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Serum Levels of Circulating Soluble Adhesion Molecules and Nitrites in Patients with Prehypertension

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Abstract Endothelial dysfunction is associated with vascular inflammation, reduced serum levels of nitric oxide, vasoconstriction and atherosclerosis.Soluble adhesion molecules (SAM) are considered markers of endothelial dysfunction and play a role in end organ damage in those patients. Prehypertensive patients suffer endothelial dysfunction. **The aim** of this study was to evaluate the serum levels of circulating soluble adhesion molecules and nitric oxide (evaluated as serum levels of nitrites) in prehypertensive non-diabetic patients. **METHODS**: Circulating levels of VCAM-1, ICAM-1 and e-selectine (ELISA RyDSystems Minneapolis USA), and serum nitrite levels (Griess method, Molecular Probes Inc. Oregon USA) were measured in 20 prehypertensive non-diabetic patients (as defined by JNC 7) and in 20 age matched normotensive controls. Statistical analysis was performed with ANOVA. **RESULTS:** Prehypertensive patients showed significantly higher levels of SAM, (VCAM-1; 530 ± 30.9 vs. 477 ± 22.5 ng/ml $p<0.001$), (ICAM-1; 285 ± 16.5 vs. 239 ± 14.9 ng/ml $p<0.001$), (E- selectin; 68 ± 6.9 vs. 52 ± 9.8 ng/ml $p<0.01$) and lower levels of nitrites (4.5 ± 0.8µmol/L vs. 6.2 ± 1.2 µmol/L $p<0.01$) than controls. **CONCLUSION**: Prehypertensive patients showed higher circulating levels of SAM and lower nitrites than normotensive subjects; which may explain why prehypertensive patients had more complications and coronary risk than normotensive patients.

Keywords: *prehypertension, endothelial dysfunction, inflammation, adhesion molecules*

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1. Background

Prehypertension, as defined by the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7), consists in the presence of systolic blood pressure (BP)between 120 mmHg to 139 mmHg and/or a diastolic BP between 80 mmHg and 89 mmHg [1].

Recent evidence suggests the role of prehypertension as risk for future hypertension, and also associated to organ damage. dividuals with prehypertension, enrolled in the Strong Heart Study, showed 2-fold higher prevalence of left ventricular hypertrophy (LVH), than their normotensive counterparts [2]. Although prehypertension-associated cardiovascular risk is unclear, evidence suggests that people with BP in the prehypertensive range may be at increased cardiovascular risk. In fact, patients with prehypertension also show increased carotid artery intimal-media thickness and arterial stiffness [3].

The endothelium maintains the integrity of vascular system, controlling vascular relaxation, thrombogenesis, and platelet adhesion. Underlying mechanism involves the interaction between nitric oxide and the vasoconstrictor factors. Endothelial dysfunction (ED) leads to a vasoconstrictor, proliferative and proinflammatory condition, including the expression of leukocyte adhesion molecules expressed on the arterial endothelium, which are able to be measured as soluble adhesion molecules (SAM) in the plasma. Noteworthy, ED promotes vascular damage and atherosclerosis; whereas circulating SAM are thought to reflect the expression of adhesion molecules at cell surface, then being considered as reliable markers of ED [4].

Manios, et al. found that the levels of C-reactive protein were higher in prehypertensive patients than normotensive subjects; however, most of the population suffered from obesity and type-2 diabetes [5]. In other study, Weil, et al. found that prehypertension associated to impaired endothelium-dependent vasodilatation, mediated by nitric oxide (NO) [6]. Inflammation and ED, due to reduced NO biodisponibility, may increase BP; but data are scanty regarding their participation in prehypertensive non-diabetic patients.

The aim of this study was to evaluate circulating levels of SAM and nitrites, these lasts reflecting NO, in prehypertensive non-diabetic patients.

2. Methods

We included 20 prehypertensive non-diabetic patients (as defined by JNC 7) and 20 age matched normotensive controls.

Venous samples were collected in the morning after a 12-h overnight fast. Circulating levels of VCAM-1, ICAM-1 and E-select in were measured by duplicate using ELISA kits commercially available (R&D Systems, Minneapolis, MN USA), following manufacturer´s recommendations. ELISA assays were performed by personnel blinded to the study, achieving intra-assay precision of 3.1 for VCAM-1, 4.1 for ICAM-1, and 3.8 for E-selectin, while inter-assays precision were 7 for VCAM-1, 7.3 for E-selectin and 7.4 for ICAM-1.

NO measurement was performed using the Griess method (Molecular Probes Inc. Oregon USA) for detection of nitrite levels. This method was preferred since NO is unstable, has a short lifetime, is highly oxygen-reactive to form nitrite or nitrates, which make complexa direct determination of NO radicals [7].

Patients with any of the following diagnoses were excluded from the study: diabetes mellitus [according to the American Diabetes Association criteria] [8]; heart, hepatic, or renal failure; evidence of valvular heart disease; heart block or cardiac arrhythmia; acute coronary syndrome or cerebrovascular disease six months before the study's initiation; autoimmune disease; pregnancy; urinary tract infection; fever; or a history of alcohol abuse and/or psychotropic drugs.

The study was conducted with the approval of the Research and Medical Ethics Committee of our hospital, in accordance with the Helsinki declaration. Participants gave written informed consent before their inclusion in the study protocol.

2.1. Statistical Analysis

Data are presented as the mean ± standard deviation. Differences in circulating SAM levels between groups were analyzed through ANOVA test. $P < 0.05$ was considered as statistically significant.

3. Results

The basal characteristics of the patients and controls are shown in Table 1.

Table 1. Basal characteristic of the subjects

	PREHYPERTENSIVE	NORMOTENSIVE	P
Age (years)	58 ± 10	57 ± 10	NS
Sex (M/F)	7/13	6/14	NS
Glycemia (mg/dl)	100±11	100±10	NS
Blood Pressure (mm Hg)	136±86	122/76	<0.01
LDL (mg/dl)	128±24	127±28	NS
Body Mass Index	29.5±7	29.8±6	NS
Nitrites (µmol/L)	4.5 ± 0.8	6.2 ± 1.2	<0.01

Prehypertensive patients showed significantly higher levels of SAM, (VCAM-1; 530 ± 30.9 vs. 477 ± 22.5 ng/ml p<0.001), (ICAM-1; 285 ± 16.5vs. 239 ± 14.9ng/ml p<0.001), (E- selectin; 68 ± 6.9 vs. 52 ±9.8ng/ml p<0.01) [Figure 1] and lower levels of nitrites (4.5 ± 0.8 µmol/L vs. 6.2 ± 1.2 µmol/L p < 0.01) when compared with the age matched normotensive controls.

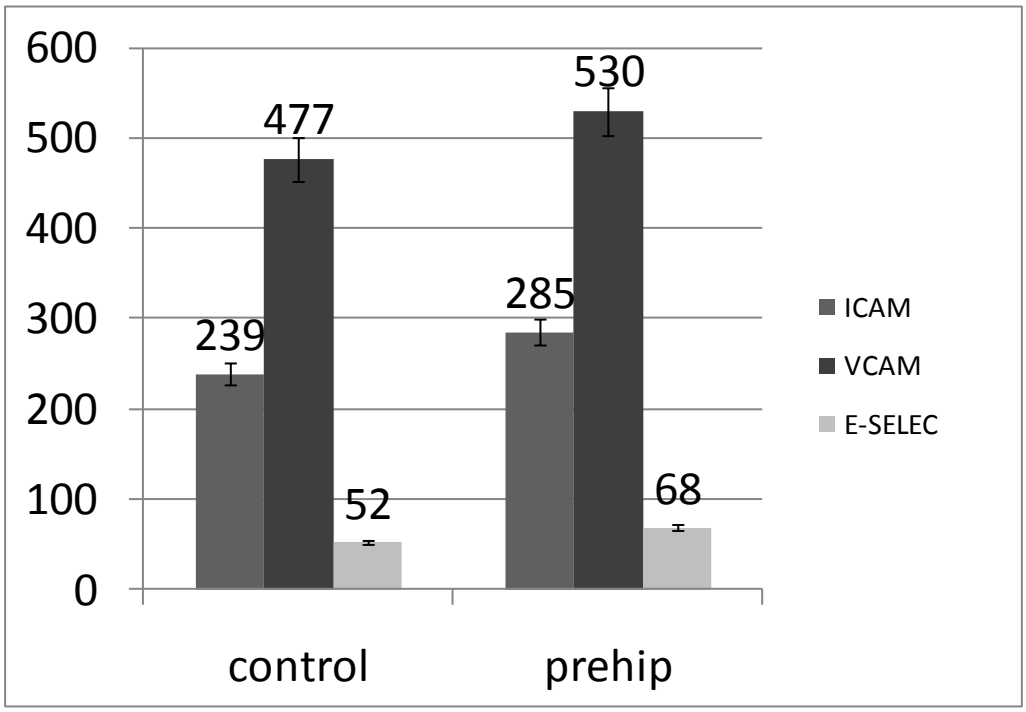

Figure 1. LEVELS OF SOLUBLE ADHESION MOLECULES IN PREHYPERTENSIVE AND NORMOTENSIVE SUBJECTS

4. Discussion

In this study we found that prehypertensive non-diabetic patients had higher circulating levels of SAM and lower NO, as reflected by plasma nitrites, than normotensive controls. Our methodology was strengthen by duplicate determinations of SAM, so intra-individual variation was taken into account, and the exclusion of diabetic patients, since diabetes mellitus may increase SAM levels with potential interference with the analysis of our results.

The endothelium maintains the integrity of the vascular system, whereas ED develops when the bioavailability of NO decreases. This reduction activates the nuclear factor κappa-B (NFkB), a regulator of several genes involved in inflammatory and atherosclerosis pathways. NFkB mediates the increase in circulating SAMs [9]: thereby, considered ED markers, and represents a potential link between reduced NO, inflammation and atherosclerosis [10].

ED and inflammatory condition found in our prehypertensive patients make sense with a paraphysiological status, possibly contributing to increased cardiovascular risk. This assumption is supported by the findings of several studies that shown that prehypertensive patients have an increased risk of coronary heart disease and myocardial infarction [11,12]. Interestingly, Femia et al. found that carotid intima-media thickness is increased in prehypertensive subjects. The increase in the thickness of the carotid intima-media, which has been directly associated with atherosclerosis in the peripheral, coronary and cerebral circulation, predicts myocardial infarction and stroke [13].

Our results agree with those observations from the ATTICA study, where prehypertensive patients had significantly higher levels of C-reactive protein and tumor necrosis factor than normotensive subjects [14]. They also enforce the growing body of research establishing the association between inflammation and values of BP; and suggest a pathophysiological mechanism explaining cardiovascular risk associated to patients with prehypertension [10].

5. Conclusion

Our study shows that prehypertensive patients develop more ED and inflammation than normotensive subjects. Further research is required to understand the clinical implications of this endothelial profile, as well as therapeutic impact of reducing inflammation and promoting vascular integrity in those patients.

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