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RELATIONSHIP BETWEEN ATHEROGENIC IMBALANCE (APOB/APOA) AND MARKERS OF OXIDATIVE STRESS IN THE DEVELOPMENT OF ARTERIAL HYPERTENSION

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Abstract:

This article explores the relationship between atherogenic imbalance, assessed through the ApoB/ApoA ratio, and markers of oxidative stress in the pathogenesis of arterial hypertension. The ApoB/ApoA ratio reflects the balance between atherogenic and anti-atherogenic lipoproteins and is considered a more precise predictor of cardiovascular risk than traditional lipid parameters. Oxidative stress, characterized by excessive production of reactive oxygen species and insufficient antioxidant defense, plays a central role in endothelial dysfunction and vascular remodeling. The review analyzes current evidence linking elevated ApoB/ApoA ratios with increased oxidative stress biomarkers and discusses their combined contribution to the initiation and progression of arterial hypertension. Particular attention is given to mechanisms involving endothelial injury, inflammation, lipid peroxidation, and impaired nitric oxide bioavailability. Understanding this interaction may improve early risk stratification and open new perspectives for targeted therapeutic strategies in hypertensive patients.

Keywords: ApoB/ApoA ratio, atherogenic imbalance, oxidative stress, arterial hypertension, cardiovascular risk, endothelial dysfunction, lipid metabolism, reactive oxygen species, inflammation, vascular remodeling.

RELEVANCE

Hypertension is the leading preventable risk factor for cardiovascular diseases (CVD) and overall mortality worldwide [1,2].

In 2010, 31.1% of the global adult population (1.39 billion people) had arterial hypertension, defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg [3].

The prevalence of hypertension is increasing worldwide due to population aging and the growing impact of lifestyle-related factors, including unhealthy diet (high sodium intake, low potassium intake) and insufficient physical activity [3]. However, trends in hypertension prevalence are not uniform across regions. Over the past two decades, high-income countries have experienced a moderate decline in prevalence, whereas low- and middle-income countries have seen a significant increase [3]. These differences suggest that healthcare systems may face a rapidly growing burden of hypertension and blood pressure–related cardiovascular diseases, often in addition to a substantial burden of infectious diseases.

A review of the literature indicates that over the past 40 years, global mean blood pressure levels have remained stable or slightly decreased [4]. The global age-standardized mean systolic blood pressure in men remained nearly unchanged between 1985 (126.6 mmHg) and 2023 (127.0 mmHg), while in women it slightly decreased over the same period (from 123.9 to 122.3 mmHg). Similar trends were observed for diastolic blood pressure: minimal changes in men and a slight decrease in women.

However, regional changes in mean blood pressure from 1985 to 2023 were heterogeneous (Figure 1). In general, high-income countries demonstrated a significant decrease in blood pressure levels, whereas low- and middle-income countries showed an increase [4].

The greatest decline in systolic blood pressure was observed in the high-income Asia-Pacific region, where it decreased by 2.4 mmHg per decade in men and by 3.2 mmHg per decade in women.

The largest reduction in diastolic blood pressure was recorded in the high-income Western region, with decreases of 1.5 mmHg per decade in men and 1.8 mmHg per decade in women.

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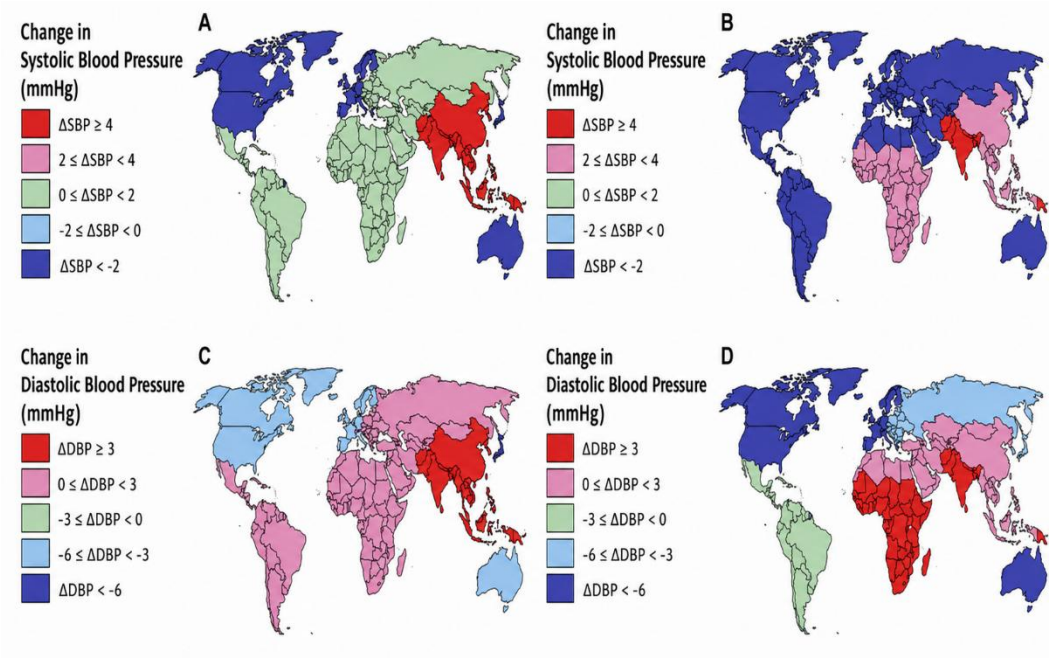
Figure 1



The relationship between dyslipidemia and endothelial dysfunction has been demonstrated in numerous studies [5–7]. Low-density lipoproteins (LDL) are responsible for the generation of reactive oxygen species (ROS) in the endothelium. Lipid peroxidation occurs through both non-enzymatic pathways (mediated by ROS produced by NADPH/NADH oxidases or uncoupled eNOS) and enzymatic pathways (involving lipoxygenases, myeloperoxidase, and cyclooxygenases).

Lipid peroxidation products form oxidation-specific epitopes on the surface of oxidized LDL [4, 8, 9]. These epitopes are recognized by receptors such as scavenger receptors, Toll-like receptors, components of the complement system, and IgM antibodies. Genetic studies have shown that deletion of lipoxygenases reduces LDL oxidation and atherosclerosis development in mice [24, 40], while OSE-specific natural IgM antibodies inhibit macrophage uptake of LDL and prevent foam cell formation [4, 1, 2].

Moreover, scavenger receptors are not downregulated in response to increased LDL levels, allowing cholesterol to accumulate easily, leading to foam cell formation—the first stage of atherogenesis. Virchow, based on autopsy data, emphasized that lipid accumulation occurs at sites of early endothelial injury [5, 4, 3].

In addition, numerous studies have shown that disturbed (turbulent) blood flow at vascular curvatures, bifurcations, and branch points promotes the development of atherosclerosis. In these regions, endothelial cells exhibit a cuboidal shape, increased turnover, and impaired barrier function, facilitating the penetration of LDL and inflammatory mediators. In contrast, areas with laminar flow are characterized by an ellipsoidal cell shape, coaxial alignment, and the presence of a glycocalyx, which protects against lipoprotein infiltration [4–7].

Interaction of arterial hypertension and dyslipidemia accelerates the development of atherosclerosis

The common vascular outcome of arterial hypertension and dyslipidemia is endothelial dysfunction, which plays a key role in the initiation and progression of atherosclerosis. These two risk factors, interacting through overlapping pathogenetic mechanisms at the endothelial level, potentiate atherogenesis.

In arterial hypertension, dyslipidemia enhances the development of atherosclerosis through several

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mechanisms. First, chronic oscillatory shear stress induces oxidative stress, disrupts redox homeostasis, and activates lipid-oxidizing enzymes, leading to the oxidation and subsequent intracellular uptake of low-density lipoproteins (LDL) [5, 6]. Second, elevated blood pressure enhances angiotensin II signaling via type 1 (AT1) receptors, promoting increased lipid accumulation in the vascular wall [5, 7].

In dyslipidemia, a reduction in nitric oxide (NO) bioavailability occurs due to LDL-induced generation of reactive oxygen species and uncoupling of endothelial nitric oxide synthase (eNOS), resulting in vasoconstriction. In addition, hypercholesterolemia increases the activity of arginase—an enzyme competing with eNOS for L-arginine—thereby further exacerbating NO pathway dysfunction. Dyslipidemia also increases the expression of AT1 receptors, enhancing the vasoconstrictive effects of angiotensin II [4, 8]. Furthermore, it has been shown that dyslipidemia increases arterial stiffness, thereby predisposing to the development of arterial hypertension [9, 6]. Finally, dyslipidemia reduces baroreflex sensitivity, impairing negative feedback mechanisms and destabilizing blood pressure regulation [1, 2].

The scale of endothelial alterations associated with the coexistence of these factors highlights the importance of the microcirculation, which represents the most extensive component of the vascular network. Microvessels account for approximately 99% of all blood vessels in the human body, with a total surface area estimated at 500–700 m² [6]. Therefore, assessment of endothelial function in the microcirculatory bed, as a key hemodynamic regulator with a vast surface area, may provide valuable information about cardiovascular status.

A reduction in the vasodilatory function of the endothelium and an inflammatory process with neointima formation in response to the adverse effects of hypertension and dyslipidemia lead to vascular remodeling. Although both conditions are indirectly associated with arterial occlusion, their distribution within the vascular bed differs [4, 6]. In hypertension, luminal narrowing is observed in small vessels and the microcirculatory bed, whereas in large vessels thickening of the intima-media layer and expansion of the vascular wall are noted. In atherosclerosis, obstructive lesions are localized in medium and large arteries.

Arterial stiffness leads to an increase in systolic and pulse pressure and a shift of reflected pressure waves toward the microcirculation. As a result, pulsatile load penetrates the microvascular bed, causing further vascular remodeling and damage to target organs [70].

This vicious cycle of hypertension progression may be significantly accelerated in the presence of comorbid conditions such as dyslipidemia due to a shared pathophysiological mechanism—endothelial dysfunction.

The increasing prevalence of arterial hypertension and dyslipidemia necessitates the development of new approaches. The assessment of endothelial biomarkers is of great importance and represents a promising tool for the future diagnosis of cardiovascular diseases. The metabolomic profile provides new insights into early changes preceding the development of hypertension [74] and dyslipidemia, paving the way toward novel therapeutic strategies. However, the limited number of prospective studies indicates the need for further research.

We conducted a cohort study with a prospective design. Patients diagnosed with arterial hypertension (AH) were included in the study.

Inclusion criteria: age ≥ 18 years; confirmed diagnosis of AH; availability of laboratory data (homocysteine, CRP, lipid profile, etc.).

Exclusion criteria: acute inflammatory diseases; oncological diseases; severe renal or hepatic failure; incomplete data.

Patients were followed up for 5 years (e.g., 12–36 months). Outcomes assessed included development of cardiovascular complications, progression of hypertension, and hospitalizations.

METHODS OF THE STUDY

In all patients, the following parameters were assessed: homocysteine, high-sensitivity C-reactive protein (hs-CRP), apolipoproteins (ApoA, ApoB), lipid profile, and blood pressure. The study design was based on the inclusion of patients with newly diagnosed arterial hypertension. Along with general clinical examination, anthropometric measurements were performed in all patients, including body mass index (BMI), calculated using the Quetelet formula (body weight, kg / height, m²), and waist-to-hip ratio (WHR), defined as the ratio of waist circumference to hip circumference.

The ankle–brachial index (ABI) was determined using the formula:

ABI = (max ankle systolic BP) / (max brachial systolic BP).

A complete blood count was performed using an automated analyzer Micro-SS and Micro-SS Plus (HTI, USA), with assessment of erythrocyte count, hemoglobin level, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelet count,

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leukocyte count, leukocyte differential, and erythrocyte sedimentation rate (ESR).

Glucose levels were measured using the glucose oxidase method ("Vector-Best", Glucose-Novo). Total cholesterol was determined by an enzymatic method ("Vector-Best", Cholesterol-Novo). High-density lipoprotein cholesterol (HDL-C) was measured by an enzymatic method ("High-Density Lipoproteins", BioSystems, Spain). Triglycerides were measured using an enzymatic colorimetric method ("Vector-Best", Triglycerides-Novo, liquid form). Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula:

$$LDL\text{-}C = TC - 0.46 \times TG - HDL\text{-}C \text{ (mmol/L)}.$$

Apolipoproteins were also analyzed as protein components of lipoproteins. Apolipoprotein A-I (ApoA-I) is the main component of HDL (approximately 90%) and plays a key role in the anti-atherogenic properties of high-density lipoproteins, preventing cholesterol deposition in atherosclerotic vascular plaques. Apolipoprotein B (ApoB) is the main structural protein of all lipoproteins except HDL. It is involved in the regulation of cholesterol synthesis and metabolism and reflects the risk of atherosclerosis development. An increase in ApoB, even in the presence of normal HDL-C levels, indicates an elevated risk of cardiovascular diseases.

Serum hs-CRP levels were determined by an enzyme-linked immunosorbent assay (ELISA) using the "Uniplan" analyzer with the Hs-CRP ELISA reagent kit manufactured by Biomerica (USA).

Here is the English translation in a scientific style:

The level of malondialdehyde (MDA) in saliva was determined using thiobarbituric acid reactive substances (TBARS) assay, based on the reaction of MDA with 2-thiobarbituric acid to form a colored complex. Unstimulated whole saliva was used for analysis, collected in the morning on an empty stomach, after rinsing the oral cavity with water and with prior abstinence from food, beverages, and tooth brushing for at least 1 hour.

Homocysteine levels in blood were measured in venous blood samples collected in the morning on an empty stomach (at least 8–12 hours after the last meal).

Comparative characteristics of parameters between groups

In the study, clinical and biochemical parameters were analyzed in patients of the main group (n = 60) and the control group (n = 51). Results are presented as mean ± standard error.

Table 1. Age characteristics of study participants

Group	Age range, years	Mean age, years (M ± m)
Main group (n = 60)	26–64	46.68 ± 1.12
Control group (n = 51)	20–60	37.84 ± 1.68

Total sample size: 111 participants

Overall mean age: 42.26 ± 1.4 years

It was found that patients in the main group were statistically significantly older compared to the control group (46.68 ± 1.12 vs. 37.84 ± 1.68; $p < 0.001$). The body mass index was also higher in the main group (24.89 ± 0.42 vs. 22.46 ± 0.38; $p < 0.001$).

Table 2.

Groups	Main group (n=60)	Control group (n=51)
Age	46.68±1.12	37.84±1.68***
BMI	24.89±0.42	22.46±0.38***
Homocysteine	19.51±1.20	14.00±0.58***
MDA	0.03±0.01	0.01±0.00**
Total cholesterol	4.49±0.08	4.10±0.05***
HDL	1.08±0.03	1.45±0.03***
LDL	3.24±0.09	2.62±0.08***
TG (triglycerides)	1.61±0.05	1.28±0.05***
Atherogenic index	3.29±0.13	1.88±0.07***
High-sensitivity C-reactive protein	3.22±0.22	1.38±0.06***

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Groups	Main group (n=60)	Control group (n=51)
CRP	2.05±0.14	2.04±0.15
Total bilirubin	18.41±0.26	19.25±0.15**
Glucose	5.00±0.11	4.35±0.04***
Apo A1	1.22±0.05	1.76±0.05***
Apo B	1.90±0.07	1.15±0.05***
Fibrinogen	3.97±0.07	3.80±0.07
LPI	0.99±0.02	1.08±0.02**

A significant increase in homocysteine levels was observed in the main group (19.51±1.20 vs 14.00±0.58; p<0.001), which may indicate a higher cardiovascular risk. Similarly, malondialdehyde (MDA) levels were elevated (0.03±0.01 vs 0.01±0.00; p<0.01), reflecting intensified lipid peroxidation processes.

The lipid profile also demonstrated unfavorable changes in the main group: total cholesterol, LDL cholesterol, triglycerides, and the atherogenic index were significantly higher, whereas HDL cholesterol levels were lower (p<0.001 for most parameters). This indicates a pronounced atherogenic dyslipidemia.

High-sensitivity C-reactive protein levels were significantly elevated in the main group (3.22±0.22 vs 1.38±0.06; p<0.001), suggesting the presence of chronic systemic inflammation. In contrast, differences in standard CRP levels were not statistically significant.

An increase in glucose levels was also noted in the main group (5.00±0.11 vs 4.35±0.04; p<0.001), which may indicate disturbances in carbohydrate metabolism.

The apolipoprotein profile was characterized by decreased Apo A1 and increased Apo B levels in the main group (p<0.001), further confirming a high atherogenic risk.

No statistically significant differences were observed in fibrinogen levels, whereas the lipid peroxidation index (LPI) was lower in the main group (p<0.01). Interestingly, total bilirubin levels were significantly lower in the main group (18.41±0.26 vs 19.25±0.15; p<0.01), which may suggest a reduced antioxidant protective effect

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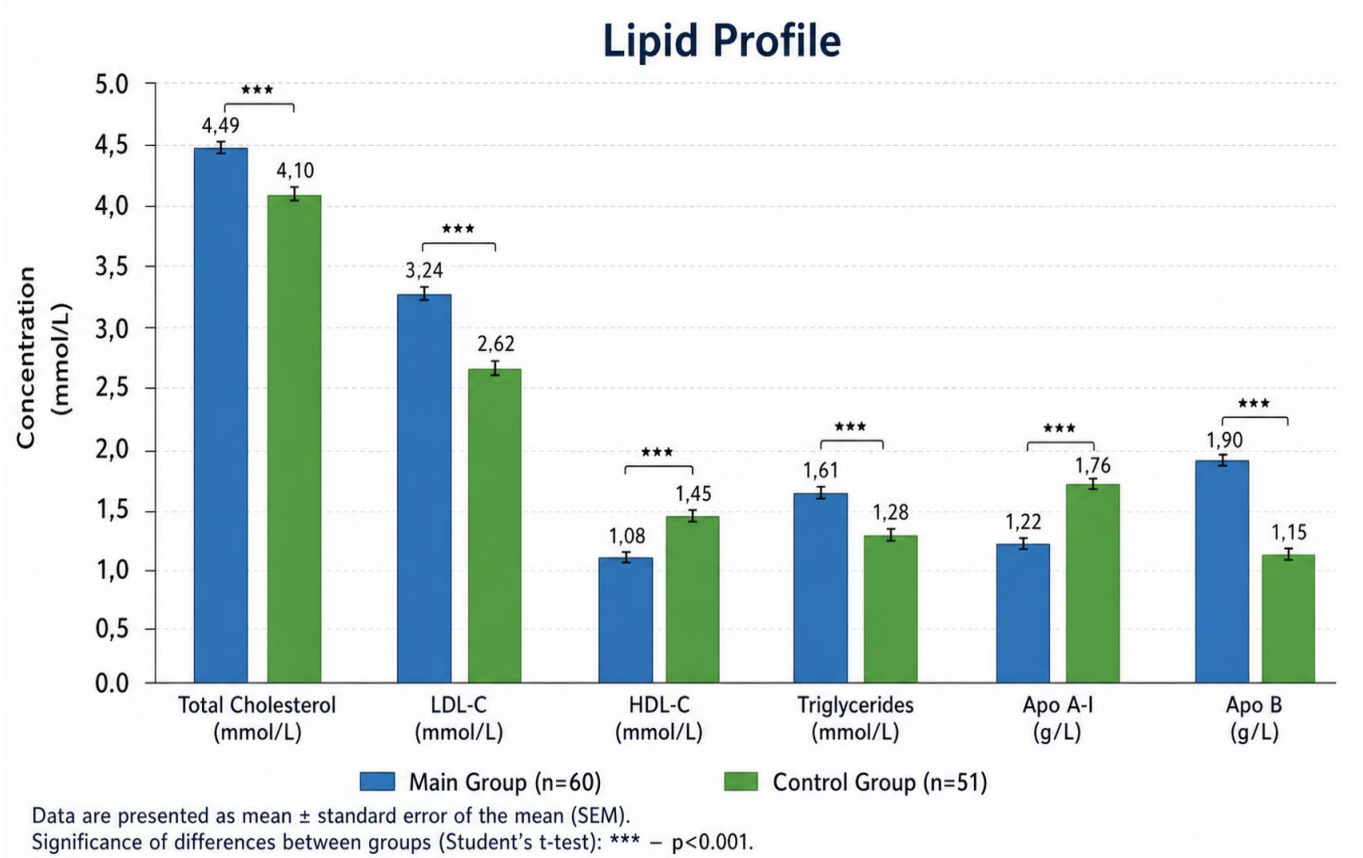

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CONCLUSION

A complex of adverse metabolic and inflammatory changes associated with increased cardiovascular risk was identified in the main group. A significant elevation of homocysteine and malondialdehyde levels indicates enhanced oxidative stress and endothelial damage.

Lipid profile disturbances, including increased total cholesterol, low-density lipoproteins (LDL), triglycerides, and atherogenic index accompanied by decreased high-density lipoproteins (HDL), indicate pronounced atherogenic dyslipidemia. Elevated levels of high-sensitivity C-reactive protein reflect the presence of a chronic inflammatory process.

The concomitant increase in glucose levels suggests possible impairment of carbohydrate metabolism. Changes in the apolipoprotein profile, characterized by decreased Apo A-I and increased Apo B levels, further confirm a high atherogenic potential. A reduction in total bilirubin may reflect a weakened endogenous antioxidant defense.

Taken together, these findings characterize the main group as having a higher risk of cardiovascular complications and emphasize the need for early diagnosis and correction of the identified abnormalities. Thus, the overall set of observed changes confirms pronounced oxidative stress, deterioration of the lipid–apolipoprotein profile, and an increased atherogenic potential, which may contribute to a higher cardiovascular risk in the examined patients.

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