ORIGINAL ARTICLE

GUT MICROBIOTA COMPOSITION AND ITS METABOLITES CHANGES IN PATIENTS WITH ATHEROSCLEROSIS AND ATRIAL FIBRILLATION

DOI: 10.36740/WLek202212117

Iryna Melnychuk, Viktor G. Lizogub
O.O. BOGOMOLETS NATIONAL MEDICAL UNIVERSITY, KYIV, UKRAINE

ABSTRACT

The aim: To check changes of gut microbiota composition and its metabolites in atherosclerosis (AS) patients with or without atrial fibrillation (AF) and special connections between them and important clinic and laboratory features of investigated groups.

Materials and methods: 300 patients were investigated. All investigated were divided into 3 groups: control group (CG) – 27 patients without AS and arrhythmias; mean group – 149 patients with AS but without arrhythmias; comparable group – 124 patients with AS and AF paroxysm. By 16-S rRNA sequencing was checked gut microbiota composition. The level of trimethylamine-N-oxide (TMAO), trimethylamine (TMA) plasma was determined by gas chromatography with mass electron detection.

Results: The mean and comparable groups have the significant abundance of total bacterial mass, *Bacteroides Spp., Faecalibacterium Prausnitzii, Actinobacter Spp.* and decreasing *Ruminococcus Spp*. In the comparable group to the mean significant increasing of *Actinobacter Spp*. and decreasing *Eubacterium Rectale*, *Ruminococcus Spp*. were checked. Bacteroides Fragilis Group/ Faecalibacterium Prausnitzii ratio was significantly higher than in patients' comparable group. In the mean group patients compared with CG significant abundance of *Streptococcus Spp*. was checked. In the comparable group compared with CG significant leak of *Eubacterium Rectale* was checked. The highest amount of correlations was between *Lactobacillus Spp*., *Streptococcus Spp*. and clinic-laboratory changes. The mean and comparable groups the significant increasing of TMA ta TMAO plasma levels were checked. In patients of comparable group compared with patients mean group the significant increasing of TMAO plasma level was revealed.

Conclusions: We checked special bacterial changes of gut microbiota that are common for patients with AS and AF comparable with AS patients. TMAO plasma levels are increased significantly for patients with AS and AF comparable with AS patients. Connections between AS and AF with TMAO plasma levels are confirmed by reliable correlations between TMAO and age, BMI, GFR, HDL levels. Special bacterial species are closely connected with age, BMI, GFR, HDL, LDL, plasma TMA and TMAO levels.

KEY WORDS: atherosclerosis, atrial fibrillation, gut microbiota composition, trimethylamine-N-oxide, trimethylamine

Wiad Lek. 2022;75(12):2994-2999

INTRODUCTION

The role of the gut microbiota and its metabolites in human health become more and more popular during last ten years. Especially occurred a lot of new data about links between gut microbiota composition and metabolic disorders. Condition of gut microbiota is an important component of human health in general. It influences on cardiovascular health directly by regulating intestinal digestion and absorption and indirectly through its metabolites as trimethylamine (TMA), trimethylamine-N-oxide (TMAO), short chain fatty acids (SHFA) [1].

Human gut microbiota is defined as complex of microorganisms, with includes bacteria and archea that lives into digestive tract. Gut microbiota changes are closely linked with metabolic disorders as obesity, type 2 diabetes mellitus, hyperlipidemia, arterial hypertension, chronic kidney diseases, fatty liver etc., which are the known risk factors of atherosclerosis (AS) and atrial fibrillation (AF) [2, 3]. But no special microbial pattern for atherosclerotic changes are not defined yet. On the one hand it is described the prevalence of Bacteroides, Escherichia coli and low level of Proteobacteria and Haemophilus for patients with AS [4]. Other authors reported abundance of *Streptococcus salivarius, Klebsiella pneumoniae and leak of Roseburia hominis in AS patients [5].* One more datum reported higher level of *Proteobacteria and Enterobacter*, *Escherichia*/*Shigella*, *Klebsiella* [6]. Differences in studies results and little groups of investigated patients shows us an importance of further gut microbiota composition features investigations in AS patients.

Moreover, it is no exact data about gut microbiota composition in patients with AF. But not far away occurred a lot of information about links between AF and gut dysbiosis [7, 8]. As we know increasing TMAO plasma levels become an evidence risk factor of AS, but by the latest data TMAO level can be the important risk factor of AF occurrence also [10]. The role of SHFA in pathogenesis of AS and AF is also stayed questionable. By some data their changes can provoke AF paroxysm [11]. Important that AF and AS can be the cause and the reason of each other in the same time. Together they form the viscous circle that's lead for increasing risk of cardiovascular events. So, their pathogenesis can be analyzed together [9].

Table I. Clinical and laboratory characteristics of investigated groups, mean ± standard error

Characteristic /group	AS	AS+AF	CG	P1-2	P2-3	P1-3
Age (years)	67,71±3,90	67,96±0,94	56,25±2,18	P>0,05	P>0,05	P>0,05
Men (%)	48,99	47,97	48,15	P>0,05	P>0,05	P>0,05
BMI (kg/m^2)	27,02±0,33	26,93±0,43	28,12±2,10	P>0,05	P>0,05	P>0,05
GFR (ml/min)	62,03±2,31	67,73±1,98	84,01±5,48	P>0,05	P<0,05	P<0,05
Smoking (%)	51,01	41,46	40,74	P>0,05	P>0,05	P>0,05
Total cholesterol (mmol/l)	5,73±0,37	6,18±0,31	4,32±0,21	P>0,05	P<0,05	P<0,05
Triglycerides (mmol/l)	2,02±0,18	1,74±0,14	1,12±0,09	P>0,05	P<0,05	P<0,05
LDL (mmol/l)	2,63±0,29	2,66±0,24	1,54±0,11	P>0,05	P<0,05	P<0,05
HDL (mmol/l)	1,46±0,13	1,23±0,14	1,74±0,12	P>0,05	P<0,05	P<0,05

According the listed it is very important to understand if there are special changes of gut microbiota composition and its metabolites in AS patients with or without AF and also are there special connections between them and important clinic and laboratory features of investigated groups.

THE AIM

To check changes of gut microbiota composition and its metabolites in atherosclerosis patients with or without atrial fibrillation and special connections between them and important clinic and laboratory features of investigated groups.

MATERIALS AND METHODS

300 patients were investigated. All investigated were divided into 3 groups: control group – 27 patients without AS and arrhythmias; mean group – 149 patients with AS but without arrhythmias; comparable group – 124 patients with AS and AF paroxysm. We excluded patients with valvular atrial fibrillation, heart failure from Class III to IV (by New York Heart Association), reported malignancies, chronic kidney disease (Glomerular Filtration Rate, GFR <60 mL/min), thyroid pathology, inflammatory bowel disease, irritable bowel syndrome, pregnancy, taking probiotics and antibiotics for a month before the study. There were no vegetarians or vegans among the examined. Informed consent was obtained from all subjects in accordance with the Declaration of Helsinki. The study was conducted at the base and was approved by the ethical commission of the Kiev City Clinical Hospital No. 12. Clinical and laboratory characteristics of investigated groups are performed in table I.

Carotid ultrasound and Holter ECG monitoring was used for diagnosis verification. Toshiba Aplio 400 color Doppler ultrasound system was used to scan the neck blood vessels by a linear probe and a frequency of 5–12 MHz. Bilateral common carotid arteries, internal and external carotid artery, vertebral artery were investigated. Cardiosens K Holter monitor was used during 24 hours. 16-S rRNA sequencing checked gut microbiota composition, that include such bacterias: *Lactobacillus spp., Bifidobacterium spp., Escherichia coli, Bacteroides spp., Faecalibacterium prausnitzii, Bacteroides thetaiotaomicron, Akkermansia muciniphila, Enterococcus spp., Blautia spp., Acinetobacter spp., Streptococcus spp., Eubacterium rectale, Roseburia inulinivorans, Prevotella spp., Methanobrevibacter smithii, Methanosphaera stadmanae, Ruminococcus spp.* The level of TMAO, TMA plasma was determined by gas chromatography with mass electron detection. They were extracted from blood plasma into acid by adding internal standards. Blood sampling from patients was performed on an empty stomach from the cubital vein on the day of hospitalization. Results were presented as mean ± standard error or [95% confidence interval (CI)] for continuous variables or as a number for categorical variables. Data were compared using Wilcoxon signed-rank test or Student t-test with two critical regions by the type of distribution and Spearman's rank correlation coefficient.

RESULTS

During our work gut microbiota composition in patients with AS without arrhythmias, patients with AS and AF and control group was compared. Result or gut microbiota comparison is shown in table II.

As we can see in the table II patients of the mean (AS) and comparable (AS+AF) groups have the significant abundance of total bacterial mass, *Bacteroides Spp., Faecalibacterium Prausnitzii, Actinobacter Spp.* and decreasing *Ruminococcus Spp*. Also comparing the comparable (AS+AF) and the mean (AS) groups significant increasing of *Actinobacter Spp*. and decreasing *Eubacterium Rectale*, *Ruminococcus Spp*. were checked. Bacteroides Fragilis Group/ Faecalibacterium Prausnitzii ratio was significantly higher than in patients' comparable group (AS+AF). In the mean group patients (AS) compared with control group significant abundance of *Streptococcus Spp*. was checked. In the comparable group (AS+AF) compared with control group significant leak of Eubacterium Rectale was checked.

The correlation analysis between components of gut microbiota and the clinical and laboratory characteristics

Table II. Gut microbiota composition changes in patients with AS and patients with AS and AF compared with control group, mean [95% CI], copy/ml

Characteristic /group	AS	AS+AF	CG	P1-2	P2-3	P1-3
Total bacterial mass	7,00E+13 [5,00E+13; 1,00E+14]	1,00E+14 [8,00E+13; 7,00E+14]	7,00E+11 [1,00E+11; 1,00E+12]	P>0,05	P<0,05	P<0,05
Lactobacillus Spp.	3,00E+06 [2,00E+06; 8,00E+06]	9,00E+05 [8,00E+05; 3,00E+06]	1,00E+08 [7,00E+07; 1,00E+08]	P>0,05	P<0,01	P<0,01
Bifidobacterium Spp.	8,00E+08 [5,00E+08; 1,00E+09]	1,00E+08 [6,00E+07; 3,00E+08]	6,00E+09 [1,00E+09; 3,00E+10]	P>0,05	P<0,01	P<0,05
Escherichia Coli	7,00E+06 [4,00E+06; 3,00E+07]	9,00E+06 [3,00E+06; 4,00E+07]	8,00E+06 [6,00E+06; 3,00E+07]	P>0,05	P>0,05	P>0,05
Bacteroides Spp.	3,50E+13 [1,00E+13; 6,00E+14]	9,00E+13 [7,00E+13; 3,00E+14]	7,00E+08 [1,00E+08; 1,00E+09]	P>0,05	P<0,01	P<0,01
Faecalibacterium Prausnitzii	2,50E+12 [1,00E+12; 8,00E+12]	8,00E+12 [4,00E+12; 5,00E+13]	1,00E+08 [1,00E+07; 6,00E+09]	P>0,05	P<0,05	P<0,05
Bacteroides Thetaiotaomicron	4,00E+10 [2,00E+10; 9,00E+10]	8,00E+09 [1,00E+09; 1,00E+10]	1,00E+09 [7,00E+07; 4,00E+09]	P>0,05	P>0,05	P>0,05
Akkermansia Muciniphila	7,00E+09 [6,00E+09; 8,00E+09]	4,00E+09 [5,00E+08; 9,00E+09]	1,00E+08 [6,00E+07; 2,00E+08]	P>0,05	P>0,05	P>0,05
Enterococcus Spp.	8,50E+05 [2,00E+05; 1,00E+06]	7,00E+05 [4,00E+05; 1,00E+06]	7,00E+05 [5,00E+05; 4,00E+07]	P>0,05	P>0,05	P>0,05
Blautia Spp.	4,00E+10 [5,00E+09; 7,00E+10]	4,00E+09 [7,00E+08; 8,00E+09]	3,00E+09 [1,00E+08; 8,00E+09]	P>0,05	P>0,05	P>0,05
Actinobacter Spp.	3,00E+07 [1,00E+07; 3,00E+08]	5,00E+09 [9,00E+08; 1,00E+10]	4,00E+05 [8,00E+04; 4,00E+05]	P<0,05	P<0,01	P<0,05
Streptococcus Spp.	6,00E+07 [9,00E+06; 1,00E+08]	8,00E+06 [6,00E+06; 4,00E+07]	8,00E+05 [1,00E+05; 1,00E+06]	P>0,05	P>0,05	P<0,01
Eubacterium Rectale	5,50E+07 [2,00E+06; 4,00E+08]	8,00E+06 [1,00E+06; 5,00E+07]	4,00E+08 [3,00E+08; 1,00E+10]	P>0,05	P<0,05	P>0,05
Roseburia Inulinivorans	5,00E+08 [8,00E+07; 1,00E+10]	6,00E+07 [3,00E+06; 5,00E+08]	3,00E+08 [8,00E+06; 5,00E+08]	P>0,05	P>0,05	P>0,05
Prevotella Spp.	7,50E+08 [2,00E+08; 4,00E+10]	7,00E+08 [2,00E+08; 3,00E+09]	3,00E+08 [1,00E+07; 6,00E+09]	P>0,05	P>0,05	P>0,05
Methanobrevibacter Smithii	4,00E+06 [1,00E+06; 7,00E+06]	3,00E+06 [1,00E+06; 7,00E+06]	5,00E+07 [1,00E+07; 3,00E+08]	P>0,05	P>0,05	P>0,05
Methanosphaera Stadmanae	9,50E+02 [0,00E+00; 1,00E+04]	1,00E+03 [9,00E+02; 4,00E+03]	8,00E+02 [0,00E+00; 4,00E+03]	P>0,05	P>0,05	P>0,05
Ruminococcus Spp.	5,00E+06 [8,00E+05; 2,00E+09]	9,00E+04 [8,00E+04; 1,00E+06]	9,00E+08 [1,00E+07; 1,00E+09]	P<0,05	P<0,01	P>0,05
Bacteroides Fragilis Group/ Faecalibacterium Prausnitzii	10,00 [8,75; 100]	11,25 [4,29; 35]	5,5 [0,12; 10]	P<0,05	P<0,05	P>0,05

Table III. Gut microbiota correlations with clinical and laboratory changes, P<0.05

Gut microbiota/ clinical and laboratory changes	Age (years)	BMI (kg/m²)	GFR (ml/min)	Total cholesterol (mmol/l)	Triglycerides (mmol/l)	LDL (mmol/l)	HDL (mmol/l)	TMA (mmol/l)	TMAO (mmol/l)
Total bacterial mass	++	++	0	+	0	+	-	+	+
Lactobacillus Spp.	-	--	0	-	-	--	+	--	--
Bifidobacterium Spp.	-	--	0	-	0	-	0	-	-
Escherichia Coli	0	0	0	0	0	+	-	0	0
Bacteroides Spp.	+	--	+	0	0	0	-	+	++
Faecalibacterium Prausnitzii	+	--	0	0	0	-	0	+	+
Bacteroides Thetaiotaomicron	0	0	0	0	0	0	0	0	0
Akkermansia Muciniphila	0	0	0	0	0	0	0	0	0
Enterococcus Spp.	0	0	0	0	0	0	0	0	++
Blautia Spp.	0	0	0	0	0	0	0	0	0
Actinobacter Spp.	+	+	+	0	+	+	-	+	+
Streptococcus Spp.	+	++	0	+	+	++	--	+	++
Eubacterium Rectale	-	0	-	-	0	--	++	--	-
Roseburia Inulinivorans	0	0	0	0	0	0	0	0	0
Prevotella Spp.	0	0	0	0	0	0	0	0	0
Methanobrevibacter Smithii	0	0	0	0	0	0	0	0	0
Methanosphaera Stadmanae	0	0	0	0	0	0	+	0	0
Ruminococcus Spp.	--	--	-	0	0	--	++	--	--

*Note: + – moderate positive correlation, 0.3< r<0.7; ++ – strong positive correlation, r>0.7; 0 – no significant correlations; - – moderate negative correlation, -0.3> r>-0.7; -- – strong negative correlation, r<-0.7

Table IV. TMA and TMAO plasma levels in patients with AS and patients with AS and AF compared with control group, mean ± standard error, mmol/l

Characteristic /group	AS	AS+AF	CG	P1-2	P2-3	P1-3
TMA	23,94±1,56	25,85±1,18	19,84±1,72	P>0,05	P<0,01	P<0,05
TMAO	2,64±0,19	4,22±0,30	2,13±0,22	P<0,01	P<0,01	P<0,05

of the examined groups was done. Spearman's correlation analysis was used to explore their correlations with species abundance. It was found that the most gut microbes enriched in the mean (AS) and comparable (AS+AF) groups had significant positive correlations with clinical and laboratory characteristics, whereas those enriched in control group had significant negative correlations with clinical and laboratory characteristics. All correlations are shown in the table 3. The largest amount of correlations was checked between gut microbiota composition and such clinical characteristics as TMAO (total number = 10), Age (total number = 9), TMA (total number = 9), BMI (total number = 8), LDL (total number = 9) and HDL (total number = 9) levels. The highest amount of correlations was between *Lactobacillus Spp., Streptococcus Spp*. and clinic-laboratory changes.

For analysis of gut microbiota metabolites changes plasma TMA and TMAO levels were investigated. Results of plasma TMA and TMAO levels in investigated patients are shown in table IV.

As we can see from the table 3 patients of the mean (AS) and comparable (AS+AF) groups the significant increasing of TMA ta TMAO plasma levels compared with control group were checked. Also, in patients of comparable group (AS+AF) compared with patients mean group (AS) the significant increasing of TMAO plasma level was revealed.

In our work, a correlation analysis was carried out between the levels of TMA and TMAO in the blood and the clinical and laboratory characteristics of the examined groups. Correlations were found between the level of TMA in blood plasma and the age of patients (r=0.584; p<0.01), BMI (r=0.351; p<0.01), LDL (r=0.320; p<0.05) and GFR (r=0.239; p<0.05). Also, blood plasma TMAO and age of patients (r=0.634; p<0.01), BMI (r=0.522; p<0.01), GFR (r=0.327; p<0.01), and more levels of HDL (r=-0.411; p<0.01) and K+ plasma levels (r=0.761; p<0.01).

DISCUSSION

AS - the formation of fibro fatty lesions in the artery wall. It is a multifocal, smoldering, immune inflammatory disease of medium-sized and large arteries fueled by lipids. Endothelial cells, leukocytes, and intimal smooth muscle cells are the major players in the development of this disease [12]. AF is the most common arrhythmia in the world. It is known connection between AF and AS occurrence, but no exact pathogenetic explanations of them has not still present. AF by itself is both the cause of atherosclerotic changes and their consequences. The incidence of AF in patients with AS is almost three times higher than in the general population. AF and AS have many common risk factors: hypertension, obesity, dyslipidemia, age, type 2 diabetes, sleep apnea, smoking and others. Also, the basic pathogenetic mechanisms underlying AS and AF are common: subclinical permanent inflammation and endothelial dysfunction [9]. Gut microbiota changes are potentially closely link with subclinical inflammation. Moreover, it is a evidenced cause of most metabolic disorders, which are known risk factors of AF and AS [4]. The gut microbiota is a promising target for the management or prevention of inflammatory and metabolic disorders in humans.

In our work we determine the composition of gut microbiota of healthy controls and patients with AS and AF or without it. In the bough investigated groups increased the total bacterial mass, *Bacteroides Spp., Faecalibacterium Prausnitzii, Actinobacter Spp*. and decreased *Ruminococcus Spp.* We compared our results with previous studies of gut microbiota composition in patients with AS [4-6] – they are not equal due to differences in their results. Decreased *Ruminococcus Spp*. are special for our group. It is known that *Ruminococcus Spp*. plays an important role in permeability features of intestinal membrane, that why their leak can be a cause of chronic inflammation [13].

We did not find the special data about gut microbiota composition in AS with AF. In our investigation patients with AS and AF were characterized by the significant increasing of *Actinobacter Spp., Bacteroides Fragilis Group/ Faecalibacterium Prausnitzii ratio and decreasing Eubacterium Rectale, Ruminococcus Spp*. Also, for this group was leak of Eubacterium Rectale compared with healthy controls. By the literature date Eubacterium Rectale plays the mean role in synthesis bytirates, which has probiotic effects and also can decrease the levels of proinflammatory cytokines [14]. For patients with AS without arrhythmia were significant abundance of *Streptococcus Spp*. compared with AS and AF group. By the literature data *Streptococcus Spp*. is the one of the mean bacteria that characterized atherosclerotic proses. It was found in atherosclerotic plaques, thrombus in case of myocardial infarction [15].

TMA and TMAO level were both increased in all investigated groups compared with controls, that is matches to previous literature data [1, 6, 8, 10]. Also, TMAO level was significantly higher in patients with AF comparing group without it. That can be explained of proinflammatory effects of TMAO and its ability to influence of lipid metabolism and processes of connecting tissue formation [10].

Correlations between gut microbiota components, its metabolites and clinical and laboratory patients' characteristics were checked and analyzed. The presence of strong negative connections between the TMAO plasma levels and *Lactobacillus Spp., Ruminococcus Spp*. and positive connections between the TMAO plasma levels and *Bacteroides Spp., Enterococcus Spp., Streptococcus Spp.* are interesting. It shows us what bacteria can be the cause of increasing TMAO through investigative groups.

CONCLUSIONS

Metagenomic analysis between the gut microbiota composition and its metabolites in patients with AS and AF was done in our study. We checked special bacterial changes of gut microbiota that are common for patients with AS and AF comparable with *AS patients: increasing of Actinobacter Spp. and decreasing Eubacterium Rectale, Ruminococcus Spp., Bacteroides Fragilis Group/ Faecalibacterium Prausnitzii* ratio was significantly higher. Also, TMAO plasma levels are increased significantly for patients with AS and AF comparable with AS patients. Connections between AS and AF with TMAO plasma levels are confirmed by reliable correlations between TMAO and age, BMI, GFR, HDL levels that are known risk factors of AS and AF. Moreover, special bacterial species, as *Lactobacillus Spp., Actinobacter Spp., Streptococcus Spp., Eubacterium Rectale, Ruminococcus Spp.* are closely connected with age, BMI, GFR, HDL, LDL, plasma TMA and TMAO levels. In further research, will be interesting to checked the ways for correction described gut microbiota composition and its metabolites changes and their influence at the risks of occurrence AF in AS patients.

REFERENCES

1. Lizogub V.G., Kramarova V.N., Melnychuk I.O. The role of gut microbiota changes in the pathogenesis of heart disease. Zaporizkiy medical journal. 2019;21(5): 672–678. doi: 10.14739 / 2310-1210.2019.5.179462.
2. Moszak M., Szulińska M., Bogdański P. You Are What You Eat-The Relationship between Diet, Microbiota, and Metabolic Disorders-A Review. Nutrients. 2020;12 (4):1096. doi:10.3390/nu12041096.
3. Hui-Qing Chen, Jin-Yu Gong et al. Pharmacomicrobiomics: Exploiting the Drug-Microbiota Interactions in Antihypertensive Treatment. Front Med (Lausanne). 2021;8:742394. doi: 10.3389/fmed.2021.742394.
4. Jingfeng Chen, Qian Qin et al. Gut Microbiome Alterations in Patients With Carotid Atherosclerosis Front Cardiovasc Med. 2021; 8: 739093. doi: 10.3389/fcvm.2021.739093.
5. Chenglin Liu, Zhonghan Sun et al. The gut microbiome and microbial metabolites in acute myocardial infarction J Genet Genomics. 2021;21:1673-8527. doi: 10.1016/j.jgg.2021.12.007.
6. Ortega-Madueño I., Modrego J. et al. Relationship between the coronary artery calcium quantification and gut microbiota composition in subjects without previous cardiovascular disease: A pilot study Clin Investig Arterioscler. 2022; 21: 0214-9168. doi: 10.1016/j.arteri.2021.11.008.
7. Gawałko M., Agbaedeng T.A. et al. Gut microbiota, dysbiosis and atrial fibrillation. Arrhythmogenic mechanisms and potential clinical implications Cardiovasc Res. 2021. doi: 10.1093/cvr/cvab292.

8. Na Li, Durgan D.J., Wehrens X.H.T. Gut microbiota - a key regulator of aging-associated atrial fibrillation? Cardiovasc Res. 2021. doi: 10.1093/cvr/cvab346.
9. Liang F., Wang Y. Coronary Heart Disease and Atrial Fibrillation: A Vicious cycle. American Journal of Physiology-Heart and Circulatory Physiology. 2020. doi:10.1152/ajpheart.00702.2020.
10. Rui Huang, Li Yan, Yuhua Lei. The Gut Microbial-Derived Metabolite Trimethylamine N-Oxide and Atrial Fibrillation: Relationships, Mechanisms, and Therapeutic Strategies Clin Interv Aging. 2021; 16:1975-1986. doi: 10.2147/CIA.S339590.
11. Jing Zhang, Kun Zuo at al. Altered synthesis of genes associated with short-chain fatty acids in the gut of patients with atrial fibrillation BMC Genomics. 2021; 22: 634. doi: 10.1186/s12864-021-07944-0.
12. Libby P., Buring J.E., Badimon L. et al. Atherosclerosis. Nat Rev Dis Primers. 2019;5(1):56. doi: 10.1038/s41572-019-0106-z.
13. Michels N., Zouiouich S. et al. Human microbiome and metabolic health: An overview of systematic reviews Obes Rev. 2022; e13409. doi: 10.1111/obr.13409.
14. Nagara Yu., Fujii D. et al. (2022) Selective induction of human gut-associated acetogenic/butyrogenic microbiota based on specific microbial colonization of indigestible starch granules. ISME J. 2022. doi: 10.1038/s41396-022-01196-w.
15. Tuomisto S., Huhtala H. et al. Age-dependent association of gut bacteria with coronary atherosclerosis: Tampere Sudden Death Study PLoS One. 2019; 14(8): e0221345. Published online 2019. doi: 10.1371/journal.pone.0221345.

ORCID and contributionship:
Iryna Melnychuk: 0000-0002-0659-1476[A-F]
Viktor G. Lizogub: 0000-0003-3603-7342[A,E,F]

Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR
Iryna Melnychuk
O.O. Bogomolets National medical university
13 Shevchenko boulevard, 01601 Kyiv, Ukraine
e-mail: ira.merkulova45@gmail.com

Received: 14.02.2022
Accepted: 14.11.2022

A - Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article