DISTURBANCE IN THE COMPOSITION OF LIPOPROTEIN PARTICLES AND CHRONIC INFLAMMATION AS PROGNOSTIC FACTORS IN THE DEVELOPMENT OF CORONARY DISEASE

POREMEĆAJI KOMPOZICIJE LIPOPROTEINSKIH ČESTICA I HRONIČNA INFLAMACIJA KAO PROGNOSTIČKI FAKTORI ZA RAZVOJ KORONARNE BOLESTI

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Summary: The study focused on 30 dyslipidemic patients (12 women and 18 men); 16 of them had coronary disease (CD). The concentrations of apoA and apoB were determined in all patients, as well as the calculated ratio between apoA and apoB. As far as inflammatory indicators are concerned, the concentrations of sensitive C reactive protein (hsCRP), albumin, fibrinogen, intracellular adhesive molecule (ICAM-1) and vascular adhesive molecule (VCAM -1) were determined. In patients with CD there were considerably higher concentrations of fibrinogen (3.1 ± 1.2 vs. 2.7 ± 0.7 g/L) and VCAM-1 (10.9 ± 3.6 vs. 8.3 ± 2.8 g/L) (p<0.05) while the numerical values of hsCRP and ICAM-1 were not significantly different in relation to the patients without CD. The concentration of apoB and the value of apoB/apoA ratio were considerably higher in patients with CD (1.7 ± 0.8 vs. 1.3 ± 0.4 and 1.3 ± 0.4 vs. 0.9 ± 0.4; p<0.05), whereas the concentration of apoA did not differ in relation to the patients without CD. The research confirmed the significance of the disturbance in the composition of lipoprotein particles and the systemic inflammatory response in the pathogenesis of atherosclerosis, whereas their significant mutual connection was not shown. This indicates their cumulative effect and different mechanisms at the base of these disturbances.

Keywords: lipoprotein, hCRP, albumin, fibrinogen, ICAM-1, VCAM-1, coronary disease

Kratak sadržaj: Ispitivanjem je obuhvaćeno 30 dislipidemičnih bolesnika (12 žena i 18 muškaraca), od kojih je 16 imalo koronarnu bolest (KB). Kod svih bolesnika određivane su koncentracije apoA, apoB i izračunavan odnos apoB/apoA. Od inflamatornih pokazatelja, određivane su koncentracije visokosenzitivnog C-reaktivnog proteina (hsCRP), albumina, fibrinogena, intracelularnog adhezionog molekula (ICAM-1) i vaskularnog adhezionog molekula (VCAM-1). Kod bolesnika sa KB postoji značajno veća koncentracija fibrinogena (3,1 ± 1,2 vs. 2,7 ± 0,7 g/L) i VCAM-1 (10,9 ± 3,6 vs. 8,3 ± 2,8 g/L) (p<0,05), dok se vrednosti hsCRP i ICAM-1 nisu značajnije razlikovale u odnosu na bolesnike bez KB. Koncentracija apoB i vrednosti apoB/apoA odnosa bile su značajno veće kod bolesnika sa KB (1,7 ± 0,8 vs.1,3 ± 0,4 i 1,3 ± 0,4 vs. 0,9 ± 0,4; p<0,5), dok se koncentracija apoA nije razlikovala u odnosu na bolesnike bez KB. Ispitivanjem je potvrđen značaj poremećaja kompozicije lipoproteinskih čestica i sistemskog inflamatornog odgovora u patogenezi ateroskleroze, pri čemu nije utvrđena značajna međusobna povezanost. Ovo ukazuje na njihov kumulativni efekat i različite mehanizme koji stoje u osnovi ovih poremećaja.

Ključne reči: lipoproteini, hCRP, albumini, fibrinogen, ICAM-1,VCAM-1, koronarna bolest

Introduction

Cardiovascular diseases (CVD) which start with atherosclerosis are the most common cause of death in the world today (50% of the total mortality value). The second most important disorder are malign tumors (22%), and the third position is occupied by lung diseases (10%). Death caused by various cardiovascular diseases amounted to 56% in Yugoslavia in 2001. The mortality value (death caused by coronary diseases) is on the increase in our country, while in other countries this value has been decreasing significantly, by over 50%, especially when cardiac arrest

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is concerned (1). This has been achieved by successfully modifying the risk factors for the development of atherosclerosis and by wide usage of hypolipemic medicines (2).

Atherosclerosis is a multifactoral process which is manifested as an excessive inflammatory response to various forms of artery wall damage (3). The main ignitor and catalyst of atherosclerosis is hyperlipidemia. It is known today that the most important processes in atherogenesis are cholesterol accumulation in the artery wall, oxygenation and modification of the LDL particles, and the onset of local inflammatory process. The lipoprotein composition disorder together with the inflammatory processes represents the basis of atherosclerosis. New research indicates that the apoprotein concentration and apoB/apoA balance disorder, together with the inflammatory process, have the most significant prognostic value for determining the development of atherosclerotic complications (4).

The inflammatory process mediated by macrofagi induces the release of the matrix of metal-proteinase, type I collagen dissolvement and fibrous cover bursting. The momentary release of IL-6 influences increased CPR production in the liver, which binds itself to the damaged membranes and proteins, locates the complement and opsonises the necrotic matter. The expression of adhesive molecules at the endothelial cells enables the binding of the trombocytes which excrete PGDF, and the procoagulative activity of the inner wall is developed (5).

The goal of the research was to determine the lipoprotein composition disorder and its relevance to the inflammatory indicators in coronary disease patients.

Patients and Methodology

This research included 30 dyslipidemic patients (12 women, 18 men) who had been treated and examined at »Vojna Bolnica« (Military Hospital) in Niš. Sixteen patients, out of total, had been diagnosed with coronary disease (CD). All patients were evaluated for apoA and apoB concentrations and their balance values. The following inflammatory factors were also being examined: highly sensitive C reactive protein concentration (hsCRP), albumin, fibrinogen, intracellular adhesive molecule (ICAM-1) and vascular adhesive molecule (VCAM-1). ApoA, ApoB, hCRP and fibrinogen were determined on turbitimer (Behring), while ICAM-1 and VCAM-1 were determined by the ELISA method (Cellcom).

Results

General characteristics of the examined patients with dyslipidemia are shown in *Table I*.

The mean age of the patients was 62.26 ± 5.49 years. There were no significant age, sex, and dyslipidemia duration differences within the examined group of patients (*Table I*).

The apoprotein concentrations and their relative values are shown in *Table II*.

The apoB and apoB/apoA concentration values were distinctively higher in the CD patients (1.7 ± 0.8 vs. 1.3 ± 0.4 and 1.3 ± 0.4 vs. 0.9 ± 0.4; p<0.05), while the apoA concentration value did not show much variation in the patients who did not suffer from CD (*Table II*).

Inflammatory indicators within the dyslipidemic patient group (with and without CD) are shown in *Table III*.

There is a significantly higher fibrinogen concentration in the CD patients (3.1 ± 1.2 vs. 2.7 ± 0.7 g/L) and VCAM-1 (10.9 ± 3.6 vs. 8.3 ± 2.8 g/L) (p<0.05), while the hsCRP, albumin, and ICAM values did not show much variation in relation to the patients without CD.

A comparative/correlative analysis was performed in order to investigate the relationship between the apoprotein concentration and inflammatory indicator values. The analysis did not show any significant correlation between the apoprotein values and

Table I Dyslipidemic patient characteristics.

	Number	Women	Men	Age (years)	Dyslipidemia duration
With CD	16	7	9	61.4 ± 6.41	4.78 ± 2.95
Without CD	14	5	9	63.25 ± 4.52	4.1 ± 2.63
Total	30	12	18	62.26 ± 5.49	4.46 ± 2.78

Table II Apoproteins and their values.

	With CD	Without CD	Total
ApoA (mmol/L)	1.28 ± 0.48	1.5 ± 0.62	1.39 ± 0.56
ApoB (mmol/L)	1.67 ± 0.84	1.29 ± 0.42*	1.46 ± 0.64
ApoB/apoA	1.3 ± 0.48	0.90 ± 0.48*	1.12 ± 0.48

* p<0.05

Table III Inflammatory indicators in the target group.

	With CD	Without CD	Total
hsCRP (mg/L)	3.37 ± 1.2	4.53 ± 1.08	3.91 ± 1.1
Albumin (g/L)	47.8 ± 2.8	46.18 ± 2.22	47.04 ± 2.6
Fibrinogen (g/L)	3.14 ± 1.19*	2.69 ± 0.72	2.93 ± 0.92
ICAM-1 (	7.16 ± 2.62	7.57 ± 3.44	7.35 ± 2.91
VCAM-1 (	10.9 ± 3.65*	8.3 ± 2.81	9.68 ± 3.2

* p<0.05

apoB/apoA relation and the inflammatory indicators of cardiovascular risk.

Discussion

Apoproteins are protein molecules which are located at the surface of lipid particles. Beside their enzymatic role, they have a receptive role which is visible in the lipoprotein particle metabolism. ApoB-100 is a kind of »identification card« of each VLDL particle, which is synthesized in the liver, and that »ID card« will remain present even during the VLDL transformation into IDL and LDL particles, and help VLDL be accepted by the hepatocytes. ApoA-I is the main apoprotein of the HDL particle which ensures its identification during the metabolic process. The significance of the apoprotein determination lies in the fact that they can be used to further determine the »number« of lipoprotein particles, thus identifying their size. By describing apoB and adequately calculating the number of atherogenic particles in patients with the metabolic syndrome, the risk for cardiovascular conditions can be predicted (6).

The concentration of apoA was slightly lower in the dyslipidemic patients with existing CD, but this finding was not statistically important (*Table II*). The apoA concentration value and apoB/apoA ratio were significantly higher in the patient group with coronary disease ($p < 0.01$).

The decreased value of apoA-I indicates that the amount of HDL lipoprotein particles is also reduced. This result can be frequently found in the DM type 2 disorder, and is tightly connected with the increased carotid intima/media ratio, especially in women, which indicates the existence of early stages of atherosclerosis (7). Numerous group studies show that the decrease in protective HDL cholesterol value represents a significant risk factor for the cardiovascular disease development (7).

A fact well known today is that increased values of LDL cholesterol have an enormous impact on the pathogenesis of atherosclerosis. However, the change of LDL lipoprotein particle composition has proved to be a more significant risk factor than the amount of cholesterol inside the particle. Research shows that a very small and condensed LDL particle is highly susceptible to oxygenation modification, and that it can easily induce an inflammatory reaction of the inner wall. In accordance with this theory is the plausible message of the AMORIS (Apolipoprotein-related Mortality Risk) study: apoA-I, apoB, and the relation between apoB/apoA-I are significant factors that predict the development of a fatal cardiac insult, to an even greater extent than the total cholesterol and TGA values, with no relation to the age of the examined group (8).

Modern understanding of the pathogenesis of atherosclerosis includes the inflammatory component during its development. It is widely believed today that this inflammatory process is a consequence of various stimuli (9).

Inflammatory risk factors (hsCRP, ICAM-1 and albumin concentration) did not indicate that a higher stage of the inflammatory process existed in the patients with CD, and the values were similar to the values from the examined groups (*Table III*). Fibrinogen and VCAM-1 concentration values were drastically higher in the group with CD in relation to the rest of the dyslipidemic patients without CD, and they indicated that a high level of inflammatory process existed ($p < 0.05$).

The levels of VCAM-1 are good indicators of the atherosclerotic process, and are the highest with acute coronary disorders, but the lowest with a stable angina pectoris. The levels of ICAM-1 are good indicators of atherosclerotic lesion presence, and do not vary much concerning the clinic manifestation of coronary atherosclerosis. Both adhesive molecules mainly have a much higher concentration value in patients with coronary diseases than in the healthy population (10).

It has been proved that some other inflammatory biomarkers can predict the risk for CV conditions, not only in patients with existing CD, but also in those who do not have any manifestations of the atherosclerotic process. These biomarkers are: fibrinogen, serum amiloid A, myeloperoxydase, and soluble CD4OL receptor (11). Among these markers, some other constant markers exist that have prognostic significance. These are: albumin concentration, white blood cell count, antibody and circulating immunocomplex concentrations, which all together points out the immense impact of the inflammatory component in the pathogenesis of atherosclerosis (12).

Recent studies have shown that increased values of the C reactive protein (CRP), as an indicator of system inflammation, influence the development of acute coronary syndromes (13). Some results indicate that hsCRP is the strongest biomarker for the appearance and development of coronary diseases, whose prognostic value surpasses LDL-C and Framingham risk score (14, 15). In addition to being a powerful risk marker, the CRP exhibits proinflammatory and proatherogenic abilities. However, its values do not show much variation between the groups with and without CD.

The significance of the lipoprotein particles composition disorder and the system inflammatory response in atherosclerosis has been confirmed by studies. No interrelation has been shown between these two units. This distinctly indicates their cumulative effect and different mechanisms which are the basis of the disorders mentioned.

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