Correlation Between High- sensitivity C-reactive Protein and Intima Media Thickness in Patients with Coronary Artery Diseases and Essential Hypertension

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The aim of this study was to investigate the correlation of intima-media thickness (IMT) and systolic hypertension (TAS) and diastolic hypertension (TAD) as well as the association of IMT and high-sensitivity C-reactive protein (hsCRP) in patients with essential hypertension and with coronary artery disease confirmed by coronarography.

Keywords: high sensitivity C-reactive protein, intima-media thickness, coronary artery disease

Cardiovascular diseases represent the major cause of mortality in Europe, both in females and males, and it refers to a large number of potentially fatal diseases including coronary artery diseases (CAD) and arterial hypertension [1]. CAD also known as ischemic heart disease, manifests in two major symptoms: angina and heart attack. The risk factors that can lead to CAD are well determined and include fixed risk factors such as age, family history, sex and modifiable risk factors that include smoking, hypertension, obesity, diabetes, hyperlipidaemia and stress.

Atherosclerosis is considered a chronic inflammatory disease of the arterial system that plays a critical role in the CAD. Atherosclerosis is caused by the dysfunction of the endothelial wall due to the accumulation of lipoproteins in the intima of the coronary vessels and Further development of the atherosclerotic lesion will imply the formation of foam cells, the migration and proliferation of smooth muscle cells in the foamy cells with the consecutive appearance of the fibrous plaque that will decrease the arterial lumen and the advance to complicated lesion that can be thrombogenic. Inflammation plays a major role in the smooth muscle cell migration and proliferation [2]. Determination of intima media thickness (IMT) represents a non-invasive method used to assess the early arterial wall alteration of the carotid artery. The IMT measurements predict the cumulative effect of atherosclerotic risk factors correlated with de future cardiovascular risk [3].

Hypertension represents the central risk factor for the appearance of cardiovascular events. Blood flow vortex that appears in hypertension can produce irreversible damage to the arterial wall, leading to an accelerated development of atherosclerosis, therefore to the CAD events. A high blood pressure level can stimulate the inflammatory response, that is now known to play a central role in the pathogenesis of atherosclerosis [4]. It was found that high sensitivity C-reactive protein (hsCRP), a biomarker of low-grade inflammation that is produced in the liver in response to IL-6 secretion, can be a predictor for cardiovascular events [5]. hsCRP was found also in the endothelium cells of the atherosclerotic lesions and it was proposed that hsCRP can stimulate the inflammatory reaction of arteriosclerosis by increasing the cell adhesion in vascular endothelial cells, idea that lead to the hypothesis that CRP could be a target for the arteriosclerosis treatment [6].

The aim of the study was to assess the relationship between hsCRP and IMT in patients with CAD and hypertension, to evaluate the predictive value of hsCRP and IMT for future cardiovascular events.

Experimental part

Materials and methods

The study was conducted on 3 lots age- and sex-matched subjects (age range: 50-70 years) after obtaining the informed consent : 26 healthy subjects in the control group (CON), 34 subjects with CAD that was confirmed by angiography (CAD group) and 39 subjects in the essential hypertension group (HTN). Clinical evaluation included physical examination, blood pressure measurements, 12-lead electrocardiogram and chest radiography. Total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglycerides were determined by enzymatically methods (Hitachi 717 analyser). Antihypertensive medication was interrupted for two weeks before the study.

Blood pressure measurements

Blood pressure was taken on the left arm after resting for minimum 5 min with the cuff placed, using a standard mercury sphygmomanometer. In each subject were taken 2 readings at 2 min intervals. Arterial hypertension was diagnosed after ESC/ESH 2007 guidelines (ESC/ESH, 2007).

IMT measurements

IMT measurements were conducted using a ALOKA ProSound SSD 4000 diagnostic ultrasound system with a frequency linear probe (7MHz), equipped with vascular bidimensional 2D colour software and spectral Doppler. The IMT value used in the study was a mean of four maximum values obtained through the investigation of the far wall of common carotid artery (CCA) left and right, at

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10 mm proximal to its bifurcation into the external carotid artery and internal carotid artery. The interpretation of the obtained values were realised in conformity with the recommendations of Mannheim consensus [7].

hsCRP measurements

The plasmatic concentration of hsCRP was determined using the quantitative method Turbolatex with Olympus CRP Latex assay Kit, AU400, SUA.

The latex particles are covered with anti CRP antibodies that agglutinate when they are mixed with the plasma probes that contain hsCRP. The agglutination will determine modifications in the extinction of the probe that cn be compared with a control solution that contains a well-known amount of hsCRP. Normal hsCRP plasmatic level ins between 0.05-3 mg/ L. American Heart Association/ Centres for Disease Control and Prevention scientific statement suggested that levels 3 mg/L be considered high [8]. The procedures followed were in accordance with the ethical standards of the Hospital Ethics Committee and with the Helsinki Declaration of 1975, as revised in 2000.

Statistical analysis

Continuous variables were expressed as means ± SD. Means were compared using analysis of variance or the Student t-test and one-way ANOVA. Pearson's correlation was used to test bivariate correlations and results were verified using the non-parametric Spearman's rank correlation test.

Statistical significance was defined as two–sided $p < 0.05$. All statistical analyses were performed using Microsoft Windows Office Excel.

Results and discussions

Table 1
BASELINE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE STUDYPOPULATIONS

	CON group (n=26)	CAD group (n=34)	*HTN group (n= 39)*
Age	55± 4.15	53± 2.75	54±3.54
Male (%)	63%	72%	68%
Systolic BP (mmHg)	115 ± 5.78	152± 13.45	162±12.45
Diastolic BP (mmHg)	66 ± 5.67	94 ± 6.94	98±8.90
Total cholesterol (mg/dl)	177± 14.56	257± 17.57	<0.001
Triglycerides (mg/dl)	89 ± 26.54	243± 42.23	<0.001
LDL-cholesterol (mg/dl)	111±9.34	189± 22.67	<0.001
HDL-cholesterol (mg/dl)	35 ± 4.55	49 ± 9.25	31±4.92

Values are means ± S.D. or frequency (%).
BP = blood pressure

The correlation between TAS and IMT was significant for CAD group (R^2=0.876) but not significant to CON group (R^2= 0.139) and HTN group (R^2=0.125).

Table 2
INDICES OF SYSTEMIC INFLAMMATION, ARTERY TENSION AND IMT IN STUDY GROUPS

Parameters	[CON] (n = 12)	[CAD] (n = 32)	[HTN] (n = 12)
TAS (mm Hg)	112.14 ± 12.26	153.09 ± 7.74	148.76 ± 11.51
TAD (mm Hg)	71.66 ± 3.96	92.04 ± 3.68	87.57 ± 2.92
IMTc (mm)	0.69 ± 0.27	1.69 ± 0.10	0.83 ± 0.30
hsCRP (mg/L)	1.95 ± 0.599	11.21 ± 1.03	3.14 ± 0.76

Note: *Data represents mean ± standard deviation; TAS= systolic arterial tension; TAD= diastolic arterial tension; IMTc= intima media-thickness of carotid artery; hsCRP= high-sensitivity C-reactive protein. $p<0.001$.*

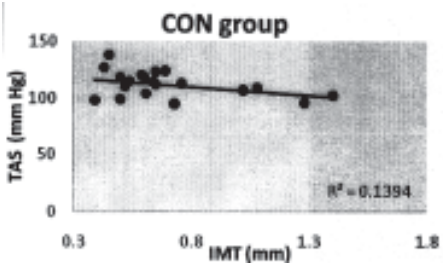


Fig. 1. Correlation between IMT and TAS in control group (CON).

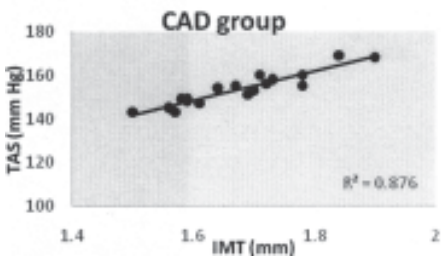


Fig. 2. Correlation between IMT and TAS coronary artery disease group (CAD).

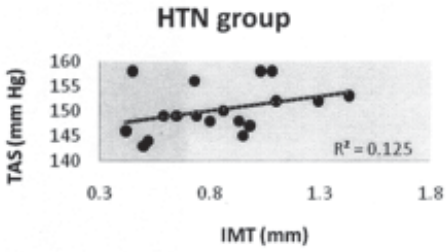


Fig. 3. Correlation between IMT and TAS hypertensive group (HTN).

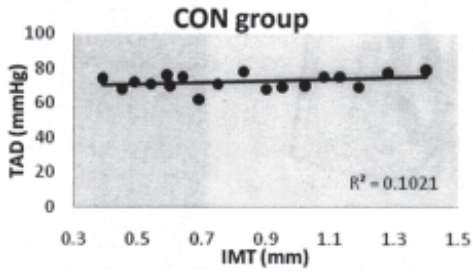


Fig. 4. Correlation between IMT and TAD control group (CON).

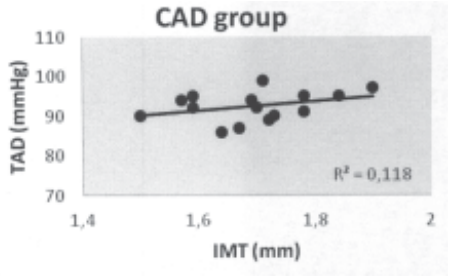


Fig. 5. Correlation between IMT and TAD coronary artery disease group (CAD).

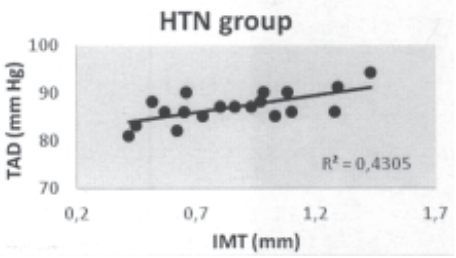


Fig. 6. Correlation between IMT and TAD hypertensive group (HTN).

We found that the correlation between TAD and IMT was moderate significant for HTN group (R^2=0.430) but not statistic significant for CON group (R^2=0.102) and CAD group R^2= (0.118).

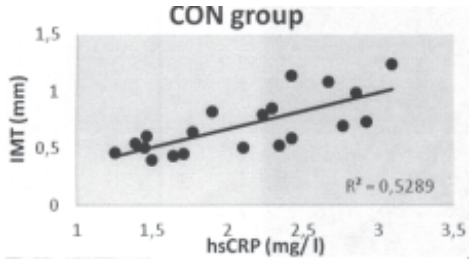


Fig. 7. Correlation between hsCRP and IMT in control group (CON).

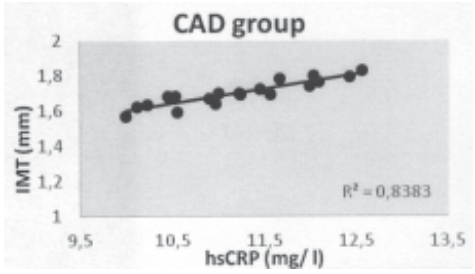


Fig. 8. Correlation between hsCRP and IMT in coronary artery disease group (CAD).

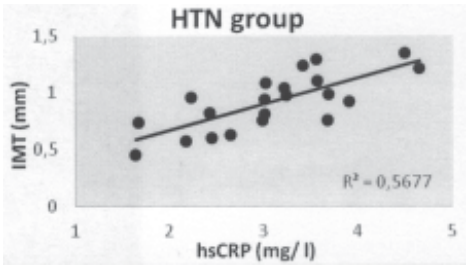
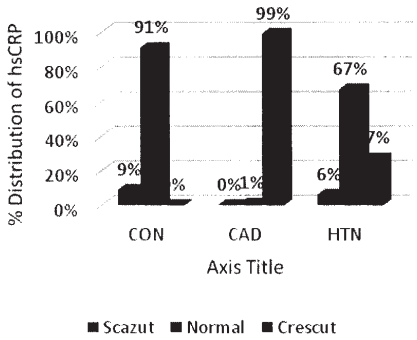


Fig. 9. Correlation between hsCRP and IMT in hypertensive group (HTN).

It was found a positive and significant correlation between hsCRP and IMT in CAD group (R^2=0.838) and a moderate, significant correlation in CON (R^2=0.528) and HTN group (R^2=0.526).

We classified the levels of hsCRP in 3 risk categories, depending on the prevalence to develop cardiovascular events: low risk category that presented a concentration of hsCRP< 1mg/ L, normal for hsCRP= 1-3 mg/ L and high risk for a value of hs CRP> 3 mg/ L. It ca be observed a 9% prevalence of low risk category present in CON group and 6% prevalence in HTN group. In the CAD group the 0% of the subjects presented a low risk. Normal hsCRP category was maximum in CON group. The prevalence for high risk category (hsCRP> 3 mg/ L) was found in CAD group, compare with CON group.



compare with CON group.

It is known the central role played by systemic inflammation and hypertension in the pathogenesis of atherosclerosis [9, 10]. There are few studies that follow the correlation between markers of inflammation and the atherosclerosis in CAD and HTN patients. We assessed the severity of the atherosclerosis by means of IMT, correlated with the levels of hsCRP, an inflammatory marker.

Also, we evaluated IMT, by high-frequency 10 MHz ultrasound transducers, as an integrated marker of atherosclerotic lesions in the presence of cardiovascular risk factors such as arterial hypertension. Carotid IMT is used as a valid indicator of atherosclerosis and to the risk of developing coronary events [11] and it reveals early atherosclerotic changes as well as vessel remodelling. We found that the levels on IMT are significant correlated with TAS, therefore TAS is an important risk factor for atherosclerosis and further development of cardiovascular events, data that is supported by previous findings of Lakka et al. [12]. Ridker et al established the role hsCRP as an independent risk factor for possible future cardiovascular events [13]. Abdushi S et al, found a strong correlation between hsCRP and IMT in CAD group, and showed that the measurements of IMT can be used as a tool to identify individuals with coronary atherosclerosis, but when the results were associated with high levels of hsCRP they revealed the destabilization of a stable CAD [14]. Another study of Lorenz M. et al demonstrated the association between cardiovascular risk factors and IMT, but did not found any association between IMT and hsCRP, the relationship between them is not casual and explained by conventional cardiovascular risk factors increasing both hsCRP and cardiovascular risk independently [15]. Gazahala I et al. confirmed that inflammation can be the cause of the stable coronary plaque transformation to an unstable plaque that can be ruptured and therefore thrombogenic [16].We observed a significant correlation between IMT and hsCRP in CAD group result that may indicate that the inflammatory process represents one

mechanism involved in atherosclerotic lesion development and progression of carotid artery, results that were moderately significant in CON and HTN group. Our results indicated an increased value of hsCRP in CAD group, results that suggest the instability of the atherosclerotic plaque and a sign of increased risk for possible future cardiovascular events.

Conclusions

A high systolic pressure can be a more important risk factor in the pathogenesis of atherosclerosis than the diastolic hypertension, and therefore a risk factor implicated in the cardiovascular events.

The measuring of IMT as a non-invasive predictor for CAD associated with the determination of hsCRP levels can have a predicting value for future coronary artery events.

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