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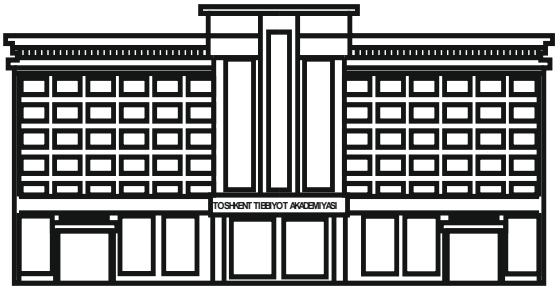

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Тошкент

THE ROLE OF ASYMMETRIC DIMETHYLARGININE AS A PREDICTOR OF CARDIOVASCULAR DISEASES

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Introduction. *Asymmetric dimethylarginine (ADMA) is an endogenous inhibitor of nitric oxide synthase (NOS), an enzyme responsible for producing nitric oxide (NO), a molecule with various cardiovascular protective effects including vasodilation and inhibition of platelet aggregation. Elevated levels of ADMA have been associated with endothelial dysfunction, inflammation, and oxidative stress, all of which are key factors in the development and progression of cardiovascular diseases (CVD).*

Key words: *Asymmetric dimethylarginine, cardiovascular disease, nitric oxide synthase, endothelial dysfunction, l-arginine.*

The development of atherosclerosis, in particular atherosclerosis of the coronary arteries, is influenced by many factors: age, gender, heredity, smoking, low physical activity, hypertension, excess body weight, dyslipidemia, diabetes [7]. These also include hyperhomocysteinemia, changes in fibrinolytic activity of the blood, and indicators of nonspecific inflammation (C-reactive protein). Recently, endothelial dysfunction has been considered as an independent risk factor for the development of atherosclerosis and other CVDs [4].

Endothelial dysfunction is accompanied by an imbalance in the production of vasoactive substances that regulate the lumen of the vessel and cell growth. Nitric oxide is one of the mediators that is of paramount importance for maintaining the functioning of endothelial cells [10, 20]. In addition to the direct vasodilating effect [1], nitric oxide, produced in endothelial cells with the help of nitric oxide synthase [9], prevents the development of atherosclerosis due to other properties: reducing the expression of leukocyte adhesion molecules, the content of pro-inflammatory cytokines, control of SMC proliferation, aggregation platelets, maintaining the balance of the blood coagulation and anticoagulation systems [13].

It has now been established that there are several pathways for the formation of nitric oxide in the human body. One of them involves the formation of nitric oxide by the action of nitric oxide synthase. There are 3 isoforms of this enzyme [5, 7, 20]. Type I nitric oxide synthase, called neuronal, is concentrated in cerebellar neurons and astroglia. Inducible nitric oxide synthase type II is expressed as a result of exposure to inflammatory cytokines [5]. Type III nitric oxide synthase is localized predominantly in the endothelium and has a constitutional nature [15]. Another pathway for the formation of nitric oxide involves the reduction of nitrates and nitrites to nitric oxide under low oxygen conditions. It should be noted that the second mechanism of nitric oxide generation, independent of nitric oxide synthase, according to some authors, may even predominate during the progression of ischemia and its transition to necrosis [2; 11].

The substrate for the synthesis of nitric oxide under the action of nitric oxide synthase is the amino acid L-arginine, the main endogenous amino acid. In addition to participating in the metabolism of nitric oxide, L-arginine is a product of the ammonia detoxification process, a metabolite of the uric acid cycle, a precursor of ornithine, urea and creatinine, and a participant in the formation of active centers of some enzymes [14]. Data from animal experiments, as well as in vitro studies, showed the combined antiaggregation, anticoagulation and profibrinolytic effects of L-arginine [6]. The administration of L-arginine as a substrate for the formation of nitric oxide leads to an improvement in endothelium-dependent vasodilation, reduces blood pressure and total peripheral vascular resistance, both in healthy individuals and in patients with cardiovascular diseases [3], improves the function of endothelial cells, quality life, tolerance to physical exercise and reduces the intensity of LDL-C oxidation during angina pectoris [4], reduces the degree of myocardial ischemia-reperfusion damage in humans in vivo [12]. Impaired L-arginine transport is observed in patients with hypertension and in normotensive individuals genetically predisposed to the development of hypertension [17]. Thus, L-arginine plays a significant role in the functioning of the cardiovascular system. In the human body, L-arginine, like other amino acids, undergoes various metabolic changes [19]. In particular, methyl groups are transferred to L-arginine residues, which are part of various proteins both in the endothelium and in other tissues, under the action of enzymes, and methylated amino acids are formed, including ADMA, which can compete with L-arginine as a substrate nitric oxide synthase and lead to the development of endothelial dysfunction [6].

ADMA is a naturally occurring compound found in the body that plays several important physiological roles. Some of the key functions of ADMA include:

a) Regulation of nitric oxide (NO) synthesis: ADMA is an endogenous inhibitor of nitric oxide synthase (NOS), which is the enzyme responsible for producing nitric oxide (NO) from arginine [11]. Nitric oxide is a critical signaling molecule involved in various physiological processes, including vasodilation, neurotransmission, and immune response. By inhibiting NOS, ADMA regulates the production of NO, thereby influencing vascular tone, blood pressure regulation, and other cardiovascular functions [8].

b) Vascular tone and blood pressure regulation: Nitric oxide produced by NOS plays a key role in regulating vascular tone by promoting vasodilation, which relaxes blood vessels and lowers blood pressure. Elevated levels of ADMA can lead to decreased NO production, resulting in impaired vasodilation and endothelial dysfunction, which are associated with conditions such as hypertension and atherosclerosis [21].

c) Endothelial function: ADMA is involved in the regulation of endothelial function, which refers to the health and integrity of the inner lining of blood vessels (endothelium) [18]. Endothelial dysfunction, characterized by impaired endothelial-dependent vasodilation and increased inflammation, is a key feature of various cardiovascular diseases. Elevated levels of ADMA have been as-

sociated with endothelial dysfunction, suggesting a role for ADMA in the pathogenesis of these conditions [2;10].

d) Inflammation and oxidative stress: ADMA has been implicated in the regulation of inflammation and oxidative stress, both of which are involved in the development and progression of cardiovascular diseases. ADMA can promote inflammation and oxidative stress by various mechanisms, including the induction of pro-inflammatory cytokines and activation of oxidative pathways [9]. Elevated levels of ADMA have been associated with increased markers of inflammation and oxidative stress, further highlighting its role in cardiovascular pathology.

e) Cell growth and proliferation: ADMA may also influence cell growth and proliferation through its effects on NO signaling pathways. Nitric oxide produced by NOS can regulate cell proliferation, apoptosis, and angiogenesis in various cell types. Dysregulation of ADMA levels may disrupt these processes, contributing to pathological conditions such as cancer, neurodegenerative diseases, and cardiovascular disorders [3].

The normal concentration of asymmetric dimethylarginine (ADMA) in the blood can vary depending on several factors such as age, sex, and underlying health conditions. However, typically, the concentration of ADMA in healthy individuals ranges from approximately 0.4 to 0.8 micromoles per liter (μmol/L) or 0.05 to 0.1 milligrams per deciliter (mg/dL) [16]. It's essential to note that these values can vary slightly depending on the laboratory method used for measurement and the specific population being studied. Additionally, levels of ADMA may be influenced by factors such as renal function, diet, and medications. Clinically, elevated levels of ADMA, beyond the normal range, have been associated with increased risk for cardiovascular diseases and other vascular disorders. Therefore, monitoring ADMA levels can be useful in assessing cardiovascular risk and guiding treatment strategies in patients with such conditions [2].

Summary

In summary, ADMA is considered a predictor of cardiovascular diseases due to its role in promoting endothelial dysfunction, inflammation, and oxidative stress, all of which are key pathophysiological mechanisms underlying the development and progression of CVD. Lowering ADMA levels has been proposed as a potential therapeutic strategy for preventing and treating CVD. Interventions aimed at reducing ADMA levels, such as lifestyle modifications (e.g., exercise, diet) and pharmacological treatments (e.g., statins, ACE inhibitors), have shown promise in improving endothelial function and reducing cardiovascular risk.

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