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Lipid metabolism correction with statins and probiotics

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Summary

The gut microbiota can be regarded as a novel "metabolic organ," involved in the regulation of metabolism. In the case of gut dysbiosis, changes in the concentration of certain bacterial metabolites can act as triggers for the development of metabolic and lipid metabolism disorders. For instance, lower levels of bacteria that produce short-chain fatty acids (SCFA), disorders of enterohepatic circulation of bile acids, elevated levels of trimethylamine (TMA)-producing gut bacteria play an important role in dyslipidemia. Undoubtedly, there are interactions between statin use and changes in the gut microbiota. The paper presents a analysis of the literature data and the results of own research concerning the effect of statins and probiotics on the lipid metabolism and on the microbiota. Considering the positive effects of some probiotics on lipid metabolism, their ability to counteract low-grade inflammation, immunomodulatory role and benefit influence on the digestive system, combining statins with specific probiotic agents appears to be a logical approach. Autoprobiotics (indigenous apathogenic benefit strains) are method of personalized therapy. They demonstrate promising results in the treatment of lipid metabolism disorders. We emphasize that autoprobiotics may be preferable over probiotics due to their safety and longer-lasting effect in the case of personalized therapy of lipid metabolism disorders. However, further research is warranted to gain a deeper understanding of the underlying mechanisms interaction of organism their microbiota including during statin, probiotic and autoprobiotic therapy patients with metabolic syndrome. in the influences and address remaining questions in this field.

Keywords: statins; probiotics; autoprobiotics, microbiota, gut, lipid metabolism, dyslipidemia

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Коррекция липидного обмена статинами и пробиотиками

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Резюме

Микробиоту кишечника можно рассматривать как новый «метаболический орган», участвующий в регуляции метаболизма. В случае дисбактериоза кишечника изменения концентрации определенных бактериальных метаболитов могут выступать в качестве триггеров для развития нарушений метаболизма и липидного обмена. Например, более низкие уровни бактерий, продуцирующих короткоцепочечные жирные кислоты (КЦЖК), нарушения энтерогепатической циркуляции желчных кислот, повышенные уровни кишечных бактерий, продуцирующих триметиламин (ТМА), играют важную роль в дислипидемии. Несомненно, существуют взаимодействия между использованием статинов и изменениями в микробиоте кишечника. В статье представлен анализ литературных данных и результаты собственных исследований относительно влияния статинов и пробиотиков на липидный обмен и микробиоту. Учитывая положительное влияние некоторых пробиотиков на липидный обмен, их способность противодействовать слабовыраженному воспалению, иммуномодулирующую роль и полезное влияние на пищеварительную систему, сочетание статинов со специфическими пробиотическими агентами представляется логичным подходом. Аутопробиотики (местные апатогенные полезные штаммы) являются методом персонализированной терапии. Они демонстрируют многообещающие результаты в лечении нарушений липидного обмена. Мы подчеркиваем, что аутопробиотики могут быть предпочтительнее пробиотиков из-за их безопасности и более длительного эффекта в случае персонализированной терапии нарушений липидного обмена. Однако необходимы дальнейшие исследования для более глубокого понимания основных механизмов взаимодействия организма и его микробиоты, в том числе во время терапии статинами, пробиотиками и аутопробиотиками у пациентов с метаболическим синдромом. в влияниях и решении оставшихся вопросов в этой области.

Ключевые слова: статины; пробиотики; аутопробиотики, микробиота, кишечник, липидный обмен, дислипидемия

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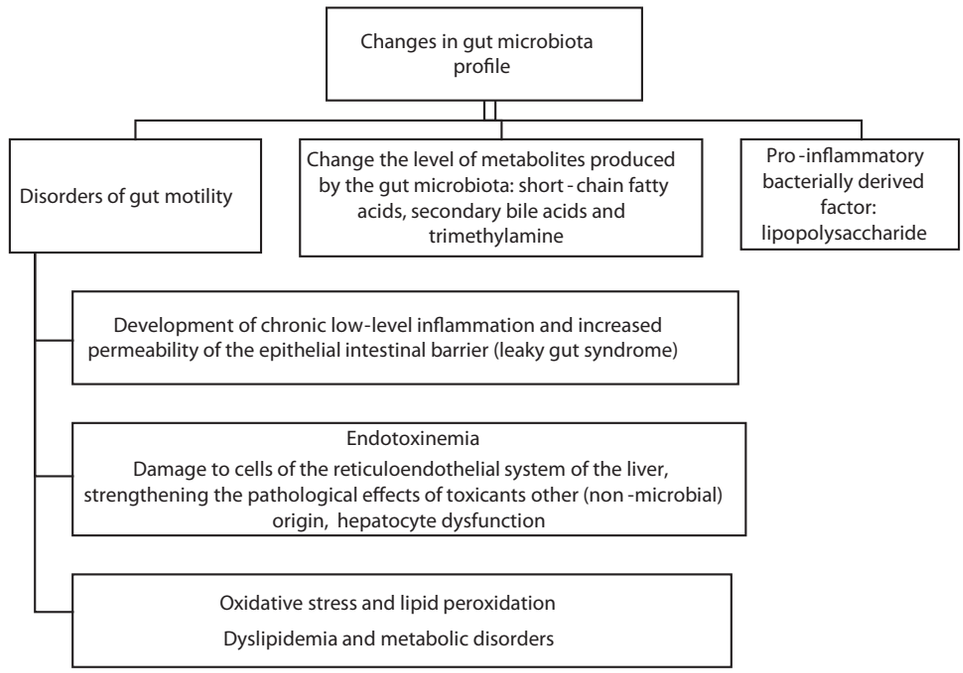
1. Introduction

The gut microbiota serves as a central regulator of host metabolism [1]. Furthermore, it can be regarded as a novel "metabolic organ," the perturbation of which may contribute to the pathogenesis of metabolic disorders, including lipid metabolism disorders [2–5]. For instance, individuals with hypercholesterolemia exhibit reduced bacterial diversity compared to those with normal blood lipid levels [6]. Patients with metabolic syndrome, as opposed to individuals without metabolic disorders, exhibit alterations in gut microbiota composition, characterized by elevated levels of *Roseburia inulinivorans*, *Ruminococcus* spp., *Prevotella* spp., *Eubacterium rectale*, *Bacteroides* spp., and *Streptococcus* spp. [7]. Phylums *Bacilliota* and *Fusobacteria* exhibit a negative correlation with low-density lipoprotein cholesterol levels, whereas phylums *Cyanobacteria* and *Lentisphaerae* exhibit a positive correlation [8]. In the case of gut dysbiosis, changes in the concentration of certain bacterial metabolites can act as triggers for the development of atherosclerosis, arterial hypertension, heart failure, obesity, and diabetes mellitus [9]. For instance, lower levels of bacteria that produce short-chain fatty acids (SCFA) (e.g., *Lactobacillus*, *Propionibacterium*, *Acidaminococcus* and *Clostridium* genera, phylum *Bacteroidota* etc.) may also be associated with increased fat accumulation through the activation of G-protein-coupled receptor 43 (GPR43) and subsequent insulin-mediated adipocyte aggregation [10]. Decreased levels of *Lactobacillus*, *Clostridium*, *Listeria*, and *Bifidobacterium* genera in the gut can impair the deconjugation of primary bile acids, leading to reduced formation of secondary bile acids [11]. Consequently, primary bile acids may accumulate abnormally, suppressing the FXR-TGR5 pathway, and ultimately resulting in elevated cholesterol levels [12, 13]. Elevated levels of trimethylamine (TMA)-producing gut bacteria belonging to the phyla *Bacilliota* and *Pseudomonadota* can lead to increased production of trimethylamine N-oxide (TMAO), which exhibits an atherogenic effect [14, 15]. In patients with gut dysbiosis following antibiotic administration, the lipid-lowering effects of simvastatin and lovastatin were diminished [16, 17]. The development of lipid metabolism disorders in individuals with alterations in gut microbiota involves several stages (*figure 1*) [13, 18–20].

Figure. 1.



Stages in the development of lipid metabolism disorders in individuals with gut microbiota changes

As can be seen above, changes in the gut microbiota are closely related to lipid metabolism disorders. Consequently, the correction of gut dysbiosis can make a significant contribution to the restoration of metabolic processes. For this purpose, various medicines can be used, for example, probiotics, prebiotics, metabiotics. For assessment of effects of statins and probiotics on lipid metabolism correction we search randomized controlled trials for the last 10 years and half (from 2013 to 2024) with keywords: probiotics, lipid metabolism, statins, gut microbiota, total cholesterol, lipoproteins and triglycerides. In common there are 1214 scientific articles with these key words, 79 from them were randomized controlled studies and clinical trials. These articles were included in our analysis

2. Effects of Statin Intake on Gut Microbiota

Subsequent to dyslipidemia and metabolic disorders, patients often undergo statin therapy. Statins are the leading medicines in the treatment of hypercholesterolemia and prevention of cardiovascular events. The precise impact of lipid-lowering drugs, such as statins, on the gut microbiota remains uncertain [21]. It is known that they influence on the gut microbiota by inhibiting HMG-CoA reductase, which is involved in the synthesis of isoprenoids by some of its representatives [22]. Multiple studies have indicated that statin therapy results in significant remodeling of the gut microbiota and disruptions in the regulation

Table 1.
The impact of various statins on gut microbiota composition

Name of statin	↓ Types of gut microorganisms	↑ Types of gut microorganisms	First author, year
Simvastatin	*Bacilliota* phylum	*Bacteroidota* phylum, *Ruminococcaceae* family *Lactobacillus* spp.	Zhang Q, 2020 [33] Zhang S, 2020 [34]
	Lactobacillus spp.		Catry E, 2015 [35]
	Bifidobacterium spp. *Lactobacillus* spp.	*Staphylococcus* spp.	L'niavina VM, 2009 [36]
Atorvastatin	*Clostridium* spp.	*Lactobacillus*, *Eubacterium*, *Faecalibacterium* and *Bifidobacterium* genera	Sun B, 2018 [37]
		Bacteroidota phylum, *Butyricimonas and Mucispirillum* genera	Kim J, 2019 [38]
	Alfa-diversity of gut microbiome *Bacilliota* phylum	Pseudomonadota and *Bacteroidota* phylums	Khan TJ, 2018 [39]
	Bifidobacterium spp., *Tyzzerella* spp., *Lactobacillus* spp. and other members of *Lactobacillaceae family*		Zhao C, 2020 [40]
	Akkermansia muciniphila		Cheng T, 2022 [41]
Rosuvastatin	*Bacilliota* / *Bacteroidota* ratio	*Bacteroidota* spp. and *Butyricimonas* spp.	Kim J, 2019 [38]
	*Bacilliot*a, *Fusobacteria* and *Pseudomonadota* phylums, *Ruminococcaceae, Lachnospiraceae, Clostridiaceae*, *Coriobacteriaceae*, *Erysipelotrichaceae* and *Akkermansiaceae* families	Bacteroidaceae, *Lachnospiraceae* and *Erysipelotrichaceae* families	Liu Y, 2018 [8] Nolan JA, 2017 [42]
Fluvastatin	SCFA-producing taxa	Escherichia/Shigella, Ruminococcaceae UCG 014, and Sutterella	Zhao C, 2020 [40]
All statins	Parabacteroides merdae	*Bifidobacterium longum*, *Anaerostipes hadrus*, *Ruminococcus obeum*	Hu X, 2021 [29]
	SCFA-producing taxa Community diversity	Bacteroidales S24.7	Caparrós-Martín JA, 2017 [24]
		Akkermansia muciniphila and Faecalibacterium prausnitzii	Khan TJ, 2018 [43]
		Ruminococcus	Ryan PM, 2017 [44]

of liver gene expression involved in lipid metabolism [23]. This phenomenon can be attributed to the erroneous modulation of liver gene expression associated with lipid metabolism and metabolic alterations in mice mediated by the nuclear pregnane X receptor (PXR) [24]. Also a number of studies have identified certain bacteria from atherosclerotic plaques and feces: *Pseudomonadota, Baciliota* and *Actinobacteria* phylums [25]. During statin administration, the abundance of butyrate-producing bacteria (crucial components influencing lipid metabolism regulation) decreases, and overall gut microbial diversity is reduced [24]. Some researchers have reported minor alterations in the gut microbiome associated with statin usage [26].

In some studies, statins have been shown to have antibacterial activity against a wide range of several representatives of the gut microbiota (*Enterococcus faecalis, Enterococcus faecium, Lactobacillus casei* and methicillin-sensitive *Staphylococcus aureus*), as well as drug-resistant microorganisms (VRE, MRSA, MRSE). It has been proven that simvastatin has the most pronounced effect, especially against enterococci, streptococci and staphylococci. In the study that directly compared all statins with each other, only simvastatin also had an antibacterial effect against MRSA. In turn, atorvastatin was more active than simvastatin against *Escherichia coli* and *Acinetobacter baumannii* [27].

However, there are also studies indicating that statin therapy is associated with a lower incidence of gut dysbiosis [28] and has the ability to modulate the gut microbiome towards a healthier state [29]. Individuals with the enterotype Bac2 tend to exhibit higher plasma concentrations of the inflammatory marker C-reactive protein [30]. In obese participants who are not typically prescribed statins, the administration of statin therapy leads to a decreased prevalence of the Bact2 enterotype [28]. Moreover, statin therapy has a significant impact on reducing plasma levels of trimethylamine-N-oxide (TMAO), partly by influencing the gut microbiota and decreasing the abundance of TMA-producing bacteria [31]. These findings suggest that the statin-mediated reduction in TMAO production may contribute to improvements in lipid profiles, reduced inflammation, and atherosclerosis [32]. The impact of various statins on gut microbiota composition is presented *on table 1.*

3. Effects of Gut Microbiota on Statin Efficacy

The microbiome is increasingly recognized as an under-explored contributor to variation in drug metabolism and pharmacological efficacy. Greater than 50 drugs display evidence for metabolism by the gut microbiome [45]. Gut microbiota can directly and indirectly influence drug response either by

interfering with drug pharmacokinetics or pharmacodynamics [46].

The intestine itself is an important drug metabolizing organ as it also expresses many drug metabolizing enzymes and drug transporters and contributes to pre-systemic metabolism and drug transport from the intestinal lumen. The gut microbiota also possess the genetic machinery necessary to produce enzymes that metabolize orally administered drugs which are focused on two main reaction types- hydrolysis and reduction [47]. Microbial activity can thus result in altered drug pharmacokinetics, activation of prodrugs, unwanted formation of toxic metabolites or inactivation of drugs [48].

The impact of gut microbiota on statins efficacy have many mechanisms with direct effects (participate in drug metabolism by hydrolysis, acetylation, etc,) and indirect (modulation of host receptor signaling, influence on gastrointestinal permeability and role of microbial derived bile acids) effects [46]. These effects of gut microbiota can lead to decreased amount of drug reaching target tissues and/or variability in FXR receptor signaling [49]. Kaddurah-Daouk R. et al (2011) identified three secondary, bacterial-derived bile acids that contribute to predicting the magnitude of statin-induced LDLC lowering in good responders [49].

4. Probiotic strains and statins

A number of studies demonstrate the role of the gut microbiota in changing the effectiveness of drugs, including statins. Some authors even call this effect an "individual reaction to drugs", when individual probiotic strains affect their effectiveness due to changes in the metabolism of medicinal products. For example, in the work of Chen S. et al (2021) studied in vitro the effect of 83 strains of *Lactiplantibacillus plantarum* and strain *Lacticaseibacillus paracasei* Shirota on the effect of lovastatin it has been found that probiotics can destroy lovastatin to varying degrees [50]. *Lactiplantibacillus* plantarum A5 (16.87%) and *Lacticaseibacillus paracasei* Shirota (17.6%) had the greatest ability to decompose lovastatin, and *Lactiplantibacillus plantarum* C3 (4.61%) had the least [50]. However, when repeating this experiment in vivo on golden hamsters with mixed hyperlipidemia, it was found that taking probiotics did not affect the effectiveness of lovastatin, but could slow down the inflammatory reaction of the liver [50]. Consequently, the positive effects of probiotics in the correction of lipid metabolism disorders may be associated with improved liver function.

Another study evaluated the hypolipidemic effect of probiotic strains of *Limosilactibacillus fermentum* FM6, *L. fermentum* FM16, *L. fermentum* FM12, *Lacticaseibacillus rhamnosus* FM9, L. fermentum Y55, *L. fermentum* Y57, *L. rhamnosus* Y59 and L. fermentum Y63. To do this, for a month male Wistar rats were fed probiotic strains diluted in water at 2 × 108 CFU/ml per rat per day in addition to a diet high in fat and cholesterol, the control group of rats received statins. The best effect in the correction of lipid metabolism was demonstrated by *L. rhamnosus* FM9, *L. fermentum* Y55, *L. fermentum* Y57, taking their action was as effective as statins in male Wistar rats [51]. It was noteworthy that in the groups of rats receiving probiotic strains, an additional decrease in body weight was observed, which is an additional positive factor [51].

It is well known that the mechanism of action of statins is based on the active suppression of the enzyme HMG-CoA reductase. On the other hand, a number of studies have found that strains of bifidobacteria in the presence of bile acid salts secrete deconjugases that convert taurine- and glycine-containing amides of bile acids into insoluble precipitates that bind thick cholesterol and ensure its excretion with feces. De-conjugase also inhibits the activity of HMG-CoA reductase, which leads to a decrease in the excretion of cholesterol by hepatocytes, and has an effect on the number of receptors for low-density lipoproteins on the surface of the formed blood elements, and can also be regarded as a statin-like effect [52]. Similar properties are observed in lactobacilli and some other intestinal microorganisms [53]. Comparative analysis of the effectiveness of the use of *L. plantarum* N-1 and simvastatin showed that their hypolipidemic effect was comparable, but with the use of simvastatin, the greater effect was in reducing cholesterol and TG, and against the background of taking *L. plantarum* N-1 – a decrease in LDLC, an increase in HDLC and short-chain fatty acids (SCFA) [54]. The use of probiotics from a mixture of *Lactobacillus plantarum* strains CECT7527, CET7528 and CECT7529, a mixture of *Lactobacillus acidophilus* La-5, *Bifidobacterium lactis* BB-12, *Bifidobacterium animalis* lactis BB-12 strains, helps to reduce the level of LDLC, total cholesterol, triglycerides, which allows them to be used as adjuvant therapy in combination with hypolipidemic drugs in dyslipidemia and multifocal atherosclerosis [55]. In patients with metabolic syndrome, non-alcoholic fatty liver disease and dyslipidemia, the use of combination therapy (statins in combination with a probiotic) was more effective in achieving target lipid levels compared with statin monotherapy [52]. THis may indicate the synergistic effect of these groups of drugs.

In addition, you should be aware of the possible side effects of statins, including from the gastrointestinal tract. For example, the instructions for atorvastatin in the section "side effects" indicate the possible development of nausea, heartburn, constipation or diarrhea, flatulence, etc. All these side effects can be reduced or eliminated through the use of probiotics, which not only restore the balance of the intestinal microbiota, but also stop the concomitant manifestations of dyspepsia as a result of reducing chronic low-level inflammation, restoring the permeability of the digestive tube, and a positive effect on liver function.

5. Probiotics and lipid metabolism

The idea of the benefits of fermented milk products for human health dates back to the early 20th century, when Mechnikov I.I. suggested that lactic acid bacteria "prevents intestinal putrefaction" and "helped maintain the forces of the body" [56].

There is promising evidence that the correction and restoration of gut microbiota disorders can lead to improvements in lipid metabolism [57, 58]. The most common used strains are different strains of bifidobacteria and lactobacillii: *Bifidobacterium*

animalis, *Bifidobacterium longum*, *Lactobacillus acidophilus*, *Lactobacillus reuteri*, *Lactobacillus bulgaricus*, *Lactobacillus sporogenes*, etc. [59]. Also in a randomized, double-blind, placebo-controlled clinical trial, it was demonstrated that *Enterococcus faecium* probiotic strain reduced cholesterol levels by 12% [59].

The results of a randomized trial demonstrated that the intake of *Lactobacillus casei* strain Shirota for 60 days resulted in a significant reduction in serum triglyceride and low-density lipoprotein cholesterol levels by 26.56% and 23.83%, respectively, compared to the control group ($P < 0.05$) [60]. In patients with type 2 diabetes mellitus, the use of a multi-strain probiotic containing seven viable strains of *Lactobacillus* spp., *Bifidobacterium* spp. and *Streptococcus* sp. showed a significant decrease in low-density lipoprotein cholesterol (LDLC) levels compared to the placebo group ($P = 0.002$) [61].

A meta-analysis of 11 smaller clinical trials revealed that probiotic supplementation has beneficial effects on serum lipid profiles, leading to a decrease in total serum cholesterol (TC) and LDLC levels. However, there were no significant differences in high-density lipoprotein cholesterol (HDLC) and triglyceride (TG) levels between the probiotic and control groups. Among the different bacterial strains, Gaio and *Lactobacillus acidophilus* strains demonstrated a greater impact [62]. Another meta-analysis focused on studies utilizing Lactobacillus formulations, which showed improvements in total serum cholesterol and LDLC levels, but no significant changes in triglycerides or HDLC levels [63]. Additionally, a separate study reported reductions in total cholesterol, LDLC, and TG levels, as well as an increase in HDLC levels, with the use of a Bifidobacterium/yeast extract [64].

Other meta-analysis of Wang L. of 32 randomized controlled trials including 1971 patients revealed that serum TC was significantly reduced in probiotics group compared with the control group. These results were with the following probiotic strains: *Lactobacillus acidophilus, Lactobacillus plantarum* and *Bifidobacterium lactis*. Also longer duration of treatment and usage of probiotics in capsules form might contribute to a better curative effect [65].

In meta-analysis Mo R. and co-authors (19 randomized controlled trials including 967) al shown next data: probiotic interventions reduced TC and LDLC compared to controls (placebo or no treatment) by –0.25mmol/L and –0.17mmol/L, respectively. No significant effects of probiotics on TG and HDLC levels were found. The effects of probiotics on decreasing TC and LDLC levels were greater for longer intervention times, certain probiotic strains, and in younger mildly hypercholesterolaemic subjects [66].

A number of studies suggest that probiotics containing microorganisms producing SCFA, including bifidobacteria, enterococci and lactobacilli, have many advantages, including anti-inflammatory and beneficial metabolic effects. [67]. The usage of various probiotics, such as *Lactobacillus plantarum*, can reduce the production of TMAO and the development of atherosclerosis in mouse ApoE – / – [68].

In a number of studies, positive effects of probiotics have been observed only when probiotics are combined with other types of therapy. Soy isoflavones and 23 probiotics supplements showed a significant synergistic effect, which was not observed in the groups receiving only supplements. [69]. In addition, exercises combined with taking probiotics stimulated an increase in HDLC cholesterol [70]. In the DiRienzo D.B. study, a significant decrease in LDLC was observed with the use of

Table 2.
The impact of various probiotics on lipid metabolism

Probiotic strain	Effect on lipid metabolism	First author, year
L. rhamnosus FM9, *L. fermentum* Y55, *L. fermentum* Y57	Simular than statins	Zafar H., 2022 [51]
L. plantarum N-1	↑ HDLC ↓ LDLC	Tian L., 2022 [54]
Combination of *L. plantarum* CECT7527, CET7528 и CECT7529	↓ TC, TG, LDLC	Oynotkinova O.S., 2020 [55]
Combination of L. acidophilus La-5, Bifidobacterium lactis BB-12, *B. animalis lactis* BB-12	↓ TC, TG, LDLC	Oynotkinova O.S., 2020 [55]
L. casei strain Shirota	↓ TG, LDLC	Li X., 2021 [60]
Combination of seven strains of *Lactobacillus* spp., *Bifidobacterium* spp. and *Streptococcus* spp.	↓ LDLC	Razmpoosh E., 2019 [61]
L. reuteri NCIMB 30242	↓ LDLC	DiRienzo D.B., 2014 [71]
Combinations of *L. acidophilus* and *B. lactis*	↓ LDLC	DiRienzo D.B., 2014 [71]
Combination of *L. acidophilus* and *B. bifidum*	↓ TC, LDLC ↑ HDLC No effect on TG	Rerksuppaphol S., 2015 [72]
L. paracasei TISTR 2593	No changes in TC, HDLC, TG	Khongrum J., 2023 [78]
B. lactis HN019	↓ TG, LDLC	Bernini L.J, 2016 [73]
Combination of *B. animalis* subspecies *lactis* MB 2409, B. bifidum MB 109B, and *B. longum* subspecies *longum* BL04	↓ TG, LDLC	Guardamagna O., 2014 [74]
Enterococcus faecium 132, *Lactobacillus paracasei* 201	↓ TC, TG, LDLC	Yang L., 2021 [79]
E. faecium GEFA01	↑ HDLC ↓ TC, LDLC, TG	Xu W., 2022 [80]
Streptococcus thermophilus	↓ TC, LDLC	Bertolami M.C, 1999 [75]
Bacillus subtilis	↑ HDLC ↓ TC, LDLC	L'niavina V.M., 2023 [76]

the following probiotic strains: *Lactobacillus reuteri* NCIMB 30242, *Enterococcus faecium* and combinations of *Lactobacillus acidophilus* and *Bifidobacterium lactis* [71]. Intake of combination of *Lactobacillus acidophilus* and *Bifidobacterium bifidum* during six weeks decreased serum TC, LDLC and increased HDLC levels in hypercholesterolemic patients. There was no effect on TG [72]. In Bernini LJ et al work was demonstrated that daily ingestion of 80 mL fermented milk with 2.72 × 10(10) colony-forming units of *Bifidobacterium lactis* HN019 showed significant reduction in TG and LDLC compared with baseline and control group values. Furthermore, in this study significant decrease in tumor necrosis factor-α and interleukin-6 was observed [73]. It can be explained by anti-inflammatory efficacy of probiotic.

In children with dyslipidemia usage of multi-strain probiotic (*B. animalis* subspecies *lactis* MB 2409, *B. bifidum* MB 109B, and *B. longum* subspecies *longum* BL04) during 3 months demonstrated a significantly decrease of TC and LDLC compared with placebo group [74].

Usage of probiotic contains *Enterococcus faecium* and 2 strains of *Streptococcus thermophilus* helps to TC decrease on 5.3% (P = 0.004), and LDLC decrease on 6.15% (P = 0.012) [75].

The influence of probiotic Bacillus subtilis on lipid metabolism were presented in the study by L'niavina et al., 2023 [76]. The investigators demonstrated that the use of probiotics as part of a comprehensive therapy regimen exhibited a significant hypolipidemic effect, comparable to the effect of statins.

6. Own research probiotic effects in metabolic syndrome therapy

The important findings regarding the influence of probiotic bacilli and enterococci on the restoration of microbiota of patients with metabolic syndrome were presented in the our previous study [76].

For evaluation the possibilities of *Enterococcus faecium* L-3 and *Bacillus subtilis* 3 and in the correction of metabolic disorders we decided to estimate of the clinical efficacy of probiotics, including in combination with statins.

Materials and methods

We included in study 100 patients with ischemic heart disease (CHD) with functional class II angina pectoris, dyslipidaemia and concomitant disorders of the gut microbiota. The ratio of men and women was 1:1.7 (35:65 people, respectively). The average age of the patients was 58.5±I.2 years. For all patients a lipidogram was performed twice: before and 30–45 days after treatment. Depending on the therapy, four groups of patients were formed. All patients signed informed consent before starting the study procedures. The work was approved by the Local Ethics Committee at the Institute of Experimental Medicine (№ 7/19, 24.10.2019). Depending on the therapy, four groups of patients were formed. All patients signed informed consent before starting the study procedures (*table 3*).

Study group 1 included 23 patients who underwent complex treatment, including a standard treatment regimen for coronary heart disease (nitrates, angiotensin converting enzyme inhibitors, beta-blockers or calcium channel blockers, antiplatelet agents), as well as a Enterococcus faecium L-3 in the amount of 10^{6-7} CFU/ml) at a dose of 5 g 3 times a day during 3–4 weeks.

Study group 2 included 26 patients, who received complex treatment, including a standard treatment regimen for coronary heart disease (nitrates, angiotensin converting enzyme inhibitors, beta-blockers or calcium channel blockers, antiplatelet agents) and a *Bacillus subtilis* 3 two capsules at a dose of 2 capsules 2 times a day during 3–4 weeks.

Study group 3 included 25 patients who, along with the standard treatment regimen, received a culture liquid of Bacillus subtilis 3 at a dose of 2 capsules 2 times a day during 3–4 weeks and simvastatin at a dose of 10 mg 1 time a day (in the evening) for 3–4 weeks.

The group 4 (comparison group) consisted of 26 patients receiving complex treatment and simvastatin at a dose of 20 mg once a day (in the evening).

Table3. Characteristics of the groups

Group	1 group	2 group	3 group	4 group
Simvastatin	+	–	–	–
E. faecium L-3		+		
Bacillus subtilis 3			+	
Bacillus subtilis 3+sumvastatin				+
Gut Microbiota [76]	Dysbiosis	Dysbiosis correction	Dybiosis partially correction	Dysbiosis

Results

After treatment course all patients showed a tendency to decrease total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL), however, a significant increase in high-density lipoprotein cholesterol (HDL) was recorded only in those patients who received probiotic therapy (group 1 – from 1.33 to 1.98, group 2 – from 1.42 to 2.09, group 3 – from 1.53 to 1.53, group 4 – from 1.28 to 1.31 mmol/l) (*fig. 2, 3, 4*).

We also saw that after use of probiotics, there is a decrease in the processes of lipid peroxidation, and after use of statins, on the contrary, an increase (*fig. 5*).

The main results of the study are presented *in table 4*.

Figure 2. The level of TC in the blood serum in CHD patients with gut dysbiosis before and after treatment

Notes: The norm – 3.6–5.2 mmol/l. Along the axis of the abscissa group of patients, along the ordinate axis – the level of TC in the blood serum (mmol/l), *- p<0.05

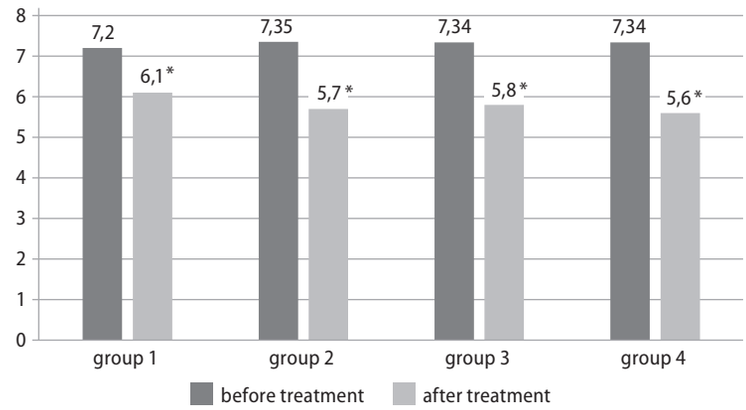


Figure 3. The level of LDL in the blood serum in CHD patients with gut dysbiosis before and after treatment.

Notes: The norm <3.4 mmol/L. Along the axis of the abscissa group of patients, on the ordinate axis is the level of LDL in blood serum (mmol/l), * – p<0.05

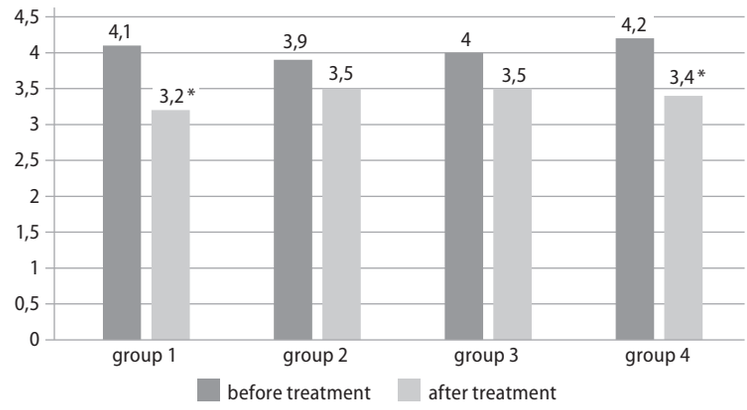


Figure 4. The level of HDL in the blood serum in CHD patients with gut dysbiosis before and after treatment.

Notes: The norm is not less than 0.9 mmol/l. Along the axis of the abscissa group of patients, along the ordinate axis is the level of HDL in blood serum (mmol/l), * – p<0.05

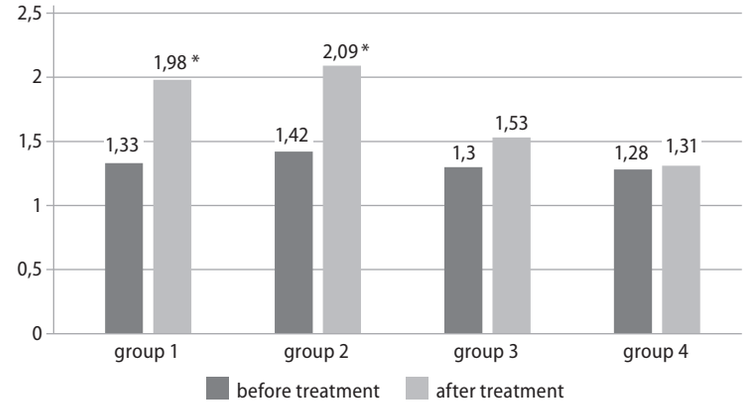


Figure 5. The level of lipid peroxidation in the blood serum in CHD patients with gut dysbiosis before and after treatment

Notes: The norm is 2.6–3.6 m/Ml. Along the axis of the abscissa are the groups of patients, along the ordinate axis is the level of lipid peroxidation in blood serum (m/Ml), *- p<0.05

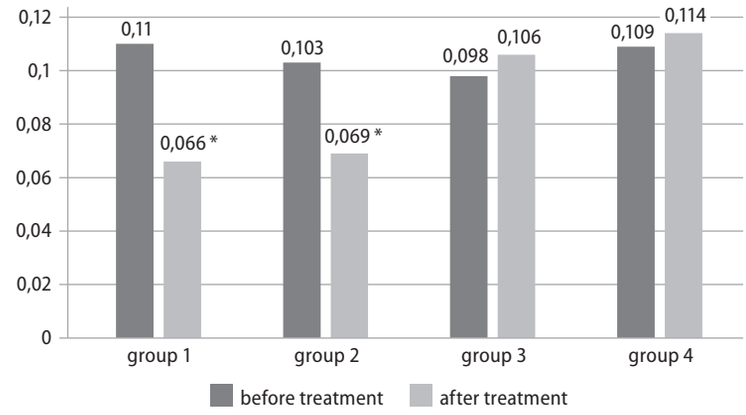


Table 4. Summary results

Group	1 group	2 group	3 group	4 group
TC	↓*	↓	↓	↓*
LDL	↓*	↓	↓	↓*
HDL	↑*	↑*	–	–
lipid peroxidation	↓*	↓*	–	–

Notes: * – p<0.05

Conclusion

The investigators demonstrated that the use of probiotics as part of a comprehensive therapy regimen exhibited a significant hypolipidemic effect, comparable to the effect of simvastatin, in reducing TC and LDLC levels. Furthermore, the probiotic E. faecium L-3 intervention resulted in an increase in the levels of antiatherogenic HDLC and fat burning (lipid peroxidation). We can hypothesize that probiotics represent effective therapeutic agents for restoring gut microbiota disorders and correcting lipid metabolism. However, their effectiveness may be limited by the phenomenon of colonization resistance and the challenges associated with transit through the small intestine and colon. Also probiotic-mediated gut dysbiosis and infections have been reported [77]. Currently, the selection of a suitable probiotic for individual patients with lipid metabolism correction remains unclear. At the same time, the most effective of them can be recommended first for most patients.

7. Autoprobiotics and lipid metabolism

The use of probiotics, despite their high safety, also has its disadvantages, such as necessarily of a long course of treatment (1 month or more). The use of probiotic strains may not have a pronounced positive effect on the gastrointestinal microbiota, because they transit through the small intestine and colon. Moreover, it remains unclear how to choose a suitable probiotic for each individual for the best effect. So the personalized symbiotic therapy technology with "personified functional food products (PFFP) usage was suggested. This technology bases on usage of autoprobiotics – beneficial indigenous microbes of the human's own microbiota in the form of PFFP, which are used for the prevention and treatment of various diseases.

One innovative approach to restore gut microbiota is through the use of autoprobiotics. Currently, Suvorov et al., demonstrated a strategy for treating dysbiosis using genetically tested bacteria obtained from patients, grown in laboratory conditions and provided by the patient in the form of fermented milk products [81].

Autoprobiotics are strains of normal microbiota, that are isolated from an individual and designed to address their unique microecology. Autoprobiotics derived from indigenous lactobacilli, bifidobacteria, or enterococci could be considered the preferred therapeutic options, as they establish immunological tolerance early in life and do not conflict with other resident microbiota in the human body [82]. Autoprobiotics have an extended residence time in the colon, which allows for shorter treatment durations. This becomes possible due to the presence of immunological tolerance to representatives of their own microbiota and the high adaptation of indigenous microorganisms in the intestinal microbiocenosis to inhabiting conditions.

Studies have already demonstrated the effectiveness of autoprobiotics based on indigenous strains of *Lactobacillus* spp. in restoring and stabilizing the levels of key representatives of normal gut microbiota (such as *Bifidobacterium* spp., *Lactobacillus* spp., and *E. coli*) in the management of dysbiotic disorders resulting from antibacterial drug usage [83]. Additionally, indigenous strains of *Enterococcus* spp. have shown promise in the treatment of intestinal pathology, neurological diseases [72, 74], and metabolic disorders [84].

The usage of indigenous enterococci (were obtained as described in Russian Patent No. 2546253 [85]) in patients with metabolic syndrome (MS) lead to statistically significant improving of lipid profile parameters: lowering of TC, LDLC, TG and higher level of HDLC [7, 86].

8. Discussion

Recent studies have established a clear association between the gut microbiome, metabolic disorders, and the use of statins [21, 87, 88]. Considering the impact of statins on the microbiota, which is likely to disrupt its stability [89], and the fact that dysregulation of lipid metabolism can lead to complications, it is crucial to carefully examine the consequences of statin usage. Statins have been found to modulate the composition of the gut microbiota and alter certain microbiota-derived metabolites, thereby influencing the cholesterol-lowering effects of these drugs [90]. Moreover, the response to statins differs among patients with different enterotypes: a gut microbiome enriched with *Bacteroides* spp. (Bac.2 enterotype) and reduced in diversity showed a more robust response to statins, while Bac.1, *Ruminococcus* spp. family (Rum.), and *Prevotella* spp. (Prev.) enterotypes exhibited a lower response [26, 91]. Patients with a favorable statin response demonstrated higher levels of microorganisms belonging to the B*acilliota* phylum, increased proportions of the genera *Lactobacillus* and *Bifidobacterium*, and greater gut microbiome diversity [8, 37]. These findings suggest a potential role of the gut microbiota in the efficacy of statins.

Considering the positive effects of some probiotics on lipid metabolism, their ability to counteract low-grade inflammation, and their immunomodulatory role in the digestive system, endocrine and nervous systems, combining statins with probiotic agents appears to be a logical approach. In case of the minor changes in the lipid profile, it is even more appropriate to consider probiotic therapy. Probiotics have shown promising hypocholesterolemic effects [92]. However, the efficacy of probiotics varies depending on the specific strains

used, the physiological characteristics of the host, and the type of diet to which the probiotics are introduced.

Positive effects of autoprobiotics are similar to probiotics. These effects include: normalization of the composition of the gut microbiota, including inhibition of the growth of pathogenic and opportunistic microorganisms due to microbial antagonism, increased local immunity, improved absorption of nutrients, reduced frequency of allergic reactions, restoration of the production of a number of vitamins, optimization of lipid metabolism, etc. At the same time, the autoprobiotic has a number of advantages such as individual composition and personalization therapy; high survival rate in gut; safety (the indigenous bacteria from autoprobiotic do not enter into conflict relations with other resident representatives of the human microbiota).

Undoubtedly, there are interactions between statin use and changes in the gut microbiota. To optimize the treatment of patients with metabolic syndrome and lipid metabolism disorders, it can be proposed to use a highly effective and safe integrated approach: a combination of statins with a probiotic/autoprobiotic. This is due to the complex positive effects of statins and probiotics/autoprobiotics on lipid metabolism, including through positive modulation of the gut microbiota and positive changes in the ratio of SCFA, bile acid concentration, TMAO and lipopolysaccharide. Also probiotics have shown positive vascular beneficial effects: a decrease in oxidative stress and restoration of the nitric oxide pathway [93]. When using probiotics and combined use of probiotics with statins decreased the level of endotoxin, peroxidation products and nitric oxide in the blood, and also increases the level of superoxide dismutase and catalase. This has a significant impact on the pathogenesis of metabolic disorders [94, 95].

However, further research is warranted to gain a deeper understanding of the underlying mechanisms and address remaining questions in this field. It cannot be excluded that the use of autoprobiotics and the prescription of targeted probiotics according to the optimal treatment regimen will avoid the introduction of statins or, as an element of complex therapy, or at least will neutralize the complications associated with their use.

Supplementary Materials:

The following supporting information can be downloaded at: www.mdpi.com/xxx/s1, Figure S1: title; Table S1: title; Video S1: title.

Author Contributions:

Conceptualization, N. Baryshnikova and E. Ermolenko; methodology, N. Baryshnikova and E. Ermolenko; software, N. Baryshnikova and E. Ermolenko; validation, N. Baryshnikova and E. Ermolenko; formal analysis, N. Baryshnikova and E. Ermolenko; investigation, N. Baryshnikova and E. Ermolenko; resources, N. Baryshnikova and E. Ermolenko; data curation, N. Baryshnikova and E. Ermolenko; writing – original draft preparation, N. Baryshnikova and E. Ermolenko; writing – review and editing, N. Baryshnikova and E. Ermolenko; visualization, N. Baryshnikova and E. Ermolenko; supervision, N. Baryshnikova and E. Ermolenko; project administration, N. Baryshnikova and E. Ermolenko. All authors have read and agreed to the published version of the manuscript."

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Дополнительные материалы:

Следующая вспомогательная информация может быть загружена по адресу: www.mdpi.com/xxx/s1, Figure S1: title; Table S1: title; Video S1: title

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References | Литература

1. Schoeler M., Caesar R. Dietary lipids, gut microbiota and lipid metabolism. *Rev Endocr Metab Disord*. 2019, 20(4):461–472. doi: 10.1007/s11154–019–09512–0.
2. Sun C., Wang Z., Hu L., Zhang X., Chen J., Yu Z., Liu L., Wu M. Targets of statins intervention in LDL–C metabolism: Gut microbiota. *Front Cardiovasc Med*. 2022;9:972603. doi: 10.3389/fcvm.2022.972603.
3. Albillos A., de Gottardi A., Rescigno M. The gut-liver axis in liver disease: Pathophysiological basis for therapy. *J Hepatol*. 2020, 72:558–77. doi: 10.1016/j.jhep.2019.10.003
4. Martinez K.B., Leone V., Chang E.B. Western diets, gut dysbiosis, and metabolic diseases: are they linked? *Gut Microbes*. 2017, 8:130–42. doi: 10.1080/19490976.2016.1270811l.
5. Sonnenburg J.L., Bäckhed F. Diet-microbiota interactions as moderators of human metabolism. *Nature*. 2016, 535:56–64. doi: 10.1038/nature 18846.
6. Rebolledo C., Cuevas A., Zambrano T. et al. Bacterial Community Profile of the Gut Microbiota Differs between Hypercholesterolemic Subjects and Controls. *Biomed Res Int*. 2017;2017:8127814. doi: 10.1155/2017/8127814.
7. Alferova L.S., Ermolenko E.I., Chernikova A.T. et al. Autoprobiotic enterococci as a component of metabolic syndrome complex therapy. Russian Journal for Personalized Medicine. 2022;2(6):98–114. (In Russ.) doi: 10.18705/2782–3806–2022–2–6–98–114.
8. Liu Y., Song X., Zhou H., Zhou X., Xia Y., Dong X., Zhong W., Tang S., Wang L., Wen S., Xiao J., Tang L. Gut Microbiome Associates With Lipid-Lowering Effect of Rosuvastatin in Vivo. *Front Microbiol*. 2018 Mar 22;9:530. doi: 10.3389/fmicb.2018.00530.
9. Drapkina O.M., Shirobokikh O.E. Role of Gut Microbiota in the Pathogenesis of Cardiovascular Diseases and Metabolic Syndrome. *Rational Pharmacotherapy in Cardiology*. 2018;14(4):567–574. (In Russ.) doi: 10.20996/1819–6446–2018–14–4–567–574.
10. Kimura I., Ozawa K., Inoue D. et al. The gut microbiota suppresses insulin-mediated fat accumulation via the short-chain fatty acid receptor GPR43. *Nat Commun*. 2013;4:1829. doi: 10.1038/ncomms2852.
11. Kumar P.S., Mason M.R., Brooker M.R., O'Brien K. Pyrosequencing reveals unique microbial signatures associated with healthy and failing dental implants. *J Clin Periodontol*. 2012;39(5):425–33. doi: 10.1111/j.1600–051X.2012.01856.x.
12. Lefebvre P., Cariou B., Lien F., Kuipers F., Staels B. Role of bile acids and bile acid receptors in metabolic regulation. *Physiol Rev*. 2009;89(1):147–91. doi: 10.1152/physrev.00010.2008.
13. Schoeler M., Caesar R. Dietary lipids, gut microbiota and lipid metabolism. *Rev Endocr Metab Disord*. 2019;20(4):461–472. doi: 10.1007/s11154–019–09512–0.
14. Zhu Y., Li Q., Jiang H. Gut microbiota in atherosclerosis: focus on trimethylamine N-oxide. *APMIS*. 2020;128(5):353–366. doi: 10.1111/apm.13038.
15. Bennett B.J., de Aguiar Vallim T.Q., Wang Z. et al. Trimethylamine-N-oxide, a metabolite associated with atherosclerosis, exhibits complex genetic and dietary regulation. *Cell Metab*. 2013;17(1):49–60. doi: 10.1016/j.cmet.2012.12.011.
16. He X., Zheng N., He J., Liu C., Feng J., Jia W., Li H. Gut Microbiota Modulation Attenuated the Hypolipidemic Effect of Simvastatin in High-Fat/Cholesterol-Diet Fed Mice. *J Proteome Res*. 2017;16(5):1900–1910. doi: 10.1021/acs.jproteome.6b00984.
17. Yoo D.H., Kim I.S., Van Le T.K., Jung I.H., Yoo H.H., Kim D.H. Gut microbiota-mediated drug interactions between lovastatin and antibiotics. *Drug Metab Dispos*. 2014;42(9):1508–13. doi: 10.1124/dmd.114.058354.
18. Samsonova N.G., Zvenigorodskaia L.A., Cherkashova E.A., Lazebnik L.B. [Intestinal dysbiosis and atherogenic dyslipidemia]. *Eksp Klin Gastroenterol*. 2010;(3):88–94. (in Russ.) PMID: 20499450.
19. Adak A., Khan M.R. An insight into gut microbiota and its functionalities. *Cell Mol Life Sci*. 2019, 76:473–93. doi: 10.1007/s00018–018–2943–4.
20. Bogiatzi C., Gloor G., Allen-Vercoe E. et al. Metabolic products of the intestinal microbiome and extremes of atherosclerosis. *Atherosclerosis*. 2018;273:91–97. doi: 10.1016/j.atherosclerosis.2018.04.015.
21. Dias A.M., Cordeiro G., Estevinho M.M. et al. Gut bacterial microbiome composition and statin intake-A systematic review. *Pharmacol Res Perspect*. 2020, 8: e00601. doi: 10.1002/prp2.601.
22. Kashtanova D.A., Tkacheva O.N., Boytsov S.A. Gut microbiota and cardiovascular risk factors. Part IV. Arterial hypertension, smoking and the gut microbiota. *Cardiovascular Therapy and Prevention*. 2016;15(1):69–72. (In Russ.) doi: 10.15829/1728–8800–2016–1–69–72.
23. Chiu H.F., Huang Y.C., Lu Y.Y., Han Y.C., Shen Y.C., Golovinskaia O. et al. Regulatory/modulatory effect of prune essence concentrate on intestinal function and blood lipids. *Pharm Biol*. 2017, 55:974–9. doi: 10.1080/13880209.2017.1285323.
24. Caparrós-Martín J.A., Lareu R.R., Ramsay J.P. et al. Statin therapy causes gut dysbiosis in mice through a PXR-dependent mechanism. *Microbiome*. 2017;5(1):95. doi: 10.1186/s40168–017–0312–4.
25. Shen X., Li L., Sun Z., Zang G., Zhang L., Shao C., Wang Z. Gut Microbiota and Atherosclerosis-Focusing on the Plaque Stability. *Front Cardiovasc Med*. 2021 Aug 3;8:668532. doi: 10.3389/fcvm.2021.668532.
26. Wilmanski T., Kornilov S.A., Diener C. et al. Heterogeneity in statin responses explained by variation in the human gut microbiome. *Med*. 2022;3(6):388–405. e6. doi: 10.1016/j.medj.2022.04.007.
27. Ko H.H.T., Lareu R.R., Dix B.R., Hughes J.D. Statins: antimicrobial resistance breakers or makers? *Peer* J. 2017 Oct 24;5: e3952. doi: 10.7717/peerj.3952.
28. Vieira-Silva S., Falony G., Belda E. et al. Statin therapy is associated with lower prevalence of gut microbiota dysbiosis. *Nature* 2020, 581, 310–315. doi.org/10.1038/s41586–020–2269-x.
29. Hu X., Li H., Zhao X., Zhou R., Liu H., Sun Y., Fan Y., Shi Y., Qiao S., Liu S., Liu H., Zhang S. Multi-omics study reveals that statin therapy is associated with restoration of gut microbiota homeostasis and improvement in outcomes in patients with acute coronary syndrome. *Theranostics*. 2021;11(12):5778–5793. doi: 10.7150/thno.55946.
30. Lim G.B. Improved gut microbiota profile in individuals with obesity taking statins. *Nat Rev Cardiol*. 2020;17(7):385. doi: 10.1038/s41569–020–0396–6.
31. Zhu Y., Li Q., Jiang H. Gut microbiota in atherosclerosis: focus on trimethylamine N-oxide. *APMIS*. 2020;128(5):353–366. doi: 10.1111/apm.13038.
32. Li D.Y., Li X.S., Chaikijurajai T., Li L., Wang Z., Hazen S.L., Tang W.H.W. Relation of Statin Use to Gut Microbial Trimethylamine N-Oxide and Cardiovascular

Risk. *Am J Cardiol*. 2022;178:26–34. doi: 10.1016/j.amjcard.2022.05.010.

33. Zhang Q., Fan X., Ye R., Hu Y., Zheng T., Shi R. et al. The effect of simvastatin on gut microbiota and lipid metabolism in hyperlipidemic rats induced by a high-fat diet. *Front Pharmacol*. 2020, 11:522. 10.3389/fphar.2020.0052.
34. Zhang S., Li H., Yuan L., Zhang J., Han L., Liu R. et al. Molecular characterization of gut microbiota in high-lipid diet-induced hyperlipidemic rats treated with simvastatin. *Int J Mol Med*. 2020 45:1601–15. 10.3892/ijmm.2020.451.
35. Catry E., Pachikian B.D., Salazar N., Neyrinck A.M., Cani P.D., Delzenne N.M. Ezetimibe and simvastatin modulate gut microbiota and expression of genes related to cholesterol metabolism. *Life Sci*. 2015;132:77–84. doi: 10.1016/j.lfs.2015.04.004.
36. L'niavina V.M. Changes in lipid metabolism in patients with ischemic heart disease associated with intestinal dysbiosis; metabolic effects of probiotics. 2009: 24 p. Available online: https://www.dissercat.com/content/izmeneniya-lipidnogo-obmena-u-bolnykh-ishemicheskoi-boleznyu-serdtsa-assotsiirovannoi-s-disb?ysclid=ljev2yyrd101039582 (accessed on 28 June 2023).
37. Sun B., Li L., Zhou X. Comparative analysis of the gut microbiota in distinct statin response patients in East China. *J Microbiol*. 2018, 56:886–92. 10.1007/s12275–018–8152-x.
38. Kim J., Lee H., An J., Song Y., Lee C.K., Kim K., Kong H. Alterations in Gut Microbiota by Statin Therapy and Possible Intermediate Effects on Hyperglycemia and Hyperlipidemia. *Front Microbiol*. 2019;10:1947. doi: 10.3389/fmicb.2019.01947.
39. Khan T.J., Ahmed Y.M., Zamzami M.A., Mohamed S.A., Khan I., Baothman O.A.S., Mehanna M.G., Yasir M. Effect of atorvastatin on the gut microbiota of high fat diet-induced hypercholesterolemic rats. *Sci Rep*. 2018;8(1):662. doi: 10.1038/s41598–017–19013–2.
40. Zhao C., Hu Y., Chen H., Li B., Cao L., Xia J., Yin Y. An in vitro evaluation of the effects of different statins on the structure and function of human gut bacterial community. *PLoS One*. 2020;15(3): e0230200. doi: 10.1371/journal.pone.0230200.
41. Cheng T., Li C., Shen L., Wang S., Li X., Fu C., Li T., Liu B., Gu Y., Wang W., Feng B. The Intestinal Effect of Atorvastatin: Akkermansia muciniphila and Barrier Function. *Front Microbiol*. 2022;12:797062. doi: 10.3389/fmicb.2021.797062.
42. Nolan J.A., Skuse P., Govindarajan K. et al. The influence of rosuvastatin on the gastrointestinal microbiota and host gene expression profiles. *Am J Physiol Gastrointest Liver Physiol*. 2017, 312: G488-g97. 10.1152/ajpgi.00149.2016.
43. Khan T.J., Ahmed Y.M., Zamzami M.A. et al. Atorvastatin Treatment Modulates the Gut Microbiota of the Hypercholesterolemic Patients. *OMICS*. 2018, 22(2):154–163. doi: 10.1089/omi.2017.0130.
44. Ryan P.M., London L.E., Bjorndahl T.C. et al. Microbiome and metabolome modifying effects of several cardiovascular disease interventions in apo-E-/- mice. *Microbiome*. 2017;5(1):30. doi: 10.1186/s40168–017–0246-x.
45. Haiser H.J., Turnbaugh P.J. Developing a metagenomic view of xenobiotic metabolism. *Pharmacol Res*. 2013 Mar;69(1):21–31. doi: 10.1016/j.phrs.2012.07.009.
46. Tuteja S., Ferguson J.F. Gut Microbiome and Response to Cardiovascular Drugs. *Circ Genom Precis Med*. 2019 Sep;12(9):421–429. doi: 10.1161/CIRCGEN.119.002314.
47. Kim D.H. Gut Microbiota-Mediated Drug-Antibiotic Interactions. *Drug Metab Dispos*. 2015 Oct;43(10):1581–9. doi: 10.1124/dmd.115.063867.
48. Sousa T., Paterson R., Moore V., Carlsson A., Abrahamsson B., Basit A.W. The gastrointestinal microbiota as a site for the biotransformation of drugs. *Int J Pharm*. 2008 Nov 3;363(1–2):1–25. doi: 10.1016/j.ijpharm.2008.07.009.
49. Kaddurah-Daouk R., Baillie R.A., Zhu H. et al. Enteric microbiome metabolites correlate with response to simvastatin treatment. *PLoS One*. 2011;6(10): e25482. doi: 10.1371/journal.pone.0025482.
50. Shen S., Wang J., Ma C., Chen Y., Ding H., Zhang J. Understanding the "individual drug reaction" from the perspective of the interaction between probiotics and lovastatin in vitro and in vivo. *Microbiome*. 2023 Sep 25;11(1):209. doi: 10.1186/s40168–023–01658-z.
51. Zafar H., Ain N.U., Alshammari A. et al. Lacticaseibacillus rhamnosus FM9 and Limosilactobacillus fermentum Y57 Are as Effective as Statins at Improving Blood Lipid Profile in High Cholesterol, High-Fat Diet Model in Male Wistar Rats. *Nutrients*. 2022 Apr 15;14(8):1654. doi: 10.3390/nu14081654.
52. Zvenigorodskaia LA, Cherkashova EA, Samsonova NG, Nilova TV, Sil'verstova SIu. [Advisability of using probiotics in the treatment of atherogenic dyslipidemia]. *Eksp Klin Gastroenterol*. 2011;(2):37–43. Russian. PMID: 21563361.

Звенигородская Л.А., Черкашова Е.А., Самсонова Н.Г., Нилова Т.В., Сильверствова С.Ю. Целесообразность применения пробиотиков в лечении атерогенной дислипидемии. Экспериментальная и клиническая гастроэнтерология. 2011; 2: 37–43.

53. Rolfe R.D. Interactions among microorganisms of the indigenous intestinal flora and their influence on the host. *Rev Infect Dis*. 1984 Mar-Apr;6 Suppl 1: S73–9. doi: 10.1093/clinids/6.supplement_1.s73.
54. Tian L., Liu R., Zhou Z., Xu X., Feng S., Kushmaro A., Marks R.S., Wang D., Sun Q. Probiotic Characteristics of Lactiplantibacillus Plantarum N-1 and Its Cholesterol-Lowering Effect in Hypercholesterolemic Rats. *Probiotics Antimicrob Proteins*. 2022 Apr;14(2):337–348. doi: 10.1007/s12602–021–09886–1.
55. Oynotkinova O.S., Nikonov E.L., Demidova T.Y., Baranov A.P., Kryukov E.V., Dedov E.I., Karavashkina E.A. [Changes in the intestinal microbiota as a risk factor for dyslipidemia, atherosclerosis and the role of probiotics in their prevention]. *Ter Arkh*. 2020 Oct 14;92(9):94–101. Russian. doi: 10.26442/00403660.2020.09.000784.
56. Nagpal R., Behare P.V., Kumar M. et al. Milk, milk products, and disease free health: an updated overview. *Crit Rev Food Sci Nutr*. 2012;52(4):321–33. doi: 10.1080/10408398.2010.500231.
57. Falcinelli S., Rodiles A., Hatef A., Picchietti S., Cossignani L., Merrifield D.L., Unniappan S., Carnevali O. Influence of Probiotics Administration on Gut Microbiota Core: A Review on the Effects on Appetite Control, Glucose, and Lipid Metabolism. *J Clin Gastroenterol*. 2018;52 Suppl 1, Proceedings from the 9th Probiotics, Prebiotics and New Foods, Nutraceuticals and Botanicals for Nutrition & Human and Microbiota Health Meeting, held in Rome, Italy from September 10 to 12, 2017: S50-S56. doi: 10.1097/MCG.0000000000001064.
58. Mu J., Guo X., Zhou Y., Cao G. The Effects of Probiotics/Synbiotics on Glucose and Lipid Metabolism in Women with Gestational Diabetes Mellitus: A Meta-Analysis of Randomized Controlled Trials. *Nutrients*. 2023;15(6):1375. doi: 10.3390/nu15061375.

59. Kumar M., Nagpal R., Kumar R., Hemalatha R., Verma V., Kumar A., Chakraborty C., Singh B., Marotta F., Jain S., Yadav H. Cholesterol-lowering probiotics as potential biotherapeutics for metabolic diseases. *Exp Diabetes Res*. 2012;2012:902917. doi: 10.1155/2012/902917.
60. Li X., Liu Y., Guo X., Ma Y., Zhang H., Liang H. Effect of Lactobacillus casei on lipid metabolism and intestinal microflora in patients with alcoholic liver injury. *Eur J Clin Nutr*. 2021;75(8):1227–1236. doi: 10.1038/s41430–020–00852–8.
61. Razmpoosh E., Javadi A., Ejtahed H.S., Mirmiran P., Javadi M., Yousefinejad A. The effect of probiotic supplementation on glycemic control and lipid profile in patients with type 2 diabetes: A randomized placebo controlled trial. *Diabetes Metab Syndr*. 2019;13(1):175–182. doi: 10.1016/j.dsx.2018.08.008.
62. Shimizu M., Hashiguchi M., Shiga T., Tamura H.O., Mochizuki M. Meta-Analysis: Effects of Probiotic Supplementation on Lipid Profiles in Normal to Mildly Hypercholesterolemic Individuals. *PLoS One*. 2015;10(10): e0139795. doi: 10.1371/journal.pone.0139795.
63. Wu Y., Zhang Q., Ren Y., Ruan Z. Effect of probiotic Lactobacillus on lipid profile: A systematic review and meta-analysis of randomized, controlled trials. *PLoS One*. 2017;12(6): e0178868. doi: 10.1371/journal.pone.0178868.
64. Ruscica M., Pavanello C., Gandini S. et al. Nutraceutical approach for the management of cardiovascular risk – a combination containing the probiotic Bifidobacterium longum BB536 and red yeast rice extract: results from a randomized, double-blind, placebo-controlled study. *Nutr J*. 2019;18(1):13. doi: 10.1186/s12937–019–0438–2.
65. Wang L., Guo M.J., Gao Q., Yang J.F., Yang L., Pang X.L., Jiang X.J. The effects of probiotics on total cholesterol: A meta-analysis of randomized controlled trials. *Medicine (Baltimore)*. 2018 Feb;97(5): e9679. doi: 10.1097/MD.0000000000009679.
66. Mo R., Zhang X., Yang Y. Effect of probiotics on lipid profiles in hypercholesterolaemic adults: A meta-analysis of randomized controlled trials. *Med Clin (Barc)*. 2019 Jun 21;152(12):473–481. English, Spanish. doi: 10.1016/j.medcli.2018.09.007.
67. Hiippala K., Jouhten H., Ronkainen A., Hartikainen A., Kainulainen V., Jalanka J., Satokari R. The Potential of Gut Commensals in Reinforcing Intestinal Barrier Function and Alleviating Inflammation. *Nutrients*. 2018 Jul 29;10(8):988. doi: 10.3390/nu10080988.
68. Qiu L., Tao X., Xiong H., Yu J., Wei H. Lactobacillus plantarum ZDY04 exhibits a strain-specific property of lowering TMAO via the modulation of gut microbiota in mice. *Food Funct*. 2018 Aug 15;9(8):4299–4309. doi: 10.1039/c8fo00349a.
69. Cavallini D.C., Manzoni M.S., Bedani R. et al. Probiotic Soy Product Supplemented with Isoflavones Improves the Lipid Profile of Moderately Hypercholesterolemic Men: A Randomized Controlled Trial. *Nutrients*. 2016 Jan 19;8(1):52. doi: 10.3390/nu8010052.
70. Dönmez N., Kısadere İ., Balaban C., Kadiralieva N. Effects of traditional homemade koumiss on some hematological and biochemical characteristics in sedentary men exposed to exercise. *Biotech Histochem*. 2014 Nov;89(8):558–63. doi: 10.3109/10520295.2014.915428.
71. DiRienzo D.B. Effect of probiotics on biomarkers of cardiovascular disease: implications for heart-healthy diets. *Nutr Rev*. 2014 Jan;72(1):18–29. doi: 10.1111/nure.12084.
72. Rerksuppaphol S., Rerksuppaphol L. A Randomized Double-blind Controlled Trial of Lactobacillus acidophilus Plus Bifidobacterium bifidum versus Placebo in Patients with Hypercholesterolemia. *J Clin Diagn Res*. 2015 Mar;9(3): KC01–4. doi: 10.7860/JCDR/2015/11867.5728.
73. Bernini L.J., Simão A.N., Alfieri D.F., Lozovoy M.A., Mari N.L., de Souza C.H., Dichi I., Costa G.N. Beneficial effects of Bifidobacterium lactis on lipid profile and cytokines in patients with metabolic syndrome: A randomized trial. Effects of probiotics on metabolic syndrome. *Nutrition*. 2016 Jun;32(6):716–9. doi: 10.1016/j.nut.2015.11.001.
74. Guardamagna O., Amaretti A., Puddu P.E., Raimondi S., Abello F., Cagliero P., Rossi M. Bifidobacteria supplementation: effects on plasma lipid profiles in dyslipidemic children. *Nutrition*. 2014 Jul-Aug;30(7–8):831–6. doi: 10.1016/j.nut.2014.01.014.
75. Bertolami M.C., Faludi A.A., Batlouni M. Evaluation of the effects of a new fermented milk product (Gaio) on primary hypercholesterolemia. *Eur J Clin Nutr*. 1999 Feb;53(2):97–101. doi: 10.1038/sj.ejcn.1600683.
76. L'niavina V.M., Baryshnikova N.V., Uspenskiy Y.P., Ermolenko E.I., Suvorov A.N. Probiotics in the correction of lipid metabolism. Problems of medical mycology. 2023; 25 (2): 85. Available at: https://mycology.szgmu.ru/images/2–2023.pdf (accessed 28 June 2023)
77. Ooi L.G., Liong M.T. Cholesterol-lowering effects of probiotics and prebiotics: a review of in vivo and in vitro findings. *Int J Mol Sci*. 2010 Jun 17;11(6):2499–522. doi: 10.3390/ijms11062499.
78. Khongrum J., Yingthongchai P., Boonyapranai K. et al. Safety and Effects of Lactobacillus paracasei TISTR 2593 Supplementation on Improving Cholesterol Metabolism and Atherosclerosis-Related Parameters in Subjects with Hypercholesterolemia: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial. *Nutrients*. 2023 Jan 28;15(3):661. doi: 10.3390/nu15030661.
79. Yang L., Xie X., Li Y., Wu L. et al. Evaluation of the Cholesterol-Lowering Mechanism of Enterococcus faecium Strain 132 and Lactobacillus paracasei Strain 201 in Hypercholesterolemia Rats. *Nutrients*. 2021 Jun 9;13(6):1982. doi: 10.3390/nu13061982.
80. Xu W., Zou K., Zhan Y., Cai Y., Zhang Z., Tao X., Qiu L., Wei H. Enterococcus faecium GEFA01 alleviates hypercholesterolemia by promoting reverse cholesterol transportation via modulating the gut microbiota-SCFA axis. *Front Nutr*. 2022 Nov 8;9:1020734. doi: 10.3389/fnut.2022.1020734.
81. Suvorov A., Karaseva A., Kotyleva M. et al. Autoprobiotics as an approach for restoration of personalised microbiota. *Front. Microbiol*. 2018; 9:1869. (in Russ.) doi: 10.3389/fmicb.2018.01869.
82. Tsapieva A.N., Borovkova E.A., Karaseva A.B., Alieva E.V., Suvorov A.N. Development of a method for identification of indigenous gut lactobacilli in the creation of autoprobiotics. *Voprosy detskoi dietologii = Pediatric Nutrition*. 2019; 17 (3): 52–59. (in Russ.) doi: 10.20953/1727–5784–2019–3–52–59.
83. Ermolenko E.I., Abdurasulova I.N., Kotyleva M.P., Svirido D.A., Matsulevich A.V., Karaseva A.B. Effects of Indigenous enterococci on the Intestinal Microbiota and the Behavior of Rats. *Neuroscience and Behavioral Physiology*, 2018, 48(4):496–505. (in Russ.) doi: 10.1007/s11055–018–0591.
84. Simanenkov V.I., Bakulina N.V., Tikhonov S.V., Ermolenko E.I., Dekkanova V.D., Kotyleva M.P., Lavrenova N.S., Voropaeva L.S., Korzheva M.D., Suvorov A.N., Tsapieva A.N. Efficacy and safety of autoprobiotic therapy in patients with type 2 diabetes mel-

litus. *Medical alphabet*. 2020;1(30):48–53. (In Russ.). doi: 10.33667/2078–5631–2020–30–48–53.

85. Simanenkov V.I., Suvorov A.N., Solovyova O.I. A method for obtaining a personalized autoprobiotic product and a method for treating irritable bowel syndrome using this product. RF Patent for invention No. 2546253 / 02.03.2015. Byul. No. 10. Available at: http://www.findpatent.ru/patent/254/2546253.html (accessed on 30 June 2023).
86. Baryshnikova N. V., Alferova L.S., Demchenko E.A., Lavrenova N.S., Tsapieva A.N., Suvorov A.N., Ermolenko E.I. The effectiveness of autoprobiotics in the correction of lipid metabolism. *Experimental and Clinical Gastroenterology*. 2023;220(12): (In Russ.) doi: 10.31146/1682–8658-ecg-220–12–97–102.
87. Vourakis M., Mayer G., Rousseau G. The Role of Gut Microbiota on Cholesterol Metabolism in Atherosclerosis. *Int J Mol Sci*. 2021;22(15):8074. doi: 10.3390/ijms22158074.
88. Sudun Liu S., Xiao C., Peng C., Liang L., He X., Zhao S., Zhang G. Probiotic strains improve high-fat diet-induced hypercholesterolemia through modulating gut microbiota in ways different from atorvastatin. *Food Funct*. 2019;10(9):6098–6109. doi: 10.1039/c9fo00444k.
89. Wang L., Wang Y., Wang H., Zhou X., Wei X., Xie Z., Zhang Z., Wang K., Mu J. The influence of the intestinal microflora to the efficacy of Rosuvastatin. *Lipids Health Dis*. 2018;17(1):151. doi: 10.1186/s12944–018–0801-x.
90. Peng Chen and Kangbao Li Statin Therapy and Gut Microbiota. doi: 10.5772/intechopen.1001098. Available at: https://www.intechopen.com/chapters/1129562 (accessed on 28 June 2023).
91. Eckel R.H., Bruce K.D. Statins, gut microbiome, LDL–C, glucose intolerance: Personalized medicine timely? *Med*. 2022;3(6):355–357. doi: 10.1016/j.medj.2022.05.006.
92. Reis S.A., Conceição L.L., Rosa D.D., Siqueira N.P., Peluzio M.C.G. Mechanisms responsible for the hypocholesterolaemic effect of regular consumption of probiotics. *Nutr Res Rev*. 2017;30(1):36–49. doi: 10.1017/S0954422416000226.
93. Oliveira P.W.C., Couto M.R., de Sousa G.J., Peixoto P., Moraes F.S.A., de Andrade T.U., Bissoli N.S. Effects of Drugs, Phytoestrogens, Nutrients and Probiotics on Endothelial Dysfunction in the Estrogen-Deficient State. *Curr Pharm Des*. 2020;26(30):3711–3722. doi: 10.2174/1381612826666200331084338.
94. Zvenigorodskaia L.A., Cherkashova E.A., Samsonova N.G., Nilova T.V., Sil'verstova S. Iu. [Advisability of using probiotics in the treatment of atherogenic dyslipidemia]. *Eksp Klin Gastroenterol*. 2011;(2):37–43. Russian. PMID: 21563361.
95. Zvenigorodskaia L.A., Samsonova N.G., Mel'nikova N.V., Cherkashova E.A. [Hypolipidemic therapy in patients with non-alcoholic fatty liver disease]. *Eksp Klin Gastroenterol*. 2010;(7):25–33. Russian. PMID: 21033080.