The Protective Effect of HDL-Cholesterol in Patients with Essential Hypertension

GERMAINE SAVOIU BALINT[1#], GHEORGHE IOVANESCU[2#], HORIA STANCA[3*], CALIN MARIUS POPOIU[2], EUGEN BOIA[2], RAMONA AMINA POPOVICI[4], SORIN LUCIAN BOLINTINEANU[2]

[1]University of Medicine and Pharmacy Victor Babes Faculty of Pharmacy, 2 Eftimie Murgu Sq., 300041, Timisoara, Romania

[2] University of Medicine and Pharmacy Victor Babes, Faculty of Medicine, 2 Eftimie Murgu Sq., 300041, Timisoara, Romania

[3] Carol Davila University of Medicine and Pharmacy Bucharest, Faculty of General Medicine, Ophthalmology Department, 37 Dionisie Lupu Str., 020021, Bucharest, Romania

[4] University of Medicine and Pharmacy Victor Babes, Faculty of Dentistry, 2 Eftimie Murgu Sq., 300041, TImisoara, Romania

High blood pressure (HPB) is considered a major health problem affecting more than one billion people worldwide. Hypertension is the most common cardiovascular disorder that increases the risk of cardiovascular morbidity and mortality. HDL-cholesterol, considered to be an independent risk factor for cardiovascular events, presents pleiotropic effects that can influence arterial status and blood pressure. The aim of this study was to determine the correlation between HDL-cholesterol levels and blood pressure in normotensive and hypertensive patients (untreated and 1-month treated with statins) and to evaluate the arterial stiffness as a marker of endothelial dysfunction in these patients.

Keywords: HDL-cholesterol, essential hypertension, arterial stiffness

Arterial hypertension, known also as high blood pressure (HBP), is the most common chronic disease at global level, affecting between a third and half the population of a country [1,2]. This pathology is more common in hypertensive western-modern societies, in which overeating, physical inactivity and stress are a feature of modern life [1,2].

The relationship between blood pressure (BP) and cardiovascular events (CV) - morbidity and mortality, has been extensively studied in an increased number of observational research [3]. Thus, it is currently well established that HBP represents a major risk factor for cerebrovascular and coronary heart disease, the risk of a hypertensive patient being closely correlated with the severity of hypertension, but also with the association with other risk factors for atherosclerosis. Moreover, in particular, it was demonstrated that systolic BP (SBP) is a better predictor of CV events than diastolic BP (DBP) [3]. The pulse pressure (defined as the difference between SBP and DBP), a parameter that reflects arterial distensibility (stiffness), is regarded as having additional prognostic role [4]. There is evidence that pulse pressure in hypertensive patients is also positively associated with various cardiovascular manifestations [5,6]. However, it is uncertain whether pulse pressure is an independent predictor of cardiovascular events, as against SBP and DBP. Although there are sufficient theoretical premises in order to consider arterial stiffness as an independent predictor of cardiovascular risk, there are still insufficient practical evidence to confirm this.

Another major risk factor for cardiovascular events is considered to be dyslipidemia, by its involvement in the development of atherosclerosis. This disease is produced when the lipoproteins metabolism is altered, particularly, it was characterized by the increase of very/intermediate/ low density lipoproteins (VLDL/IDL/LDL-cholesterol) accompanied by the decreased of high density lipoproteins (HDL-cholesterol). HDL-cholesterol it is known by its beneficial effects on cholesterol metabolism, being responsible for the *retrograde transport* of cholesterol from extra-hepatic tissues (especially from blood vessels) to liver, where cholesterol is catabolized, thus HDL-cholesterol is considered to the anti-atherogenic lipoprotein. Indeed, studies have concluded that patients with normal/ high levels of HDL-cholesterol present a lower risk to develop cardiovascular diseases, and now HDL-cholesterol is considered to be an independent risk factor [7]. Beside the anti-atherosclerotic effects, HDL-cholesterol exerts an antioxidant activity, manifested by the presence of HDL associated enzymes (paraoxonase) and HDL apolipoproteins [8-10].

It is known that HBP and high cholesterol, dyslipidemia are risk factors for developing cardiovascular diseases. In individuals who both risk factors, their effects are not additive, but multiplicative, dyslipidemia is often associated with HPB, whereas HBP does not lead to dyslipidemia. There are few studies showing the interrelationship between HBP and HDL-cholesterol. Evidence of a reversed has been found in hypertensive patients with chronic alcoholism or obesity [11]. The plausible link between HDL-cholesterol and HBP may be represented by endothelial dysfunction. The decrease of HDL-cholesterol levels is correlated with an increase in arterial stiffness, which is known to be involved in the onset of hypertension, and also associated with increased endothelial dysfunction [6,12].

Some studies were also carried out in the analysis of compounds used in the therapy of high cholesterol levels [13-18], by instrumental techniques, such as thermal analysis and spectroscopic techniques [19-29].

The aim of this study is to determine the correlation between HDL-cholesterol and HBP in untreated and recently diagnosed patients with hypertension compared to one month treated patients with statins (atorvastatin - 20mg/day) and normotensive patients and to evaluate the arterial stiffness as a marker of endothelial dysfunction in these patients.

* email: hstanca@yahoo.com

# These authors contributed equally to this work.

Experimental part

Material and methods

The present study was conducted over a period of 5 months in Clinical Hospital CFR Timisoara, and included a total number of 45 patients (age range: 45-69, males: 54%, females 46%). The study groups were as follows:

- Control: clinically healthy patients without hypertension (n = 15)
- Group HBP - M: Hypertensive patients recently diagnosed, untreated (n = 30)
- Group HBP + M: Hypertensive patients (n = 30)

The patients in the HBP + M group were form the previously group (HBP – M), but after one-month treatment with atorvastatin (20mg / day). After one month they returned to the hospital for consultation, in order to determine again BP and arterial stiffness.

To evaluate the direct relationship between HDL-cholesterol concentration and arterial stiffness, a group of 15 clinically healthy subjects were divided into two groups according to plasma levels of HDL-cholesterol, as follows:

- HDL**n**: patients with a serum level of HDL-cholesterol normal (n = 8)
- HDL**d**: patients with a serum level of HDL-cholesterol decreased (n = 7)

Blood pressure measurement

Blood pressure measurement was realized after the new AHA (American Heart Association) Recommendations for Blood Pressure Measurement [30], with a mercury sphygmomanometer (Gima, 32703) with the Korotkoff 's sound technique, and interpreted as shown in table 1.

Arterial stiffness measurement

The measurement of Pulse Wave Velocity (m/s) - PWV, represents a non-invasive method of assessing the status of arterial / arterial stiffness. The PWV measurement was recorded with two electrodes (one placed at the base of the neck, at the level of common carotid artery and the other on the forearm, at the level of femoral artery), that measured the period of time in which the pulse wave travels the distance between the two electrodes. The PWV is influenced by the elastic properties of arteries, their thickness and density of blood flow. Thus, when the vessel distensibility is lower, the wave propagation speed is higher. Thus, the speed of the pressure pulse indicates the arterial stiffness and at the same time it is used as a parameter for evaluation of endothelial dysfunction.

The normal PWV is considered to be 9.6 m/s, any increase over 10 m/s is considered to be pathological.

Statistical analysis

The results are presented as mean (M) ± standard deviation (SD). The statistical processing of the data was performed using Microsoft Office Excel 2013 and GraphPad Prism5. For the comparison of data we used the simple analysis of variance (one - way ANOVA) and t-Student test. The interpretation of the level of significance was as follows: ***: $p \leq 0.001$; **: $p \leq 0.01$; *: $p \leq 0.05$.

Results and discussions

Due to the existence of different values of HDL-cholesterol between males and females, we studied the correlation of BP with HDL-cholesterol concentration by gender. The results revealed that when we compared the levels of HDL-cholesterol in the males of the HBP-M group, we observed a significant decrease in HDL-cholesterol levels, as compared to the healthy subjects ($p^{***} \leq 0.001$). We observed no significant differences between the HDL-cholesterol in group HBP + M vs. control ($p > 0,05$), but these values were significant increased in group HBP + M compared to HBP-M group ($p \leq 0.05$) (fig. 1).

When we compared the level of HDL cholesterol in females, we obtained the same changes as in the case of males, as presented in figure 2.

When comparing SBP/DBP values we observed a significant differences between (HBP-M) compared to the SBP/DBP in patients treated with statins for one month (HBP + M) ($p \leq 0.05$), presented in figure 3 and 4.

At the correlation of HDL cholesterol with SBP and DBP, we obtained a moderate correlation within Control group

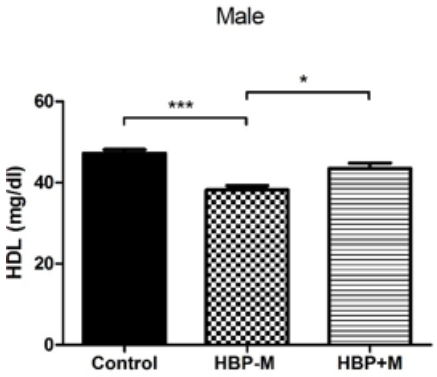

Fig. 1. Average HDL-cholesterol concentration of males in all studied groups

	SBP (mmHg)	DBP (mmHg)
Normal	119 or lower	79 or lower
Prehypertension	120 to 139	80 to 89
Stage 1 hypertension	140 to 159	90 to 99
Stage 2 hypertension	160 or higher	100 or higher

Table 1
CLASSIFICATION OF HYPERTENSION (AFTER CHOBANIAN AV, ET AL. HYPERTENSION, 2003)

	Control	HBP - M	HBP + M
SBP (mmHg)	120.2 ± 7.61	154.2 ± 11.3	139.2 ± 13.01
DBP (mmHg)	70.33 ± 4.46	99.33 ± 9.28	83.32 ± 8.13
HDL-cholesterol females (mg/dl)	55.17 ± 4.45	45.17 ± 2.70	51.17 ± 2.43
HDL-cholesterol males (mg/dl)	47.17 ± 2.40	38.17 ± 2.62	43.47 ± 3.32

Table 2
MEAN VALUES OF THE PARAMETERS DETERMINED IN ALL STUDIED GROUPS

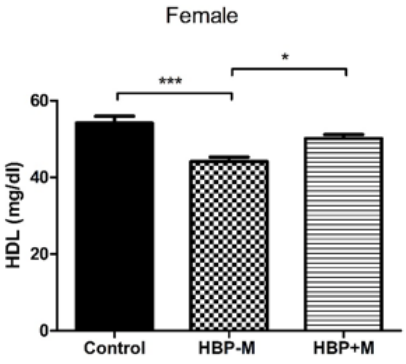

Fig. 2. Average HDL-cholesterol concentration of females in all studied groups

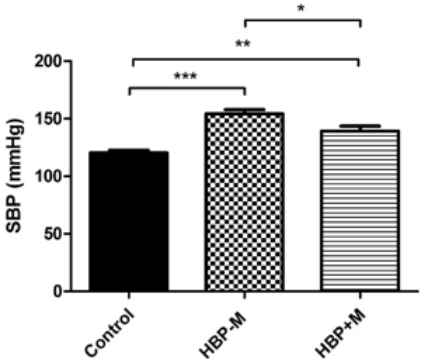

Fig. 3. Average SBP values in all studied groups

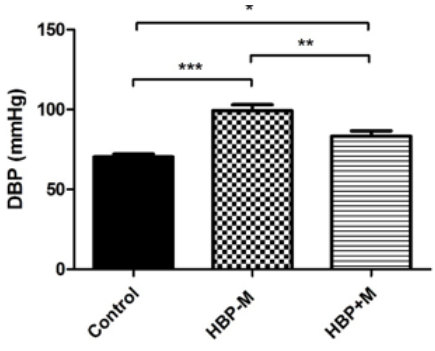

Fig. 4. Average DBP values in all studied groups

(R^2= 0.347 for males and R^2= 0.271 for females, data not shown). In HBP – M we obtained modest correlations with SBP (R^2=0.349 males and R^2=0.224 females) and with DBP (R^2=0.201 males and R^2=0.119 females). For the correlation of HDL cholesterol with SBP and DBP in HBP + M we obtained strong and negative correlations, as presented in figure 5 A and B.

When compared the values of PWV with HDL-cholesterol, we observed a decline in the group HDLd vs. HDLn ($p \leq 0.05$). Moreover, the correlation of PWV values obtained from HDLn were weakly correlated (R^2 = 0.2805), whereas PWV values obtained from HDLd were correlated moderately (R^2 = 0.4214).

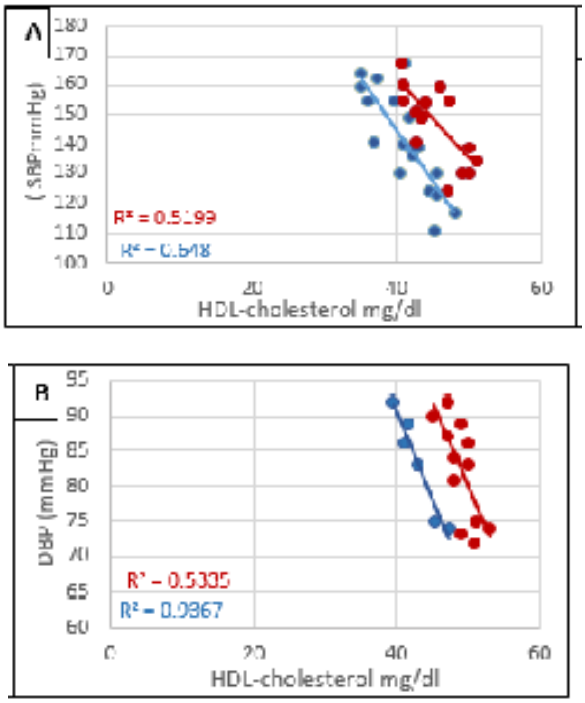

Fig. 5. Correlation between SBP (A) and DBP (B) with HDL-cholesterol in females (red line) and males (blue line).

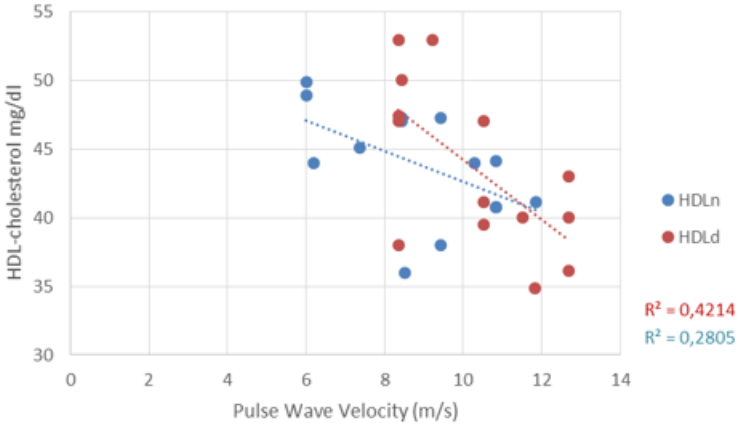

Fig. 7. Correlation of PWV with HDL-cholesterol between the group with normal HDL concentration (HDLn) and decreased HDL concentration (HDLd)

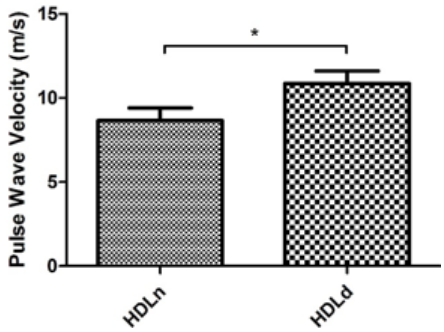

Fig. 6. Comparison of PWV values between the group with normal HDL concentration (HDLn) and decreased HDL concentration (HDLd)

The present study was aimed to determine the correlation between HDL-cholesterol and BP in patients diagnosed with hypertension, untreated and patients diagnosed with hypertension after one month of treatment with statins (atorvastatin- 20mg / day).

Hypertension and dyslipidemia are considered risk factors for developing cardiovascular disease [31]. A large number of studies have shown that HBP is directly correlated with higher levels of lipid proportion [32]. Among the purposed mechanisms that link dyslipidemia with HBP are: i) atherosclerosis that causes a reduction of the elasticity of large and medium arteries and ii) endothelial dysfunction, by altering the vasomotor function dyslipidemia decreases nitric oxide biodisponibility, which in turn produces vasoconstriction and therefore increased blood pressure [12]. The HBP decrease observed as a response to statin therapy indicates the presence of a common mechanism in the two diseases that needs to be investigated in more detail [12]. Studies reported also an improvement of endothelial function as a response to treatment with atorvastatin, with a consecutive decrease

Table 3
VALUES OF THE PWV (m/s) DETERMINED IN ALL STUDIED GROUPS

	HDLn (mg/dL)	HDLd (mg/dL)
Pulse wave velocity (m/s)	8.652 ± 0.7567	10.85 ± 0.7540

of cardiovascular events [33]. However, a high predictive value for future cardiovascular events is achieved by the measurement of intima media thickness (IMT) accompanied with the determination of high sensitive C reactive protein (hsCRP) [34].

Due to differences between HDL cholesterol levels in men and women, this study was also aimed at evaluating the relationship between HDL-cholesterol and BP, considering gender. In the male sex, we observed a significant decrease of HDL-cholesterol in untreated hypertensive patients compared to the control group. As expected, this difference was not present between the control group and hypertensive patients, due to the effects of atorvastatin on HDL-cholesterol. When we compared the level of HDL-cholesterol in females, we obtained the same changes as in the case of males. We found a negative correlation between HDL-cholesterol levels and SBP/DBP, regardless the gender in control group. This finding is supported by the study of Harperin et al. [35] that have also negatively correlated HDL-cholesterol with the incidence hypertension.

The pulse wave velocity, the speed at which the pulse wave propagates in human arteries, is one important parameter used for the assessment of arterial stiffness. In our study, we aimed to assess this parameter in relation to the level of HDL-cholesterol and BP. Other studies have shown an increase in the pulse wave velocity in hypertensive persons [36]. The results obtained indicated that a decrease of HDL-cholesterol level is associated with an increase of this parameter and thus with the increase in arterial stiffness. These results may suggest that another mechanism by which low levels of HDL-cholesterol is involved in HBP and in the increase of cardiovascular events.

Conclusions

The highly negative correlation obtained between HDL-cholesterol concentration and BP suggests a major interrelation between them, in untreated hypertensive individuals. There is also a moderate negative correlation between HDL-cholesterol and BP in treated patients, therefore suggesting that statins may reduce moderately the BP by increasing plasma levels of HDL-cholesterol, or by lowering LDL-cholesterol. Moreover, this study demonstrated that persons with low levels of HDL-cholesterol present an increased pulse wave velocity and hence an increased arterial stiffness. This inverse correlation suggests that any treatment that leads to the raise of HDL-cholesterol levels can result in an improvement of vascular function. Together, these results support the beneficial effect of increasing plasma levels of HDL-cholesterol and statin treatment on blood pressure, both systolic and diastolic.

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