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Comparative analysis of tryptophan and downstream metabolites of the kynurenine and serotonin pathways in patients with arterial hypertension and coronary artery disease

Aim	To compare serum concentrations of tryptophane (Trp) and its metabolites in subjects with no cardiovascular disease (CVD) and patients with CVD. including arterial hypertension (AH) and ischemic heart disease (IHD).
Material and Methods	This study included 131 participants; 58 participants (11 of them with documented peripheral atherosclerosis) were included into the AH group. 46 participants were included into the IHD group. and 27 participants with no signs of CVD were included into the control group. Plasma concentrations of Trp and its metabolites were measured by high-performance liquid chromatography in combination with a triple quadrupole analyzer.
Results	Comparison of the three study groups revealed significant differences in concentrations of Trp (p=0.029). kynurenine (p<0.001). kynurenine/Trp ratio (p<0.001). quinolinic acid (p=0.007). kynurenic acid (p=0.003). serotonin (p<0.001). and 5-hydroxyindoleacetic acid (5-HIAA) (p=0.011). When the AH group was subdivided into subgroups without and with documented peripheral atherosclerosis. the intergroup differences remained for concentrations of kynurenine. kynurenine/Trp ratio. quinolinic acid. kynurenic acid. serotonin. and 5-HIAA. Also. correlations were found between concentrations of Trp metabolites and laboratory and instrumental data. primarily inflammatory markers.
Conclusion	Analysis of serum concentrations of Trp and its metabolites in CVD patients showed increases in kynurenine. kynurenine/Trp ratio. quinolinic acid. kynurenic acid. and 5-HIAA along with decreases in concentrations of Trp and serotonin in the groups of AH. AH with documented peripheral atherosclerosis. and IHD.

Keywords	Tryptophane; tryptophane catabolism; arterial hypertension; ischemic heart disease
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Introduction

Recent studies have demonstrated the involvement of pro-inflammatory cytokines in the development and progression of atherosclerosis [1]. The CANTOS study also have shown the efficacy of anti-inflammatory therapy in reducing cardiovascular mortality in patients with a history of myocardial infarction [2]. The increased activity of pro-inflammatory cytokines is assumed to cause endothelial dysfunction. increased proliferation of smooth muscle cells and activation of macrophages [3]. Cell activation is accompanied by metabolic changes. such as alternation of glycolysis- tricarboxylic acid pathway. b-oxidation. and oxidative phosphorylation of fatty acids. disruption of amino acid synthesis and metabolism. Tryptophan catabolism is an important component of the regulation of systemic inflammation and immune response. a shift in the metabolic pathways of which occurs at earlier. including preclinical. stages of the development of cardiovascular diseases (CVDs). Tryptophan (Trp) is an essential amino acids that contains the aromatic indole nucleus in its structure. The kynurenine pathway (KUP) is the main metabolic pathway of Trp. in which the indole ring is disrupted by oxidation catalyzed by indoleamine-2.3 dioxygenase (IDO) or tryptophan-2.3 dioxygenase to form kynurenine. Kynurenine. being a substrate for various enzymes. is converted in turn to anthranilic. kynurenic. xanthurenic. and quinolinic acids. KUP is ultimately completed by the production of the nicotinamide adenine dinucleotide (NAD+) coenzyme from quinolinic acid [4]. Trp is less spent on the formation of serotonin and

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melatonin by tryptophan hydroxylase. and is partially spent on bacterial degradation resulting in the formation of indole acids and indole [4]. Given the large variety of tryptophan cycle derivatives obtained in one of the three transformation pathways (kynurenine. serotonin and indole) (Figure 1). the involvement of Trp metabolites in pathological processes is actively studied now.

Thus. the role of serotonin pathway metabolites in neuropsychiatric diseases. such as schizophrenia. depressive disorders. chronic insomnia. cognitive impairment. etc.. is most well studied at present [5–8]. Also. the role of Trp in systemic inflammation has been widely studied in relation to CVDs over recent years [9–11]. The study of KUP activity is of the greatest interest in relation to the regulation of inflammation. The activation of the IDO expression by pro-inflammatory cytokines is believed to contribute to the breakdown of Trp via the KUP with the increased production of quinoline and xanthurenic acids. Moreover. the expression of kynurenine monooxygenase increases. which increases the formation of quinoline and xanthurenic acids. It should be noted that the latter makes a significant contribution to the development of metabolic syndrome and diabetes [4]. The shift in Trp metabolism towards KUP due to cytokine activation suggests that KUP metabolites may reflect systemic inflammation and their plasma levels can change in CVDs. which in turn may help to identify these diseases at earlier stages. Although. the studies of Trp catabolism in CVDs are becoming more common. there are no comparative analyses of metabolite levels in clinically healthy individuals. patients with risk factors for atherosclerosis. and patients with symptomatic atherosclerosis. Thus. we have formulated a hypothesis that. as a CVD develops and progresses. the levels of Trp metabolites progressively change. which means that the concentration of circulating metabolites may be an indicator of the disease at an early (preclinical) stage.

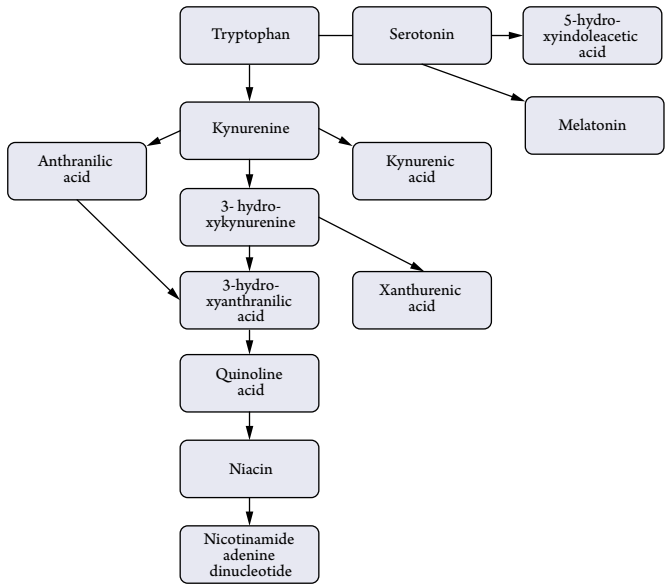
Objective

Perform a comparative analysis of the levels of Trp and its metabolites in blood serum in patients with CVDs (arterial hypertension (AH). coronary artery disease (CAD)) and in individuals without signs of CVDs.

Material and methods

In this study. 131 patients were examined in the Department of Cardiology No. 1 of the Sechenov University (Moscow. Russia) in 2018–2020. The study protocol was approved by the local ethics committee of the Sechenov University. The study was conducted following the ethical principles for medical research involving human subjects established in the Declaration of Helsinki. The control group consisted of individuals without CVDs (n=27. Group 1).

Figure 1. Kynurenine and serotonin pathways of tryptophan catabolism



Patients with AH (n=58. Group 2) and patients with CAD (n=46. Group 3) were included in the study. Patients were included in the AH and CAD groups if they had verified AH or CAD. respectively. in accordance with the relevant clinical guidelines [12. 13]. Doppler ultrasound of the brachiocephalic arteries (BCAs) and lower limb arteries was performed to detect peripheral atherosclerosis. which and 11 patients with stenosing peripheral atherosclerosis were identified in the AH group. Coronary artery angiography (CAG) or multislice computed tomography (MSCT) was performed to visualize and assess the extent of coronary artery (CA) involvement depending on the pre-test probability (PTP) of CAD. which was calculated using the CAD Consortium score [14].

Exclusion criteria included secondary AH. acute and chronic heart failure. acute myocardial infarction. acute cerebrovascular accident. acquired and congenital heart defects. hemodynamically significant valvular lesions. cardiomyopathies. bronchial asthma. and acute exacerbation of chronic obstructive pulmonary disease. connective tissue diseases. cancer. chronic viral infections. acute exacerbation of gastrointestinal and hepatobiliary diseases. chronic kidney disease stage 4–5.

All patients underwent anthropometric measurements. physical examination (measurement of office systolic and diastolic blood pressure (SBP. DBP). biochemical and hormone blood tests. echocardiography) (see Table 1 and Table 2 in the supplementary materials published in the journal's website). The numbers of male and female patients were comparable in both groups. but the groups differed in patient age. body mass index (BMI). and the presence of dyslipidemia. At the time of inclusion. 58.6% of

patients with AH received combination antihypertensive therapy: angiotensinconverting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) (75.9%). beta-blockers (BBs) (43.1%). calcium channel blockers (CCBs) (22.4%). diuretics (34.5%). CAD patients were treated with ACE inhibitors or ARBs (60.9%). BBs (63.0%). CCBs (19.6%). diuretics (28.3%). antiplatelet drugs (65.2%). Lipid-lowering therapy was administered to 34.5% of patients in the AH group and 65.2% in the CAD group.

Metabolites associated with tryptophan catabolism were profiled at the laboratory of pharmacokinetics and metabolome analysis in the Institute of Translational Medicine and Biotechnology of the Sechenov University (Moscow. Russia). Venous blood was collected for the metabolome analysis after an overnight fast in two ethylenediaminetetraacetic acid potassium salt dehydrate tubes. To assess the profile of tryptophan degradation products. endogenous compounds of the kynurenine and serotonin pathways were quantified (Figure 1). A mixture of isotope labeled standards of the compounds of interest was used for the assay.

High performance liquid chromatography and tandem mass spectrometry were performed using an Agilent 1200 liquid chromatograph coupled to a 6450C three quadrupole mass spectrometer (Agilent Technologies. Palo Alto. CA. USA). Chromatographic separation was performed on a Discovery PFP HS F 52.1×150.3 μm column (Supelco Inc.. USA) using a Waters WAT084560 pre-column (Waters Inc.. USA) (see the metabolome analysis report presented in the supplementary materials published in the journal's website).

The statistical analysis of findings was carried out using Statistica 10.0 (StatSoft. USA). Table 1 and Table 2 in the supplementary materials provide descriptive data. Quantitative indicators were assessed for normal distribution using the Shapiro–Wilk test (is less than 50 subjects) or the Kolmogorov–Smirnov test (if more than 50 subjects). The data were described using the medians (Me) and lower and upper quartiles [Q1 – Q3] or the absolute and relative values (%). The three groups were quantitatively compared using the non-parametric Kruskal–Wallis test. Pairwise post-hoc comparisons between the groups were performed using the Dunn's test with and Holm correction. The direction and

Table 1. Differences in the levels of Trp and its derivatives between the control group and the groups with CVDs: AH without atherosclerosis. AH with documented peripheral atherosclerosis and CAD

Metabolites	Group 1 (control; n=27)	Group 2a (AH without atherosclerosis; n=47)	Group 2b (AH with atherosclerosis; n=11)	Group 3 (CAD; n=46)	p
Trp	49 823.09 (45 302.29;55278.25)	47 192.10 (41 652.91;51 621.69)	45 930.12 (42 207.88;52 200.23)	45 323.39 (40 254.81;49 533.31)	0.068[a]
Kynurenine	1204.02 (979.91;1368.74)	1304.26 (1092.89;1477.26)	1513.81 (1261.41;1720.65)	1491.02 (1302.16;1656.96)	<0.001[a] p_{1-3}=0.002[b] p_{2a-3}=0.033[b]
Kynurenine:Trp ratio	0.0224 (0 0.0195; 0.0264)	0.0272 (0.0243; 0.0311)	0.0339 (0.0265;0.0384)	0.0320 (0.0282; 0.0370)	<0.001[a] p_{1-2a}=0.049[b] p_{1-26}=0.002[b] p_{1-3}<0.001[b] p_{2a-3}=0.008[b]
Quinoline acid	53.31 (41.53;78.26)	65.23 (48.09;90.05)	91.24 (64.96;130.09)	78.98 (60.17;108.30)	0.003[a]
Anthranilic acid	7.89 (4.53;10.16)	10.02 (6.22;12.84)	13.32 (7.11;16.45)	10.56 (6.82;14.76)	0.056[a]
Xanthurenic acid	16.43 (10.08;32.14)	15.82 (8.55;30.27)	25.01 (7.13;29.34)	19.57 (9.95;30.51)	0.818[a]
Kynurenic acid	13.37 (9.95;16.69)	13.25 (10.90; 18.95)	17.38 (12.47; 23.84)	17.16 (13.96;20.33)	0.004[a] p_{1-3}=0.023[b]
Serotonin	77.28 (24.09;182.43)	45.04 (14.72;105.65)	31.52 (19.39;77.08)	14.34 (7.26;44.27)	<0.001[a] p_{1-3}=0.009[b]
5-HIAA	11.98 (9.93;15.56)	14.6 (10.07;17.93)	17.61 (15.08;24.45)	16.03 (13.72;22.56)	0.002[a]

[a] Kruskal–Wallis test. [b] post-hoc pairwise comparison of groups using the Dunn's test Holm correction.
The data is presented as Me (Q1 – Q3). AH. arterial hypertension; CAD. coronary artery disease;
Trp. tryptophan; 5-HIAA. 5-hydroxyindoleacetic acid.

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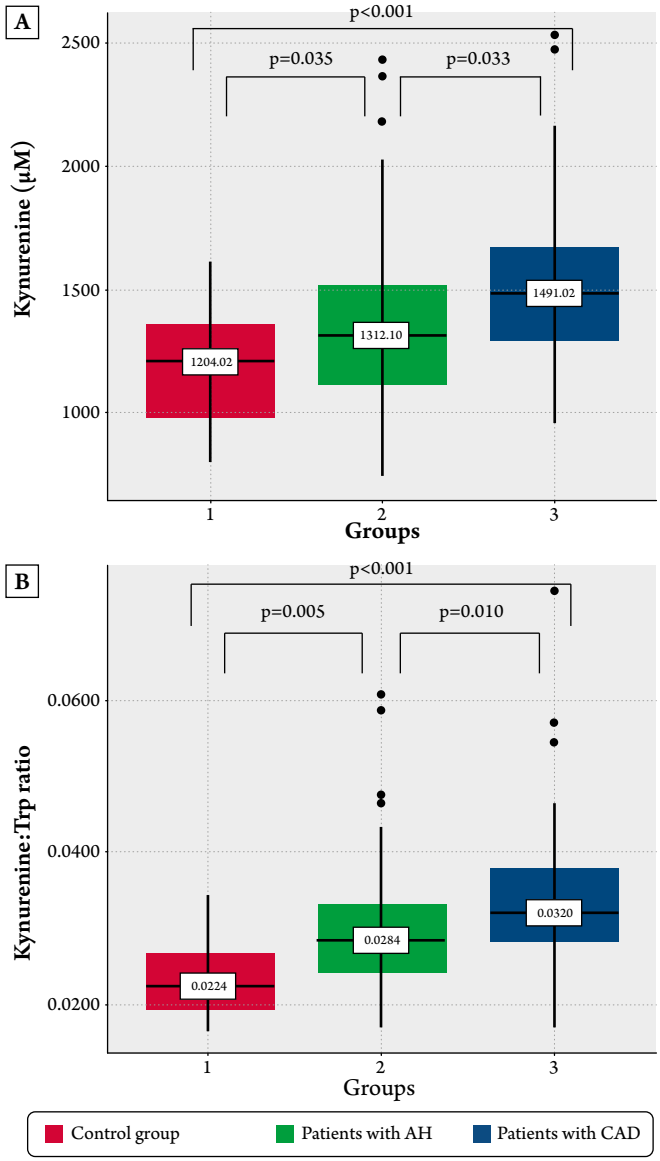
tightness of a correlation between two quantitative measures were estimated using either the Spearman's rank correlation coefficient (non-normal distribution) or the Pearson correlation coefficient (normal distribution). Multivariate analysis was performed using linear regression. Differences were statistically significant with p less than 0.05.

Results

The data analysis showed that all groups were comparable by patient sex. however. patients with AH and CAD belonged to the older age cohort (see Table 1 in the supplementary materials published in the journal's website). It should be noted that the levels of tryptophan metabolites increased most significantly. except reduced levels of tryptophan and serotonin. in the CAD group. The comparison of the three groups revealed statistically significant differences in the levels of Trp (p=0.029). kynurenine (p<0.001). kynurenine:Trp ratio (p<0.001). quinoline (p=0.007) and kynurenine (p=0.003) acids. serotonin (p<0.001). 5 hydroxyindoleacetic acid (5 HIAA) (p=0.011) between the control group and patients with AH and CAD. A pairwise comparison of the groups showed significant differences between all three groups in kynurenine levels (p1–2=0.035; p1–3<0.001; p^2–3=0.033) and kynurenine:Trp ratio (p1–2=0.005; p1–3<0.001; p^2–3=0.010) (Figure 2). between the control group and the CAD group in the levels of Trp (p1–3=0.024). quinoline acid (p1–3=0.005). kinurenic acid (p1–3=0.003). serotonin (p1–3<0.001). 5 HIAA (p1–3=0.008). between the control group and the AH group in the levels of quinoline acid (p1–2=0.036). and between the AH and CAD groups in serotonin levels (p^2–3=0.002).

Given the data obtained. we analyzed additionally the levels of Trp and its derivatives in the healthy individuals and patients with CVDs at various stages of atherosclerosis. Accordingly. groups of AH patients without atherosclerosis (n=47). AH patients with documented peripheral atherosclerosis (n=11). and patients with CAD (n=46) were identified among patients with CVDs. Significant differences remained between the groups in the levels of kynurenine. serotonin. quinolinic acid. 5 HIAA. and the kynurenine:Trp ratio. Significance of differences in the levels of tryptophan decreased. but the trend of intergroup differences continued. The comparisons showed a statistically significant difference in the kynurenine:Trp ratio between the AH group with documented peripheral atherosclerosis and the control group (p=0.002). and a statistically significant difference in the levels of kynurenine and the kynurenine:Trp ratio between the AH group without atherosclerosis and the CAD group (p=0.033 and p=0.008. respectively). Interestingly. there were no differences in circulating metabolites between the AH group with atherosclerosis and patients with CAD (Table 1).

Figure 2. Kynurenine (A) and kynurenine:Trp ratio (B) plots by groups



AH, arterial hypertension;
CAD, coronary artery disease; Trp, tryptophan

The correlations between the levels of metabolites of interest and laboratory and clinical examination parameters were studied using correlation analysis. The detected correlations are presented in Figure 3.

Due to the fact that the control individuals were relatively younger than patients with CVDs. we carried out additional statistical data processing. which revealed only a weak or moderate correlation between the levels of circulating metabolites and age. and the resulting regression models adjusted for age did not lose statistical significance.

Discussion

Low-level systemic inflammation is currently considered to be a key mechanism of the progression of atherosclerosis and endothelial dysfunction (ED). Damaged

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vascular endothelium triggers immune response. which leads to the activation of cytokines and T-cells. and further aggravation of ED. Among pro-inflammatory cytokines. special attention is given to interleukin-6 (IL-6) and interferon-γ acting as mediators and inducers of tryptophan metabolism [11]. At the same time. Trp catabolism products. such as kynurenine. are considered as regulators of immune responses contributing to the regulatory T-cell differentiation. Thus. it can be suggested to study tryptophan metabolism to find new CVD markers and possible therapeutic targets [14–18].

Under physiological conditions. nicotinic acid (vitamin B3) is formed from Trp. which means that Trp is able to positively influence. indirectly through niacin. the carbohydrate metabolism. lipid profile. microcirculation (vasodilation). promote cellular energy homeostasis by NAD+ which is a common redox cofactor in various biological processes [19]. However. reduced levels of Trp and the predominance of other KUP subpathways in CVDs contribute to a decrease in niacin levels. On the other hand. the role of other metabolites of the main tryptophan degradation pathway in the development and progression of CVDs. including atherosclerosis. is not fully understood. However. it has been suggested that some KUP metabolites (kynurenine. xanthurenic acid) may contribute to the regulation of vascular tone. especially in inflammation [20]. An interesting experimental study in mice showed that IDO deficiency in vascular smooth muscle cells contributes to plaque calcification and instability. On the other hand. the intraperitoneal administration of kynurenine slowed down the progression of intima calcification [21]. The association KUP metabolites and systemic inflammatory response was shown by Farouk et al. during coronary artery bypass graft surgery [22]. Increased intraoperative levels of kynurenine. IL-6. and plasma levels of white blood cells were noted. and the Trp:kynurenine ratio was decreased; a positive correlation of white blood cells with IL-6 and a negative correlation with the Trp:kynurenine ratio were revealed.

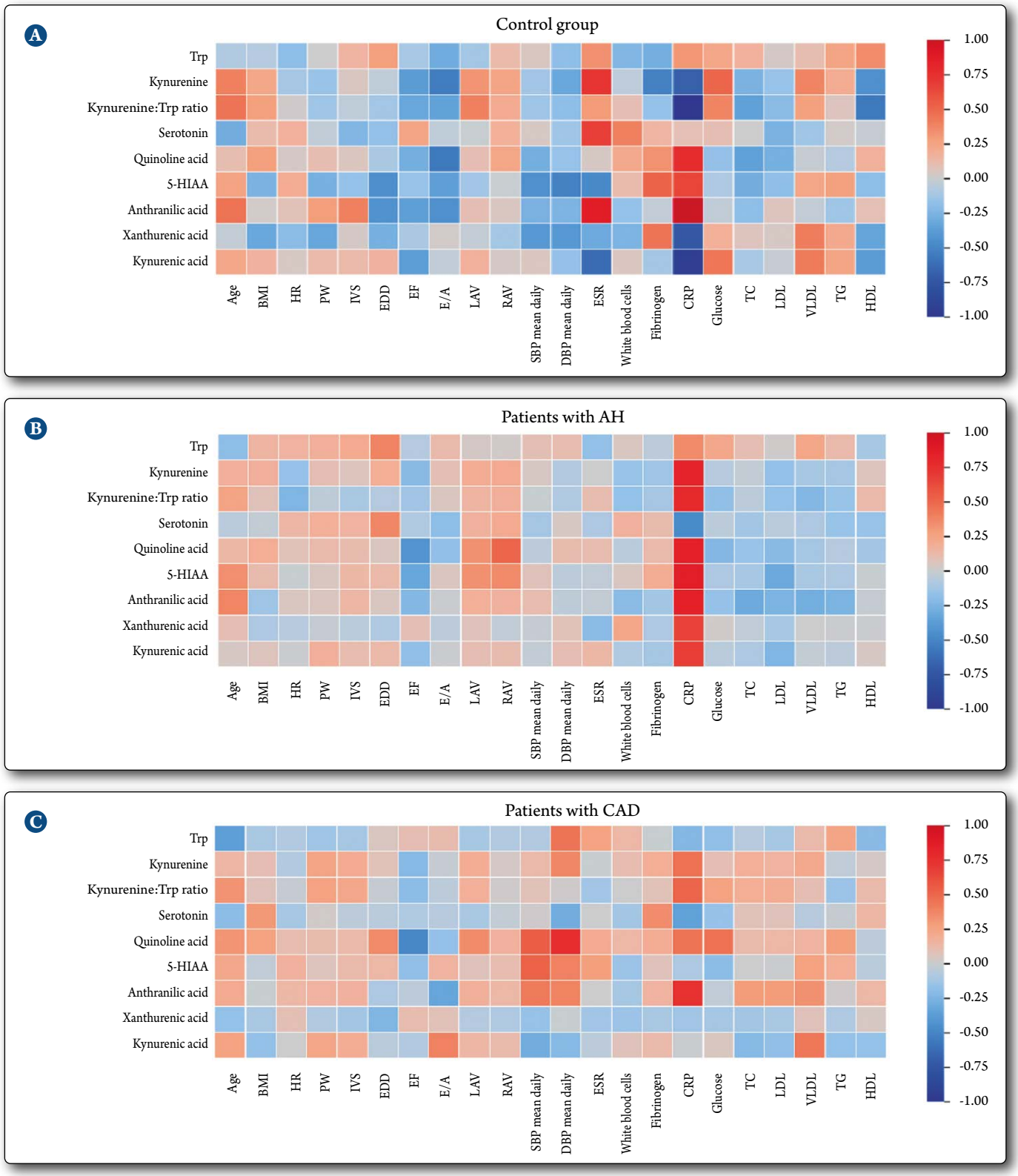
The results obtained in this study demonstrated a significant alternation of the levels Of all KUP metabolites and serotonin in patients with CVDs compared to healthy individuals. Moreover. the levels of five metabolites and the kynurenine:Trp ratio gradually increased in AH patients without signs of atherosclerosis. AH patients with clinical signs of peripheral atherosclerosis. and patients with CAD in a cross-sectional comparison. We have also established positive correlations of KUP metabolites with C-reactive protein (CRP) in the AH and CAD groups. Interestingly. patient age was positively correlated in the study groups with the levels of kynurenine and serotonin pathway metabolites and negatively correlated with the levels of Trp. These results are consistent with several clinical trials [14–18. 22. 23]. Accordingly. Wirleitner et al. showed a decrease in the levels of Trp and an increase in the blood levels of kynurenine and kynurenine-tryptophan ratio in patients with CAD and coronary artery atherosclerosis confirmed by CAG [23]. Another multicenter randomized trial PREDIMED showed the prognostic role of kinurinic acid and Trp in the development of cardiovascular events (myocardial infarction or any other cause of cardiovascular death) in patients at high cardiovascular risk [14]. Unlike previous trials. we studied the levels of metabolites associated with tryptophan catabolism at different stages of the cardiovascular continuum and showed that the first changes occur at the early stage of preclinical manifestation of atherosclerosis and are aggravated as CVDs progress.

Although it was shown in our and some other studies that the levels of tryptophan and its metabolites depend on age [24. 25]. it should be noted that differences in the metabolite levels remained in the study groups in the age-adjusted analysis.

The serotonin pathway of Trp catabolism is also of particular scientific interest. Serotonin is able to affect vascular tone by acting on serotonin receptors. which in turn causes tachycardia with preceding brief reflex bradycardia. increased atrial wall motion. atrial arrhythmias and pulmonary arterial hypertension through the impact on smooth muscle contraction and vascular remodeling [4]. However. serotonin is mostly absorbed in the blood by platelets and its plasma levels are unstable. Nevertheless. our study showed a significant difference in the levels of serotonin and its derivative 5 HIAA between patients with CVDs and healthy individuals.

Thus. we tried in the present study to answer whether changes in the levels of Trp metabolites are associated more with arterial hypertension or atherosclerosis and at what stage of the cardiovascular continuum significant changes appear. The demonstrated differences in the levels of Trp and its metabolites between the AH group. the AH group with documented peripheral atherosclerosis. and the CAD group. suggested that Trp metabolites are more associated with the development of atherosclerosis. which allows them to be considered as early markers of atherosclerosis. We cannot completely exclude the effects on the studied metabolites of early atherosclerotic changes in the isolated subgroup of AH patients without atherosclerosis who did not have clinical signs of atherosclerosis. The association of KUP metabolites with markers of inflammation in patients with CAD is also noteworthy. as it indirectly confirms the correlation between Trp catabolism and inflammation. Thus. further research of Trp catabolism regulation may suggest new targets in the treatment and prevention of CAD.

Figure 3. Correlations between the levels of Trp and its metabolites and laboratory and clinical examination parameters: (A) control group; (B) AH group; (C) CAD group



The strength and direction of the correlation is shown by the color intensity: red is a strong positive correlation, blue is a strong negative correlation. AH, arterial hypertension; DBP, diastolic blood pressure; E/A, ratio of early (E) to late (A) left ventricular filling velocity; PW, posterior wall; CAD, coronary artery disease; B, body mass index; EDD, end-diastolic dimension; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein; IVS, interventricular septum; LAV, left atrial volume; RAV, right atrial volume; TC, total cholesterol; SBP, systolic blood pressure; ESR. erythrocyte sedimentation rate; CRP, C-reactive protein; TG, triglycerides; Trp. Tryptophan; TSH, thyroid-stimulating hormone; EF, ejection fraction; 5-HIAA, 5-hydroxyindoleacetic acid.

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Conclusions

Our findings show that. as CVDs develop and progress. abnormalities gradually worsen in the KUP. which is one of the main etiological factors of systemic inflammation. Based on the results of the analysis of changes in the serum levels of tryptophan and its metabolites in patients with CVDs. we observed a consistent increase in the levels of kynurenine. the kynurenine:Trp ratio. quinoline. kynurenine and 5 HIAA and a decrease in the levels of tryptophan and serotonin in the groups of patients with AH. AH and documented peripheral atherosclerosis. and CAD. The demonstrated dependence is the basis for further research of these metabolites as potential markers of early atherosclerosis and possible therapeutic targets.

Limitations

Our study is limited by the small number of subjects and non-randomized design. The limitations also include a small sample of the subgroup with AH and peripheral atherosclerosis and the inability to completely exclude the influence of the early atherosclerotic changes on the metabolites of interest in the isolated subgroup of AH patients without atherosclerosis. On the other hand. the advantage of our work is a stricter selection of patients. specifically the exclusion of any conditions associated with inflammation (cancer. autoimmune diseases. respiratory and gastrointestinal inflammatory diseases). which allows excluding the possible effect of other pro-inflammatory conditions on changes in the tryptophan metabolism and interpreting the results from the perspective of the association with the presence of atherosclerosis.

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No conflict of interest is reported.

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