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ENDOTHELIAL PROTECTIVE FUNCTIONS OF HIGH DENSITY LIPOPROTEINS

The development of cardiovascular diseases inversely depends on the cholesterol level of high density lipoproteins (HDLs). On the other hand, it is known that pathogenesis of many cardiovascular diseases is based on endothelial dysfunction. Such facts indicate a special role of this class of lipoproteins in the functioning of endothelial cells. Upon binding to various receptors on endothelial cells, HDLs initiate the induction of endothelial nitric oxide synthase, enhance the production of NO, and stimulate the synthesis of prostacyclin, thus leading to vasorelaxation. By suppressing the synthesis of intercellular adhesion molecules, HDLs prevent the migration of leucocytes and monocytes/macrophages into the vascular wall, exerting anti-inflammatory action. HDLs inhibit the production of reactive oxygen species, prevent apoptosis, and stimulate the proliferation and migration of endothelial cells. Understanding the mechanisms of the protective action of HDLs on vascular endothelium is a necessary stage in the development of new therapeutic agents with the endothelial protective properties.

Keywords: endothelial cells, high density lipoproteins, apoptosis, angiogenesis, cardiovascular diseases.

Introduction. Vascular endothelium, which is located on the boundary between circulating blood and cells of organs and tissues, performs not only the barrier function. It is the key regulator of vascular homeostasis, which maintains a balance between vasodilation and vasoconstriction, inhibition or stimulation of the migration and proliferation of myocytes, fibrinolysis and thrombosis, and is involved in the regulation of intercellular adhesion and aggregation of thrombocytes. Endothelial dysfunction underlies the pathogenesis of many cardiovascular diseases [3].

Reactive oxygen species (ROS), oxidized low density lipoproteins (LDLs) and very low density lipoproteins (VLDLs), and free radicals disturb the ability of endothelium to synthesize nitric oxide (NO). The action of inflammation mediators and proinflammatory cytokines leads to the synthesis of P- and E-selectins on the endotheliocyte membrane as well as monocytic chemotactic protein-1 (MCP-1), tumor necrosis factor a**The regulation of vascular tone.** It is known that binding, internalization and transport of HDLs through endothelial cells are carried out by the following proteins: scavenger receptor class B type I (SR-BI), ATP-binding cassette transporter G1 (ABCG1), endothelial lipase, and ecto-F1-ATPase. Each of them contributes to vascular homeostasis. In addition, endothelial cells express sphingosine-1-phosphate receptors (S1PR) for S1P – the bioactive lipid, 50-70% of which is transferred by HDLs (S1P-HDLs) [43]. The binding of HDL/apoA-I or S1P to receptors not only leads to transendothelial transport of lipids, but also triggers some intracellular signaling events that are accompanied by potential vasoprotective effects (Fig.1). HDLs initiate the induction of endothelial nitric oxide synthase (eNOS), which enhances the synthesis of NO and leads to vasorelaxation; they suppress the synthesis of endothelial adhesion molecules and prevent the migration of leucocytes and monocytes/macrophages into the vascular wall, thus exerting anti-inflammatory action. HDLs inhibit reactive oxygen species and apoptosis; they provide the proliferation and migration of endothelial cells, angiogenesis and re-endothelialization [35,49]. It was shown that HDLs in obese persons with diabetes and dyslipidemia lose their ability to endothelial protection [52].

Nitric oxide is the key signaling molecule for maintaining the normal functioning of vessels by regulation of the vascular tone. It prevents the endothelial inflammation and activation of thrombocytes and also diminishes the growth of myocytes. The activity of eNOS can be regulated by physiological concentrations of HDL/apoA-I through phosphorylation by Ser1179 enzyme [36]. The HDL-induced release of NO decreased under the action of N-nitro-L-arginine methyl ether (L-NAME) – a nonselective inhibitor of eNOS. In bovine aorta endothelial cells (BAEC), colocalization of apoA-I and eNOS was revealed using confocal microscopy with immunostaining of these proteins. The interaction between apoA-I and eNOS proceeds most likely in the perinuclear region rather than on the membrane [24]. Antibodies to apoA-I block the HDL-induced activation of eNOS in isolated plasmatic membranes of endothelial cells [35].

The ability to stimulate eNOS in endothelial cells can be mediated by different HDL binding sites. The molecular mechanism of activation can start from the interaction of HDLs with SR-BI and stimulation of phosphatidyl inositol-3-kinase (PI3K), which in its turn gives rise to the parallel activation of serine/threonine protein kinase B (Akt) and mitogen-activated protein kinase (MAPK)/Erk1/2 with subsequent activation of eNOS, which generates NO and vascular relaxation [36,37]. In aortic cell culture of transgenic mice expressing apoA-I$^{-/-}$, a decrease in the amount of phosphorylated proteins Akt and Erk1/2 was observed [25]. This signaling pathway was partially suppressed when SR-B1 was knocked down using small interfering RNA (siRNA), and induction of SR-BI by inhibitors of HMG-CoA reductase (statins) enhanced the activation of eNOS [32].

Another activation mechanism of eNOS starts from the interaction of S1P-HDL with S1PR. S1P exerted a strong vasodilatory action on the wild-type mice aorta. In HUVEC cells, the effects of S1P on phosphorylation of Akt and eNOS depended on its concentration and disappeared completely after the pretreatment with L-NAME. In endothelial cells of mice with a deficit of S1P, phosphorylation of Akt and an increase in [Ca^{2+}] in response to HDLs and S1P were considerably diminished. Earlier it was shown that activation of eNOS is achieved due to mobilization of [Ca^{2+}] from internal supplies and is a prerequisite for the Akt-dependent

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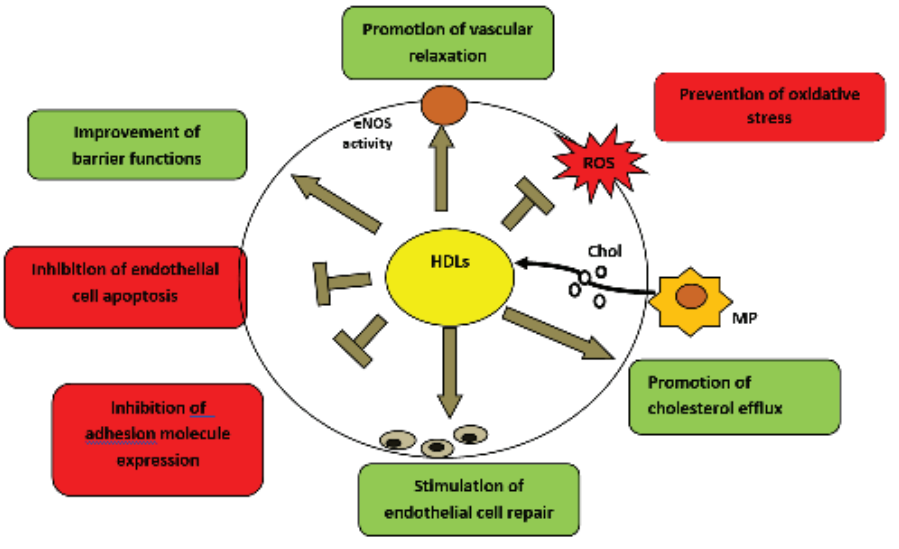

Vasoprotective effect of HDLs on the functions of endothelial cells [adapted from 49]. MP – macrophage, ROS – reactive oxygen species, eNOS – endothelial nitric oxide synthase, Chol – cholesterol, and HDLs – high density lipoproteins.

activation of eNOS and NO-dependent vasorelaxation [26].

By now, the effect of HDLs on the NO production via ABCG1 receptors and their interaction with the structural component of caveolae, a cholesterol-binding protein – caveolin, has been studied. Caveolae and caveolins are the most important modulators of signaling transduction in the cell. Caveolins interact with the signaling molecules and modulate their activity; in most cases, they serve as inhibitors [2]. An increase in the cholesterol content in endothelial cells of the lungs of mice on a high-cholesterol diet enhances the interaction between caveolin and eNOS, thus suppressing the catalytic activity of the enzyme and diminishing the release of NO. HDLs abolished the inhibition of eNOS in endothelial cells, but had no effect in mice with a deficit of caveolin. Stimulation of the outflow of cholesterol and oxysterols, which are detected in a large amount in atherosclerotic plaques, with ABCG1 decreases the interaction of eNOS with caveolin and the subsequent phosphorylation of eNOS [14].

It was shown recently that ecto-F1-ATPase is the single receptor involved in the stimulation of NO production by endothelial cells and NO-dependent vasorelaxation, which are induced by the lipid-free apoA-I. The activation of ecto-F1-ATPase under the action of apoA-I in human endothelial cells and in mice aorta led to Ser1179 phosphorylation of eNOS protein through the signaling pathway of various kinases, including Akt, protein kinase A, AMPK, and calcium/calmodulin-dependent protein kinase type II (CaMKK2) [38].

An increase in the level of eNOS protein under the action of HDLs was demonstrated also in endothelial progenitor cells (EPC), which are a subpopulation of stem cells that can differentiate into mature endothelial cells and take part in re-endothelialization and neovascularization processes [12]. In addition, HDL/apoA-I can increase the amount of eNOS protein not by changing the gene transcription, but rather by increasing the half-life of the eNOS protein in endothelial cells of human vessels via the activation of PI3K, Akt and p42/44 MAPK [38].

Studies with experimental *in vitro* and *in vivo* models showed that HDLs stimulate endothelial cells to produce prostacyclin, thus increasing the inflow of arachidonic acid and the expression of cyclooxygenase-2 (COX-2), which produces prostacyclin (PGI2) – a metabolite of arachidonic acid, the vasoactive endothelial lipid mediator. Prostacyclin is a powerful factor that prevents the aggregation of thrombocytes and initiates vasodilation. Different HDL_2 and HDL_3 subtypes promoted the release of PGI2 in endothelial cells in a dose-dependent manner, which was blocked by a specific inhibitor of COX-2 – rofecoxib. The knockdown of SR-B1 receptors also significantly decreased the release of PGI2 [5]. In diabetes mellitus type 2, glycated HDLs lose their ability to enhance the expression of COX-2 and the release of PGI_2 in HUVEC endothelial cells. However, the addition of S1P to dysfunctional HDL restores this ability. The regulation of COX-2 expression included phosphorylation of the signaling pathway MAPK/ERK, which increased phosphorylation of the nuclear transcription factor CREB [51]. The potential contribution of HDLs to vascular homeostasis via increasing the synthesis of PGI2 can be enhanced by statins [33]. Along with the favorable effect on vasodilation, HDL inhibits the synthesis of thromboxane A2, which is a powerful vasoconstrictor of endothelial cells [40].

In persons with familial hypoalphalipoproteinemia and a low level of HDLs, a sharp decrease in both the basal and stimulated activity of NO was observed; this was accompanied by endothelial dysfunction, which was estimated using venous occlusion plethysmography. A single injection of the reconstructed HDLs (rHDLs) consisting of apoA-I and phosphatidylcholine resulted in complete restoration of vasomotor functions [41]. The *in vivo* effect of HDLs was proved also with the use of apoA-I mimetic peptides, which are the artificially synthesized peptides possessing the biological properties of native apoA-I. Oral administration of the peptide imitating the action of apoA-1 (D-4F) to mice with the knockout of LDL receptor (i.e. hypercholesterinemia) improves the endothelium-dependent vasodilation and decreases the thickness of the arterial wall [18].

The regulation of apoptosis. The oxidized LDLs cause a stable increase in the concentration of intracellular calcium, which leads to the death of endothelial cells. It was shown that the rHDLs, which consist of apoA-I, cholesterol and phospholipids, inhibited the apoptosis in endothelial cells. Therewith, the enrichment of rHDLs with plasmalogens or sphingomyelins enhanced their anti-apoptotic activity [46]. Besides, HDLs retained the anti-apoptotic activity also after the knockdown of eNOS with the use of its inhibitor – L-NAME, which testifies that anti-apoptotic activity of HDLs does not depend on the activation of eNOS [42].

HDLs prevent the apoptosis of HUVEC endothelial cells caused by various stimuli. The mechanism of the endothelial anti-apoptotic effect of HDLs depends on the stimulus of apoptosis. Suppression of the apoptosis induced by TNF-α is related to a decrease in the induction of caspase 3, which is a component of all primary apoptotic pathways. The inhibition of apoptosis in the absence of growth factors in a medium is associated with weakening of the mitochondrial pathways of apoptosis. Therewith, HDLs decrease spreading of mitochondrial potential, generation of ROS, release of cytochrome C into cytoplasm, and activation of caspases 3 and 9. By activating Akt, HDLs give rise to phosphorylation of

the Akt target – BAD (Bcl-2, the associated agonist of cell death), which facilitates the detachment of Bcl-2 from Bcl-xL and suppression of apoptosis [35,42]. It was revealed that HDLs isolated from the blood of patients with stable myocardial ischemia or acute coronary syndrome, which contain an increased amount of apolipoproteins C-I or C-III, transformed into strong inductors of apoptosis in vascular myocytes and endothelial cells due to the increased activity of Bcl-2 and expression of proapoptotic protein tBid [37].

The overwhelming majority of proofs of the anti-apoptotic action of HDLs on endothelium were obtained from observations of cell cultures. The effect of HDLs *in vivo* was established when studying the apoA-I mimetic (D-4F) as the anti-apoptotic agent in a rat model of diabetes; D-4F was shown to improve the vascular reactivity and decrease the fragmentation and desquamation of endotheliocytes [16].

The regulation of angiogenesis. Endothelial cells are able to proliferate, migrate and participate in angiogenesis; this ability underlies neovascularization and maintains integrity of the vascular wall. HDLs (in the concentration of 50, 100 and 500 μg/ml) in a dose-dependent manner for 72 h increased the proliferation of HUVEC cells by a factor of 2-5 compared to the control group. Therewith, already in 24 h HDLs reliably increased the migration of such cells and enhanced their ability to form vessel-like endothelial tubes [23]. Fluorescence microscopy using Alexa-568 dye demonstrated a significant increase in lamellipodia (a sign of cell migration) in endothelial BAEC cells under the action of HDLs, which was comparable with the action of vascular endothelial growth factor (VEGF), the main regulator of angiogenesis [7]. D-4F restored re-endothelialization, which was disturbed in the presence of oxidized HDLs, thus promoting the proliferation and migration of human aortic endothelial cells (HAEC) and the formation of lamellipodia. Proliferation of the cells was revealed by immunostaining on PCNA (the nuclear factor involved in replication and reparation of DNA in proliferating cells). The endothelial migration of cells and re-endothelialization were verified by wound repair and transwell analysis (a test for investigating the migration reaction of endothelial cells to angiogenic inductors or inhibitors) [7].

The mechanisms controlling the angiogenic reactions in response to HDLs are related to an increase in the number of receptors for VEGF (VEGFR) and its rapid phosphorylation, i.e. activation. VEGFR2 was shown to be the main receptor for VEGF that mediates angiogenesis in endothelial cells under the action of HDLs. The expression of VEGFR2 depended on the time and HDL dose. The blockade of VEGFR2 activation by SU1498 inhibitor significantly abolished the proangiogenic ability of HDLs. Moreover, S1P3 inhibitor (suramin) prevented the expression of VEGFR2 as well as the subsequent migration of endothelial cells and formation of new vessels, whereas S1P1 agonist (CYM-5442) and S1P2 (JTE-013) inhibitor did not exert any effect [23]. Under normal conditions, HDLs induce through various receptors (ABCG1, S1P and SR-BI) the activation of many signaling pathways that are necessary for physiological angiogenesis, particularly PI3K/AKT, Gi/Ras/ERK and eNOS. This enhances the migration and proliferation of endothelial cells, mobilization of EPC, re-endothelialization, and tubulogenesis [50].

HDLs play the key role in the regulation of angiogenesis caused by hypoxia. When the content of intracellular oxygen decreases, HDLs modulate post-translational modification of HIF-1a (the transcription factor induced by hypoxia 1-a), after which it is translocated into the nucleus. This stimulates the expression of proangiogenic mediators, such as VEGF, angiopoietin, fibroblast growth factor and others. HDLs, after binding to SR-BI receptor on the cell surface, mediate angiogenesis at hypoxia via the signaling pathway PI3K/Akt, modulation of HIF-1α/VEGF, and enhancement of the eNOS activity [50]. The introduction of rHDL/apoA-I increased the levels of VEGF mRNA, facilitated an increase in the density of sural capillaries in the ischemic hind limbs in mice with streptozotocin-induced diabetes mellitus. Local administration of HDLs restored the angiogenesis and formation of coronary collaterals and facilitated wound healing [28].

To confirm re-endothelialization *in vivo*, the area of vascular wall denudation after perivascular electrical injury is measured. This model made it possible to demonstrate that the vascular endothelialization disturbed by electrical injury can be restored by inserting the human apoA-I gene into somatic cells of transgenic mice expressing apoA-I$^{-/-}$ [27]. The effect on the restoration of endothelium *in vivo* was demonstrated in mice on a high-cholesterol diet with the carotids injured by electricity. Healing was slower in the experimental group compared to the control mice: in the 5th day, healing constituted only 27.8% against 48.2%, respectively. The introduction of D-4F enhanced the restoration of endothelium in mice up to 43.4%. In the process, a considerable inverse correlation between healing of endothelium and plasma markers of oxidative stress was observed [13].

In addition, HDLs can stimulate re-endothelialization and neovascularization at the injured sites through differentiation of EPC into mature endothelial cells and their adhesion to the vessel walls [12]. The apoA-I mimetic, D-4F, increased the amount and functional activity (proliferation, migration and formation of capillary tubes) of mice and human EPC [19]. HDLs promoted the angiogenesis disturbed by ischemia via stimulating the differentiation of EPC using the signaling pathway PI3K/Akt [22].

ApoA-I increased the expression of angiopoietin 4 (the protein growth factor that stimulates the formation of blood vessels from the earlier existing ones) in human aortic endothelial cells. This signaling pathway acted through PI3K/Akt/FOX01 (forkhead box protein O1 – a transcription factor) [30].

In mice with the brain injure similar to human amyotrophic lateral sclerosis, apoA-1 decreased the death of endothelial cells in the mice brain (mBEC) via the signaling pathway PI3K/Akt, which was verified by the inhibition with wortmannin (the PI3K inhibitor). Therewith, apoE did not exert such an effect on the cell culture. A considerable increase in the death of endothelial cells upon inhibition of the apoA-I action by monoclonal antibodies has been proved [19].

The effect on barrier functions. HDL-S1P ensure stability and permeability of vessels [22]. In genetically modified mice (apoM–/–), a strong decrease in the plasmatic level of S1P increased plasma exudation into the extravascular tissues [31]. Besides, in apoM–/– mice, two-photon microscopy, which is employed to obtain brain images *in vivo*, revealed an increase in hematoencephalic barrier permeability for small molecules (fluorescent albumin, 45 kDA) and a flow of large proteins mediated by transcytosis (sodium fluorescein, 365 Da and Alexa fluor488, 643 Da). For example, the transfer of fluorescent albumin in arterioles increased by a factor of 3-10. The S1PR1 agonist (SEW2871) rapidly normalized the disturbed permeability and maintained it in all brain microvessels [10]. Earlier it was shown that the absence of apoM in mice disturbed the endothelial barrier in the lungs and brown adipose tissue [47].

HDLs facilitate the integrity of the HUVEC endothelial barrier via the process including S1PR1 and activation of Akt [43]. Recently it was revealed that stimulation of the barrier integrity in human

endothelial cells of microvessels under the action of S1P signaling leads to phosphorylation of AMPK [45].

D. Svensson [11] analyzed the ability of the wild-type apoA-I to weaken the detrimental effect of cathelicidin peptide (LL-37) on the viability of HUVEC endothelial cells. LL-37 is synthesized by granulocytes, lymphocytes and monocytes; after binding to the cell membranes it can initiate the formation of pores in the membrane, thus reducing the cell viability. The apoA-I binding to LL-37 led to a structural rearrangement of the peptide, which decreased its antibacterial action and cytotoxicity. The siRNA knockdown of the apoA-I gene for decreasing the expression of protein in the HepG2 cells, which produce apoA-I, increases the LL-37-induced cytotoxicity.

The anti-inflammatory action. An important property of HDL is the direct action on endothelium, which is associated with its anti-inflammatory effect. In particular, HDLs weaken the expression of adhesion molecules VCAM-1, ICAM-1 and E-selectin in cultured endothelial cells [9,53]. This process is mediated by SR-BI and S1P receptors, PI3K and eNOS [35]. The S1P-HDL induced phosphorylation of AMPK in inhibiting the expression of adhesion molecules was confirmed *in vitro* in HUVEC cells and *in vivo* in mice aortic endothelial cells. The introduction of the AMPK activator (AICAR) in mice under natural conditions for three days stimulated the phosphorylation of AMPK followed by activation of eNOS and inhibiting the expression of VCAM-1, migration of monocytes and their adhesion to endothelial cells. Therewith, the activation of AMPK and eNOS was completely suppressed by siRNA to CaMKK2 lying above the AMPK level, or STO-609, the specific inhibitor of CaMKK2 [34].

The key role in the modulation of cell responses to inflammation belongs to the nuclear transcription factor NF-kB. In the inactive state, the NF-kB factor forms a heterodimeric complex localized in cytosol; the complex consists of two subunits, p50 and p65, which are associated with the inhibiting protein IkB. When the NF-kB factor is activated by high concentrations of glucose, reactive oxygen species, and inflammatory cytokines, the IkB protein is phosphorylated and becomes degraded. As a result, the release of p50/p65 heterodimer occurs, which is translocated into the nucleus and initiates the nuclear transcription of the genes involved in the development of inflammatory reactions of endothelium, particularly the cell adhesion molecules (ICAM-1 and VCAM-1), Willebrand factor, and E- and P-selectins; this leads to dysfunction of endothelial cells [20]. The anti-inflammatory action of HDLs is associated with inhibiting the production of various factors, including E-selectin, cell adhesion molecules and cytokines [6]. It was shown that apoA-I decreased the activation of NF-kB induced by palmitate in cultured endothelial cells [35]. Positive effects associated with the anti-inflammatory action of apoA-I in different cells were discussed in recent reviews [20,43].

In endothelial cells, delipidized apoA-I and rHDL suppressed the expression of adhesion molecules, thus enhancing the activity of heme oxygenase-1. Heme oxygenase-1 (HO-1) is an inducible enzyme that neutralizes ROS, which are formed by NADPH oxidase under the action of oxidized LDLs. In HUVEC cells, D-4F increased the expression of HO-1 in dependence on the dose and time of action. The action mechanism of D-4F is associated with the activation of HO-1 enzyme through the route Akt/AMPK/eNOS/HO-1 [48]. D-4F suppressed the accumulation of oxidized LDLs and migration of monocytes and inhibited the expression of adhesion molecules and MCP-1, which led to the restoration of migration and reparation of HAEC cells *in vitro* [13]. In Sprague Dawley rats, oral administration of D-4F *in vivo* decreased the iodixanol-induced inflammation by inhibiting NADPH oxidase, production of ROS and formation of peroxynitrite ($ONOO^-$) [17]. Thus, D-4F *in vitro* and *in vivo* prevents endothelial dysfunction, oxidative stress, and inflammation.

HDL decreases inflammation in endothelial cells by increasing the expression of annexin (lipocartin) in them, which is followed by inhibiting the activation of phospholipase A2. In TNF-α activated endothelial HUVEC cells, HDLs increased the level of annexin A1 via the SR-BI receptor by involving the ERK, p38MAPK, Akt and PKC signaling pathways. The HDL-induced annexin A1 inhibited the expression of cell adhesion molecules (VCAM-1, ICAM-1) and E-selectin as well as the secretion of MCP-1, IL-8, VCAM-1 and E-selectin, thus suppressing the adhesion of monocytes. Special inhibitors of the above listed signaling pathways decreased *in vitro* the inhibiting effect of HDLs on the adhesion of monocytes to the TNF-α activated endothelial cells. In the *in vivo* experiments, HDLs (10 mg/kg) induced the expression of annexin in thoracic aorta endothelial cells and prevented its decrease under the action of TNF-α [6].

Conclusion. The facts presented in the review testify to the essential role of HDLs in the functioning of endothelial cells. HDLs carry out their regulatory function via receptors on the membrane of endothelial cells (SR-BI, ABCG1 and S1PR) and also via the activation of endothelial lipase and ecto-F1-ATPase. Thus, binding of HDLs to receptors is necessary not only for transendothelial transport of lipids, but also for triggering the intracellular signaling events, particularly PI3K/Akt, AMPK and MAPK. As a result, HDLs initiate the induction of endothelial nitric oxide synthase, enhance the production of NO, and stimulate the synthesis of prostacyclin, thus leading to vasorelaxation. By suppressing the synthesis of intercellular adhesion molecules, HDLs prevent the migration of leucocytes and monocytes/macrophages into the vascular wall and exert the anti-inflammatory effect. HDLs inhibit the production of reactive oxygen species and prevent apoptosis; they also stimulate the proliferation and migration of endothelial cells. Understanding the mechanisms of the protective action of HDLs on vascular endothelium is a necessary stage in the development of advanced therapeutic agents with the endothelial protective properties.

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PROADRENOMEDULLIN AS A BIOMARKER OF COVID -19 POOR OUTCOME: META-ANALYSIS AND SYSTEMIC REVIEW

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The aim of this study was to analyse and summarise all researches about proadrenomedullin (pro-ADM) prognostic value as covid-19 severity and mortality early predictor. After a literature search and selection, we found 19 articles eligible to inclusion in a meta-analysis. We found pro-ADM had significantly high values in patients both admitted to the general department and ICU-patients with unfavourable outcomes. The Pro-ADM measurement in the admission or early stages of the hospitalisation can be used for the patient's risk stratification, to making a decision and a differential treatment approach.

Keywords: coronavirus disease COVID-19, biomarker, proadrenomedullin, severity score, mortality prognosis.

Introduction. The objective assessment of the disease severity and outcome prediction are essential components to make a decision in the patient's management and appropriate treatment definition. Stratification problems and patient's transferring based on the disease severity and the risk of unfavourable outcomes acquired crucial and priority when there are large number of cases and inevitable excessive burden on healthcare systems. These requirements are particularly relevant in diseases with a wide variability of clinical course and rapidly developing severe complications, an example of which was the new coronavirus infection COVID-19.

Currently, different prognostic scales (APACHE II, SOFA, SAPS II, CURB-65, NEWS) and laboratory biomarkers (leukocytes and platelets level, D-Dimer, C-reactive protein (CRP), Interleukin-6, Interleukin-10, Tumor Necrosis Factor-α, procalcitonin and etc.) are used in the Covid-19 severity assessment [8]. However, none of these scale and laboratory tests has any benefits in Covid-19 prognostic effectiveness with low sensitivity and specificity, it requires further searches of reliable predictive biomarkers of disease's severity.

Covid-19 pathways investigation found the key role of endothelial damage which correlate with infection's severity [16]. Therefore, findings of early indicator with high predictive value considering covid-19-associated endothelitis are reasonable. One of the newest biomarker is adrenomedullin (ADM) – hormone with cytokine-like effects, it consist of 52 amino acid peptide and released by endothelial and vascular smooth muscle cells and widely distribute in tissue and this production increased during infections [1]. ADM has vasodilative immunomodulate and anti-inflammatory effects, it's used as early marker in lower respiratory tract infections, community-acquired pneumonia and sepsis [2]. ADM has low metabolic stability and brief half-life, its splits in 1:1 ratio with precursor called mid-regional proadrenomedullin (pro-ADM) and it can proportionally represent the ADM level and it is used in tests. The biomarker showed direct correlation with increased procalcitonin level and prognostic scales (APACHE II, SOFA, SAPS II, CURB-65, NEWS). The Pro-ADM level in sepsis and septic shock were 1,8 (0,4-5,8) nmol/L and 4,5 (0,9-21,0) nmol/L respectively [2,4]. In several single studies pro-ADM level interpretation and combination with other biomarkers and scales demonstrated efficiency in making a decision about admission in ICU or save transferring out, antibiotics escalation or de-escalation and poor prognosis prediction [1].

In view of the above, our research summarised current studies to evaluate proADM as an early biomarker of severity and mortality predictions.

Purpose of the study was combined and analyse articles to assess pro-ADM prognostic ability as an early marker of severity and mortality in Covid-19 patients.

Materials and Methods. In PubMed, EMBASE (Experta Medica), Cochrane Central Register of Controlled Trials, Scholar Google and e-library we selected article were had been published in English and Russian till 25.11.2022 with pro-ADM levels, severity and outcomes information. The search strategy was used with key words and combinations: «new coronavirus infection», «COVID-19», «predict», «midregional

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