptococcus, Actinomyces, Citrobacter, Enterobacter, Reptostreptococcus,*

Veillonella, Bacillus, Pseudomonas, Eubacterium, Acidinococcus, Aerovibrio, Corynebacterium. Anaerobes from childbirth are less common *Anaerobiospirillum, Megasphaera, Bilophila Metanobrevibacter, Gemiger*Simplest *Chilomastix, Endolimax, Entamoeba, Enteromonas*, as well as intestinal viruses. As for the latter, during the COVID-19 pandemic, it was found that the SARS-CoV-2 virus affects not only the respiratory system with the provocation of autoaggressiveness of the immune system (confirmed by the appearance of extracellular DNA) [71], but infects and multiplies in GI cells. This is confirmed by the detection of viral RNA and infectious viral particles in fecal samples of COVID-19 patients, even in cases with absent or mild respiratory symptoms [94].

Despite some fluctuations in the above-mentioned composition, GM has a more or less stable character, performing many important functions for the host body, in particular, antitoxic, antimutagen, anticarcinogenic, etc. Due to the symbiosis of various bacterial cultures, the gas composition of the internal environment is controlled, the effect on water-salt, energy, protein, carbohydrate and fat metabolism occurs.

In addition, there is many evidence that a change in GM can act as both a motive and a consequence of pathological disorders. With regard to the first, it has been clarified, for example, how a certain kind of deviation in the microbiocenosis of the colon cavity plays the role of a harbinger of undesirable shifts not only in the microbiocenosis of other parts of the intestine, but also in the physiological status of the human body as a whole. Unfortunately, it is not always possible to find out what is the primary or so-called "trigger" of the pathological process, but the main thing is well known - the imbalance of the human intestinal microflora is characterized not only by local disorders, but also by systemic ones.

When studying GM, it is also necessary to take into account several fundamental points. Firstly, in order to determine such expressions as "pathological changes in the GM", "impaired GM", "deviations in the GM", etc., it is necessary to have a standard for comparison. It is clear that we can use the reference values of the

norms of a particular type of bacteria, but it should be emphasized that the term "healthy gut microbiota" does not exist today, because it still requires careful study of the relevant criteria. At the same time, it is known that such GM should be diverse, and therefore, using only one of these factors, we are already able to find differences between the control group of healthy and sick [165, **141**]. Diversity is usually understood as a diversity α that describes a characteristic within the same host sample system. For example, how many species are present in the same department (type) *Firmicutes*, while β-diversity is determined between individual biotopes of the human body or two individuals dissimilar to each other. Another indicator of γ-diversity is used. Each of them has its own mathematical models. And as for the term "dysbiosis", it also does not have a clear definition [8].

Despite the problems of determining dysbiosis, or dysbiosis, as well as healthy GM, there is still a list of criteria listed in the literature for the phenotype of a healthy person and a patient with obesity, IR and DM.

Secondly: GM is a decisive factor in weight gain and thirdly, it is a key mechanism for the formation and functioning of the immune system. Mice freed from GM showed resistance to obesity, which was deliberately provoked by diet [26], and mice that were raised in aseptic conditions were characterized by an underdeveloped immune system. After systemic infection *Listeria monocytogenes* and antibiotic therapy, experimental rodents showed pathogen overload and rapid death. Instead, recolonization of bacteria-free mice with a diverse and rich microbiota repaired myelopoiesis defects and developed resistance to *Listeria monocytogenes* [125]. In another study, injecting microbe-free mice with only one type of bacteria, *Enterobacter cloacae*, which is associated with obesity, contributed to weight gain, impaired glucose tolerance, decreased adiponectin content, and increased lipopolysaccharide [81]. The obesity phenotype can still be transmitted through GM.

3.3. The relationship of the intestinal microbiota with the appearance of pathological conditions related to endocrinopathies

The GM effect goes far beyond the regulation of the intestine itself. A cursory glance indicates the effect of GM on protein (bacterial proteases hydrolyze proteins into amino acids), carbohydrate (synthesis of glucose, fructose, lactose, etc.), as well as on fat metabolism (cholesterol and bile acids under the action of bifidobacteria and lactobacilli are converted into insoluble compounds and excreted in feces).

The death of beneficial microflora or its failure has a tangible impact on the health of the body as a whole. So, for example, in the case of systemic inflammatory response syndrome (SIRS) compared to healthy ones, there was a significant decrease in the total number of anaerobes (especially *Bifidobacterium* and *Lactobacillus*) and the growth of pathogenic groups of aerobes, such as *Staphylococcus and Pseudomonas* [219].

In the face of dysbiosis, an imbalance of SCFA can stimulate intestinal chromaffin cells to produce 5-hydroxytryptamine, which, interacting with the 5-HT3 receptor of the intestinal vagus nerve, inhibits the afferent activity of the vagus nerve from the intestine to the brain. It was previously known that oppression *nervus vagus*, as part of the parasympathetic nervous system can stimulate the heartbeat, cause gastric motility disorders, etc. And now they have found that once in the bloodstream, 5-hydroxytryptamine can cause vasoconstriction and affect blood pressure through blood circulation and damage to the blood-brain barrier [275]. In addition, the hydrogen sulfide produced by GM can also regulate a variety of physiological processes, including vasodilation, angiogenesis, and hypotension [69].

A bacterium lives in the intestines *Bilophila wadsworthia*, that inhaling taurine produces hydrogen sulfide through desulfonation reactions using sulfite lyase isethionate. Hydrogen sulfide (hydrogen sulfide) deficiency precedes the onset of hypertension, because hydrogen sulfide has cardioprotective properties. In particular, an exogenous hydrogen sulfide donor protects rats from spontaneous hypertension

[69]. Hydrogen sulfide is also involved in a number of different mechanisms, including inhibition of oxidative stress, inflammation and, mediated by ion channels, relaxation of vascular smooth muscles [219]. However, its excess has been linked to colorectal cancer and irritable bowel syndrome because it damages the mucous layer of the intestinal epithelium. And during antibiotic treatment, hydrogen sulfide can provoke the growth of opportunistic bacteria and cause resistance to antibiotic therapy.

GM also has a direct effect on the renin-angiotensin system. Rich in GM partially alleviates angiotensin II-induced hypertension and vascular dysfunction due to vascular immune cell infiltration and inflammation, in particular through the effects of MCP-1/IL-17 [120]. There are reports that the probiotic strain *Enterococcus faecalis* Increases the activity of angiotensin-converting enzyme inhibitors. In experimental studies on rats, antihyperglycemic and anti-insulin-resistant effects and generally positive effects on the components of metabolic syndrome were found [144].

Animal experiments have shown that the introduction of donor feces of hypertensive animals into the intestines of healthy mice leads to an increase in blood pressure, demonstrating the unconditional role of GM in the development of hypertension [**57**, **73**]. During clinical observations, it was possible to find out that in patients with hypertension, microbiological diversity and balance deteriorate significantly, and the ratio *Firmicutes/Bacteroidetes* grows [42]. TMA-N-oxide should be added to the effect on the cardiovascular system through the gastrointestinal tract. Its precursor is trimethylamine, which is formed from the food intake of phosphatidylcholine and L-carnitine (mainly from meat products) by GM bacteria. In the liver, trimethylamine is transformed into TMA-N-oxide under the influence of flavin monooxygenase. The concentration of TMA-N-oxide in the blood (serum or plasma) has a dose-dependent relationship with the risk of hypertension directly, and is generally associated with cardiovascular and metabolic manifestations, which was found on the basis of the results of a meta-analysis of 18 observational studies [**14**, **266**].

3.4. The role of meta-inflammation and immune abnormalities in the development of endocrinopathies and comorbid conditions

Overall, there is strong evidence that the three-way interaction between the host's GM, its immune system, and inflammatory processes are critical participants in the pathogenesis of obesity and type 2 diabetes [**104**, 211]. The gut microbiota has many important functions, one of which is to limit the invasion of pathogens competing for essential nutrients. To establish and maintain this symbiotic balance, it is important that the host develops tolerance to intestinal microbial antigens at an early age. Proper induction in childhood builds immune resistance against intestinal bacteria throughout an individual's life [129]. Immunoglobulins control GM and prevent bacterial invasion by directly binding to microorganisms. Despite this, immunoglobulins neutralize microbial toxins [135]. IgA is a major player in the formation of GM in experimental mice and in humans [36]. And a change in the intestinal immunoglobulin response was recorded in patients and mice with inflammatory bowel disease [182], with obesity [152], as well as in conditions of malnutrition [123].

Only in recent years has it been found that immunoglobulins play an important role in intestinal homeostasis, and through it can affect the progression of metabolic diseases [181]. Taking into account the mediation of the immune system in the chain of interaction between GM and carbohydrate metabolism, there is a reasonable assumption about its regulatory capacity in both directions. For example, obese mice were found to have fewer IgA+ immune cells and IgA secretion, higher levels of macrophages in adipose tissue, and more systemic endotoxins despite impaired glucose tolerance, and metformin increased IgA [152].

T-cells, such as helper follicular T-cells, induce immune and antibody responses [187]. Immune cells formed in the intestine under the influence of an altered intestinal microbiota can contribute to the pathogenesis of systemic autoimmune diseases and can even alter the outcome of cancer immunotherapy [271]. The depletion of T-cells and their function with age reduced the activity of IgA in the intestine and caused the development of metabolic syndrome. An unexpected discovery was also made that flagellin (flagellum) of intestinal commensal bacteria *Clostridiales*belonging

to the family *Lachnospiraceae*, serve as immunodominant antigens in both experimental mouse colitis and patients with Crohn's disease [236].

GM, as a partial immunomodulator, is directly related to low-grade metabolic inflammation - meta-inflammation, both local and systemic. Slight increases in inflammatory factors accompany or cause IR, DM-2 due to impaired insulin and/or insulin secretion [**91**, **140**, 194].

This hypothesis is confirmed by the observation that in people with metabolic syndrome, the level of cytokines increases, which have a negative effect on the sensitivity of peripheral tissues to glucose and obesity in particular [**148**, **167**]. The mini-review with the pilot study had the following two goals: to review the latest literature data of the international electronic resource PubMed on interleukins as markers of inflammation in D2M and to analyze the parameters that together assess redox disorders and the adverse effects of D2M on patients. Significant differences were observed in serum indicators of redox and inflammatory status according to protein oxidation end products (AOPPs), of glycation end products (AGEs), CRP, CRP/HDL, CRP/IL-6, IL-10/IL-6 ratios, two oxidation-inflammatory status indices (IH1 and IH2) between patients with D2M compared to controls. Glycemic control strongly influenced inflammatory status biomarkers: glycemia was positively correlated with inflammatory parameters (CRP/IL-10) and inversely with anti-inflammatory parameters (IL-10, IL-10/IL-1β ratio) [240].

On the other hand, weight loss reduced the concentration of a number of inflammatory cytokines in obesity by 10% [160]. Adipose tissue was one of the first tissues to be extensively studied for IR and inflammatory markers, and one of the first cytokines to be discovered expressed and secreted by adipose tissue macrophages was TNF-α. Its increase is typical for people with type 2 diabetes and obesity [189]. TNF-α expression in adipose tissue is inversely correlated with insulin sensitivity in obese people without type 2 diabetes compared to healthy people [124]. We find confirmation in the experiment: infusion of TNF-α in rats induced IR on the first day of manipulation [201]. At the same time, mice deficient in TNF-α and receptors for it were protected from IR, which they tried to induce with appropriate nutrition. Neutralization of TNF-

α by infusion of reactive immunoglobulins in rats improved insulin-stimulated glucose uptake, and weight loss in obese patients improved insulin sensitivity and decreased expression of TNF-α in adipose tissue, suggesting a key role for obesity in inflammation and insulin sensitivity. Therefore, TNF-α inhibition has been proposed infliximab for the treatment and prevention of type 2 diabetes [68]. Infliximab is a monoclonal antibody that binds in a specific way TNF-α, leveling its activity. A clinical case is described 53-year-old a patient suffering from melanoma with existing liver metastases, lungs and lymph nodes, as well as immunodeficiency colitis. After two doses of combination treatment with ipilimumab and nivolumab (immunoblockade), the patient developed hypocalcemia as a result of immune-mediated hypoparathyroidism, which was treated with calcium and vitamin D replacement therapy. Immunoblockade provided complete remission from melanoma. Against the background of a maintenance dose of nivolumab and glucocorticoids, an increase in blood glucose ($HbA_{1c,}$ which was 11.6%). Autoantibodies to islet cells were positive, so insulin therapy was prescribed. Since the patient also developed more active oligoarthritis, we started infliximab therapy to block FNP-α. Treatment with infliximab contributed to the restoration of β cell function and eliminated IR, and therefore insulin therapy was discontinued. The patient's restoration 2 months after the last insulin injection and infliximab dose demonstrated long-term complete remission of his DM [237]. An inspiring example of the effectiveness of infliximab points to a poorly understood pathogenetic link in the development of DM in relation to the β cells of the islets of Langerhans. It became known that D2M β cells produce both immunoglobulins and pro-inflammatory cytokines [54].

In the experiment, it was found that islet β cells are related to the development of DM, since mice with zero β cells have less IR caused by a high-fat diet. As in adyrocytes, macrophages accumulate in the β cells of the islets of Langerhans, with a corresponding increase in secretion FNP-α that against the background of a fat diet, leads to impaired insulin production, due to dysfunction These cells, and peripheral IR [254].

At the same time, a number of pharmacological agents based on cytokines "friendly" to humans reduced the manifestations of inflammation and had a positive effect on glucose sensitivity in humans and animals. For example, a new hybrid cytokine IL-233 from a genetically modified *Escherichia coli*, which is obtained by fusing mouse IL-2 and mouse IL-33 and protected mice from ischemic-reperfusion kidney damage more effectively than any cytokine alone; prevented the development of type 2 diabetes, obesity and diabetic nephropathy in mice, regulating, as the authors write, numerous pathogenesis factors [203]. Other treatments include blocking the IL-1 receptor [17], antagonism of IL-1β [37], the use of IL-25, which improves wound healing in mice with experimental diabetes [143], inhibition of the intracellular pro-inflammatory pathway NF-κB [82]. Obese mice and people with DM-2 have lower IL-10 expression and higher pro-inflammatory signals [153] compared to individuals without metabolic syndrome [76], which is consistent with the study that the increase in the cytokine IL-10 content by M2 macrophages protected mice from IR [103, 153]. In addition, increased expression of IL-10 in mouse muscle tissue improved insulin sensitivity even under high-fat diet conditions [103].

Another useful cytokine is IL-22, which is necessary to maintain the antimicrobial response and ensure the functionality of the intestinal barrier [176]. Its production is induced by intestinal type 3 innate lymphoid cells, as the main stationary source and under the influence of bacterial metabolites of tryptophan, which balance the reactivity of the mucous membrane on the example of mice [**244**, **265**]. It was discovered that What is against the background of infection *Citrobacter rodentium* the induction of IL-22 from congenital lymphoid cells and CD4 T-cells in obese mice is impaired, especially in the colon [251]. This indicates an inadequate immune response to pro-inflammatory bacteria. Mice that did not have an IL-22 receptor on a high-fat diet developed metabolic syndrome, and the administration of IL-22 eliminated the phenomena of hyperglycemia and IR [**72**, 251]. Butyrate, obtained as a result of the degradation of dietary fiber, is also able to induce the secretion of IL-22 by congenital lymphoid cells of the pancreas, affecting β cell proliferation and inflammation [166]. A decrease in the activity of IL-22 (next to IL-23) due to the weakening of the intestinal

barrier in mice, leads to uncontrolled multiplication of pathogenic bacteria, an increase in lipopolysaccharides and TMA [80]. Inhibition of intestinal TMA formation reduced the formation of foamy macrophage cells and the development of atherosclerotic lesions in mice [252].

Another such cytokine is IL-36, the expression of which increased in obese patients and was negatively correlated with high blood glucose levels [87]. Mice that were excluded from the endogenous IL-36 receptor inhibitor restored insulin sensitivity, had better glucose tolerance, and increased intestinal numbers *Akkermansia muciniphila*, the integrity of the intestine was restored, mucin was formed [87].

The anti-inflammatory cytokine IL-10 is also important for inhibiting the inflammatory response against intestinal bacteria [169]. As with IL-22, microbiota-derived SCFAs protect IL-10 [228]. And the elimination of IL-10 in experimental mice causes colitis [216].

Other anti-inflammatory cytokines such as IL-4, IL-13 are less studied, but no less important because they affect glucose tolerance and inhibit adipogenesis [238]. However, despite their anti-inflammatory properties, they also have the ability to alternatively activate macrophages [**154**, **242**]. Therefore, we will look at such scientific papers, which record that both cytokines next to the above-mentioned anti-inflammatory IL-10 increased in obesity compared to the control group of thin individuals, which was believed to be associated with lower physical activity. At the same time, it has been confirmed a significant increase in IL-5, IL-10, IL-12, IL-13, IFN-γ and TNF-α in general obesity and IL-5, IL-10, IL-12, IL-13 and IFN-γ in conditions of central obesity in patients with a BMI≥30 kg/m2 [212].

Another study found an increase in the above-mentioned anti-inflammatory cytokines in IR and their positive correlation with hyperglycemia. However, the experiment showed that when obese mice become obese, the activity of IL-13Rα2 increases, which inactivates and depletes IL-13 [163]. Therefore, there is a mechanism for leveling the anti-inflammatory properties of IL-13 in the blood, and therefore an increased content of IL-13 can be apparent and lead to false conclusions. We observe a problem with the correct identification of the role and the IL-6. On the one hand, IL-

6 increases the activity of suppressor of cytokine signaling 3 (SOCS3), which further inhibits a number of insulin receptor signaling mediators [115]. However, knocking out the IL-6 receptor from immune cells, although it disrupts the immune homeostasis of mice, does not protect them from the development of IR [260]. In another study, administration of IL-6 increased insulin secretion by increasing glucagon-like peptide 1 incretin from gut L-cells and pancreatic α cells of experimental mice [234]. It appears that IL-6 acts as a pro-inflammatory and anti-inflammatory cytokine, because it is known to indirectly inhibit TNF-alpha, IL-1 and activate IL-10.

A group of cytokines, also called chemokines, is also able to attract immune cells to tissues with metabolic properties [92]. Monocytic chemoattractant protein-1 (MCP-1) is considered a potent chemokine for monocytes and its expression was increased not only in experimental animals, but in a clinical study of obese women. Data analysis of 51 obese women was carried out after gynecological surgery Foundthat alterations in the production of inflammatory biomolecules precede increased infiltration of immune cells in visceral adipose tissue. In addition, serum resistin and leptin are involved in the specific regulation of adipose tissue macrophages in patients with moderate obesity or early metabolic dysfunction [119].

The islets of Langerhans also express and secrete MCP-1. Overexpression of MCP-1 in mouse β cells led to increased macrophage infiltration and spontaneous development of DM [162]. An increase in the concentration of pro-inflammatory elements such as lipopolysaccharide also leads to an increase in MCP-1 expression [60]. Lipopolysaccharide is key component outer membrane gram-negative bacteria, which ensures the structural integrity of microorganisms and protects the membrane from various kinds of damage. At the same time, it can play a role endotoxin, which induces immune responses.

In the liver, too, there is an increase in infiltration by macrophages (and various immune cells). This causes the production of inflammatory cytokines, the appearance of hepatic IR against the background of type 2 diabetes and metabolic-associated fatty liver disease and/or non-alcoholic steatohepatitis [**138**, **178**]. As it turned out, liver

macrophages produce insulin-like growth factor-binding protein 7 (IGFBP7), which directly alters insulin receptor signaling in the liver [171].

Drawing on the latest arguments from recent studies, it is confirmed that inflammatory biomolecules, such asonocyte chemoattractant protein-1, precede increased macrophage infiltration followed by cytokine secretion in adipose tissue, leading to IR due to obesity, which ultimately accelerates the development of DM. Despite the large list of cytokines that are associated with metabolic disorders and affect them, only a few representatives interleukins (IL-22, IL-23, IL-36) play the role of components of the pathogenesis of obesity, type 2 diabetes and IR through the intestinal microbiota. However, this in no way detracts from the pathogenetic effect of the cytokines listed above.

Based on the literature, the relationship between GM and carbohydrate metabolism can be depicted through changes in processes in the immune system and adipose tissue mediated by inflammatory markers.

From the available data, it becomes clear that dysregulation of the immune system is closely intertwined with obesity, metabolic-associated liver disease, and type 2 diabetes. In addition, in the pathogenesis of type 2, along with the involvement of the immune system, low-grade inflammation is involved, which is called "meta-inflammation". This indicates that in contrast to the acute inflammatory response to pathogens and/or tissue damage, the low-grade chronic inflammation seen in obesity and type 2 diabetes has detrimental effects on human health.

3.5. Embryos of metabolic disorders in the pathogenesis of diabetes mellitus through the prism of changes in the gut and its microbiota

In 2019, 463 million people in the world suffered from diabetes. It is predicted that by 2030 these figures will increase to 578 million patients [204]. The emergence of type 2 diabetes is largely caused by the obesity pandemic. In the pathogenesis of type 2 diabetes, a key link is occupied by IR - a condition in which the action of insulin on peripheral tissues, including skeletal muscles, liver, adipose tissue, vascular

endothelium, is disrupted. As a result of IR, there is a decrease in insulin-stimulated glucose utilization, lipolysis and glucose production in the liver are activated through gluconeogenesis and glycogenolysis [172]. In the initial stages of IR, the pancreas tries to compensate for the weakened peripheral action of insulin by increasing its synthesis and release into the bloodstream. But over time, the β cells of the pancreas are depleted and are no longer able to meet the need for insulin. As a result, the first signs of hyperglycemia develop. The appearance of hyperglycemia incessantly leads to damage to the micro- and macrovascular bed.

Starting closer to specific representatives of the intestinal microflora, you can pay attention to the study that revealed an increase in the number of *Bacteroides caccae, Bacteroides massiliensis* and *Bacteroides vulgatus* in women with gestational diabetes and patients with type 2 diabetes, which may be associated with hyperglycemia [221]

As mentioned above, SCFAs are involved in the development of metabolic disorders. SCFAs, which include acetate, propionate, butyrate, isovaleric acid and others, are the result of the treatment of dietary fiber by certain bacteria [40]. For example, a reduced amount of *Faecalibacterium prausnitzii* associated with a violation of the production of SCFA [194].

Let's look at the ambiguous results of various studies on the level of diabetes mellitus and their relationship to the pathogenesis of diabetes mellitus and obesity. One study recorded an increased production of SCFA in obesity [56], which could indicate an increased supply of energy resources to the host's body [214]. And in another project, a reduced level of SCFA was recorded in DM [194, **215**]. After administration of low concentrations of propionate, the occurrence of IR was found due to stimulation of glucagon and FABP4 production [235]. In this regard, it is worth recalling the data of Canadian and Dutch scientists, who estimated that 5-10% of the individual's daily energy pool comes from fermentation processes in GM [211]. The clarification of the discrepancies mentioned above is ordered in the original article by the research team after a targeted clinical follow-up. The analysis involved 952 normoglycemic individuals who underwent genotyping, study of the metagenomic sequence of GM,

determination of the level of SCFA in the feces. Combining the results obtained, a bidirectional Mendelian randomization analysis was used to assess causation and found that a genetic increase in butyrate production was associated with an improved insulin response after an oral glucose tolerance test (p= 9.8 × 10−5), while abnormalities in the production or absorption of another SCFA, namely propionate, were causally associated with an increased risk of developing type 2 diabetes (R= 0,004) [208]. Instead, another representative of SCFA, acetate, despite its positive effect on glucose-stimulated insulin secretion, has been implicated in weight gain in mice [186].

Despite the established connections, one should not discount the fact that the real turnover of SCFA is very difficult to calculate, because, in particular, butyrate is constantly consumed by enterocytes of the colon as a source of energy [200]. On the other hand, not all SCFAs have a beneficial or only beneficial effect on the human body, and only for three of the SCFAs (acetate, butyrate, propionate) a connection has been established between GM, the immune system, inflammation, and carbohydrate metabolism.

The intestinal wall also plays a role in the pathogenesis of endocrinopathies and related conditions, since its resistance prevents the penetration of bacteria and their particles into the systemic circulation. In particular, literary sources mention inflammatory bowel diseases [188], liver disease [83], metabolic syndrome [32].

An increase in the concentration of lipopolysaccharides, as bacterial particles, in the blood accompanied patients with metabolic syndrome, T2D and T1D [**88**, **139**]. Lipopolysaccharides are thought to enter the systemic circulation via chylomicrons or through increased intestinal permeability [86]. In mice, chronic infusion of lipopolysaccharides impaired glucose tolerance by inducing hepatic IR, interfered with glucose-stimulated insulin secretion [32]. Lipopolysaccharides and long-chain saturated fatty acids, such as palmitate, act synergistically in the direction of macrophage activation [137], which justifies the etiopathogenetic relationship between the so-called Western diet rich in saturated fatty acids [49], and postprandial inflammation. In addition to lipopolysaccharides, imidazole propionate, a metabolite of histidine, enters the systemic circulation, which also enhances IR [131].

There is also a reverse process, when hyperglycemia through Glut2-dependent reprogramming of epithelial cells weakens the intestinal barrier of the intestine and increases its permeability to peripheral organs [232]. Accordingly, there have been attempts to detect, by measuring or sequencing 16s ribosomal RNA of bacteria, their abnormal movement to peripheral tissues. And this approach was crowned with success. Bacterial DNA (predominantly proteobacteria) was recorded in greater abundances in DM patients, in an experiment on obese mice compared to control groups [21]. DNA translocation of gram-negative bacteria to adipose tissue in obese women showed an inverse correlation with adiponectin [239].

Bile acids also play an important role in glucose metabolism [217]. After postprandial contraction of the gallbladder, they enter the duodenum. Primary FAs can be deconjugated and dehydroxylated by intestinal bacteria to form secondary FAs. Later, intestinal FAs are actively reabsorbed in the terminal ileum and return to the liver, where, after reconjugation, they are again secreted into the gallbladder, and from there they enter the intestine. As a result of this enterohepatic circulation, only a small part of the FA is excreted in the feces. These of them, which have entered the systemic circulation, regulate lipid homeostasis, glucose, energy consumption, inflammation processes, intestinal motility, composition and growth of bacteria in it [217]. For example, cholic acid changes the composition of GM and reduces systemic adiponectin levels in rats [110]. In the systemic circulation, FAs bind to their two main receptors, the farnesoid X receptor (FXR) and TGR5, which are involved in glucose metabolism [185] and liver regeneration [**106**]. In an experiment in mice, the use of an intestinal agonist for FXR induced GLP-1 secretion, altering the gut microbiota, and improving glucose tolerance [185]. At the same time, FXR, despite improving insulin sensitivity, provokes obesity [**192**, **253**], and its elimination in experimental mice prevented obesity and metabolic changes in mice [184]. Immune cells also express FXRs, which simulate the functioning of innate immunity cells and gut integrity on the example of experimental colitis in mice As a result, it was found that aFXR activation increased the expression of I-BABP, FXR and SHP mRNA in the colon, decreased the expression

of mRNA IL-1β, IL-2, IL-6, TNF-α, IFN-γ and alleviated the course of the disease [243].

GM also produces a number of other substances: lactate, histamine, methane and many others. The metabolites of the three metabolic pathways tryptophan, histidine, and phenylalanine can affect various inflammatory conditions such as obesity, diabetes, arthritis, colitis, atherosclerosis, and neuroinflammation [261].

Lactic acid fermentation is the main process during the fermentation of vegetables and dairy products. The genera of lactic acid bacteria include *Lactobacillus, Lactococcus, Pediococcus, Enterococcus, Streptococcus, Leuconostoc, Weissella* etc. Lactate has an antimicrobial and immunomodulatory effect. Lactic acid regulated the polarization state of macrophages and inhibited the expression of pro-inflammatory cytokines *in vivo* and *in vitro* [229]. It should be noted that there are two types of lactate: L(+) lactate and D(-) lactate. Human and animal tissues produce almost exclusively L(+), while microorganisms can produce D(-) lactate or, occasionally, a combination of L(+). It has been observed that lactate L(+) increases with DM, oncopathology, thiamine deficiency, liver dysfunction, injuries, excessive physical activity. In an experiment on mice with streptozotocin diabetes, glucose and lactate levels increased markedly [146]. Its high level is also found in the meat of slaughtered animals.

Histamine-producing microflora includes *Klebsiella spp., Enterobacter spp. Histamine* plays an important role in various physiological processes such as cell proliferation, wound healing, allergic reactions, regulation of immune cells, etc., acts as one of the most important neurotransmitters in the brain. In the intestine, histamine is produced mainly by enterochromaffin cells. microorganisms) that develop on undigested food debris can also release histamine, which causes allergic reactions.

Experimental study on mice whose intestines colonized by the fecal microbiota of patients with irritable bowel syndrome who had high levels of histamine in the urine developed visceral hyperalgesia and mast cell activation. When the mice changed their diet by reducing the fermented carbohydrate content, it was observed that the animals experienced a decrease in visceral hypersensitivity and the accumulation of mast cells

in the colon. It was found that *Klebsiella aerogenes*, which was most common in patients with irritable bowel syndrome, contains a variant of the histidine decarboxylase gene responsible for the production of histamine. When histamine receptor blockade 4 was used *in vivo* The accumulation of mast cells in the colon along with visceral hyperalgesia decreased [58].

The most typical representative of methanogens in human GM is *Methanobrevibacter smithii*. In obese mice, microorganisms of the class *Archaea spp. (species Methanobrevibacter smithii)*, which have the ability to increase the fermentation process of polysaccharides and produce methane [27]. In addition, methane slows down intestinal transit due to increased tone of the intestinal wall and causes constipation. For example, adults with functional constipation had a decrease in the amount of *Bifidobacteria* and *Lactobacilli* in fecal samples, and also recorded an increased level of methane in respiration, compared to control subjects [62].

There is also such a problem as excessive bacterial growth of the small intestine. Bacterial overgrowth syndrome, for example, occurs after prolonged use proton pump inhibitors. The risk of the syndrome increases with age, complicates the course of a number of diseases and has a pathogenetic effect on their course. First of all, bacterial growth syndrome is associated with gastrointestinal diseases (functional dyspepsia, irritable bowel syndrome, functional flatulence, functional constipation and/or diarrhea, lactase deficiency, Crohn's disease, etc.), as well as with metabolically associated fatty liver disease, DM, hypothyroidism, hyperlipidemia, acromegaly, heart failure and many other pathologies. In the pathogenesis of the syndrome, there is a slowdown in the time of orocecal passage, which reduces the clearance of bacteria from the small intestine to the distal sections. In particular, this phenomenon can be observed in DM, when autonomic diabetic polyneuropathy develops, or in the absence of a normal level of thyroid hormones in hypothyroidism, when their stimulating effect on peristalsis decreases [74].

4. OWN RESEARCH AND ANALYSIS OF THE KEY COMPONENTS OF THE PATHOGENETIC PICTURE OF THE DEVELOPMENT OF THE STUDIED ENDOCRINOLOGICAL PATHOLOGIES

To assess the structural and functional state of GM, using multiplex pyrosequencing of the 16S fecal rRNA gene, thirty-two indicators of GM were obtained, which are shown in Fig. 4.1.

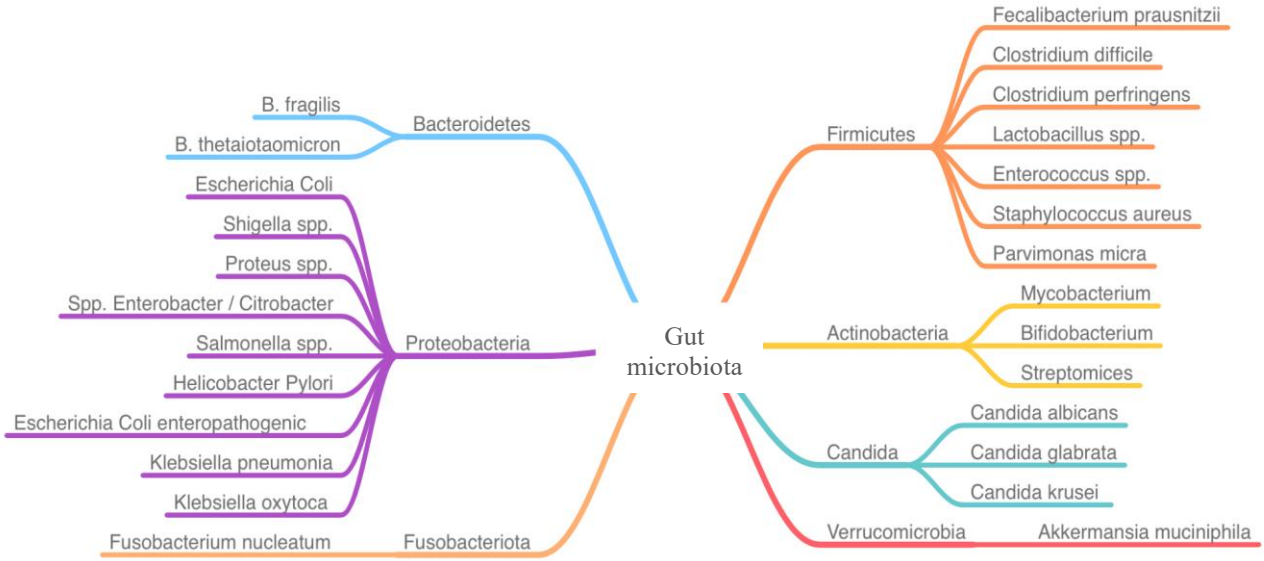

Fig. 4.1. Scheme of the GM examined by us, grouped by type, indicating genera and species

The selection of patients by groups obeyed a clear logic. The first three groups reflected the pathogenesis of type 2 diabetes, starting with obesity due to prediabetes to type 2 diabetes. From the third to the sixth group, the pathogenetic course of autoimmune thyroid disease from AIT was traced, through hypothyroidism to Graves' disease. Since iodine deficiency with the development of endemic goiter is observed in the west of Ukraine, patients with endemic goiter, as a common comorbidity, were included in the first three groups. At the same time, patients in the fourth and fifth groups had IR as a common background with the first two groups of patients. The group of patients with Graves' disease had to show the opposite picture to all previous groups, since these were patients who were progressively losing body weight, did not

have IR and did not have any disorders of carbohydrate metabolism. So, with regard to carbohydrate metabolism disorders, for the convenience of studying and analyzing GM, the groups were arranged in the following order: obesity and endemic goiter appeared in the first group, prediabetes with endemic goiter appeared in the second, type 2 diabetes mellitus against the background of endemic goiter, and in terms of thyroidology, patients with AIT and IR were involved in the fourth group, patients with hypothyroidism with existing IR were involved in the fifth group, and to the sixth - patients with Graves' disease. For comparison with patients, a control group was created, which included healthy individuals who did not express complaints, and their laboratory parameters did not go beyond the reference values.

First of all, a comparative analysis was carried out between all patients in general and the control group. As a result of a comprehensive study, it was found for the first time that in healthy people selected for the control group, after multiplex pyrosequencing of the 16S fecal rRNA gene, numerous differences from the reference norms in the GM were revealed. This came as a certain surprise, since healthy people who did not have a burdensome history, clinical complaints and abnormalities in biochemical and hormonal examinations were selected for the control group. Therefore, it was assumed that 32 parameters of the studied MC would also have no deviations. Instead, it turned out that in each so-called healthy person who, according to the above-mentioned criteria, fell into the control group, from 30 to 50 % of the MC indicators went beyond the reference values. The results obtained are confirmed by the observations of scientists who underestimated the term "healthy gut microbiome", since GM is an extremely sensitive and highly variable structure, although it has certain stable parameters (Meijnikman A. S. et al., 2017). At the same time, it should be noted that both the first and second components of the GM (more variable and mostly stable) require further study and clarification, because they are not known for certain.

To describe pathogenetic links, changes in biochemical and enzyme-linked immunosorbent parameters that are generally known and understood were taken as a basis. On them, as a basis, we will superimpose what was discovered for the first time in the structural and functional state of the GM.

Insulin resistance is a pathogenetic condition of reduced biological response of tissues to the action of insulin at its sufficient or increased concentration in the blood. IR is a key factor in the development of type 2 diabetes, prediabetes, and part of the course of other pathological conditions such as thyroid disease, cardiovascular disease, etc.

The main pathogenetic mechanisms for the development of IR include:

- Impaired insulin signal transduction: decreased expression of insulin receptors, impaired autophosphorylation of these receptors, decreased activity of insulin receptor 1 substrate and phosphatidylinositol-3-kinase, and impaired translocation of glucose transporter 4 (GLUT4) to the cell membrane [**164**, **245**].
- Accumulation of intracellular lipids: excessive intake of free FAs leads to the accumulation of TG and other lipid metabolites that inhibit the activity of insulin receptor 1 and phosphatidylinositol-3 kinase [53].
- Chronic inflammation: Pro-inflammatory cytokines such as TNF-α and IL-6 secreted by adipocytes and macrophages disrupt insulin signaling [67].
- Mitochondrial dysfunction: decreased oxidative phosphorylation and increased production of reactive oxygen species lead to oxidative stress and inflammation that disrupts insulin signaling [132].
- Genetic predisposition: There is a genetic predisposition to develop IR [134].

All nutrients that the human body needs enter the cells of the body through the direct participation of GM. Therefore, the pathogenetic effect of GM on the development of IR can hardly be overestimated.

The mechanisms by which GM is able to influence the development of IR:

- SCFA production: Microbiota bacteria ferment undigested carbohydrates to form SCFAs such as acetate, propionate and butyrate. Butyrate is the main source of energy for colonocytes and has anti-inflammatory properties. Propionate affects gluconeogenesis in the liver, and acetate can affect lipid metabolism. Violation of the production of SCFA in dysbiosis can contribute to the development of IR. For

example, reducing the number of butyrate-producing bacteria (e.g., *Faecalibacterium prausnitzii*), associated with inflammation and IR [55].

- Effects on inflammation: dysbiosis can lead to increased intestinal barrier permeability and translocation of bacterial lipopolysaccharides into the systemic circulation. Lipopolysaccharides, which is a component of the cell wall of gram-negative bacteria (for example, *Escherichia coli*), is a powerful factor in stimulating inflammation, which, due to the activation of the immune response, leads to chronic inflammation and the development of IR [199]. An increase in the number of gram-negative bacteria in the intestines can aggravate this process.
- Regulation of bile acid metabolism: GM is involved in the metabolism of FAs, which affect the regulation of glucose and lipids. Some bacteria, such as *Clostridium, Bacteroides, Lactobacillus, Bifidobacterium* and *Enterococcus*, participate in the deconjugation of primary FAs. Disruption of this process in dysbiosis can contribute to the development of IR [116].

So, starting from the first group of patients and gradually moving on to the final, sixth (after all, it was mentioned that a certain pathogenetic logic is embedded in the formation of groups), we present new data that were revealed as a result of the scientific research.

The appearance of obesity is accompanied by a direct correlation between BMI and the "Others" group, species of the genus *Shigella spp., the* species *Staphylococcus aureus* and the inverse with species of the genus *Bifidobacterium spp.,* the species *Escherichia coli* and the species *H.pylori.* Obesity leads to impaired carbohydrate metabolism in the form of morning hyperglycemia and IR. Then we observe that *Shigella spp.* also directly correlates with glucose levels and the HOMA-IR index.

Obesity and prediabetes are characterized by certain manifestations of dyslipidemia (LDL level, total cholesterol, AC), hypertriglyceridemia. At this stage, we record that the HOMA-β, LDL, VLDL and CA index directly correlate with the ratio of *Bacteroides fragilis group / Faecalibacterium prausnitzii*. The total bacterial mass directly correlates with the Caro index, and vice versa with VLDL. From the group of obligate representatives of GM*, the species Bacteroides thetaiotaomicron*

directly correlates with LDL and inversely with VLDL. Species of the genus *Enterobacter spp*. and/or *Citrobacter spp.* directly correlate with the Caro index and HDL.

Gradually, prediabetes is transformed into type 2 diabetes, where we find that the type *of Actinobacteria* directly correlates with HbA1c. The species *Faecalibacterium prausnitzii* is inversely correlated with insulin and the HOMA-β index and directly with the Caro index, as well as with creatinine. uric acid, and species of the genus *Shigella spp.* in addition to direct correlation with glucose levels, the HOMA-IR index is also directly correlated with creatinine. And the species *Akkermansia muciniphila* shows an additional direct correlation (in addition to that of HbA1c) with creatinine.

The advanced state of CD-2 is accompanied by the exhaustion of the work of the β islets of Langerhans, the appearance of complications. Species of the genus *Enterococcus spp.* show a direct correlation with glucose and the Caro index, as well as an inverse relationship with HOMA-β, and species of the genus *Salmonella spp.* show a direct correlation with glucose, the HOMA-IR index, and creatinine. The species *Parvimonas micra* also correlates with creatinine, showing a direct relationship

Autoimmune thyroiditis is accompanied by an increase in antibody titers. And in our case, the patients still had confirmed IR. Anti-TPO were directly correlated with *Fusobacterium nucleatum*.

Autoimmune thyroiditis usually turns into subclinical hypothyroidism, and then into manifest hypothyroidism with low levels of thyroid hormones and elevated TSH levels, dyslipidemia. *Staphylococcus aureus* correlated with cholesterol levels, namely: directly - with LDL, inversely - with VLDL. *Candida krusei* was characterized by the appearance of a correlation with HbA1c.

As a result of impaired carbohydrate metabolism, hypothyroidism develops insulin insensitivity. At this stage, we observe that *Candida spp.* shows an inverse correlation with anti-TPO and the HOMA-IR index, as well as a direct correlation with total cholesterol, LDL, triglycerides, AC. Bacteria of the *Firmicutes type* were

inversely correlated with fT3 levels. Representatives of *the Bacteroidetes phylum* showed a direct correlation with fT3, anti-TG.

On the basis of an autoimmune disorder, the pathogenetic picture of Graves' disease, opposite in clinical signs and laboratory tests, develops. Here there is an increase in antibodies (TPO, TG) along with the main marker antibodies to the TSH repeator (TSHR-Ab), TSH is clearly reduced and thyroid hormones (fT3, fT4,) increase. So, at this stage of pathogenetic development, we find that the species Clostridium perfringens directly correlates with the levels of fT3, fT4, TSHR-Ab, AbTG.

Among fungi of the genus Candida, only Candida krusei was characterized by the appearance of a correlation of direct relationship with TSHR-Ab. The species H. pylori, despite the direct correlation with TSHR-Ab, is still directly correlated with antibodies to thyroglobulin. The "Others" group shows an inverse relationship with the level of fT4.

An additional observation was the detection of an inverse correlation of fungi of the genus *Candida* with age in the absence of a probable difference between age groups under 35 years and over 35 years.

It is worth noting that the appearance of fungi of the genus *Candida* was not characteristic in the group of patients with obesity and endemic goiter

5. NATURAL AND MOTIVATING FACTORS CAN INFLUENCE THE GUT MICROBIOTA

5.1. Geographical location, ethnicity, diet and physical activity

It is proved that geographical location and ethnicity are determining factors of diversity and aggregate composition of GM. Among different populations and crops, the composition of the microbiome varies.

A 2013 study conducted by L. Prideaux et al. [193], attracted Caucasians and (on the example of representatives of China) living in the United States and Hong Kong. It was found that the microbial composition differed between countries and ethnic groups of the same country. T. Yatsunenko with colleagues [263] analyzed 531 fecal samples from healthy children and adults from the state of Amazonas of Venezuela, rural areas of Malawi, and metropolitan areas of the United States, including mono- and dizygotic twins. All study groups confirmed common features of gut microbiome development during the first three years of life, including age-related changes in genes involved in vitamin biosynthesis and metabolism. At the same time, the phylogenetic composition of the fecal microbiota was significantly altered between individuals living in different countries, including in the United States, including Indians, and in Malawi, in the following age groups: 0–3, 3–17 and over 17 years. Bacterial diversity increased with age in all three populations, with the microbiome of the U.S. population having the least diversity.

T. Yatsunenko with colleagues [263] analyzed sets of microbiome indicators of breastfed children (n=110: 24 infants (0.6–5 months), 60 children and adolescents (6 months to 17 years), and 26 adults) in order to find out which bacterial taxa monotonously change with age and between the three populations studied. In all infants, despite the dominance of bifidobacteria in fecal samples, representatives of the genus *Bifidobacterium* and their number decreased proportionally during the first year of life. Age- and population-related changes have also been noted. A total of 476 enzymes were identified as differing significantly in breastfed infants and from the

United States compared to Malawian and American Indian infants ($p<0.001$). The most notable differences in GM concerned pathways related to vitamin biosynthesis and carbohydrate metabolism. Malawian and American infants (but not adults) had more enzymes, which are components of the biosynthetic pathway vitamin B2 (riboflavin). The microbiome of infants, compared to adults, has been enriched with enzymes involved in the removal of glycans present in breast milk and intestinal mucosa (mannans, sialylated glycans, galactose and fucosilloligosaccharides), with some of these genes occurring more frequently in the microbiomes of children from Malawi and Indians. The representation of the urease gene was significantly higher, but decreased with age in the microbiomes of Malawian and Native American children, in contrast to the inhabitants of the United States, in whom it was low from childhood to adulthood. The typical American diet is rich in protein, while corn and cassava predominate in the diet of the Malawi population and Indians. Urea, which contains up to 15% nitrogen and is present in human breast milk, is broken down by urease into ammonia, which can then be used for microbial biosynthesis of essential and non-essential amino acids. Therefore, urease plays a decisive role in nitrogen recirculation, especially if there is a protein deficiency in the diet.

The differences between the microbiomes of the United States and Malawi or American Indians are due to differences in their habitual diets and resemble the pattern that exists between predators and herbivorous mammals [174]. Enzymes involved in amino acid degradation have been widely represented in the fecal microbiomes of U.S. adults, including aspartate, proline, ornithine, and lysine, as well as enzymes involved in the catabolism of simple sugars (glucose-6-phosphate dehydrogenase and 6-phosphofructokinase), sweeteners (L-iditol-2-dehydrogenase, which breaks down sorbitol), and host glycans (α-manosidase, β-manosidase, and α-fucosidase). Conversely, the microbiomes of Malawians and Indians had an overrepresentation of α-amylase, which is involved in starch degradation and reflects a corn-dominated diet. Perhaps due to the fat-rich diet of the representatives of the United States, GM was characterized by a significant number of enzymes involved in the biosynthesis of

vitamins (cobalamin, biotin, lipoic acid), metabolism of xenobiotics (phenyl acetate-CoA ligase), hydrolase of bile salts (choloylglycine hydrolase), etc.

With regard to the studies of mono- and dizygotic twins, as mentioned above, D. S. Yankovsky, V. P. Shirobokov, G. S. Dyment, analyzing a number of literature sources, came to the conclusion that the GM of such family members did not show a more pronounced similarity compared to unrelated individuals within the same geographical and/or cultural region [13].

In our study, it was found that when comparing the control group with the total number of all patients, it was found that there was a pattern of predominance of *Bacteroidetes* over *Firmicutes* in all examined individuals, which is reflected in Table 5.1. Please note that despite the significantly higher amount of CFU/cm3 of the total bacterial mass of the control group, this ratio is maintained. It is also necessary to note the presence of homogeneity in the percentage values of *Actinobacteria* and the generalized group "Others" in all examined persons. We can make an assumption that this distribution of the main bacterial indicators is typical for the residents of the Lviv region.

Table 5.1

Comparison of the generalized indicators of the gut microbiota of the control group and all patients in general

Indicator of the gut microbiota	Control group, Me (Q1–Q3)	In general, all patients, Me (Q1–Q3)	*p*
Total bacterial mass, CFU/cm3	8,00x1011 (2,00x1011–2,00 x1012)	4,00x1011 (8,75x1010 – 2,00x1012)	0,66
Firmicutes,%	31,60 (19,06–47,68)	33,91 (23,64–47,97)	0,70
Bacteroidetes, %	42,90 (35,54–58,57)	49,69 (37,69-56,38)	0,78

Continuation of Table. 5.1

Indicator of the gut microbiota	Control group, Me (Q1–Q3)	In general, all patients, Me (Q1–Q3)	*p*
Actinobacteria, %	4,56 (3,41–7,95)	4,51 (3,02–5,91)	0,90
Other, %	10,88 (9,43–14,62)	11,35 (9,43–14,00)	0,73

Diet is one of the most important factors influencing GM, since differences in nutrition are associated with the distinct characteristics of bacterial colonies. In particular, a varied and complex diet is associated with a more diversified microbiome. C. de Filippo and colleagues compared the GM of children aged 1–6 years in rural Africa, where the population is subsistence farming, as in the Neolithic era, with the GM of children from Italian Florence of the same age, where eating habits and living conditions are typical for developed countries [55]. The researchers note that traditionally, African children are breastfed until the age of two, after which their vegetarian diet low in fat and animal protein is enriched with starch, plant polysaccharides and fiber. Food resources are located near the village, cultivated and harvested on site. The dietary content of carbohydrates, fiber and proteins of non-animal origin is very high. Animal protein intake concerns mainly chicken and termites, which are available during the rainy season. Instead, European babies are breastfed for up to a year, after which they consume a typical Western diet high in animal protein, sugar, starch and low-fiber fat. The average calorie intake between the two populations also differed (African children aged 1–2 years – 672 kcal/day, 2–6 years – 996 kcal/day; European children aged 1–2 years – 1068 kcal/day, 2–6 years – 1512 kcal/day).

Multiplex pyrosequencing of the 16S rRNA gene proved that 94.2% of the sequences in all African and European samples belonged to the four most common types of bacteria: *Actinobacteria*, *Bacteroidetes*, *Firmicutes* and *Proteobacteria*, which is consistent with previous studies that describe the types mentioned as constituting the majority of human GMs. At the same time, the following differences were identified: *Actinobacteria* and *Bacteroidetes* are more widely represented in the African than in the European microbiota of children (10.1% vs. 6.7% and 57.7% vs. 22.4%,

respectively), while *Firmicutes* and *Proteobacteria* are more common in European than African children (63.7% versus 27.3% and 6.7% versus 0.8%, respectively). *Firmicutes* were twice as large in European children, as evidenced by the different ratio between *Firmicutes* and *Bacteroidetes* (ratio F/B±SD, 2.8±0.06 in European children and 0.47±0.05 in African children) [55].

Bacteria that produce SCFAs have been found in both populations. However, bacteria such as *Xylanibacter, Prevotella, Butyrivibrio, Treponema*, which use xylan, xylose and carboxymethylcellulose to produce high levels of SCFA and play a protective role against intestinal inflammation, have only been found in African children. African children had higher rates of total SCFA than European children, with a fourfold increase in butyrate and propionate. The authors concluded that there is a correlation between the microbiota degrading polysaccharides and the calories that the host can get from its diet, potentially affecting the survival and fitness of the host. It has been suggested that the microbiome of African children evolved along with their diet, aiding in energy storage and producing high levels of SCFA [55].

In people adhering to the "Western" diet, an impoverishment of the microbial biodiversity of the intestine is observed with a parallel increase in the incidence of obesity, coronary artery disease, metabolic syndrome, impaired glucose tolerance, diabetes mellitus and some malignant neoplasms. The low content of dietary fiber in such a diet is associated in particular with increased permeability of proteobacteria through the mucous membrane [220].

Instead, a study of a diet fortified with whole grains (with the simultaneous prescription of prebiotics, which are essentially also complex carbohydrates) was characterized by a decrease in typical pro-inflammatory taxa of bacteria *Enterobacteriaceae* followed by a decrease in the level of LPS-binding protein (a protein that binds lipopolysaccharides), several markers of inflammation, and an increase in the concentration of adiponectin [259]. It can be assumed that the dietary-determined growth of adiponectin is an effective tool for influencing metabolic abnormalities such as obesity and type 2 diabetes through GM.

The predominance of fiber in the diet contributed to an increase in the number of bacteria that produce SCFA. This improved glucose tolerance, in particular by increasing GLP-1 levels in people with type 2 diabetes [270]. This role is played by inulin through its propionic ester, which increases insulin sensitivity and lowers IL-8 as a marker of inflammation [39]. The rich content of complex carbohydrates (fiber) in the diet of mice strengthened the intestinal barrier due to sufficient production of SCFA [155].

J. Zimmer et al., applying classical microbiological culture, analyzed and compared the fecal flora of a large group of healthy volunteers who followed a strict vegetarian or vegan diet and age- and sex-appropriate omnivorous subjects [273]. The fecal microbiota of vegetarians and vegans showed significantly less *Bifidobacterium, Bacteroides*, *E. coli* and *Enterobacteriaceae* and lower stool pH than that of omnivorous representatives of clinical observation. And although according to other data, the decrease in *Bacteroides* (known for their ability to break down fibers of complex carbohydrates [220, **224**]) led to an impoverishment of the level of SCFA [159], different results were observed in vegans and vegetarians. The indigestible polysaccharides of a plant-based diet, which contains more carbohydrates and fiber, are fermented by the gut microbiota to form SCFAs. The production of SCFA is associated with a decrease in the pH of the intestinal lumen. In the lower pH ranges (5.5–6.5), growth and development *E.coli* and *Enterobacteriacea* inhibited, since they prefer mainly proteins as the main source of energy. That is why the concentration of the above-mentioned bacterial cultures in vegans or vegetarians is definitely lower. At the same time, vegans and vegetarians have a greater variety of GMs.

Opposite conclusions can be found in other literary sources. In one of the meta-analyses, they found that fiber intake, on the contrary, contributes to an increase in the amount of *Bifidobacterium spp.* and *Lactobacillus spp.*, increasing the concentration of butyrate in the feces [223]. This is confirmed by another group of scientists who believe that the Western diet low in dietary fiber is associated with a decrease in beneficial bacteria *Firmicutes* [220].

The alternative, and in fact mutually contradictory views recorded by us differ only in the fixation or fixation of leading bacteria according to certain dietary preferences of the individual, but the fact of such a connection is not refuted. All researchers have no doubt that the diversity of the intestinal microbiome can serve as a marker of long-term consumption of so-called healthy foods as opposed to unhealthy ones and indicate the probable development of pathological conditions.

The peculiarity of the results obtained by us reflects the difference in the intestinal microbiota of the inhabitants of the Lviv region from the features of the European and African diets described above **[55]** (Table 5.2). The data we collected reflect the ratio of gut microbiota indicators as a result of the combination of traditional Ukrainian cuisine with the recent emergence of access to the "Western diet".

Table 5.2

Comparison of the generalized indicators of the gut microbiota of all the patients we examined with those of C. de Filippo and colleagues

Indicator of the gut microbiota	Generally all examined, Mean	Africa (Burkina Faso), mean	Europe (Tuscany, Italy), mean
Firmicutes,%	36,8	27,3	63,7
Bacteroidetes, %	45,9	57,7	22,4
Actinobacteria, %	5,3	10,1	6,7
Others (incl. *Proteobacteria*)	11,9	0,8	6,7

The results obtained may be related to the peculiarities of Ukrainian history and being in the conditions of artificial restriction of the "Iron Curtain" of the Soviet regime, and subsequently to the period of independence and the corresponding emergence of access to food products characteristic of the Western diet. We believe that the percentage results reflect a gradual shift in diet-related bacterial diversity, which changes under the influence of historical events from the household to industrial food production, which is dominated by sugar, starch and fats.

Since diet is an important factor in the formation of GM [149], a dietary intervention in the form of increasing the intake of plant fiber and reducing food additives, such as artificial sweeteners, has been put forward as an attractive means of improving the functional and compositional aspects of the intestine [165]. At the same time, the success or failure of a particular dietary approach can be predicted by taking into account the basic composition of the microbiota, as evidenced by a number of studies [**50**, **264**].

Therefore, a more pronounced microbial diversity is characteristic of a diet high in fruits, vegetables, and dietary fiber in general, in contrast to a Western diet rich in fats, sugars, animal protein and low in fiber.

Interesting observations relate to physical activity. On the one hand, they have a positive effect on the state of GM, and on the other hand, the body can perceive them as stress, simulating adverse reactions accordingly. It turned out that it depends on the duration, intensity and type of exercise. For example, intense exercise (≥60–70% VO2max) causes a classic picture of stress with an increase in cortisol and adrenaline levels. At the same time, the blood supply to the intestinal epithelium deteriorates, followed by reperfusion, which damages the intestinal barrier, increases permeability and triggers inflammatory reactions in the gastrointestinal tract [93]. Therefore, according to the researchers, it is necessary to carefully calculate the details of the protocol of physical activity for experimental animals, since through them it is possible to obtain both a favorable reaction from the gastrointestinal tract (in particular, an effect on the GM) and a destructive one, in the form of a stress model. In an experiment on male mice, stress increased the phenotype of Parkinson's disease associated with dysfunction of the enteric-brain axis [65].

A number of scientific papers have been published on the positive effects of physical activity. In an experiment on mice that were given an acceleration run for two weeks, their concentration increased *Firmicutes* and the content decreased *Bacteroidetes* and *Tenericutes*, improved memory, cognitive abilities [118]. In a similar experimental study [16], where intense running alternated with short intervals of the softened version of running, the content of *Eubacteria*, *Roseburia* and *Clostridia*

in AD mice and the level of *Prevotella, Bacteroides, Bacteroides fragilis* and *L.johnsonii*. At the same time, the researchers recorded a decrease in the manifestations of histological changes characteristic of Alzheimer's disease (the average number of plaques in the hippocampus and the average percentage of plaque areas covered). Level *B.thetaiotaomicron* directly strongly correlated with the deterioration of results in the Morris maze test, and the content *L.johnsoni* positively correlated with beta-amyloid content. In the case of using a combination of physical activity of different levels of intensity, the cognitive functions of mice improved and the content of GM microorganisms involved in the exacerbation of the disease decreased, due to an increase in the number of bacteria that produce SCFA.

5.2. Prebiotics, probiotics and intestinal microbiota transplantation

Modern prebiotics are selectively fermented ingredients that contribute to specific changes in the composition and/or activity of the GI microbiota [198]. Usually complex carbohydrates are prebiotics, but polyphenols and polyunsaturated fatty acids also have a prebiotic effect [207]. Prebiotics – as a source of SCFA, improve the consistency of the stool and have a number of beneficial effects on the health of the host [207]. It should be noted that SCFAs include acetic, propionic and butyric acids, which are the main end products of GM metabolism in the human body. Due to their small size, SCFAs are able to diffuse into the bloodstream and treat not only local problems of the gastrointestinal tract, but also distant organ systems. For example, in experimental studies of genetically obese mice, the administration of several types of dietary fiber not only mitigated the course of colitis with improved intestinal wall permeability [149], but also restored its integrity, reduced endotoxemia [33]. In other studies in genetically obese mice, oligofructose, in addition to reducing inflammation, improved glucose homeostasis and leptin sensitivity [78]. In rats, prebiotics stimulated the appearance of additional L cells, contributing to an increase in the production of GLP-1 [34].

According to clinical observations, the prebiotic inulin, enriched with oligofructose, altered the GM of obese children, reduced body fat and systemic IL-6 [177].

During a 12-week open-label study *Bifidobacterium infantis M-63* stated an improvement in mental well-being compared to placebo among patients with irritable bowel syndrome. Lower β-diversity was associated with distress and depression, and lower concentration *Lachnospiraceae* was associated with a higher rate of depression, while patients with anxiety were characterized by an increased content of *Bacteroidaceae* [113].

S. Kumar and co-authors analyzed the effects of algae on GM in an experiment. Bioactive polysaccharides from many different seaweed have been found to exhibit anti-inflammatory activity. In research *in vivo* and *in vitro* it has been determined that dietary fiber and SCFAs (in particular, propionate and butyrate), which are formed during the bacterial fermentation of dietary fiber as prebiotics, weaken the production of pro-inflammatory cytokines such as IL-8, IL-6 and FNP-α [136]. Berberine acted in the same way, demonstrating higher glucose tolerance by increasing the production of intestinal SCFAs and reducing inflammation in obese rats [269].

In general, a significant number of experimental studies have been conducted on the effect of prebiotics on glucose tolerance with the study of changes in bacterial taxonomic units, biochemical, immunological parameters and inflammatory markers, but there are few identical results in clinical studies. The need for clinical trials is extremely urgent.

Probiotics are living organisms that are beneficial to the health of the host in adequate doses. Probiotics are used as natural means of intestinal inoculation in order to treat and prevent a number of diseases in infants and adults. Although probiotics are considered a priori safe to become a drug, they must be taxonomically defined and follow an appropriate pathway, just like any drug supported by an appropriate evidence base [102].

The use of probiotics, both single-strain and multi-strain, has been studied during the treatment of irritable bowel syndrome [101]. In particular, a "new

generation" probiotic *Faecalibacterium prausnitzii* is promising for the treatment of intestinal dysbiosis. A smaller number *F. prausnitzii* found in chronic inflammation of the intestine, infections caused by *Clostridioides difficile* and COVID-19. Since this strain of bacteria produces butyrate, it has an anti-inflammatory effect and also improves the function of the intestinal barrier [99]. Probiotics have been successfully used to prevent and treat obesity in children and adults [255]. Despite the fact that they cannot achieve a clinically significant reduction in HbA1c levels in patients with type 2 diabetes, they clearly reduce HOMA-IR and show a moderate effect on fasting glucose and insulin levels [267].

It has been widely reported that *Bifidobacterium*, as a probiotic, has a protective effect against the cardiovascular system [151] and against metabolic diseases [126]. Probiotic bacteria *Lachnospiraceae* (group NK4A136), butyrate-producing bacteria reduce the risk of preeclampsia and at the same time act as markers of preeclampsia in the third semester of pregnancy [249]. In extreme studies, markers of eclampsia also include *LachnospiraceaeUCG010, Olsenella, RuminococcaceaeUCG009*, *Ruminococcus2*, *Anaerotruncus*, *Bifidobacterium*, *Intestinibacter* with gestational hypertension, *Eubacterium* (group *ruminantium*), *Eubacterium* (group *ventriosum*), *Methanobrevibacter*, *RuminococcaceaeUCG002*, *Tyzzerella3*, *Dorea* and *RuminococcaceaeUCG010* [256]. *Methanobrevibacter* (as Methanogenic archaea) from this list can be converted trimethylamine-N-oxide (TMAO), which increases in eclampsia, to methane, respectively reducing the risk of preeclampsia [195]. A low level *Tyzzerella3*mentioned above, which produces formic and butyric acidAssociated with acute myocardial infarction [98]. A wide field of opportunities opens up for the creation of new probiotics in order to affect the serious diseases and conditions listed above.

Probiotics can be prescribed from an early age, which Athalye-Jape and colleagues established by conducting a meta-analysis of 25 randomized controlled trials (n=5895) to find out whether probiotic supplementation affects complete enteral feeding in preterm infants. It turned out that the use of probiotics reduced the period of full feeding (mean difference: −1.54 days; 95% CI: −2.75, −0.32 days; p=0.01;

I2=93 %). Despite this, probiotic supplements reduced length of hospital stay, feeding intolerance, and duration of indirect hyperbilirubinemia, as well as contributed to weight gain and growth rate in children [24]. In addition, a Cochrane review of 24 randomized controlled trials (n=5529) found that adding probiotics to the diet of preterm infants reduced the risk of necrotizing enterocolitis and all-cause mortality in the study group [20].

In adult patients with type 2 diabetes, a number of studies have also been conducted with the addition of prebiotics, probiotics or a complex of them (synbiotics) with positive results. Most often, dosage forms contained species *Lactobacillus* or *Bifidobacterium* [226]. However, there is too much conflicting data in clinical studies, as we mentioned earlier, so the authors of the article, describing the pros and cons of prescribing probiotics, rightly consider ways to improve the quality of evidence, transparency, public awareness and regulation of their use.

Today, there are more experimental studies in the arsenal of scientists, which usually do not contradict each other, but for greater certainty, meta-analyses are increasingly carried out. Yes, in the case of prescribing to mice *Lactobacillus reuteri* improved insulin sensitivity and intestinal permeability [175], but in combination with *Bifidobacterium* glucose homeostasis, macrophage infiltration improved, and the gut microbiota changed [250], improved liver function, inflammation, and insulin sensitivity in genetically obese mice [147]. According to the authors of the meta-analysis [202], probiotics are more effective in mice and rats, but have little effect on human GM.

However, two meta-analyses were recorded in which a slight improvement in glucose levels was recorded without probable changes in insulin content against the background of probiotic prescribing; the effect on HbA1s was also inconclusive [227]. Therefore, the question arises whether probiotics colonize the human intestine during the course of treatment [262], as there are small pilot studies with positive treatment results. For example, despite the lack of effect of probiotics on the mass [183], a slight decrease in LDL and RH was observed [202]. Several studies have seen a decrease in CRP, although no positive changes in TNF levels have been recorded [202, 262].

Therefore, some authors have concluded that the effect of probiotics depends on the individual perception of the host and a certain initial constitution of his GM, undermining the versatility of this method of treatment [274].

Obviously, a greater effect can be achieved by prescribing probiotic and/or prebiotic complexes. For example, a positive effect on carbohydrate metabolism was observed when a mixture of several probiotics was used in patients with type 2 diabetes, and for comparison, a group of patients with obesity and normal glucose levels was formed [**18**, **206**].

Back in 2018, the authors of another publication put forward a revolutionary proposal to use known strains of bacteria for the production of bioactive compounds [100]. For example, you can encourage *L. reuteri*, produce genetically modified IL-22, which in an experiment on mice can improve liver function, inflammation and bacterial translocation. Since then, science has not stood still, and therefore we will look at the latest article on this topic [97]. D. Hamade and colleagues found out the role of *Limosilactobacillus reuteri* as an IL-22 release agent and an effective radiation mitigator in a mouse ovarian cancer model. It was stated that IL-22 from *L. reuteri* not only improved overall survival in mice when combined with a PD-L1 inhibitor by inducing differential gene expression in irradiated stem cells, but also induced PD-L1 protein expression in ovarian cancer cells and mobilized CD8+ T-cells in irradiated mice throughout the abdomen. The authors of the study suggested that the addition of IL-22 to a combination treatment with fractional abdominal irradiation and systemic chemotherapy and immunotherapy regimens could facilitate a safe and effective protocol to reduce the burden of the tumor, increase survival and improve the quality of life of patients with locally limited ovarian cancer. However, if the release of IL-22 in order to help cancer patients can have a positive effect, then for patients with obesity, hypertension, it is rather the opposite, since height accompanies these two pathologies.

The search for new prebiotics continues. Such a new bacterium is *Akkermansia muciniphila*, which was opened in 2004 M. Derrien and W. de Vos Wageningen University (Netherlands). During clinical and experimental studies, it was found that this symbiote inversely correlates with the body weight of humans and rodents [77].

Appointment *A. muciniphila* in obese mice improved insulin sensitivity, reduced manifestations of inflammation in adipose tissue [77], and its isolated strain optimized intestinal barrier function in diabetic mice amid obesity [190]. In clinical studies *Akkermansia muciniphila* had some effect on increasing insulin sensitivity, reducing inflammatory markers, and therefore a drug made from this probiotic is considered promising and safe [61].

Note the fact that GM has evolved. It maintains the stability and functional adaptability of the body, complementing our biology in new mutually beneficial ways [25]. And, obviously, it evolves further. The emergence of previously unknown types of bacteria, or the isolation of the decisive ones from a number of ordinary ones, are waiting to be discovered.

Transplantation of the intestinal microbiota is a radical therapeutic method for changing the GM, which consists in the transfer of unfiltered homogenized suspension of feces or its filtered solution, obtained from a healthy donor/donors after a thorough screening, into upper gastrointestinal tract (duodenum) or infusions into the lower gastrointestinal tract (colon). For the first time, such a procedure was recorded in the IV century. A.D. in ancient China for the oral treatment of food poisoning called "yellow soup" [268]. The procedure received a new breath in 1958, when in the United States a case of transferring suspended feces using an enema was described to four patients with pseudomembranous colitis who were in a life-threatening condition after complicated antibiotic therapy [75]. Fecal transplantation is also used to treat infection *Clostridium difficile* [2].

Now, fecal transplantation, or intestinal microbiota transplantation, is carried out using enemas, nasogastric intubation, enteral intubation, using a colonoscope, gastroscope, using capsules containing freeze-dried fecal material. As it turned out, the extreme of the options does not always work, since the upper intestines are not ready to perceive the contents of the colon.

In 2012, the results of a pilot study (nine participants with obesity and metabolic syndrome) on the effect of GM infusion from lean donors to male recipients with metabolic syndrome on recipient microbiota composition and carbohydrate

metabolism were published. The study subjects were randomly divided into groups that were injected into the small intestine with infusions of allogeneic (from a donor) or autologous microbiota (their own). Six weeks after infusion of GM from thin donors, the sensitivity of recipients to insulin, the diversity of GM, in particular the content of butyrate-producing bacteria, increased. The study authors concluded that GM can be used as a therapeutic agent to increase insulin sensitivity in humans [248].

Five years later, a similar study confirmed the previous findings [133]. Other researchers have put forward the thesis of "rational design of personalized 'cocktails' for fecal transplantation" because they found that recipients of the same donor demonstrated varying degrees of GM production, indicating individual characteristics of microbiome resistance and the compatibility of the donor with the recipient [145]. Thus, a new view of the resistance of the recipient's GM to the donor's GM has appeared. Indeed, after a certain time (on average 18 weeks), the composition of the recipient's GM returns to the baseline level [133].

Methods of influencing and correcting the gut microbiota are available in a variety of variants, and require further research into the pathogenesis of type 2 diabetes mellitus in the context of thyroid dysfunction.

As a result of this work, we can testify that the structural and functional state of the gut microbiota is a complex and insufficiently studied milestone in medicine, which requires further research, in-depth study and analysis, especially in the pathogenesis of type 2 diabetes mellitus in the context of thyroid dysfunction.

TEST QUESTIONS TO STUDY:

1. What is the role of the gut microbiota in the formation of metabolic disorders?

- Able to form a harmful fetal microbiome
- Does not affect health
- Causes infections
- Reduces immunity
- Increases stress levels

2. What microorganisms are most often found in neonatal meconia?

- Bifidobacterium
- Escherichia coli
- Lactobacillus
- Streptococcus
- Bacteroides

3. Which of the following conditions is not associated with negative changes in the mother's microbiota during pregnancy?

- Preeclampsia
-Prematurity
- Necrotizing enterocolitis
-Allergy
- Metabolic dysfunction

4. What microbiotic changes occur in children with maternal gestational diabetes?

- Growth of actinobacteria
- Loss of bifidobacteria

- Reducing the number of lactobacilli
- The emergence of Clostridium difficile
- Only the skin microbiota changes

5. Which of these bacteria produces short-chain fatty acids?
- Coprococcus
- Streptococcus
- Actinobacteria
- Escherichia coli
- Clostridium

6. How does dietary fiber affect the microbiota?
- Increase the risk of metabolic diseases
- Reduce microbiota diversity
- Increase the production of beneficial metabolites
- Promote dysbiosis
- Reduce the immune response

7. Which of these axes is not the connection of the intestine with other systems?
- Intestines - brain
- Intestines - skin
- Intestine – eye
- Intestines - heart
- Intestines - immune system

8. What causes dysfunction of the gut microbiota?
- Healthy eating
- Antibiotic therapy
- Lack of physical activity
- Normal stress levels

- High levels of fiber in the diet

9. Which of these bacteria is a marker of hypertension?

- Bilophila wadsworthia
- Lactobacillus reuteri
- E. coli
- Akkermansia muciniphila
- Enterococcus faecalis

10. Which of the pathogenetic mechanisms is not a factor in the development of IR?

- Impaired insulin signal transmission
- Accumulation of lipids
- Pro-inflammatory cytokines
- Sleep disturbances
- Genetic predisposition

11. What bacteria are not probiotics?

- Lactobacillus
- Bifidobacterium
- Escherichia
- Saccharomyces
- Streptococcus

12. Which of these groups is a characteristic of the microbiota of a healthy person?

- Reduction of Bacteroidetes
- Reduction of Firmicutes
- Increased Proteobacteria
- Increase in microbial diversity

- Decreased Actinobacteria

13. Which of these indicators characterizes dysbiosis?
- High levels of beneficial bacteria
- Reduced microbiota diversity
- Normal production of SCFA
- Stable glucose levels
- Increased immunity

14. Which of these factors will have the least impact on the gut microbiota?
- Method of birth
-Diet
-Genetics
-Age
- Water availability

15. Which microbiota is characterized by ultrasound?
- D-peptide
- Synthesis of SCFA
- Normalization of immunity
- Lactate production
- High variety

16. Which of these bacteria is considered pathogenic for the intestinal microflora?
- Streptococcus pneumoniae
- Bifidobacterium adolescentis
- Lactobacillus rhamnosus
- Clostridium difficile
- E. coli (probiotic strains)

17. Which of the mentioned axes in scientific medicine is not yet explained?

- Intestines - brain
- Intestines - skin
- Intestines - lungs
- Intestines - heart
- Intestines - muscles

18. Which microorganism is associated with autoimmune diseases?

- Clostridium
- Lactobacillus
- Bifidobacterium
- Firmicutes
- Enterobacter

19. What role does butyrate play in the gut microbiota?

- Is toxic to cells
- Promotes inflammation
- Is a source of energy for colonocytes
- Increases glucose
- Displaces good bacteria

20. Which of the following factors does not affect the microbiota during breastfeeding?

- Method of birth
- Mother's diet
- Mother's health
- Mother's age
- Genetic factors

LIST OF QUESTIONS FOR SELF-CONTROL OF KNOWLEDGE.

1. What is the relevance of the topic of diabetes mellitus (DM) in the context of world data?

2. What is the number of diabetic patients in the world predicted for 2040?

3. How many patients with DM were officially registered in Ukraine as of January 1, 2017?

4. What percentage of the population of Ukraine are patients with diabetes?

5. What is the annual increase in DM in Ukraine?

6. What comorbid diseases are associated with DM?

7. What is the prevalence of thyroid dysfunction in patients with type 2 diabetes?

8. What pathogenetic mechanisms are associated with DM and thyroid dysfunction?

9. How does the gut microbiota affect the function of other organs?

10. What endocrinopathies are associated with the microbiota?

11. What is the role of the intestinal microbiota in the regulation of metabolism?

12. What is the structure of the gut microbiota in healthy people?

13. What are the main types of bacteria present in the human intestine?

14. What is the relationship between the microbiota and depression?

15. How many neurons are contained in the enteric nervous system?

16. How does the neurological activity of the enteric nervous system affect metabolism?

17. What factors influence the formation of the microbiota in newborns?

18. What is the role of childbirth in the formation of the baby's microbiota?

19. How does the method of feeding affect the microbiota of the newborn?

20. What is the role of breastfeeding in the formation of the intestinal microbiota?

21. How does ancestral nutrition affect the microbiota of today's children?

22. What is the difference between the microbiota of premature babies and full-term babies?

23. What are the effects on the microbiota of the mother's condition during pregnancy?

24. How does gestational diabetes affect the baby's microbiota?

25. What changes in the microbiota are observed in children of mothers with diabetes?

26. What agents influence the colonization of the microbiota during childbirth?

27. What is the role of Coprococcus and Streptococcus bacteria in maintaining gut health?

28. What mechanisms influence the formation of the microbiota at an older age?

29. What changes in the microbiota are observed in the elderly?

30. What is the difference between the microbiota of young people and the elderly?

31. How many bacteria in the intestine exceed the total number of human cells?

32. What is the role of short-chain fatty acids in metabolism?

33. How does the presence of gram-negative bacteria in the intestines affect health?

34. What are the effects on the microbiota of various ways of eating?

35. What features of the microbiota are related to geographical location?

36. How does the microbiota change in response to exercise?

37. What are the consequences of using antibiotics for the microbiota?

38. How does the microbiota affect the cardiovascular system?

39. What is the relationship between the microbiota and the immune system?

40. How do thyroid hormones affect the microbiota?

41. What is the role of metabolites of the watch diet in energy metabolism?

42. What factors can provoke dysbiosis in the intestines?

43. What impact do GI diseases have on the microbiota?

44. What is the role of metabolic syndrome in diseases of the cardiovascular system?

45. How is the microbiota related to the risk of developing DM?

46. What is the importance of the predominance of Firmicutes in the microbiota?

47. What nutritional patterns have a positive effect on the microbiota?

48. How does the microbiota affect the aging process?

49. What synthetic substances can affect the microbiota?

50. What is the role of probiotics in the treatment of DM?

51. How does the microbiota respond to stressors?

52. Can the microbiota be a source of inflammatory processes?

53. How does a reduced level of various bacteria affect carbohydrate metabolism?

54. What microbiota genes are associated with certain diseases?

55. How are changes in the composition of the microbiota related to diseases of compact organs?

56. What pathogenic organisms can reduce life expectancy?

57. What is the role of the microbiota in the context of obesity mechanisms?

58. How do environmental pollution affect the microbiota?

59. What nuance in the evolution of the microbiota is associated with the use of antibiotics?

60. What is the role of the microbiota in the regulation of metabolic disorders?

61. What specific microbiotic agents exhibit protective properties?

62. How does the microbiota affect uric acid metabolism?

63. What effects have food supplements had on the microbiota?

64. How does the duration of breastfeeding affect the microbiota?

65. What is the role of the transformed microbiota in cancer therapy?

66. How does the microbiota change during menopause?

67. What is the role of the garlic diet in the formation of the microbiota?

68. What new microbiota can be useful for treatment?

69. How do probiotics affect recovery after antibiotic therapy?

70. What is the role of the transfection microbiota in the regulation of inflammation?

71. How do diets enriched with live cultures affect health?

72. What are the main symptoms of intestinal dysbiosis?

73. How do the bacterial bases of remote control function?

74. What physiological mechanisms regulate microbiotic balance?

75. How does the microbiota's response to stress change in young and old?

76. What effects do sugars have on the microbiota?

77. What is the role of iodine in the metabolism of the microbiota?

78. What is the relationship between the microbiota and skin diseases?

79. How can proper nutrition restore the microbiota?

80. What is the role of the intestinal microbiota in the formation of autoimmune diseases?

81. How does reducing sugar in the diet affect the microbiota?

82. What effect do probiotics have on fat metabolism?

83. What is the role of the microbiota in the pathogenesis of heart disease?

84. How does the function of the microbiota change with age?

85. What factors affect the bioavailability of nutrients?

86. What is the role of the Mediterranean diet in health?

87. How does the microbiota influence mental well-being?

88. What diseases are associated with a decrease in cell infection?

89. How can neuronal engagement work through the microbiota?

90. What is the role of the expression of compounds in health?

91. What is the role of the endocrine tract in the regulation of metabolism?

92. What is the role of the microbiota in receptor sensitization?

93. What is the mechanism for recognizing the microbiota?

94. What assumptions are palpable about the term of the functional microbiota?

95. What is the role of the microbiota in the prevention of serious diseases?

96. What is the relationship between the microbiota and autoimmune diseases?

97. What is the role of glucose in microbiotic metabolism?

98. What treatment strategies are successful in the treatment of dysbiosis?

99. How does stress affect the formation of the intestinal microbiota?

100. What is the role of the microbiota in the general homeostasis of the human body?

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LIST OF SYMBOLS

AC	Atherogenicity coefficient
AH	Arterial hypertension
AIT	autoimmune thyroiditis
ALT	alanine aminotransferase
Anti-TG	thyroglobulin antibody
Anti-TPO	thyroperoxidase antibody
AST	aspartate aminotransferase
BMI	Body mass index
CNS	central nervous system
CRP	C-reactive protein
CVDs	cardiovascular diseases
DM	Diabetes
FA	fatty acids
FMT	fecal microbiota transplantation
FXR	farnesoid X receptor
GI	gastrointestinal canal
GLP-1	Glucagon-like peptide-1
GLUT4	glucose transporter 4
GM	Gut microbiota
HbA1c	glycated haemoglobin A1c (glycated hemoglobin A1c)
HDL	high-density lipoproteins
HOMA-IR	homeostasis model assessment of insulin resistance (B)
HOMA-β	Homeostasis Model Assessment of β-cell function
IGFBP7	insulin-like growth factor-binding protein 7
IL	Interleukin
IR	insulin resistance

LDL	low-density lipoproteins
MCP-1	Monocytic chemoattractant protein-1
nACh-receptor	nicotinic acetylcholine receptors
NAFLD	non-alcoholic fatty liver disease
PCR	polymerase chain reaction
SCFA	short-chain fatty acids
SOCS3	suppressor of cytokine signaling 3
T1(2)D	type 1 (2) diabetes mellitus
T3 (fT3)	triiodothyronine (free triiodothyronine)
T4 (fT4)	thyroxine (free thyroxine)
TG	Triglycerides
TMA	Trimethylamine
TMAO	Trimethylamine-N-oxide
TNF, TNF-α	tumor necrosis factor, tumor necrosis factor α
TPO	Thyroperoxidase
TSH	thyroid-stimulating hormone
TSHR-Ab	antibody to the thyroid-stimulating hormone receptor
VLDL	very low-density lipoproteins

T E X T B O O K

K. Moskva

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