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A.E. GULAYEV[1], SH. D. SERGAZY[1], A.K. ZHASHKEYEV[2], ZH.SH. ZHUMADILOV[1], G.T. ABUOVA[3]
[1] National Laboratory Astana, Nazarbayev University, Astana, Kazakhstan
[2] Karaganda Medical University, Karaganda, Kazakhstan
[3] South Kazakhstan Medical Academy (SKMA), Shymkent, Kazakhstan

THE INTESTINAL MICROBIOME AS A POTENTIAL TARGET FOR THE DEVELOPMENT OF STRATEGIES FOR REDUCING THE RISK OF CARDIOVASCULAR EVENTS IN CORONARY HEART DISEASE

Resume: *The modern period in healthcare is characterized by the preservation of the leading positions of cardiovascular diseases due to mortality in the presence of an extensive arsenal of drugs that affect risk factors for CVD. For this reason, research into new treatments for atherosclerosis continues. One of these ways of influencing atherogenesis is to change the intestinal microbiome, as an impact on the stage of atherosclerosis pathogenesis. Many scientific publications consider trimethylamine N-oxide (TMAO) as one of the predictors of atherosclerosis. This metabolite is directly dependent on the composition of the gut microbiome. The literature review includes an analysis of foreign scientific publications of scientific electronic databases Elsevier, PubMed, Web of Science, Google Scholar, as well as research results presented in domestic publications.*
Purpose: *Based on domestic and foreign scientific publications, to systematize possible strategies for influencing the intestinal microbiota to reduce the risk of cardiovascular events in IHD, including new prebiotics based on polyphenols.*
Results and conclusions: *An analysis of the literature data has shown that microbiota remodeling can indeed be recognized as an approach to reduce circulating TMAO levels. In addition to the use of probiotics and prebiotics or a plant-based diet, polyphenols can effectively promote the remodeling of the gut microbiota. In particular, polyphenols are effective antimicrobial agents against certain TMA-producing bacterial strains. Overall, these studies provide strong evidence for polyphenol-mediated microbiota remodeling resulting in lower TMAO levels and suggest that polyphenol-rich diets and/or supplements may be considered as a novel approach to the treatment and/or prevention of CVD. The discovery of an evidence-based relationship between gut microbiota metabolites and cardiovascular events provides opportunities for the development of both new diagnostic tests as biomarkers of predisposition to myocardial infarction, stroke, and new therapeutic approaches for the prevention of cardiovascular events after myocardial infarction and the correction of myocardial remodeling. In this regard, we highlight probiotic and dietary therapy using polyphenols as the most promising.*
Keywords: *gut microbiome, trimethylamine oxide (TMAO), polyphenols, cardiovascular disease, healthcare.*

А.Е. Гуляев[1], Ш.Д. Сергазы[1], А.К. Жашкеев[2], Ж.Ш. Жұмаділов[1], Г.Т. Абуова[3]
[1]National Laboratory Astana, Назарбаев Университеті, Астана, Қазақстан
[2]Қарағанды медицина университеті, Қарағанды, Қазақстан
[3]Оңтүстік Қазақстан медицина академиясы (ОҚМА), Шымкент, Қазақстан

ІШЕК МИКРОБИОМАСЫ КОРОНАРЛЫҚ АРТЕРИЯ АУРУЫНДАҒЫ ЖҮРЕК-ҚАН ТАМЫРЛАРЫ ОҚИҒАЛАРЫНЫҢ ҚАУПІН АЗАЙТУ СТРАТЕГИЯЛАРЫН ӘЗІРЛЕУДІҢ ӘЛЕУЕТТІ НЫСАНЫ РЕТІНДЕ

А.Е. Гуляев[1], Ш.Д. Сергазы[1], А.К. Жашкеев[2], Ж.Ш. Жумадилов[1], Г.Т. Абуова[3]
[1]National Laboratory Astana, Назарбаев Университет, Астана, Казахстан
[2]Медицинский университет Караганды, Караганда, Казахстан
[3]Южно-Казахстанская медицинская академия (ЮКМА), Шымкент, Казахстан

КИШЕЧНЫЙ МИКРОБИОМ КАК ПОТЕНЦИАЛЬНАЯ МИШЕНЬ ДЛЯ РАЗРАБОТКИ СТРАТЕГИЙ СНИЖЕНИЯ РИСКА СЕРДЕЧНО-СОСУДИСТЫХ СОБЫТИЙ ПРИ ИШЕМИЧЕСКОЙ БОЛЕЗНИ СЕРДЦА

Түйін: денсаулық сақтаудағы қазіргі кезең ЖҚА үшін қауіп факторларына әсер ететін дәрілік заттардың кең арсеналы болған кезде өлім-жітімге байланысты жүрек-қан тамырлары ауруларының жетекші позицияларының сақталуымен сипатталады. Осы себепті атеросклерозды емдеудің жаңа әдістерін зерттеу жалғасуда. Атерогенезге әсер етудің бір жолы-атеросклероз патогенезінің сатысына әсер ету сияқты ішек микробиомасының өзгеруі. Көптеген ғылыми басылымдар N-триметиламин оксидін (ТМАО) атеросклероздың болжаушыларының бірі ретінде қарастырады. Бұл метаболит ішек микробиомасының құрамына тікелей байланысты. Әдебиеттерге шолу Elsevier, PubMed, Web of Science, Google Scholar ғылыми электрондық дерекқорларының шетелдік ғылыми басылымдарын талдауды, сондай-ақ отандық басылымдарда ұсынылған зерттеу нәтижелерін қамтиды.

Мақсаты: отандық және шетелдік ғылыми жарияланымдар негізінде АЖЖ-дағы жүрек-қан тамырлары оқиғаларының, соның ішінде полифенол негізіндегі жаңа пребиотиктердің қаупін азайту үшін ішек микробиотасына әсер етудің ықтимал стратегияларын жүйелеу.

Нәтижелер мен қорытындылар: әдеби деректерді талдау микробиотаны қайта құруды шын мәнінде айналымдағы ТМАО деңгейін төмендету тәсілі ретінде тануға болатынын көрсетті. Пробиотиктер мен пребиотиктерді немесе өсімдік негізіндегі диетаны қолданудан басқа, полифенолдар ішек микробиотасының қайта құрылуына тиімді ықпал етуі мүмкін. Атап айтқанда, полифенолдар ТМА шығаратын белгілі бір бактериялық штамдарға қарсы тиімді микробқа қарсы агенттер болып табылады. Тұтастай алғанда, бұл зерттеулер ТМАО деңгейінің төмендеуіне әкелетін полифенол арқылы микробиотаны қайта құрудың күшті дәлелдерін береді және полифенолға бай диеталар және / немесе қоспалар ЖҚА емдеуге және / немесе алдын алуға жаңа тәсіл ретінде қарастырылуы мүмкін екенін көрсетеді. Ішек микробиотасының метаболиттері мен жүрек-қан тамырлары оқиғалары арасындағы дәлелді байланыстың ашылуы миокард инфарктісіне, инсультке бейімділіктің биомаркерлері ретінде жаңа диагностикалық сынақтарды және миокард инфарктісінен кейінгі жүрек-қан тамырлары оқиғаларының алдын алу және миокардты қайта құруды түзету үшін жаңа терапевтік тәсілдерді әзірлеуге мүмкіндік береді. Осыған байланысты біз ең перспективалы ретінде полифенолдарды қолданатын пробиотикалық және диеталық терапияны бөліп көрсетеміз.

Түйінді сөздер: ішек микробиомасы, триметиламиноксид (ТМАО), полифенолдар, жүрек-қан тамырлары аурулары, денсаулық сақтау.

Резюме: Современный период в здравоохранений характеризуется сохранением лидирующих позиций сердечно-сосудистых заболеваний по причине смертности при наличий обширного арсенала лекарственных средств влияющих на факторы риска для ССЗ. По этой причине продолжается исследование новых методов лечения атеросклероза. Одним из таких путей влияния на атерогенез является изменение микробиома кишечника, как воздействие на этап патогенеза атеросклероза. Много научных публикаций рассматривают N-оксида триметиламина (ТМАО), как один из предикторов атеросклероза. Этот метаболит напрямую зависит от состава кишечного микробиома. Обзор литературы включает анализ зарубежных научных публикаций научных электронных баз данных Elsevier, PubMed, Web of Science, Google Scholar, а также результаты исследований, предсавленные в отечественных изданиях.

Цель: На основе отечественных и зарубежных научных публикаций провести систематизацию возможных стратегии влияния на кишечную микробиоту для снижения риска сердечно-сосудистых событий при ИБС, в том числе новых пребиотиков на основе полифенолов.

Результаты и выводы: Анализ литературных данных показал, ремоделирование микробиоты действительно может быть признано подходом к снижению уровней циркулирующего ТМАО. Кроме использования пробиотиков и пребиотиков или растительной диеты, полифенолы могут эффективно способствовать ремоделированию микробиоты кишечника. В частности, полифенолы являются эффективными противомикробными средствами против определенных бактериальных штаммов, продуцирующих ТМА. В целом, эти исследования предоставляют убедительные доказательства опосредованного полифенолами ремоделирования микробиоты, приводящего к снижению уровня ТМАО, и предполагают, что диеты, богатые полифенолами, и / или добавки могут рассматриваться как новый подход к лечению и / или профилактике ССЗ. Открытие доказательной взаимосвязи между метаболитами кишечной микробиоты и сердечно-сосудистыми событиями предоставляет возможности для разработки как новых диагностических тестов в качестве биомаркеров предрасположенности к инфаркту миокарда, инсульту так и новых терапевтических подходов для профилактики сердечно-сосудистых событий после инфаркта миокарда и коррекции ремоделирования миокарда. В этой связи, мы выделяем пробиотическую и диетическую терапию с использованием полифенолов, как наиболее перспективные.

Ключевые слова: микробиом кишечника, триметиламиноксид (ТМАО), полифенолы, сердечно-сосудистые заболевания, здравоохранение.

Introduction. Coronary heart disease (CHD) currently continues to occupy the first place due to fatal outcomes for humans [1]. In society, the opinion has formed that the lower the level of LDL cholesterol, the better. However, there are reports that in patients with no risk factors and on active statin therapy, even if low-density lipoprotein cholesterol (LDL-C) reaches the target level, (≥70 mg/dL in the US) and (<55 mg/dl in Europe), CV risk is still present [2,3].

As one of the most intensively discussed strategies for reducing the risk of cardiovascular events in coronary heart disease, the intestinal microbiome is present as one of the fundamentally important regulators of some links in the pathogenesis of atherogenesis and related diseases. Trimethylamine N-oxide (TMAO) is currently being considered, which depends on the

composition of the intestinal microbiome [4]. TMAO, a microbiota-dependent dietary metabolite, is the first and most studied of the many metabolic products of microbiota bacteria, with some evidence of its role in the development of cardiovascular disease. Risk stratification of cardiovascular events (MACE-Major Adverse Cardiac Events) in coronary heart disease using the assessment of TMAO levels remains a clinical problem [5].

Materials and methods. The literature review includes an analysis of foreign scientific publications of scientific electronic databases Elsevier, PubMed, Web of Science, Google Scholar, as well as research results presented in domestic publications. The inclusion criteria for this review were: studies containing experimental data on microbiome corrections and on the study of the pharmacological properties of polyphenols that modulate the microbiota according to the TMAO indicator with an effect on cardiovascular events in IHD in English and Russian for the last 12 years (2010-2022).

Results. Part 1. The microbiome and cardiovascular disease. The brief overview of the composition of the human gut microbiome presented below anticipates the characterization of the microbiome and its metabolites in CVD and CAD in particular. The human gut is thought to contain >1014 microbiome units [6]. The term gut microbiota refers to all microorganisms colonized in the intestinal tract, and the gut microbiome collectively means the genes and genomes of the microbiota, as well as their by-products and the host environment [7]. The composition of a healthy person's gut microbiome can differ markedly from that of another person [8], however, this composition is relatively stable over time [9]. The gut microbiota refers to the complex community of different types of microorganisms found in the gastrointestinal tract. Although most microorganisms belong to the category of bacteria, nevertheless, there are organisms of different classes, including fungi, viruses, protozoa and archaebacteria [10]. Overall, a large number of studies over the past decade have shown that gut microbiome dysbiosis is strongly associated with CVD [11]. The available literature contains the results of studies that attempted to identify strains of microorganisms associated with coronary artery disease in the experiment and in the clinic. Differences in the gut microbiome between patients with cardiovascular diseases and healthy people have been noted for a long time [12]. Kelly T., et al [13] find lower alpha diversity of Faecalibacterium, Subdoligranulum, Turicibacter, Rothia, Lachnospira, Haemophilus, Dialister, Bifidobacterium, Oscillibacter, and Megamonas at high CV risk compared to low risk patients CVD. Yin J et al. [14] comparing the fecal microbiota community using 16S rRNA gene sequencing in 141 patients with stroke and transient ischemic attack and 94 controls found more opportunistic pathogens such as Enterobacter, Megasphaera, Oscillibacter and Desulfovibrio in stroke, and fewer commensal or beneficial genera such as Bacteroides, Prevotella, and Faecalibacterium. Emoto et al. [15] compared the fecal microbiota for the terminal restriction fragment length polymorphism (T-RFLP) of 16S rDNA amplicons in 39 patients with coronary heart disease (CHD) and 30 control patients without CAD, comparable in age and sex, found that the ratio Frimicutes/ Bacteroidetes and Lactobacillus and reduction of Bacteroides plus Preveotella in CAD.

Part 2. Gut microbiota remodeling to reduce TMAO levels and cardiovascular risk

Therapeutic strategies developed to manage the composition of the gut microbiota and/or their metabolism known to date include dietary interventions; treatment with probiotics, prebiotics and antibiotics; as well as fecal transplants. In a double-blind, placebo-controlled, randomized clinical trial in 44 patients with myocardial infarction undergoing percutaneous coronary intervention [16], it was found that probiotic capsules containing 1.6 × 109 colony-forming units of bacteria for 3 months provided a significant decrease in serum concentrations of TGF-β and TMAO levels compared with the placebo group, as well as improved echocardiographic parameters and left ventricular ejection fraction. A small, double-blind, placebo-controlled study using Saccharomyces boulardii [17] showed that patients with stable heart failure after a heart attack for 3 months of probiotic treatment provided significant improvements in both ejection fraction and left atrial diameter. The results of some clinical intervention studies in patients with cardiovascular disease and microbiota exposure to antibiotics have been inconsistent in their results [18] and we chose not to analyze their results in this review. Fecal transplantation, as well as a method for correcting the microbiome in coronary heart disease, is currently being tested in several clinical regimens in acute coronary syndrome and decompensated heart failure [19]. In principle, gut bacteria are well suited for genetic modification to obtain desired properties, including a particular metabolic activity or the ability to produce a particular metabolic product [20].

In the context of microbiota remodeling, dietary interventions (including diets rich in fiber and antioxidants, use of prebiotic and probiotic supplements) appear to be novel and useful approaches to treat diseases associated with high TMAO levels [21]. The case of trimethylamine N-oxide (TMAO) [22], a microbiota-dependent metabolite derived from consumed foods, represents the first and most studied of the many metabolic products of bacteria in the microbiota, with some evidence of its role in the development of cardiovascular diseases. TMAO is formed in the liver from trimethylamine (TMA), which, in turn, is the result of the processing of carnitine, choline, betaine and lecithin by the intestinal microbiome [23]. Plasma levels of TMAO are believed to be determined by several factors, including consumption of its metabolic precursors, drugs, and FMO flavin monooxygenase activity in the liver [24]. The main microbial species responsible for the degradation of another TMAO source, L-carnitine, are the Proteobacteria and Bacteroides phyla and the Prevotellaceae family [25]. The fact that elevated plasma levels of TMAO in patients are associated with an increased risk of adverse cardiovascular events has been reported since 2013 [26], which has subsequently been confirmed many times. In a study of patients with acute coronary syndrome (ACS), elevated TMAO was found to be a high predictor of long-term mortality risk [27]. Subsequently, both experimental and clinical studies found a close relationship between the risk of cardiovascular events and the level of TMAO [28]. In the last decade, numerous reviews have been published on the association between circulating trimethylamine N-oxide (TMAO) levels and cardiovascular risk [29, 30, 31, 32]. The first meta-analysis

has also been published, showing a positive dose-dependent relationship between the concentration of circulating TMAO and the risk of stroke [33]. There is the most comprehensive (6879 patients, mean follow-up 5.0 years) systematic review to date [34] describing the association between plasma TMAO levels and the occurrence of major cardiac events (MACE) and all-cause mortality in adults with heart failure confirms the importance of TMAO: elevated plasma TMAO levels in patients with heart failure are associated with worse prognosis [35] suggests that elevated TMAO levels are associated with an increased incidence of MACE in patients with CAD [36].

Part 3. Dietary Use of Polyphenols as a Microbiome Altering Strategy

It is estimated that about 90–95% of the total amount of polyphenols consumed remains unabsorbed, and colon bacteria act enzymatically on their basis, producing metabolites with different physiological significance [37].

Early animal studies demonstrated the ability of polyphenols, in particular resveratrol, to reduce TMAO levels in mice [39]. It turned out that resveratrol is effective in remodeling the composition of the microbiota by increasing the growth of Lactobacillus and Bifidobacterium [39], increasing the ratio of Bacteroidetes / Firmicutes and reducing the growth of Enterococcus faecalis [38]. Chen et al. [39] conducted an animal study demonstrating the TMAO-reducing effect of resveratrol in ApoE-/- mice. Interestingly, antibiotic treatment reverses the effects of lowering TMAO levels [40]. At the same time, a decrease in the expression of mRNA of pro-inflammatory genes, including nuclear factor-κB (NF-κB), interleukin (IL) -1β, IL-6 and cyclooxygenase-2 (COX-2), as well as the expression of proteins NF-κB and COX- 2 in liver tissue [41]. A randomized, placebo-controlled, cross-over clinical trial was conducted in healthy subjects evaluating the efficacy of a nutraceutical formulation containing grape pomace polyphenolic extract microencapsulated with maltodextrins, registered as Taurisolo®, in acid-resistant capsules [42]. After 4 weeks, TMAO levels were significantly reduced in the treatment group compared to placebo (63.6% vs. 0.54%, respectively, P<0.0001). The results of an experimental study published somewhat later with the same dietary supplement based on grape polyphenols [43] made it possible to reveal the counteraction of cytotoxicity caused by TMAO and high glucose content in the cell culture of H9c2 cardiomyoblasts [44]. Based on this evidence, microbiota remodeling can indeed be recognized as an approach to reduce circulating TMAO levels [45]. In particular, polyphenols are effective antimicrobial agents against certain TMA-producing bacterial strains, including Clostridia and Bacteroides [46]. Based on these studies, it is clear that dietary polyphenols and their metabolites promote gut health by acting as a prebiotic by positively modulating gut microbial composition, which stimulates the growth of beneficial microbes while pathogens are suppressed [47].

We also reviewed domestic studies on the relationship between the gut microbiome and MACE in CHD and targeted correction of TMAO levels in patients with cardiovascular diseases through the impact on the microbiome. We found a few original [48,49,50] and review articles reflecting only one of the aspects of our study. For example, at the Medical University of Karaganda, a study was conducted on the relationship between the level of TMAO and cardiovascular risk among the population of central Kazakhstan. The relationship between elevated TMAO titers and high cardiovascular risk was revealed, general pathogenetic mechanisms in the development of MACE were shown, and the prognostic value of TMAO among residents of Central Kazakhstan was confirmed [48]. In studies [49,50] based on the Laboratory of Human Microbiome and Longevity, Center for Life Sciences, National Laboratory Astana, Nazarbayev University, some progress has been made in studying the remodeling of the intestinal microbiota by prebiotics.

Conclusions. At present, our understanding of the interaction between the gut microbiome and risk factors for coronary heart disease and myocardial infarction can only be considered the tip of the iceberg, and the role of targeted interventions in the gut microbiota remains uncertain due to the lack of sufficient clinical research. -vascular events provides opportunities for the development of both new diagnostic tests as biomarkers of predisposition to myocardial infarction, stroke, and new therapeutic approaches for the prevention of cardiovascular events after myocardial infarction and the correction of myocardial remodeling. In this regard, we highlight probiotic and dietary therapy using polyphenols as the most promising. Data on the bidirectional interaction of polyphenols on the gut microbiota and their resulting effects in humans still need to be refined. Of course, a better understanding of aspects of the interaction of the gut-heart axis is indispensable to obtain a definition of the basis of new therapeutic approaches, as well as clinical studies themselves.

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Information about the authors:
Gulyaev Alexander Evgenievich - MD, PhD, professor, leading researcher, Laboratory of Epidemiology and Public Health, National Laboratory Astana, Nazarbayev University, Astana, Republic of Kazakhstan, 53 Kabanbay Batyr Avenue, akin@mail.ru, ORCID ID 0000-0001-5098-4675
Sergazy Shyngys Dauletkhanuly - PhD, Senior Research Fellow, Laboratory of Epidemiology and Public Health, National Laboratory Astana, Nazarbayev University, 53 Kabanbay Batyra Ave, Astana, Kazakhstan, shynggys.sergazy@nu.edu.kz, ORCID ID 0000-0002-6030-620X
Zhashkeyev Azamat Kenzhinovich - PhD doctoral student at Karaganda Medical University, Laboratory of Human Microbiome and Longevity, Astana National Laboratory, Nazarbayev University, Karaganda, Republic of Kazakhstan, Researcher ID: EIJ-7330-2022
Zhumadilov Zhaksybay Shaimardanovich - MD, PhD, professor, leading researcher, Laboratory of Epidemiology and Public Health, National Laboratory Astana, Nazarbayev University, Astana, Republic of Kazakhstan, 53 Kabanbay Batyr Ave. zzhumadilov@nu.edu.kz, ORCID ID 0000-0003-3855-6429
Abuova Gulnara Turganbaevna - PhD in biology, associate professor, South Kazakhstan Medical Academy (SKMA), Shymkent, Republic of Kazakhstan, 1, Al-Farabi sq., Scopus ID: 57193756741