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Review Article

ROLE OF GUT MICROBIOTA IN LIPID METABOLISM

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ABSTRACT

Researchers have studied the connection between cholesterol and microbiota for a long time. The results of widely published data demonstrate that the relationship between the lipid balance of the blood and the composition of the intestinal microbiota is apparent. The oblective of this study was, we tried to find the path through which this connection is carried out. Furthermore, the aim was to analyze the studies, which demonstrate the decrease of blood lipids as the result of different prebiotics and probiotics prescribtion. Also, the screening of different data from previous years was done for comparing the changes in the pathogenesis.

Keywords: Gut microbiota, Lipid profile, Cholesterol, Short chain fatty acids, Probiotics, Prebiotics.

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INTRODUCTION

The relationship between the healthy microflora (microbiota) of the intestine and the host organism is one of the examples of the cooperation of metabolic and immune reactions, the importance of which is difficult to overestimate for the state of human health. According to the literature, the mass of the microbiota of the gastrointestinal tract (GIT) in an adult reaches 2.5–3.0 kg [1]. The number of microorganisms in the intestine according to the data of different researchers is 1012–1014 cells. At the beginning of the 20-century I.I. Metchnikoff compared the intestinal microbiota with liver function and proposed to consider the intestinal microbiota as a separate organ. For announcing all the genetic material, which the microbiota contains, the term "microbiome" was approved. The number of genes of the "microbiome" is three orders of magnitude higher than the own genes of the human body, which served as the basis for considering the amount of all microorganisms as a "superorganism" [2].

HYPOCHOLESTEROLEMIC POTENTIAL OF GUT MICROBIOTA

It is known that the intestinal microbiota can be attributed to an essential element of the endocrine system that performs the enzymatic transformation of complex steroid compounds and nitrogen derivatives, classified as prohormones. Recently, a relationship has been established between the activity of microbiota and the functional characteristics of the nervous system. The molecular mechanism of such a bond can be realized through the interaction of low-molecular metabolites of bacteria, which form normal gut biocenosis with sensory endings in the submucosal nerve plexus (Meissner) region of the intestinal wall. The signal about the presence of specific chemicals (metabolites of bacterial hydrolysis), as a result of this interaction, is transferred to the enteral nervous system and simultaneously plays the role of a chemical signal for the formation of the corresponding endocrine and nervous reactions of the whole organism [3,4].

The metabolic activity of the microbiota manifests itself not only in the fermentation of proteins, fats, and carbohydrates but also in the processes of deconjugation of bile acids, the cholesterol metabolism, the excess of which in the blood plasma serves as a biomarker for the development of atherosclerosis. It should be noted that the digestive function of the microbiota is determined by the participation of the indigenous microflora in the food substrates utilization, enzymes activation, parietal digestion, GIT motility, the enhancement of absorption processes of calcium, iron, trace elements, and vitamins. Its role in the hydrolysis of lactose and proteins, carbohydrates fermentation, fats saponification, cellulolytic ability, metabolism of bile acids, bilirubin, amino acids, some hormones, and enzymes has been established [5,6]. Normal intestinal microflora develops mainly in anaerobic conditions and a source of energy for its life support is the fermentation of carbohydrates, contained in dietary fiber, that are not practically hydrolyzed by human enzyme systems, but are utilized by normal microflora. The microbial type of digestion of carbohydrates is carried out through fermentation. In the process of fermentation, short chain fatty acids (SCFAs) are formed, such as butyrate, acetate, succinate, and propionate [7].

These fatty acids are the primary source of energy for colonocytes and digestive and transport function of the colon, as well as an important source of energy for the body, including up to 30% of the total amount of energy needed. It is known that SCFAs are absorbed into the cytoplasm of the colonocyte, where mitochondria form adenosine triphosphate from it. SCFAs molecules supply 70% of energy to support local processes in the colon, and the remaining 30% of this energy is expended for the needs of the whole organism [8]. Particularly active SCFAs are involved in the synthesis of energy-intensive products. Changes in the composition of intestinal microbiota were researched, and those were attributed to the patients with obesity, in particular, a decrease in the population level of saccharolytic Bacteroides that influence the intensity of metabolic processes [9].

It is known about the presence in the GIT of bacteria that reduces cholesterol. Cholesterol is the part of the fat, which includes 90% of lipids coming from food. Digestion of fats occurs in the small intestine under the influence of pancreatic lipase, and phospholipids, and cholesterol esters - pancreatic phospholipase and cholesterol esterase. A small part of fat (about 10%) is hydrolyzed in the stomach by the action of the lingual lipase, which enters there with the food lump and saliva [10]. The initial - the first stage of fats digestion - consists in the physical destruction of droplets of fat into small particles, since water-soluble enzymes-lipase only act on the surface of the droplets of fat. This process is called emulsification of fats, and it begins in the stomach. Further, the main stage of emulsification of fats is carried out in the duodenum under the action of bile and lecithin. Lecithin, in particular, is very important for the emulsification of fats. Since fats

are water-insoluble compounds, they can be exposed to water-soluble lipases only at the water/fat border [11-13]. Therefore, the action of enzymes is preceded by the emulsification of fats (after emulsification their diameter becomes <1 mm), which occurs under the effect of bile salts. Bile acids are synthesized in the liver from cholesterol and excreted into the intestine with bile. Lipid hydrolysis products - fatty acids, cholesterol, and fatty acid salts form structures in the intestine mucosa, called mixed micelles, which diffuse through membranes into the enterocytes. Together with the products of lipid hydrolysis, fat-soluble vitamins and bile acids are absorbed. The last ones, through the portal vein, enter the liver, and from the liver are secreted into the gallbladder and again participate in the emulsification of fats in the intestine. This way of bile acids is called "enterohepatic circulation" [14].

In the assimilation of lipids, the symbiotic microflora of the GIT is very important, since it could absorb cholesterol. There is evidence that microorganisms with enzyme lipase can break down fat-like substances, and *Bifidobacteria* and *Lactobacilli* in the process of symbiont digestion can precipitate and assimilate bile acids [15]. Under the influence of enzymes of microorganisms in the distal part of the ileum, bile acids are deconjugated, and the bile acids are converted from primary (cholic and chenocholic), synthesized in the liver from cholesterol to secondary (deoxycholic, chenodeoxycholic, lithocholic, and ursodeoxycholic) bile acids [16]. It has been established that *Bacteroides* and *Lactobacilli* are involved in this process [17]. Under physiological conditions, 80–95% of bile acids are reabsorbed and included in the process of fats digestion. The rest is excreted in feces in the form of bacterial metabolites, which contribute to the formation of fecal masses by inhibiting the absorption of water and their dehydration. Exogenous and endogenous lipids are regularly exposed to the intestinal microflora with the establishment of hydroxy acids with a long chain of carbon atoms, such as hydroxystearic acid [18-20].

Bile acids are formed exclusively in the liver and are the main component of bile. Daily 250–500 mg of bile acids are synthesized and lost in feces. Synthesis of the bile acids is regulated by the mechanism of negative feedback. A decrease in the bile acids return to hepatocytes, during the enterohepatic circulation with portal blood, leads to an increase in their synthesis [21].

MECHANISMS OF THE CHOLESTEROL-LOWERING EFFECTS OF INTESTINAL MICROBIOTA

The microbiota actively affects the metabolism of cholesterol. In experiments, two mechanisms for removing cholesterol by *Bifidobacteria* were established: By assimilation and precipitation. In a comparative study of *Bacteria* anti-cholesterol effect, *Bifidobacterium breve* and *Lactobacillus amylovorus* growing in a culture medium, which contained bovine bile or taurocholic acid, were able to remove cholesterol [22]. In this case, the removal of cholesterol was associated with the precipitation of cholesterol with *Lactobacilli* metabolites, while *Bifidobacteria* are characterized by assimilation and precipitation. To study the mechanism of cholesterol assimilation, *Lactobacillus acidophilus* and *Bifidobacterium bifidum* cells were cultured in the presence of cholesterol and bovine bile. During the growth of bacteria, cholesterol and bile salts were both precipitated. The degree of precipitation depended on the cultivation conditions. If *L. acidophilus* RP32 cells were cultured under acidification conditions, the level of deconjugated bile salts precipitation was higher than in case of pH 6.0. Cholesterol in cultivation with *Lactobacilli* during the acidification conditions, precipitated together with bile salts, while this was not observed in pH-controlled cultures. Coprecipitation of cholesterol during cultivation was the result of the formation of deconjugated bile salts, which had a reduced solubility at pH values below 6.0. It is believed, that the removal of cholesterol from the culture by *Bifidobacteria* and *Lactobacilli* is not associated with the absorption of cholesterol, but is the result of deconjugation of its bile salts [23,24].

In the rat model, the hypocholesterolemic effect of *Lactobacillus gasseri*, affecting the composition of microflora, the content of lipids in blood serum, bile acids, and steroids in feces was established. Recently, a high hypocholesterolemic activity of *Bifidobacteria* isolated from healthy individuals has been demonstrated. Researchers, discussing the therapeutic properties of *Lactobacilli*-fermented products, noted its role in recycling bile acids and cholesterol and maintaining a balance of microbial populations after taking antibiotics. The fact, that in such products there is a significant amount of lactic acid, which is an antiseptic for the body, and calcium and phosphorus in it acquire more digestible form for the host body, plays an essential role in supporting this theory. Furthermore, with the optimal amount of *Lactobacilli*, the synthesis of Vitamin B6 improves, which contributes to the production of Vitamin B3 from tryptophan, one of the essential amino acids [25,26].

Other studies, where 19 cultures were grown at 37°C in a particular setting, supplemented with sodium thioglycolate, sodium taurocholate, and phosphatidylcholine cholesterol, showed, that the deconjugation activity was maximal in the late exponential growth phase, which also coincided with the maximum of cholesterol assimilation [27].

A significant variation was observed among cultures of *L. acidophilus* in case of their ability to grow in the presence of bile, deconjugate sodium taurocholate, and assimilate cholesterol, but these differences were not statistically significant. Later, a comparison was made of 304 freshly isolated human strains of *L. acidophilus* from the intestine of a human by the ability to assimilate cholesterol during growth. The resistance of *Lactobacilli* to bile, the ability to deconjugate bile salts and to absorb cholesterol during growth was assessed. Of the 123 isolates identified as *L. acidophilus*, only five could be classified as candidates for probiotic use to reduce cholesterol in human blood plasma [28].

Interesting data were obtained by studying the effect of the children's formula, supplemented with probiotics, on the composition of plasma lipids in infants with atopic reaction. Therapy with the probiotics use is a new promising approach to alleviating the condition of patients with allergic symptoms. The beneficial effect of probiotic for allergy is associated with different degrees of absorption and utilization of food allergens. Thus, 15 infants with atopic eczema at the pediatric clinic received a *Bifidobacterium* Bb-12 or *Lactobacillus rhamnosus* GG, or placebo (a randomized, placebo-controlled, and double-blind study). The formula with *L. rhamnosus* GG did not affect the amount of alpha-linolenic acid, while the method with *Bifidobacterium* Bb-12 increased the relative content of this acid from 0.13±0.03 to 0.24±0.03. The results indicate that the physiological effect of gut microbiota may be related to the interaction between probiotic bacteria and digestive fatty acids [29-31].

One more unusual study was dedicated to the effect of *Lactobacilli*, *Bifidobacteria*, and *Enterococcus*, isolated from humans, on the plasma cholesterol level. The ability of seven potential probiotic strains to decrease cholesterol level *in vitro* (*Lactobacillus fermentum* F53, *L. fermentum* KC5b, *Bifidobacterium infantis* ATCC 15697, *Streptococcus bovis* ATCC 43143, *Enterococcus durans* DSM 20633, *Enterococcus gallinarum*, and *Enterococcus faecalis*) was evaluated. Bacteria *L. fermentum* KC5b was able to stay viable for 2 h at pH 2. It could grow in a condition with 4000 mg/l of bile acids and remove as much as 14.8 mg of cholesterol per gram of bacterial cells from the culture, which indicated the possibility of its use as cholesterol-reducing probiotic [32,33].

IMPACT OF PREBIOTICS AND PROBIOTICS ON LIPID PROFILE

Although, not without exception, the results of animal experiments and human studies indicate a moderate decrease in cholesterol using food products, fermented with certain strains of lactic acid bacteria. It is believed that probiotic bacteria ferment non-digestible carbohydrates from food by means of SCFAs formation in the large intestine, which, apparently, cause a decrease of lipids level by inhibiting the cholesterol synthesis in the liver and its redistribution from plasma to the liver. Furthermore, some bacteria can interfere with the cholesterol absorption in the intestine by bile salts deconjugating or by direct assimilation of cholesterol.

For prebiotic drugs, in particular, inulin and oligofructose, in animal experiments, convincing data were obtained on the cholesterol decrease in case of oral intake [34,35]. The reports of its effect on the human body are not sufficient. In studies, where the humans with normal lipid range took part, two studies did not document the impact of inulin or oligofructose on serum lipid levels, while the other two data reported a significant reduction in triglycerides (19% and 27%, respectively) with insignificant changes in total cholesterol and low-density lipoproteins (LDL) in blood plasma. Data suggest that in individuals with elevated plasma lipid levels, the lowering effect is initially associated with a decrease in cholesterol, whereas in subjects with normal cholesterol content, the action on plasma triglyceride levels predominates [36-39].

Similar observations were obtained in the study of the hypocholesterolemic activity of *Bifidobacteria*, isolated from healthy Korean residents. The authors evaluated the hypocholesterolemic activity of three strains: *B. breve* K-110, *B. breve* K-111, and *B. infantis* K-525. The intake of *B. breve* K-110 and K-111, together with high-cholesterol food, provided significant protection against an increase of total cholesterol and LDL in comparison with the same food without *Bifidobacteria*. Adding 0.5% *B. breve* K-110 and K-111 into the meal reduced the total cholesterol and LDL in the plasma by 57 and 55%, respectively. The *Bifidobacteria* consumption had also inhibited the deposition of lipids on the aorta surface. *B. breve* K-111 activity on normalizing blood cholesterol level was higher than *B. breve* K-110. The results suggest that human *Bifidobacteria* could play a role in the atherosclerosis prevention [40].

Another data demonstrate that the long-term use of fermented foods for 6 months increases the content of high-density cholesterol lipoproteins. The study included 29 healthy women, aged 19–56 years, 15 of whom had normal cholesterol, and 14-elevated cholesterol. The concentration of high-density lipoproteins (HDL) did not differ between the normo and the hypercholesterolaemic groups, whereas the level of LDL in the hypercholesterolaemic group was significantly higher. They received 300 g of yogurt, containing 3.5% fat, cultures of Streptococcus thermophilus and *Lactococcus lactis* daily (control group) or the same amount of yogurt, enriched *L. acidophilus* 145, *Bifidobacterium longum* 913, additionally, and 1% oligofructose (synbiotic) [41]. Cross-sectional experience consisted of 3 periods (7 weeks each): First period - control yogurt for all 29 women; the second phase included probiotic yogurt for 18 and control yogurt for 11 women (the women were randomly designated to receive either control or probiotic yogurt during the next 6 weeks); and the third stage consisted of probiotic yogurt for 11 women, control - for 18 women. After the second period, the women, consuming control yogurt in the second period of the study, had to get probiotic yogurt in the third period and vice versa. The average concentrations of total cholesterol and LDL in the serum of the women, participating in the experiment, did not depend on the intake of the symbiotic. The concentration of HDL increased significantly by 0.3 mmol/l. The ratio of LDL/HDL (an index of atherogenicity) decreased from 3.24 to 2.49. Thus, prolonged consumption of yogurt (control and synbiotic) increases the content of HDLs and leads to the improvement in LDL/HDL ratio. The results did not show a cholesterol-lowering effect of the *L. acidophilus* 145 and *B. longum* 913, but there was a significant increase in the HDL level [42].

In vivo assessment of cholesterol reduction by lactic acid bacteria has been performed on a laboratory model. It was marked, that one of the key issues in the probiotics is the determination of live microorganisms minimal effective dose, that can be applied without adverse effects (translocation from the intestinal lumen to the internal environment of the body) for the human body. There is a biological model, which allows estimating the reduction of cholesterol using lactic acid bacteria and determining the minimum dose of probiotic microorganisms [43,44].

The particular interest is attended to lactulose and its analogs. These drugs can influence bacterial metabolism, which are confirmed by many years of experience in their use for the hepatic encephalopathy treatment. In addition to lactulose-containing medicines, the use of inulin and butyrate for localized and systemic disorders of the lower GIT is etiopathogenetically justified. Inulin stimulates the development of its *Bifidobacteria* and *Lactobacilli* in the large intestine, whereas butyrate can affect colon cells by encouraging the transport of sodium and water ions from its lumen, and then incorporating them into enterohepatic circulation [45,46]. One more research, which central idea was the inulin impact on lipid plasma level, has demonstrated the increase of *Faecalibacterium prausnitzii*, detected in human feces [47]. Other well-described effects of inulin consist of elevating the abundance of *Bifidobacterium* and *Lactobacillus* with the concomitant improvement of specific metabolic parameters. However, non-digestible oligosaccharides such as inulin have also shown opposite results. It has been found that in 9–12-week-old pigs such pathobionts as *Klebsiella* spp. used this carbon as the source for growth and proliferation [48].

CHOLESTEROL-REDUCING ACTIVITY OF BACTERIA PROBIOTIC STRAINS

Previous investigations were based on the impact of a few widely popular types of bacteria. However, year by year, many gut species have been discovered. And now, they know about 70 bacterial, 13 archaeal divisions in the microbiota (including such bacterial sections, as *Firmicutes* (*Clostridium*, *Eubacterium*, *Faecalibacterium*, *Ruminococcus,* and *Roseburia*), *Bacteroidetes* (*Alistipes*, *Bacteroides*, *Parabacteroides*, *Porphyromonas*, and *Prevotella*), *Actinobacteria* (*Bifidobacterium* and *Collinsella*), *Proteobacteria* (mainly *Escherichia coli* and relatives), *Verrucomicrobia* (*Akkermansia*), and *Fusobacteria* (*Fusobacterium*) [49].

It is known, that microbes can biohydrogenation linoleic acid into the saturated fatty acid, stearic acid, and similar biotransformation of linoleic acid has been marked in numerous strains of human gut bacteria *in vitro*. In later studies, substantial linoleate isomerase activity was detected in such bacterial groups as *Roseburia* spp., *Butyrivibrio fibrisolvens*, and *Propionibacterium freudenreichii* subsp. *Shermanii* and a level of metabolic products such as conjugated linoleic acids and vaccenic acid were discovered [50,51].

A great deal of work on known lipid-degrading bacteria has also been conducted with a focus on bacterial lipases. Bacterial lipases have been identified in numerous bacteria, including some typical gut microbial genera or species: *Achromobacter*, *Acinetobacter*, *Alcaligenes*, *Bacillus*, *Pseudomonas*, *Enterococcus*, *Lactobacillus*, *Propionibacterium*, *Proteus vulgaris*, *Staphylococcus*, and *Serratia marcescens*. However, most of these genera are not dominant members of gut microbiota, and little is known regarding degradation of lipids by the more dominant bacterial members. Although, not directly isolated from the gut, a new study has found that *Enterobacter aerogenes*, an ordinary human gut bacterium, has very high lipase activity *in vitro* and is capable of degrading different fatty acids types, ranging from saturated (palmitic and stearic) and unsaturated (oleic and linoleic) fatty acids to triglycerides [52,53].

Apparently, the part of the dietary fat, which reaches the colon, could be partially metabolized by gut bacteria. Although it is well known that cholesterol is degraded by gut microbiota to the metabolic end product coprostanol, thus increasing its excretion in feces, ultimate consequences of it on human health are poorly understood [54,55].

Consumption of a probiotic strain DSM 9843 of *Lactobacillus plantarum* by men with carotid atherosclerosis showed some beneficial effects for the host, associated with an increase of the bacterial diversity in the gut and with changes of specific short-chain fatty acids level in the colon [56]. Similarly, other researchers demonstrated that strain 299v of *L. plantarum* was able to reduce several cardiovascular disease risk factors in smokers including positive metabolic changes, decrease the level of proinflammatory cytokine interleukin (IL)-6 and reduce the adhesion of monocytes to endothelial cells [57]. On the other hand, administration of *Lactobacillus delbrueckii* in apoE-null mice fed on a hypercholesterolemic diet had the slightly atheroprotective effect. Limited antiatherogenic impacts of human intestinal microbiota

in case of uptake of a high-fat diet (HFD) may be explained by the positive association of some human commensals such as *Firmicutes* and *Bacteroidetes* with obesity due to the increased capability of these microbes to metabolize fiber into SCFAs, that could be converted to fat in high lipid load. In mice fed a HFD, consumption of probiotic bacteria *L. rhamnosus* GG and *Lactobacillus sakei* NR28 had beneficial anti-obesity effects through the reduction in the small intestine of the frequency of obesity-associated commensals *Firmicutes* and *Bacteroidetes*, decrease of epididymal fat mass and downregulation of liver lipid-synthesizing enzymes [58-61].

One more unusual study has been proven, the aim of which was to evaluate the effects of kefir (a natural complex probiotic, which comprises more than 50 species of microorganisms, includes *Lactobacillus* spp. and *Lactococcus* spp., acetic acid bacteria, and yeast such as *Candida* spp. and *Saccharomyces* spp.) on obesity and non-alcoholic fatty liver disease in the obese mouse model by the composition of the intestinal microbiota. Experimental mice were randomly divided into two groups (10 mice each), the kefir group and control group, and the initial body weights were measured. For the development of diet-induced obesity, mice in both groups were provided 60% HFD, and the feed intake of each group was measured weekly. The kefir group was orally administered 0.2 ml of kefir milk, while the control group was given 0.2 ml of sterilized milk as a negative control. The mice orally administered kefir for 12 weeks weighed significantly less than those that consumed milk. Adipose tissues and livers of mice in the kefir group were significantly lower in weight and smaller than those of the control mice. Mice in the kefir group exhibited significantly lower plasma levels of total cholesterol and LDL cholesterol than the control group of mice. These data indicated that kefir administration has a cholesterol-lowering effect in the HFD-induced obesity mouse model. There were no significant differences in the plasma concentrations of the proinflammatory cytokines IL-1β and TNF-α between mice in the control and kefir groups. In contrast, kefir-fed mice exhibited significantly lower plasma concentrations of IL-6 than the control mice, suggesting that kefir administration might ameliorate the systemic low-grade inflammation in HFD-fed mice [62].

CONCLUSION

Thus, at present, the pathogenetic role of dysbiosis microflora in maintaining different chronic inflammatory processes, lipid distress syndrome and in the atherosclerosis development is not in doubt. The involvement of intestinal microbiota into the variety of metabolic processes, the provision of cells and tissues with energy, hydrolysis of proteins, fats, carbohydrates, cholesterol exchange, and bile acid recycling demonstrates, how necessary is the stabilization of the microbial ecology in maintaining human health. Further work on identifying lipid-degrading bacterial strains is required to improve the existing knowledge of the microbiota primary role in fat metabolism.

AUTHOR CONTRIBUTIONS

Khrystyna Kvit and Viacheslav Kharchenko were equally involved in the development of the manusript's framework and gathering of the necessary information. Both authors discussed, drafted and wrote the manuscript.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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