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HYPERLIPIDEMIA-SPECIFIC BIOMARKERS WOULD IMPROVE CLINICAL DIAGNOSIS AND THERAPEUTIC TREATMENT AT EARLY DISEASE STAGES.

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Annotation: Arterial hypertension and dyslipidemia are among the most prevalent cardiovascular risk factors in the general population and are major contributors to the global burden of atherosclerosis-related cardiovascular diseases. Epidemiological evidence indicates that their coexistence substantially increases the risk of adverse cardiovascular outcomes, including an approximately eightfold higher risk of ischemic stroke and an elevenfold increase in cardiovascular mortality. The implementation of fixed-dose combination therapies targeting blood pressure and lipid levels represents an effective population-based strategy for improving adherence and reducing overall cardiovascular risk in both primary and secondary prevention settings.Cardiometabolic diseases remain the leading cause of morbidity and mortality worldwide. Arterial hypertension, dyslipidemia, obesity, and type 2 diabetes mellitus represent the most prevalent and modifiable risk factors contributing to cardiovascular disease development. Importantly, growing epidemiological evidence suggests that the clustering of these risk factors often begins in early adulthood. Abdominal obesity, characterized by excess visceral adipose tissue, has been recognized as a stronger predictor of cardiometabolic risk than general obesity. Visceral fat acts as an active endocrine and inflammatory organ, secreting adipokines, cytokines, and hormones that directly contribute to insulin resistance and systemic inflammation. In this context, C-peptide and insulin resistance markers have gained increasing attention as early indicators of metabolic dysfunction.

Keywords: Abdominal obesity, cardiovascular diseases, dyslipidemia, inflammation, endothelial cells

The link between dyslipidemia and endothelial dysfunction has been shown in many studies. Low-density lipoprotein (LDL) is responsible for endothelial ROS production. Lipid peroxidation occurs through nonenzymatic processes (by ROS derived from NADPH/NADH oxidase or uncoupled eNOS) or enzymatic processes (performed by lipoxygenases, myeloperoxidase, and cyclooxygenases). Lipid peroxidation products generate oxidation-specifc epitopes (OSEs) on the surface of oxidized LDL (oxLDL) molecules [2]. An OSE is recognized by receptors (i.e., scavenger receptors, toll-like receptors, mediators of the complement system, or IgM antibodies). Genetic research has shown that deletion of lipoxygenases decreases LDL oxidation and the process of atherosclerosis in mice [6], and OSE-specifc natural IgM antibodies inhibit the uptake of LDL by macrophages and prevent foam cell formation in mice [3]. Endothelial cells and macrophages—as major sensors of OSE—uptake oxLDL, which has a wide array of proatherogenic properties. Additionally, scavenger receptors are not downregulated by an LDL increase; therefore, LDL can easily accumulate and generate foam

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cells—the frst step of atherosclerosis. Virchow, based on autopsy studies, emphasized that lipid accumulation occurs at the sites of early endothelial lesion formation [1]. Moreover, several studies have shown that disturbed patterns of fow observed in arterial curvatures, bifurcations, and side branches favor the development of atherosclerosis. In such regions, endothelial cells display cuboidal morphology, higher cell turnover, and an impaired endothelial barrier function, leading to migration of LDL and infammatory mediators. In contrast, regions exposed to laminar fow exhibit ellipsoidal cell morphology, coaxial alignment, and glycocalyx, providing protection from lipoprotein extravasation [4]. In hypertension, dyslipidemia may aggravate the development of atherosclerosis through the following mechanisms. First, chronic oscillatory shear stress—driving oxidative stress, redox imbalance, and upregulation of lipid oxidation enzymes—leads to LDL oxidation and internalization [5]. Second, elevated blood pressure enhances angiotensin II binding to the angiotensin type 1 (AT1) receptor, which results in augmented lipid uptake in the vessel wall [55, 57]. In dyslipidemia, through stimulation of LDL to ROS production and through eNOS uncoupling, NO bioavailability is diminished, which contributes to vasoconstriction. Second, hypercholesterolemia enhances arginase activity—an enzyme competing with eNOS for L-arginine, which results in eNOS uncoupling with its further consequences. Third, dyslipidemia leads to upregulation of the AT1 receptor, enhancing the vasoconstrictive efect of angiotensin II [2]. Fourth, it has been proven that dyslipidemia increases arterial stifness, predisposing to the development of hypertension [5]. Finally, dyslipidemia by reducing barorefex sensitivity impairs the negative feedback loop and dysregulates blood pressure control [61, 62]. The magnitude of the reactions taking place at the endothelium level directs our considerations toward microcirculation—the part of a vascular tree having an area advantage over other parts. Microvessels constitute approximately 99% of all vessels in the human body, and their total surface area is estimated at 500 to 700 m2 [3]. Therefore, assessment of the endothelium in the microcirculation area-such a hemodynamically signifcant modulator with an impressive surface —may provide insights into CV status. A decline in endothelial-vasodilating properties and infammation process generating a neointima in response to the deleterious efect of hypertension and dyslipidemia lead to vascular remodeling. Although both diseases are indirectly associated with arterial occlusion, the distribution pattern of these diseases in the arterial tree is diferent [4]. In hypertension, the lumen narrowing process is observed in small vessels and microvascular bed, while in large vessels, intima media thickening and vessel enlargement occur. In atherosclerosis, obstructive lesions are localized in medium and large vessels. Cross talk between micro- and macrocirculation aggravates and accelerates these unfavorable alterations in the CV system. Small arteries are the major determinant of total peripheral resistance. Microvessel remodeling, manifested as a reduced lumen diameter and an increased wall-to-lumen ratio, leads to an increase in total peripheral resistance and blood pressure values [6]. Additionally, stif components are loaded in the arterial wall, subsequently enhancing large artery stifness, which is related to a decreased ability to accommodate the volume of blood ejected from the left ventricle [2]. Arterial stifness leads to an increase in systolic and pulse pressures and a shift of refection sides toward microvessels. Then, pressure pulsatility penetrates the microcirculation, resulting in further vessel remodeling and organ damage [7]. This vicious circle of successive hypertension processes might be dizzyingly accelerated by accompanying diseases such as dyslipidemia due to the common pathophysiological background taking place in endothelial dysfunction. . Some were revealed in

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the aforementioned studies to be signifcant in hypertension development, contributing to endothelial dysfunction by inhibiting endothelium-derived vasodilating mediators or stimulating endothelium-dependent vasoconstrictors [8]. For instance, ceramides, by inhibiting the eNOS-serine/ threonine protein kinases-heat shock protein 90 signaling complex and enhancing thromboxane A2, lead to endothelial disability and vasoconstriction. These data elucidate the role of lipidomic pathways in blood pressure regulation and the etiopathogenesis of hypertension. Since the metabolic pathways of hypertension and dyslipidemia partially overlap, the frequent coincidence of these two diseases seems obvious. Therefore, therapy focused on both hypertension and dyslipidemia may multiply its benefcial efects and result in greater CV disease risk reduction.

Hyperlipidemia is an important public health problem with increased incidence and prevalence worldwide. Current clinical biomarkers, triglyceride, total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol lack the necessary specificity and sensitivity and only increase significantly after serious dyslipidemia. Therefore, sensitive biomarkers are needed for hyperlipidemia. Hyperlipidemia-specific biomarkers would improve clinical diagnosis and therapeutic treatment at early disease stages. The aim of metabolomics is to identify untargeted and global small-molecule metabolite profiles from cells, biofluids, and tissues. This method offers the potential for a holistic approach to improve disease diagnoses and our understanding of underlying pathologic mechanisms. This review summarizes analytical techniques, data collection and analysis for metabolomics, and metabolomics in hyperlipidemia animal models and clinical studies. Mechanisms of hypolipemia and antilipemic drug therapy are also discussed. Metabolomics provides a new opportunity to gain insight into metabolic profiling and pathophysiologic mechanisms of hyperlipidemia. Metabolomics in dyslipidemia provides a potential revolution in the prevention, prediction, and individualization of patients with cardiovascular disease. The translation of metabolomic results clinically will provide earlier, faster, and more accurate diagnosis not only for cardiovascular disease but also for many disease states in general.

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