PATHOGENETIC ASPECTS OF HYPOLIPIDEMIC DRUGS
ANTIMICROBIAL POTENTIAL IN METABOLIC SYNDROME
THERAPY: A THEORETICAL STUDY

Topicality. Metabolic syndrome (MS) is an extremely common medical and social problem. However, there is no modern understanding of the MS etiopathogenetic mechanisms. Debates about MS discuss different versions of the development of this symptom complex, when each of the clusters can be primary in the pathogenesis of MS. Therefore, any metabolic processes disorders in the human body are always accompanied with and lead to a changes in quantitative and qualitative microbiocenoses composition, and vice versa, microbiota imbalance may induce the development of pathological states including MS.

Aim. To analyze the published data that concern antimicrobial potential of modern drugs with lipid-lowering properties used in complex therapy of MS.

Materials and methods. Lipid-lowering agents and their direct or indirect antimicrobial effect may cause the microbiota imbalance in the human body. While studying the data, we analyzed antimicrobial potential of modern drugs with lipid-lowering properties used in complex therapy of MS. We studied recent research in the field of microecology and the results of significant effect in normal microflora on metabolic processes.

Results and discussion. According to modern concepts, an important pathogenic link in the obesity and MS development is the imbalance in normal intestinal microflora. At the same time, lipid-lowering agents can have a direct or indirect antimicrobial effect and, consequently, cause an imbalance of microbiota in the human body. Thereby, it is important for the therapy effectiveness to take into account the significant antimicrobial potential of drugs used in the correction of metabolic disorders.

Conclusions. The future complex antimicrobial properties study of drugs used in the correction of described pathological states has a good perspective.

Key words: metabolic syndrome; antimicrobial activity; dyslipidemia
**INTRODUCTION**

Metabolic syndrome (MS) is defined as a complex of dynamic metabolic disorders and hormonal balance of the body. Today, MS is an extremely common medical and social problem. World Health Organization (WHO) experts note an increase in the incidence of MS among people in many countries around the world: in Western Europe, Australia and the United States the MS prevalence is on average 25-35 %, in China the incidence of MS has reached epidemiological proportions [1, 2, 3]. In addition, if earlier MS was considered a “disease” of the elderly, now this state is registered in young people, including children [4, 5]. The MS prevalence depends on sex, age, ethnicity and the diagnostic criteria used, and its highest occurrence is observed in economically developed countries [6, 7]. The criteria for MS are abdominal obesity, hypertension, lipid spectrum alterations, and carbohydrate metabolism disorders [8, 9].

However, at present there is no common understanding of the etiopathogenetic mechanisms of MS development. Therefore, much attention is paid to study of the reasons that caused MS. Most often insulin resistance (IR) is indicated as a primary pathogenetic mechanism [10, 11]. Also, in recommendations of WHO (1998), European Group for the Study of Insulin Resistance (EGR, 1999) and American Association of Clinical Endocrinologists (AACE, 2003) IR was identified as the main component of MS. However, a number of researchers consider obesity to be the main link in the MS pathogenesis [11, 12]. In addition, the leading role of arterial hypertension and lipid metabolism disorders in the MS pathogenesis is not excluded [13, 16]. There are a number of studies showing that dyslipidemia can be a predictor of MS development, and lipid metabolism in the form of deficiency in polyunsaturated fatty acid cells is the cause of the IR development [14, 15, 16]. Debates about MS discuss different versions of the development of this symptom complex, when each of the clusters can be primary in the pathogenesis of MS [17, 18].

Recent research in the field of microecology demonstrates a significant effect of normal microflora on metabolic processes. Microorganism metabolites can be effectors, cofactors and signal molecules that regulate the rate and severity of metabolic reactions both in normal and in pathological processes [19, 20]. In addition, the microbiological model has changed today—unicellular microorganisms are considered as integral microbial associations, representing a separate organ — microbiota [21]. And the relationship "the human body – the intestinal microbiota" is evaluated as a single macroecological system of the body. Therefore, any metabolic processes disorders in the human body are always accompanied with and lead to a changes in the quantitative and qualitative microbiocenoses composition, and vice versa, imbalance of the microbiota can induce the development of pathological states including MS.

One of the factors that caused the changes in human microbiota is the repeated and repeated effects of various antibacterial drugs, especially in industrially developed countries [22, 23], which correlates with the prevalence of pathological changes in MS. Because of these states polyethiologic nature, medicinal preparations of various pharmacological groups are used to their pharmacological correction. The drugs that used have a number of side effects, the development mechanisms of which in most cases have not steel explained and can be directly or indirectly related to the antimicrobial activity of these drugs. We previously identified possible antimicrobial effects in individual groups of drugs used in the treatment of type 2 diabetes mellitus, as in one of the main disorders of carbohydrate metabolism in MS [24].

**The aim is to** analyze the antimicrobial potential of modern drugs with lipid-lowering properties used in the MS complex therapy. Currently, the following groups of drugs are used to hyperlipidemia pharmacological correction: 3-hydroxy-3-methylglutaryl-coenzyme A-reductase inhibitors (statins), bile acid sequestrants (BAS), fibrolitic acid derivatives, nicotinic acid and omega-3 polyunsaturated fatty acids (PUFAs).

**MATERIALS AND METHODS**

Lipid-lowering agents and their direct or indirect antimicrobial effect may cause the microbiota imbalance in the human body. While studying the data, we analyzed antimicrobial potential of modern drugs with lipid-lowering properties used in complex therapy of MS. We studied recent research in the field of microecology and the results of significant effect in normal microflora on metabolic processes.

**RESULTS AND DISCUSSION**

Statins are still remained unconditional leader among drugs for the dyslipidemia treatment [25]. The statins mechanism of action is associated with competitive inhibition of the enzyme – hydroxymethylglutaryl-CoA re-
fibrolic acid derivatives – fibrates – stimulate peroxisome proliferation and activate peroxisome enzymes, transmitting the signal to the gene level through a specific receptor – peroxisome proliferator-activated receptor alpha (PPARα), which is a transcription factor. This leads to the lipoprotein lipase activation that increases the expression of triglycerides and apolipoprotein B. Fibrates have the ability to enhance the hypoglycemic drugs action that gives them an advantage in treating hyperlipidemia in patients with diabetes mellitus. By lowering the level of triglycerides, fibrates cause local anti-inflammatory effect in the vascular wall affected by the atherosclerotic process, inhibiting the production anti-inflammatory substances by macrophages and as a consequence inhibit atherogenesis. Side effects of their use include: dyspeptic disorders such as abdominal pain, nausea, vomiting, diarrhea, and flatulence, moderate allergic reactions, leukopenia, as well as increased hepatic enzymes activity and cholestasis. While we study the question of the possible antimicrobial effect of fibrates, we encountered single publications on the activity of fenofibric acid and dolibrate against eukaryotes [30, 31]. Apparently, this effect is associated with the ability of fibrates to inhibit the intracellular lipid molecules transfer. Along with this, in the scientific literature there is no information on the direct antibacterial activity of fibrates, however, taking into account the above-mentioned effects, one can assume their negative effect on the normomicrobiocenosis of the intestine.

Bile acid sequestrants (ion exchange resins) are used as second-line drugs in combined therapy with statins to obtain an additional effect at a high level of cholesterol-LDL (LDL-Ch). BAS disrupt bile salts enterohepatic circulation. Bile acid recycling interruption increased excretion with feces and depletion of cholesterol in the liver – all these mechanisms lead to an increase in the expression of LDL receptors in hepatocytes, which in turn leads to a decrease in the blood plasma cholesterol level. BAS continuous administration stimulates the reductase HMG-CoA activity (secondary effect), so they are often combined with statins. Their side effects are mainly due to the fact that they in the intestine adsorb not only bile acids but also some digestive enzymes (digestion, bloating, heartburn, flatulence and liquid stool may be altered). Long-term administration of BAS high doses can also disrupt the absorption of fat-soluble vitamins (A, D, E), folic acid and other medications taken. However, the binding of fatty acid (FA) salts may inhibit their antimicrobial action and can cause excessive bacterial growth and lead to the microecological abnormalities development. The normoflora influence on fat metabolism, metabolism of FA salts, cholesterol, glucose, energy homeostasis is well-known. Therefore, there is a necessity of special studies on the BAS therapy effect on the intestinal microflora composition [32].

Like bile acid sequestrants, nicotinic acid is a traditional lipid-lowering drug and is used for about 35 years. Nicotinic acid in lipid-lowering doses suppresses the free fatty acids (FFA) release from adipose tissue adipocytes and accordingly lowers their plasma concentration, which is accompanied by a decrease in the total amount of synthesized cholesterol-VLDL (VLDL-Ch) and apo-B. Because LDL-Ch is formed as a result of VLDL catabolism, a decrease...
in the amount of cholesterol produced by the VLDL-Ch can be accompanied by a decrease in plasma LDL-Ch concentrations of and total cholesterol. In addition to this mechanism, the main ways to reduce the concentration of triglyceride (TG) can be nicotinic acid mediated suppression of de novo lipogenesis, as well as suppression of the esterification process, i.e. formation of TG from FA in hepatocytes. It was recently found that nicotinic acid not only normalizes the lipoprotein exchange, but also affects the immune system cells by stimulating their receptor - G protein-coupled receptor (GPR)109A activity and this leads to a decrease in the intensity of the vascular sclerosis inflammatory component [33]. Serious complications of nicotinic acid administration include impaired liver function and increased blood glucose level. Another relatively frequent group of side effects are gastrointestinal: nausea, diarrhea, less often - heartburn, vomiting, increased or decreased appetite. Taking into account the above, we can assume the effect of nicotinic acid on the autoflora of the intestine.

Thus, lipid-lowering agents have different mechanisms of action, differ in pharmacodynamic and pharmacokinetic parameters, and some of them, according to the type of cell-receptor interaction and the chemical nature, can have a direct or indirect antimicrobial effect and, consequently, cause a microbiota imbalance in the human body.

Recently, numerous scientific reports have reported the possible role of intestinal normoflora in the obesity and MS pathogenesis [34, 35]. It has been experimentally proved that the degree of severity of microbiota alterations correlates with the excess body weight indices, and in people with excess body weight, the total metabolic activity of obligate microorganisms has decreased [36]. It was shown that food with a high fat content caused an increase in the proportion of intestinal Gram-negative microbiota, thus contributing to an increase in the bacterial lipopolysaccharides intestinal absorption. And this led to the "metabolic endotoxemia" development as one of the factors of the obesity progress [35].

In addition, one of the main microflora functions is the carbohydrate utilization. As is known, the main end products of indigestible carbohydrate fermentation are short-chain fatty acids (SHFAs), which are an energy substrate for many body tissues. SHFAs are not only directly participate in energy metabolism, but also perform a signal function by activating GPRs. Thus, GPR43 is expressed in most cells of the gastrointestinal tract, as well as in adipose tissue and immune cells. And the activation of this receptor enhances the immune response against the intestinal pathogenic flora [37]. GPR43 is expressed in neuroendocrine cells and sympathetic ganglion cells [38]. It was experimentally shown that activation of this receptor led to energy expenditure in laboratory animals, which confirms the participation of SHFAs in maintaining the energy homeostasis in the body.

It is interesting that in non-microbial animals much more cholesterol is accumulated in the liver than in the control group, the bile FA concentration increased in several times, and the cholesterol absorption also increased by not less than in 25% [39]. Moreover, recent studies have shown that the presence of microflora is necessary for the FA metabolic effects development.

CONCLUSIONS

Thus, an important pathogenic link in the obesity and MS development is the normal intestinal microflora imbalance. In turn, metabolic disorders lead to an imbalance of dynamic equilibrium in the macro-organism-microorganism system. From these positions, it is interesting not only to study the possible antimicrobial effect of individual drugs, but also to analyze the possible interaction of different pharmacological drug groups concerning antimicrobial potential. Despite this, we have not seen any data about such studies. However, it is important to consider the significant antimicrobial potential of drugs used for the metabolic disorders correction in order to increase the therapy effectiveness. The future complex antimicrobial properties study of drugs used in the correction of described pathological states has a good perspective.

Conflict of Interests: authors have no conflict of interests to declare.

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Рекомендовано д. біол. н., професором А. Л. Загайком
Надійшла до редакції 06.06.2017 р.