

## **The role of serum lipid profile in the pathogenesis of arterial hypertension**

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### **Abstract**

Hypertension is a key contributor to the high global burden of cardiovascular morbidity and mortality, due to its increasing prevalence worldwide. In clinical practice, dyslipidemia and hypertension often coexist, possibly because they share similar underlying causes, such as endothelial dysfunction and obesity. Consequently, this review article presents the collective findings on the role of lipid profile parameters in arterial hypertension. Individuals with hypertension often have significantly higher mean serum levels of triglycerides (TG), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C), while exhibiting lower mean serum levels of high-density lipoprotein cholesterol (HDL-C) compared to those without hypertension. TC and HDL-C play an important role in the pathogenesis of arterial hypertension. However, there is a lack of studies explaining the link between TG and LDL-C and arterial hypertension. Future studies are necessary to fully elucidate the exact mechanisms by which the mentioned lipid parameters contribute to arterial hypertension.

**Key words:** arterial hypertension, lipid profile, atherosclerosis

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## Introduction

Hypertension is a chronic disorder presented with consistently high blood pressure. It represents an important public health concern and adds to the total burden of cardiovascular (CV) morbidity/mortality worldwide. The world trend of hypertension incidence is rising globally, with an estimated increase to nearly 30% by 2025 (1).

In 2010, nearly 31% of people (i.e. 1.38 billion adults) exhibited hypertension, defined as systolic blood pressure (BP)  $\geq$  140 mmHg and/or diastolic BP  $\geq$  90 mmHg<sup>2</sup>. Moreover, hypertension prevalence is increasing globally in parallel with unhealthy dietary habits, sedentary lifestyle and obesity (2-6).

Hypertension, as a multifactorial disease, is tightly connected with oxidative stress and inflammation, as well as with endothelial dysfunction, being its major pathophysiological underlying feature (7).

Under physiological condition, antioxidants diminish and/or prevent the harmful effects of the reactive oxygen and nitrogen species (ROS, RNS). Once this antioxidant-pro-oxidant balance becomes exhausted due to overwhelming ROS/RNS accumulation, negative side-effects on target cells occur (7, 8). The activity of endothelial NOS is diminished by ROS/RNS, along with reduced NO synthesis, leading to vasoconstriction (7, 8).

Visceral compartments of the adipose tissue are significant contributors to increased pro-oxidant and pro-inflammatory milieu due to increased secretion of cytokines and adipokines, thus favoring insulin resistant state and atherogenic dyslipidemia, as another underlying feature of hypertension and CV risk (9-11).

Currently, the standard practice to assess the CV risk of an individual involves examining the serum lipid profile, which consists of four key measurements: triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C)<sup>12</sup>. Typically, this test is conducted using a blood sample obtained after fasting (12).

Dyslipidemia refers to an imbalance of lipid biomarkers, including TG, TC, LDL-C, and HDL-C. This condition can lead to serious complications, mostly cardiovascular disease (CVD), which can be influenced by factors like an unhealthy diet, smoking, or genetic predisposition (13). Dyslipidemia and hypertension share the common pathophysiological mechanisms, both of them being major risk factors for CVD, and there is a complex relationship between them (14, 15). These two entities act synergistically concerning the dysfunction of endothelial cells (15).

In hypertension, the dysfunction of endothelial cells forces the onset/progression of the adverse effects of dyslipidemia, and vice versa – the process of hypertension is aggravated due to structural/functional alterations of the vascular wall found in dyslipidemia (15).

Atherosclerosis is a state accompanied by the deposition of fatty plaques in the arteries, leading to modifications in the walls of arteries, i.e. narrowed lumen and stiffened

arteries. Increased LDL-C levels, i.e. LDL oxidation, are the key risk factor for atherosclerosis (15).

Over time, atherosclerosis can reduce the elasticity of the arteries and further increase BP, contributing to the development of hypertension. Atherosclerosis can lead to endothelial dysfunction. This dysfunction can reduce the ability of blood vessels to dilate properly, which can, in turn, raise BP. In clinical practice, it is common for individuals to have both dyslipidemia and hypertension, potentially due to shared underlying causes (16, 17).

Serum lipid and lipoprotein abnormalities are established as an important risk factor for both CVD and essential hypertension. Dyslipidemia is more frequent among individuals with newly diagnosed hypertension (18). Both hypertension and dyslipidemia can cause inflammation within blood vessels, promoting the development and progression of atherosclerosis. One metabolic and inflammatory marker that can predict CV risk is the TG-HDL-C ratio (19-21). According to a previous study, poorly controlled hypertension patients showed a significantly higher TG-HDL-C ratio compared to well-controlled hypertension patients (22). Patients with hypertension who had increased TG levels and LDL-C/HDL-C ratio also faced a higher risk of developing diabetes, with these factors interacting to influence diabetes onset (23).

Patients with hypertension exhibited serum lipid levels that varied depending on age and sex, with non-elderly individuals being more prone to dyslipidemia compared to the elderly. Female patients exhibited higher TG, LDL-C, and TC levels compared to males (24).

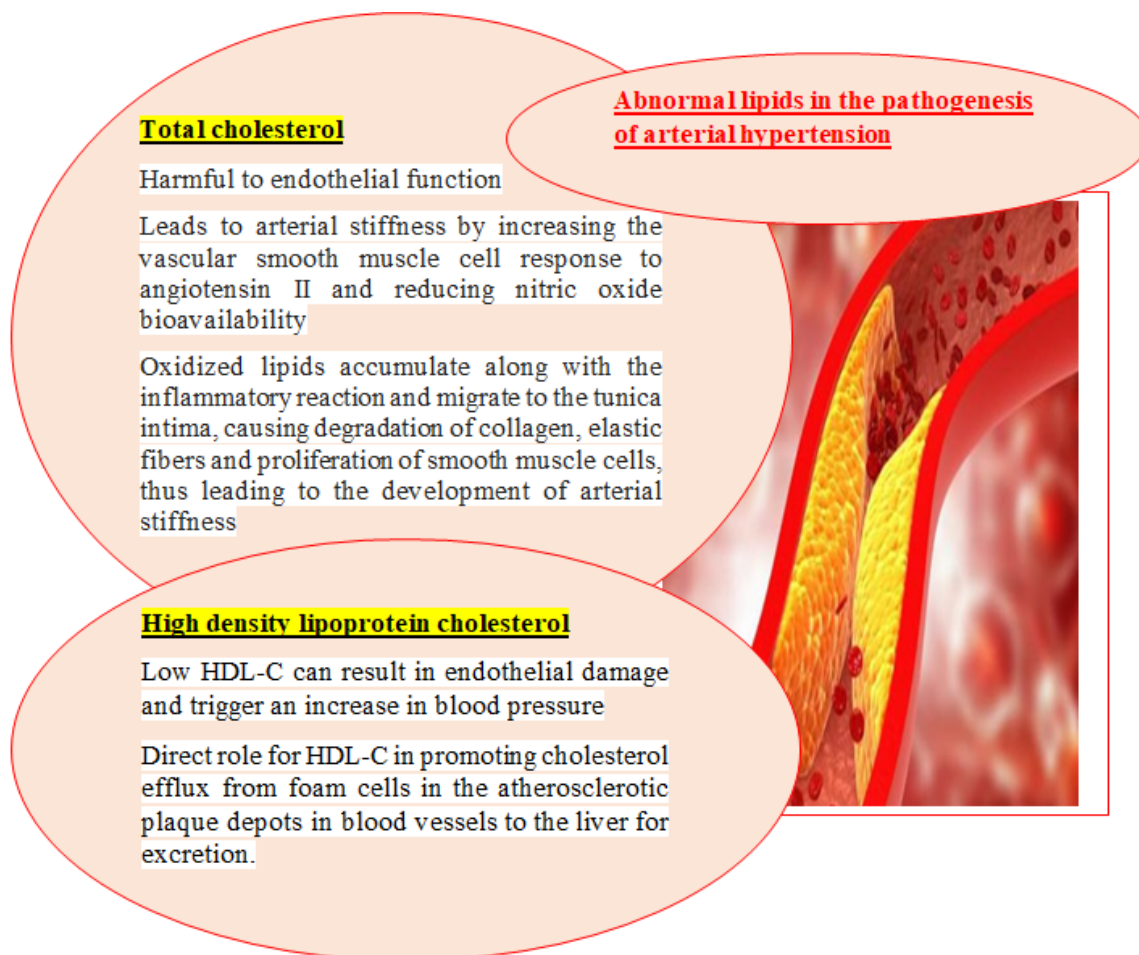
Similarly, in a study conducted on an urban population in Bangladesh, the association between serum lipid status and hypertension was investigated (25). The findings indicated that individuals with hypertension had significantly higher levels of TG, LDL-C and TC in comparison with normotensives. Additionally, lower HDL-C was recorded in hypertensive individuals compared to normotensives (25). There were significant associations between TC and systolic BP, as well as TG and diastolic BP. However, systolic and diastolic BP did not show statistically significant associations with the other lipid parameters (26). Nevertheless, it is important to note that there are diverse populations and patterns where dyslipidemia and hypertension may not be consistently linked.

Hence, this review article focuses on the role of lipid profiles in the development of arterial hypertension, an aspect that has not been extensively reported in the literature on hypertension. It specifically summarizes the role of serum levels of TG, LDL-C, HDL-C and TC in the pathogenesis of arterial hypertension.

### **The role of lipid profile in arterial hypertension**

This review article is focused on the influence of serum levels of TC, TG, HDL-C and LDL-C in arterial hypertension. In Figure 1, the lipid profile's contribution to the pathogenesis of arterial hypertension is illustrated. Moreover, a summary of studies which

explained the role of major lipid profile parameters in the development of arterial hypertension is presented in Table I.



**Figure 1. Effects of total cholesterol and high density lipoprotein cholesterol in hypertension development**

**Slika 1. Uticaj ukupnog holesterola i holesterola iz lipoproteinskih čestica velike gustine na razvoj hipertenzije**

**Table I** Summary of studies which explained the role of major lipid profile parameters in the development of arterial hypertension

**Tabela I** Sažeti prikaz studija koje objašnjavaju ulogu glavnih parametara lipidnog profila u razvoju arterijske hipertenzije

First author	Lipid profile	The key finding of lipid profile in arterial hypertension
Osuji et al. (18)	TC	Hypertensive patients have been found to have significantly higher serum TC concentrations compared to normotensive individuals.
Anika et al. (26)	TC	A significant association between systolic BP and TC and a significant correlation between TG levels and diastolic BP was found.
Satoh et al. (36)	TC	No significant interactions between blood pressure and TC have been observed for stroke. The joint effect of high BP and high TC levels can enhance the risk of death from coronary heart disease, but not from stroke.
Chen et al. (42)	TC	Arterial stiffness was found to act as a mediator between hyperlipidemia and BP, linking the risk factors of TC and arterial stiffness to high BP.
Tomita et al. (44)	TG	Significant associations were observed between serum TG levels and the onset of hypertension.
Raposeiras-Roubin et al. (45)	TG	Hypertriglyceridemia was related to endothelial inflammation and subclinical atherosclerosis, even in individuals with normal LDL-C levels in subjects with low-moderate CV risk.
Kawamoto et al. (46)	TG	TG levels modulated the correlation between serum uric acid and prehypertension.
Fletcher and Bulpitt (48)	TG, HDL-C	The risk of ischemic heart disease in individuals with low HDL-C and high TG was not directly correlated with systolic or diastolic BP values.
Trimarco et al. (51)	HDL-C	The U-shaped correlation between HDL-C levels and the risk of CV events in hypertensive males were demonstrated.
Chruściel et al. (52)	HDL subfractions	The relationship between total HDL-C and HDL-3 subfraction values and the tendency for hypertension onset in young subjects.
Ivanišević et al. (53)	HDL subfractions	The correlation between hypertension and relative proportion of paraoxonase (PON)-1 on HDL <sub>3c</sub> subclasses in pregnant women was shown.
Pavithran et al. (54)	HDL-C	Changes in lipid profile, including a lowering of HDL-C, can lead to endothelium damage and increased BP that can contribute to its significant predictive value for coronary heart disease.
Chen et al. (57)	HDL-C	In a large sample-size study that included nearly 63,000 males in China, a positive association between HDL-C and hypertension after adjustment for the BMI was observed.
Al-Jarallah et al. (58)	HDL-C	In rats with normal BP, HDL-C was found to protect against myocardial ischemia/reperfusion damage.
Tsukinoki et al. (60)	LDL-C	The first epidemiological study to investigate the joint impact of LDL-C and BP on different subtypes of CVD in population of Asia.

### **The role of dyslipidemia in the pathogenesis of hypertension**

Changes in lipid metabolism can lead to abnormal concentrations of serum lipids and lipoproteins, which are closely related to hypertension. Dyslipidemia has been shown to have a significant impact on the prognosis of individuals with hypertension (27). Research on the association between hypertension and dyslipidemia, as well as the underlying mechanisms, is growing. Hypertension and dyslipidemia not only share common underlying factors and metabolic abnormalities, but also interact with each other through various mechanisms. Firstly, dyslipidemia contributes to increased BP and vascular endothelial damage. The connection between hypertension and hyperlipidemia is likely mediated by the function of the vascular endothelium. Vascular endothelial activity plays a crucial role in regulating artery contractility. Abnormal lipids can indirectly affect arterial elasticity and lead to hypertension by interfering with the control of vascular endothelial cells (28). Oxidized low-density lipoprotein (ox-LDL) is a crucial component in the impact of hyperlipidemia on vascular endothelial damage. Ox-LDL primarily induces damage and dysfunction in the endothelium, favoring the development of atherosclerosis (24, 28). The process of LDL oxidation is not clearly defined. The scavenger receptors on the macrophages' surface recognize LDL, which further becomes internalized in large amounts and transformed into the foam cells. The expression of adhesion molecules on the surface of cells is induced by ox-LDL. The adhesion of leukocytes and their adherence to the endothelium, as well as their migration into the intima, along with the activation of macrophages to secrete pro-inflammatory mediators and ROS, further aggravate the destabilization of atherosclerotic plaque (29).

### **The role of total cholesterol (TC) in the pathogenesis of hypertension**

Hypertensive patients have been found to have significantly higher serum TC concentrations compared to normotensive individuals. A positive correlation between serum TC and both systolic and diastolic BP was observed in both patients with hypertension and control subjects (18). Similarly, Anika et al. (26) confirmed the association between systolic BP and TC.

Borghetti (30, 31) and Pereira (32) presumed that the pathogenic influence of hypercholesterolemia on hypertension may be strongly connected with its impact on peripheral vascular tone and the function of the tissue renin-angiotensin system. Research has also indicated that high TC levels may affect arterial stiffness, suggesting a potential connection between hypercholesterolemia and BP through these factors (32, 33). TC is considered to impair endothelium function, and increased serum TC levels lead to arterial stiffening by enhancing the response of vascular smooth muscle cell to angiotensin II and diminishing the availability of nitric oxide (34, 35).

It has been observed that elevated systolic BP increases the risk of mortality due to intraparenchymal haemorrhage and ischemic stroke, while high TC levels decrease such risk. However, no significant relationship was observed between BP and TC for stroke. In the Asian population, the coexistence of high BP and elevated TC levels can enhance the risk of death from coronary heart disease, which is not the case for stroke (36).

The accumulation of oxidized lipids caused by inflammation and their migration to the tunica intima of blood vessels contribute to the breakdown of collagen, smooth muscle cells proliferation, and the elongation of elastic fibres. These processes collectively contribute to the onset of arterial stiffness (37-39). Moreover, the buildup of lipid plaque in the arteries leads to narrowing, worsening arteriosclerosis, and ultimately resulting in an increase in systolic BP (40-41).

Arterial stiffness was found to act as a mediator between hyperlipidemia and BP, linking the risk factors of TC and arterial stiffness to high BP. To diminish the risk of CVD, clinicians need to pay attention to maintaining optimal blood lipid levels, especially in individuals with hyperlipidemia and hypertension, to delay or alleviate arterial stiffness and the subsequent increase in BP. However, when prescribing statins to individuals with hyperlipidemia, the onset of arterial stiffness and changes in BP need to be monitored. If necessary, strategies for treating or reversing aortic stiffness need to be implemented, as this can enable the prevention of the development of hypertension and manage BP effectively (42).

### **The role of triglycerides (TG) in the pathogenesis of hypertension**

TG, the most common fatty molecules found in organisms, can lead to hypertriglyceridemia when present in high levels in the bloodstream. Hypertriglyceridemia can arise from various pathophysiological conditions and disorders, such as obesity, non-alcoholic fatty liver disease, diabetes mellitus, etc. (43, 44). Even in the absence of high TC or LDL-C levels, elevated TG values are linked with atherosclerosis and increase the CVD risk (5, 21, 45). Hypertriglyceridemia was related to endothelial inflammation and subclinical atherosclerosis, even in individuals with normal LDL-C levels in subjects with low-moderate CV risk (45). In a study conducted on a workplace population in Japan, significant correlations were observed between serum TG levels and the development of hypertension (44). Additionally, Anika et al. (26) found a significant correlation between diastolic BP and TG levels.

The relationship between higher serum uric acid and TG was shown to be an independent indicator of systolic BP, although not of diastolic BP. Elevated serum uric acid levels were correlated with prehypertension in individuals without hypertriglyceridemia, although not in those that exhibited high TG levels. The correlation between serum uric acid and prehypertension was modified by TG levels (46). Other studies have also confirmed the association between serum uric acid levels and higher BP and an independent association between waist-to-hip ratio and systolic BP (47).

In another study involving older white males without pre-existing CVD, a notable finding showed that the risk of ischemic heart disease in individuals with low HDL-C and high TG was not in direct relationship with systolic or diastolic BP levels. Furthermore, the U-shaped correlation between the risk of ischemic heart disease and treated diastolic BP, as previously described, was observed only in men with low HDL-C and high TG (48).

Jeppesen et al. (49) proposed a potential clarification for the paradox in which BP reduction did not lead to the expected decrease in ischemic heart disease risk among hypertensive patients. They suggested that investigators in BP-lowering studies did not account for specific treatment effects in patients with hypertension without and with this particular dyslipidemia (49).

### **The role of high-density lipoprotein cholesterol (HDL-C) in the pathogenesis of hypertension**

HDL is one of the five main categories of lipoproteins, which are complex particles consisting of multiple proteins that transport fat molecules through the body's extracellular fluid. Each HDL particle is composed of an average of 80-100 proteins and is structured by one, two, or three apolipoprotein A proteins. HDL particles grow as they circulate, accumulating fat molecules and carrying hundreds of them per particle (50).

Recent research has shown that high levels of HDL-C in circulation are related to an increased risk of mortality. However, the link between HDL-C and specific CV events has not been studied in hypertensive individuals. Trimarco et al. (51) demonstrated a U-shaped relationship between HDL-C levels and the risk of CV events in hypertensive males.

A low level of HDL-C has long been recognized as a strong predictor of increased CV risk (18). Another study suggested an association between total HDL-C and HDL<sub>3</sub> subfraction levels with the tendency for hypertension development in youngsters (52). Ivanišević et al. (53) showed the correlation between hypertension and relative proportion of paraoxonase (PON)-1 on HDL<sub>3c</sub> subclasses in pregnant women. Furthermore, Pavithran et al. (54) explained that changes in lipid metabolism, including lower HDL-C, can lead to the damage of endothelium and increased BP, which may contribute to its significant predictive value for coronary heart disease.

In another study, it was suggested that isolated lower HDL-C levels might be a usual lipid abnormality in a specific region of Nigeria, and this condition was exacerbated with the presence of hypertension. HDL-C can assume the role of endothelial damage and BP elevation. Experimental studies indicate that HDL-C takes part in removing cholesterol from atherosclerotic plaque deposits in blood vessels, a process known as reverse cholesterol transport. HDL-C also possesses strong anti-inflammatory and antioxidant properties, which contribute to its protective effects against atherosclerosis (18, 55, 56). Low HDL-C levels have also been associated with the presence of other atherogenic risk factors, according to research (18).

While HDL-C levels were negatively associated with CV events, HDL-C was found to be positively correlated with hypertension, which is recognized as an impairing endothelial function factor. In a large sample-size study that included nearly 63,000 males in China, a positive association between HDL-C and hypertension after adjustment for BMI was observed (57).



Hypertension significantly influences the onset/progression of CVD and can alter the function and composition of HDL-C. However, the precise role of HDL-C in CV problems associated with hypertension has remained unclear. In rats with normal BP, HDL-C was found to protect against myocardial ischemia/reperfusion (I/R) damage. It was uncertain whether enhancing the composition or function of HDL-C in spontaneously hypertensive rats (SHR) would offer protection against myocardial I/R damage. A unique cardioprotective and anti-hypertensive action of HDL-C against myocardial I/R damage in SHR was revealed, and the magnitude of this protection was closely related to the levels of expression of cardiac scavenger receptor class B type-I (SR-BI). Continuous HDL-C therapy preserved the SHR hearts via the process of reduction of inflammation and autophagy (58).

### **The role of low-density lipoprotein cholesterol (LDL-C) in the pathogenesis of hypertension**

LDL-C is a cholesterol which is transported by LDL lipoprotein particles throughout the body in extracellular fluids. It is widely recognized as a primary CVD risk factor and clinical evidence supports the effectiveness of lowering LDL-C levels in reducing atherosclerotic disease events (59). Both LDL-C and BP contribute to the risk of ischemic stroke and coronary artery disease (CAD). Tsukinoki et al. (60) conducted an epidemiological study that was the first to investigate the combined impact of LDL-C and BP on different subtypes of CVD in the population of Asia. Although no significant interaction between LDL-C and BP was found, the data revealed that the CAD risk connected with hypertension or prehypertension was higher in subjects with high LDL-C values compared to those with normal LDL-C values. Hence, it is crucial to control both BP and LDL-C in patients in Japan with hypertension, prehypertension, and high LDL-C values to prevent CAD at an early stage. Additionally, further comprehensive epidemiological research is needed to thoroughly examine the association between LDL-C, BP, and the prevalence of specific CVD subtypes in Asian populations (60). Furthermore, among dyslipidemia outpatients with hypertension in China, low rates of achieving their LDL-C and BP goals were observed, particularly in the departments of endocrinology. Combination therapy was not connected with increased rates of achieving target LDL-C and BP values (61).

It is of utmost importance to note that hypertension is a multifactorial condition influenced by various factors, including genetics, lifestyle, and other comorbid conditions. Dyslipidemia is just one of the many factors that can contribute to the onset or exacerbation of hypertension.

### **The effect of drugs used for dyslipidemia treatment on blood pressure**

Effective management of arterial hypertension often involves addressing multiple risk factors and adopting a universal approach to cardiovascular health (61). Lifestyle changes that include a healthy diet, moderate physical activity, managing stress, and smoking cessation are important strategies for managing both hypertension and

dyslipidemia (62, 63). Additionally, medication may be prescribed when necessary to control lipid levels and BP, reducing the overall risk of CVD.

Statins are crucial medications for the treatment of dyslipidemia, i.e., for lowering LDL-C, due to their efficacy, low cost and safety. The mechanism of action of statins is related to an increase in the expression of LDL receptors at hepatocytes, with consequent LDL-C uptake. The beneficial effects of adding a statin to antihypertensive medications in patients with hypertension has also been confirmed, showing lower BP in these patients (64, 65). Moreover, the favorable properties of statins on BP can be indirectly attributed to their ability to reduce ROS and mediators of inflammation, thus improving endothelium function (65). Statins also downregulate endothelin-1 and angiotensin II-type one receptors and enhance nitric oxide (NO) bioavailability, thus inhibiting the proliferation of vascular smooth muscle cells, improving endothelial-dependent vasodilation and reducing the stiffness of large arteries (65).

Cholesteryl ester transfer protein (CETP) enables the transfer of TG from particles that contain apoB to HDL particles, as well as cholesteryl esters from HDL particles. CETP inhibitors have been shown to have more beneficial properties on LDL-C reduction than on HDL-C increase (66). Namely, the first generation of these drugs (i.e., dalcetrapib, torcetrapib) mostly exhibited off-target effects or increased HDL-C, whereas their second generation (i.e., evacetrapib, anacetrapib) exhibited beneficial properties in LDL-C reduction and were proven to be safe and effective in reducing CV risk. CETP inhibitors have also been shown to improve insulin sensitivity and glucose tolerance, and diminish the risk of new-onset diabetes (66). However, limited unfavorable effects on BP by CETP inhibitors were shown in the first generation of these drugs (67). Anacetrapib led to a mean increase of systolic BP of 0.7 mmHg (68), whereas a mean increase of systolic BP of 0.6 mmHg was shown with dalcetrapib (69). On the other hand, evacetrapib showed no effect on BP (70). Further studies are needed to confirm the properties of CETP inhibitors and clinical trials are currently ongoing (67).

## **Conclusion**

The relationship between hypertension and dyslipidemia is influenced by various factors, including genetics, diet, physical activity, and lifestyle choices. Therefore, the development of these conditions is multifactorial and individual responses can vary. Lipid profile has a significant role in the pathogenesis of hypertension due to its influence on the development of atherosclerosis, which can lead to the narrowing and stiffening of arteries, which in turn can increase BP. This review article emphasized the importance of lipid panels, including TG, LDL-C, HDL-C and TC, in the development of arterial hypertension. Future studies are necessary to elucidate the exact mechanisms by which these lipid profiles contribute to the development of arterial hypertension. It is suggested that managing lipid profiles through lifestyle modifications (e.g., diet and exercise) and medications (when necessary) can help to reduce the risk of developing hypertension and its complications. Monitoring lipid levels is an important aspect of CV assessment and management, as it can provide valuable insights into an individual's overall risk of hypertension and related CVDs.

## **Conflicts of Interest**

The authors declare no conflict of interest.

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## **Authors' Contributions**

All authors contributed to the conception and design of this study. The first draft of the manuscript was written by Saira Rafaqat. Data collection was performed by all three authors. A. Klisić critically revised the manuscript. All authors have read and approved the final version of the manuscript.

## **Availability of Data**

Not applicable.

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# **Uloga lipida u serumu u patogenezi arterijske hipertenzije**

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## **Kratak sadržaj**

Hipertenzija je glavni doprinoseći faktor u pojavi kardiovaskularnog morbiditeta i mortaliteta, zahvaljujući porastu prevalence ovog poremećaja. U kliničkoj praksi, dislipidemija i hipertenzija su često udružena stanja, vjerovatno zahvaljujući zajedničkim patofiziološkim karakteristikama, tj. disfunkciji endotela i gojaznosti. Shodno navedenom, ovaj revijski članak predstavlja zbirni prikaz uloge lipidnog profila u arterijskoj hipertenziji. Osobe sa arterijskom hipertenzijom često imaju više vrednosti ukupnog holesterola i triglicerida, više vrednosti koncentracije holesterola niske gustine, a niže vrednosti koncentracije holesterola velike gustine, u poređenju sa osobama koje nemaju hipertenziju. Ukupni holesterol i koncentracija holesterola niske gustine igraju značajnu ulogu u patogenezi arterijske hipertenzije, ali je nedovoljno studija koje ispituju povezanost triglicerida i koncentracije holesterola velike gustine u patogenezi arterijske hipertenzije. Buduće studije su potrebne kako bi rasvijetlile ulogu dislipidemije u hipertenziji.

**Ključne reči:** arterijska hipertenzija, lipidni profil, ateroskleroza

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