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Research Article

Role of Inflammation on the Control of the Arterial Hypertension among Patients with Metabolic Syndrome.

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Abstract

Background: It is widely accepted that hypertension is a pro-inflammatory disease and that the immune system plays a vital role in mediating hypertensive outcomes, end organ damages. And modulation of hypertensive pathology [2]. Patient with MetS usually present increased levels of C-reaktive protein (CRP) wich is a prototypic marker of inflammation [5], however the data of the influence of incresed levels of CRP on the control of the aterial hypertension in patients with MetS, are scarce.

Objective: We sought to determine the incresed CRP levels influence on the control of the aterial hypertension in patients with MetS.

Methods: We conducted a multicenter observational cross-sectional study. The study population recruited from a coule of outpatient clinic between june 2018 and june 2019. The population study consisted of 420 patients with MetS aged $\geq$ 18 years, divided in two groups: 211 with level of CRP>3mg/l , and 209 participans with CRP level <3mg/l.

Results: Among those with CRP level > 3mg/l (N=211) controlled BP according to evidence and current guidelines, was achieved in 23.6% of participans, whereas among those with CRP level <3mg/l(N=209) controlled BP was achived in 48.3%; p=0.000). There was independent association of CRP levels >3mg/l with uncontrolled BP (OR=3.1, 95%CI 2.06 - 4.75). There were significacant association of uncontrolled BP with: uncontrolled glycemia (OR =1.4, 95%CI 0.97-1.84); increased BMI (OR=4.4; 95%CI 3.02-4.05) and five risk factors for MetS.(OR=2.3, 95%CI 1.93-2.81).

Conclusions: We think,we brought some good evidence,in our present study ,that patients with MetS and higher CRP level have a higher prevalence of unconrolled BP.

Key words: C-reactive protein; control of BP in patient with Metabolic Syndrome.

Used abbreviations in the text:

MetS   –   Metabolic Syndrome
CRP   –   C-reactive protein
BW   –   Body weight
BMI   –   Body mass index
BP   –   Blood pressure
SBP   –   Systolic blood pressure
DBP   –   Diastolic blood pressure
T2DM   –   Diabetes Mellitus type 2
WCi   –   Waist circumference
HDL-C   –   High density lipoproteins cholesterol
TG   –   serum triglycerides

ESC/ESH   -- Europian society of Cardiology /Europian society of Hypetension

Introduction

Despite enhanced screening and therapeutic management, hypertension remains the most prevalent chronic disease worldwide and the leading cause of heart disease, chronic kidney disease, and stroke in both men and women[1]. In recent years, a vast body of evidence has accumulated indicating the role of the immune system in the regulation of blood pressure and modulation of hypertensive pathology. It is widely accepted that hypertension is a pro-inflammatory disease and that the immune system plays a vital role in mediating hypertensive outcomes and end organ damages [2].

Metabolic syndrome (MetS), is a clouster of metabolic risk factors that includes high blood pressure, hyperglicemija, dyslipidemija and abdominal obesity, has been an increasing health problem worldwide for the last three decades, is associated with advers cardiac events [3]. Patient with MetS usually present increased levels of C-reaktive protein (CRP) wich is a prototypic marker of inflamation[4], however the influence of icresed levels of CRP on control of aterial hypertension in patient with MetS, data are scarce.

We set out to determine the influence of inflammation (assessed by icresed levels of CRP) on control of aterial hypertension in patients with MetS. We set out to teste hypothesis: Patients with MetS and high level of CRP have higher prevalence of uncontrolled arterial hypertension than patients with MetS and lower level of CRP. These findings might lend further insight into inflammation-immune reactivity in arterial hypertension strategies for the controll of arterial hypertension in patients with MetS.

Objective

We sought to determine the influence icresed levels of CRP on control of aterial hypertension in patients with MetS.

Methods

Study design.

We conducted a multicenter observational cross-sectional study. The study population was recruited from our outpatient clinic between juni 2018 and juni 2019. Subjects who fulfilled the criteria for MetS according to the results of recent laboratory tests were prospectively evaluated.

The population consisted of 420 patients with MetS aged $\geq$ 18 years, divided in two groups: 211 participans (100 females and 111 males) with level of CRP>3mg/l, and 209 participans (104 females and 105 males) with level of CRP<3mg/l).

All participants underwent a comprehensive medical history and physical examination. Resting ECG, anthropometrics, measuring of blood pressure according to standard protocol (obtained after 10 min of rest in the sitting position, expressed as the average of 3 consecutive measurements), the mean systolic and diastolic blood pressure recording during the study period, were calculated. Hypertension was defined be current ESC/ESH guidelines for the management of arterial hypertension as office systolic blood pressure (SBP) values $\geq$140 mmHg, and/or diastolic blood pressure (DBP) values $\geq$90 mmHg and/or current anti-hypertensive therapy [6]. Uncontroled BP, was defined defined be current ESC/ESH guidelines for the management of arterial hypertension [5]. The blood pressure was considered to be controlled if the calculated mean systolic and diastolic blood pressure recording during the study period was found to be less than 140/90mmHg. Among adults younger than 60 years and less than 150/90mmHg.in general population aged $\geq$60 years. Diabetes mellitus was defined as a fasting serum glucose level $\geq$126 mg/dL and/ or current medical therapy with an oral hypoglycemic agent and/or insulin[6].Body mass index (BMI) was calculated as weight (kg) divided by the square of the height (m[2)].Weight was measured with weight balance scales, and height with stadiometer. Waist circumference WCi, was reported in cm.

An overnight fasting blood sample, was drawn from each patient to determine: blood glucose, lipid profile tests total serum cholesterol (TC), serum High density lipoproteins cholesterol (HDL-C), serum triglycerides (TG).The sample analysis was performed using standard biochemical analytical methods. Plasma CRP levels was measured using latex particle-enhanced immunoassay with the mephelometry (Roche Swiss). Consistent with recommendations from Centers for Disease Control and Prevention [7] (a CRP cutpoint of 3.0mg/L), was used to differentiate high-risk and low-risk group.

Exclusion criteria, included a diagnosis of dementia senilis, secondary hypertension, serum creatinine level >2mg/dl, age under 18 years and over 79 years.

MetS was defined according to the harmonized definition of the International Diabetes Federation and other organizations [8], that three or more out of five following criteria are considered as MetS: (1) central adiposity {Waist circumference (WCi)} >102 cm in men and >88cm in women [9]); (2) serum HDL-C < 50 mg/dL in women or < 40 mg/dL in men; (3) serum triglyceride levels > 150 mg/dL; (4) SBP $\geq$ 140mmHg or DBP $\geq$ 90mmHg or use of antihypertensive drugs;(5) the presence of diabetes mellitus(DM) or use of anti-diabetic drugs. A standardized case report form was used to collect data from medical record and was send to the central data management unit.

The study is in compliance with the Declaration of Helsinki. All patient that participated in this study were written informed, consent was obtained from all participating patients before they were enrolled into the study.

Statistical Analysis

Results are expressed as mean and ±SD, or as percentage. A simple descriptive analysis was performed for the general characterization of the sample and distribution of variables. The distribution of variables was tested for normality using the Kolmogorov-Smirnov test, and the heterogeneity of variances was evaluated by Levene's test. To compare baseline characteristics and echocardiographic findings between groups, we used Student,s unpaired t test for continuous data, Mann-Whithey U -test for continuous data with abnormal distribution, and X^2-test for categorical data. The association between variables were analyzed using logistic regression. Odds ration (OR) and 95% confidence interval (CI) were estimated by logistic regression. A, p value <0.05 was considered statistically significant for a confidence interval of 95%.Data were coded, entered and analysed using SPSS software package (SPSS 19.0).

Results:

A total of 420 subjects with MetS enrolled in our study, stratified in two groups:209 participans (47.5% females and 50.2% males) with level of CRP < 3mg/l, and 211 participans (47% females and 53% males) with level of CRP > 3mg/l, completed the survey and had data for 1-year medical record review. A mean of 3.4 BP recordings were obtained for each participans.

Baseline demographic, anthropometric and laboratory, characteristics by group are displayed in **(Table 1)**

Variables		Gr-I. CRP< 3mg/l (N.209)			Gr.II. CRP > 3mg/l (N.211)			p-value
		N. (%)	Men	±SD	N. (%)	Mean	±SD	
Gender	Females	104 (47.8)			100(47%)			0.77
	Males	105 (50.2)			111(53%)			0.78
Age (year)			61.6	±8.6		60.4	±9.3	0.11
BMI(kg/m^2)			25.6	±4.2		31.1	±4.7	**0.000**
SBP(mmHg)			132.3	±18.5		140.7	±14.5	**0.000**
DBP(mmHg)			80.5	±4.5		85.7	±5.8	0.07
T2DM (p.)		159 (76.1)			146(69.1)			0.52
WCi(cm.)		160 (76.5)	95.8	±7.8	181(85.7)	102.3	±3.8	**0.00**
HDL-C (p;mmol/l)		143 (68.4)	0.92	±0.1	158(74.1)	0.95	±0.01	0.36
Trig. (p;mmol/l).		124 (59.3)	2.01	±0.2	147(69.6)	2.08	±0.1	0.11
glyc.(con;mmol/l)		133 (63.6)	6.4	±0.8	81(38.3)	6.8	±0.6	**0.003**
CRP(mg/l)			2.7	±0.1		7.7	±2.5	**0.000**
Three MetS. riskfactor		140 (66.9)			101(47.8)			**0.003**
Four MetS. risk factor		55 (26.3)			72(34.1)			0.2
Five MetS. risk factor		14 (6.7)			38(18)			**0.000**

Table 1: Basic demographic, anthropometric and laboratory characteristics of study population. (MetS N.420).

Values are mean ± SD;y=year; BMI:body mass index;SBP:systolic blood presure;DBP:diastolic blod presure;T2DM(p: presence of diabetes mellitus type 2;serumHDL-C(p)-high.density cholestero ppresence;serum Triglicerides;hs-CRP: C-reative protein;WCi:presence of increased weist circumference;BPH-presemnce od artrial hypertension;glic:glicemia controll; No significant differences in: age, gender. Diastolic BP, were observed between groups. Participans with level of CRP >3mg/l had significantly higher means: SBP (140.7 ±14.5 vs. 132.3±18.5 p= 0.000), BMI(31.1 ±4.7 vs. 25.6±4.2 p=0. 000), WCi (102.3 ±3.8 vs. 95.8 ±7.8 p=0.00); uncontrolled glycemia(6.8±0.6 vs. 6.4±0.8 p=0.003) and number of risk factors for MetS {frequency of presence five risk factor for MetS was higher among participans with level of CRP > 3mg/l (18 % vs. 6.7%; p= 0.000)} (Table 2), presens the frequency of controlled BP in participans with MetS and different level of CRP. Among those with level of CRP > 3mg/l (N=211) controlled BP according to evidence and current guidelines, was achieved in 23.6% of participans,whereas among those with level of CRP< 3mg/l(N=209) controlled BP was achived in 48.3%; p=0.000).The diference was found to be statistically significant.Chi-square: 13.1; p = .0003

Study Groups: patient with MetS stratified by level of CRP (n-420)

Gr-I. (CRP< 3mg; No. 209)			**Gr. II.** (CRP > 3mg; No.211)	
Frequency of controlled BP				
Count (No.)		**101**	**50**	**P = .0003**
Percent (%)		**48.3**	**23.6**	

Table 2. Frequency of controlled BP among patients with MetS stratified by CRP levels (No.420).

Over all frequency of controlled BP (in all participans enrolled in present study), was 38%.In a logistic regression (Table. 3), there was independent association of CRP levels >3mg/l with uncontrolled BP (OR=3.1, 95%CI 2.06 - 4.75). There were signi-fiacant association of uncontrolled BP with: uncontrolled glycemia (OR =1.4,95%CI 0.97-1.84); increased BMI (OR=4.4; 95%CI 3.02-4.05) and five risk factors for MetS. (OR=2.3, 95%CI 1.93-2.81).

	OR	Significance	95% CI for Exp (B)	
			Lower	Upper
Uncontrolled BP	3.1	.000	2.06	4.75
Uncontrolled glycemia	1.4	.000	0.97	1.84
BMI	4.6	.000	3.02	4.52
MetS-RF n.5	2.3	.000	1.934	2.815

BP:blood presure;MetS-RF n.5-:five risk factors for MetS;DM:Diabetes Mellitus and BMI:Body mass index. OR* >1.

Table 3. Logistic Rgresion Model: Association of uncontrolled BP with: CRP levels (>3.0mg/L), uncontrolled glycemia, increased BMI and five risk factor for MetS.

Discussion:

In this study we found that patients with MetS and higher levels of CRP had significantly higher prevalence of uncontrolled BP than did those with MetS and lower levels of CRP. Results that confirmed our hypothesis. Low-grade inflammation is now a recognized hallmark of hypertension, and ther is an expanding literature regarding the role of inflammation and inflammatory cells in hypertension, in particular T lynphocites are now thought to have a central role in the development of hypertension and related organ injury [10] Based on the cenral role played by the cytokine milieu in determining lymphocyte differentiation and activation, differences of cytokines levels likely contribute to observed difference on the prevalence of uncontrolled BP in present study, and will impact the overall physiological outcome of an inflammatory response. The CoLaus Study reported that serum CRP, interleukin-6 and THF-α levels were positively associated with BP [11,12] Also, Grundy SM et all, suggests a significant association among inflammation, hypertension, and the metabolic syndrome [13]. Nevertheless, despite an association between high CRP levels and hypertension, a causal relationship has not been demonstrated. In fact, Smith et al. used a Mendelian randomization approach to examine a possible causal relationship analyzing the association of the 1059G/C polymorphism in the human CRP gene with hypertension, the work failed to confirm a causal relationship between CRP and blood pressure [14].

In our study, BP was controlled at 38% patient only. This result is consistent with previous findings that patients with hypertension and MS have an elevated prevalence of uncontrolled BP [15,16]. The study results allow evaluating the effetivity of hypertension treatment as for drug choise, decrease of sBP and dBP associated with a certain drug, a drug combination, and therapeutic inertia in these patients.

We also found that BP control was worse among patients with MetS and higher CRP levels in the presence of more MetS risk factors. It appears that there is an interaction between hypertension and metabolic disorder factors, although the mechanisms that are involved in this interaction remain unclear. Results in present study are consistent with previous findings [17]. It has been suggested that metabolic disorder factors have additive effects on BP control and cardiovascular disease. Arcucci *et al*. have reported that BP control worsens in the presence of more metabolic disorder factors [17] These data sugest that presence of more metabolic disorder factors, decrease the probability of BP control. We found association of number of risk factors of MetS and higher levels of CRP. However, it is unknown whether the number of MetS risk factors can influence the levels of CRP. Previeous study demonstrated that number of risk factors did not influence the levels of CRP in patients with MetS [18]. Also in present study we found association of highe levels of CRP in patient with uncontrolled BP and elevated levels of triglycerides, low HDL levels, obesity and uncontrolled glycemia. Results in present study are consistent with previous findings [19-21].

Study limitations

The study employed a cross-sectional design, and as such, the results could show only factors associated with uncontrolled hypertension. Study design limited to make causal inferences regarding increased CRP levels and control of arterial hypertension in patient with MetS. A larger sample would certainly increase the statistical power of the study, and probably some differences would therefore become more expressive. Despite some methodological limitations, this study clearly demonstrated a relationship between increased CRP levels and control of BP in patient with MetS.

Clinical Implications

These data provide further evidence that poor BP control is common in patients with MetS, and further investigations on the immune reactivitiy in hypetension may result in the identification of new strategies for the treatment of the disease. Therapeutic interventions to reduce activity of immunity may prove beneficial in reducing consequences of hypertension including: myocardial infarction, heart failure, renal failure and stroke.

Conclusions

We think, we brought some good evidence, in our present study, that patients with MetS and higher CRP level have a higher prevalence of unconrolled BP. These results indicate that presence of an subclinical inflammatory process in the natural history of MetS, through presence of high CRP levels, negatively affect BP control in patients with MetS. Measurement of this inflammatory protein may help to determine individuals cardiovascular risk and activity of immune system, it might be a novel therapeutic target for the treatment of high blood pressure in these individuals.

Materials- Agim Zeqiri;Dali Lala, Fatmir Ferati;Arben Mirto;*Data collection/pro-cessing*-Sotiraq Xhunga;Artur Serani;Ylber Jani; *Analysis/interpretation*-Ylber Jani;Ahmet Kamberi;Atila Rexhepi; Bekim Pocesta;*Literature Search*- Ylber Jani;Agin Zeqiri;Dali Lala; Fatmir Ferati;Artur Serani. *Critical Reviews*-Ahmet Kamberi.

All authors read and approved the final manuscript.

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