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-reactive protein (CRP) which is a prototypic marker of inflammation [5], however the data of the influence of increased levels of CRP on the control of the arterial hypertension in patients with MetS, are scarce.

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

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

Results: Among those with CRP level > 3 mg/l (N = 211) controlled BP according to evidence and current guidelines, was achieved in 23.6% of participants, whereas among those with CRP level < 3 mg/l (N = 209) controlled BP was achieved in 48.3%; p = 0.000). There was independent association of CRP levels > 3 mg/l with uncontrolled BP (OR = 3.1, 95%CI 2.06 - 4.75). There were significant 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).

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

Keywords: C-Reactive Protein; Control of BP in Patient with Metabolic Syndrome

Abbreviations

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: European Society of Cardiology/European Society of Hypertension

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 cluster of metabolic risk factors that includes high blood pressure, hyperglycemia, dyslipidemia and abdominal obesity, has been an increasing health problem worldwide for the last three decades, is associated with adverse cardiac events [3,4]. Patient with MetS usually present increased levels of C-reactive protein (CRP) which is a prototypic marker of inflammation [5], however the influence of increased levels of CRP on control of arterial hypertension in patient with MetS, data are scarce.

We set out to determine the influence of inflammation (assessed by increased levels of CRP) on control of arterial 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 control of arterial hypertension in patients with MetS.

Objective of the Study

We sought to determine the influence increased levels of CRP on control of arterial 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 June 2018 and June 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 ≥ 18 years, stratified in two groups:211 participants (147 females and 153 males) with level of CRP > 3 mg/l and 209 participants (155 females and 145 males) with level of CRP < 3 mg/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 minutes 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 ≥ 140 mmHg, and/or diastolic blood pressure (DBP) values ≥ 90 mmHg and/or current anti-hypertensive therapy [6]. Uncontrolled BP was defined be current ESC/ESH guidelines for the management of arterial hypertension [6]. 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 140/90 mmHg. among adults younger than 60 years and less than 150/90 mmHg. In general population aged ≥ 60 years. Diabetes mellitus was defined as a fasting serum glucose level ≥ 126 mg/dL and/or current medical therapy with an oral hypoglycemic agent and/or insulin [7].

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 nephelometry (Roche Swiss). Consistent with recommendations from Centers for Disease Control and Prevention [8] (a CRP cut point of 3.0 mg/L),was used to differentiate high-risk and low-risk group.

Exclusion criteria included a diagnosis of dementia senilis, secondary hypertension, serum creatinine level > 2 mg/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 [9], that three or more out of five following criteria are considered as MetS: (1) central adiposity {Waist circumference (WCi)} > 102 cm in men and > 88 cm in women [10]); (2) serum HDL-C < 50 mg/dL in women or < 40 mg/dL in men; (3) serum triglyceride levels > 150 mg/dL; (4) SBP ≥ 140 mmHg or DBP ≥ 90 mmHg 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-Whitney 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 ratio (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 participants (47.5% females and 50.2% males) with level of CRP < 3 mg/l and 211 participants (47% females and 53% males) with level of CRP > 3 mg/l, completed the survey and had data for 1-year medical record review. A mean of 3.4 BP recordings were obtained for each participants.

Baseline demographic, anthropometric and laboratory, characteristics by group are displayed in table 1. No significant differences in: age, gender, diastolic BP, were observed between groups. Participants with level of CRP > 3 mg/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 participants with level of CRP > 3 mg/l (18% vs. 6.7%; p = 0.000)}.

Table 2 presents the frequency of controlled BP in participants with MetS and different level of CRP. Among those with level of CRP > 3 mg/l (N = 211) controlled BP according to evidence and current guidelines, was achieved in 23.6% of participants, whereas among those with level of CRP < 3 mg/l (N = 209) controlled BP was achieved in 48.3%; p = 0.000). The difference was found to be statistically significant.

Variables N. (%)		Gr-I. CRP < 3mg/l (N.209)			Gr.II. CRP > 3mg/l (N.211)			p-value
		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/m²)			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. Risk factor		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; Serum HDL-C(p): High Density Cholesterol Presence; Serum Triglicerides; hs-CRP: C-Reative Protein; WCi: Presence of Increased Weist Circumference; BPH: Presence of Arterial Hypertension; glic: Glycemia Control.

Gr-I. (CRP< 3 mg; No. 209)		Gr.II. (CRP > 3 mg; No.211)		
Frequency of controlled BP				
Count (No.)	101	50		P = .0003
Percent (%)	48.3	23.6		
Chi-square: 13.1; p = .0003				
Study Groups: patient with MetS stratified by level of CRP (n-420)				

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

Overall frequency of controlled BP (in all participants enrolled in present study), was 38%.

In a logistic regression (Table 3), there was independent association of CRP levels > 3 mg/l with uncontrolled BP (OR = 3.1, 95%CI 2.06 - 4.75). There were significant 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

Table 3. Logistic Regression Model: Association of uncontrolled BP with: CRP levels (>3.0 mg/L), uncontrolled glycemia, increased BMI and five risk factor for MetS.
BP: Blood Pressure; MetS-RF n.5-: Five risk factors for MetS; DM: Diabetes Mellitus and BMI: Body Mass Index. OR > 1.*

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 there is an expanding literature regarding the role of inflammation and inflammatory cells in hypertension, in particular T lymphocytes are now thought to have a central role in the development of hypertension and related organ injury [11]. Based on the central 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 [12,13]. Also, Grundy SM., *et al.* suggests a significant association among inflammation, hypertension and the metabolic syndrome [14]. 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 [15].

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 [16,17]. The study results allow evaluating the effectivity of hypertension treatment as for drug choice, 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 [18]. 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 [18]. These data suggest 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. Previous study demonstrated that number of risk factors did not influence the levels of CRP in patients with MetS [19]. Also in present study we found association of high 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 [20-22].

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 reactivity in hypertension 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.

Conclusion

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

Author's Contribution

Materials-Agim Zeqiri; Dali Lala, Fatmir Ferati; Arben Mirto; Data collection/processing-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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Disclosure

Bibliography

1. "Heart Disease and Stroke Statistics-2019. Update: a report from the American Heart Association". *Circulation* 139 (2019): e56-528.

2. Tomasz P., *et al*. "Adaptive Immunity in Hypertension". *Current Hypertension Reports* 21 (2019): 68.

3. Ford ES. "Prevalence of the Metabolic Syndrome Defined by the International Diabetes Federation among adults in the U.S". *Diabetes Care* 28.11 (2005): 2745-2749.

4. Ford ES., *et al*. "Prevalence and correlates of metabolic syndrome based on a harmonious definition among adults in the US". *Journal of Diabetes* 2.3 (2010): 180-193.

5. Haffner SM. "The metabolic syndrome: inflammation, diabetes mellitus and cardiovascular disease". *The American Journal of Cardiology* 97.2A (2006): 3A-11A.

6. Bryan Williams., *et al*. "2018 ESC/ESH Guidelines for the management of arterial hypertension". *European Heart Journal* 39.33 (2018): 3021-3104.

7. America Diabetes Association. "Standards for medical care for patient with diabetes mellitus". *Diabetes Care* 25.1 (2002): S33-S49.

8. Center for disease control/American Heart association Workshop on inflammatory Markers, and Cardiovascular Disease: Application to clinical and public health practice: Atlanta, Ga. Centers for Disease Control and Prevention (2002).

9. Ford ES., *et al*. "Prevalence and correlates of metabolic syndrome based on a harmonious definition among adults in the US". *Journal of Diabetes* 2.3 (2010): 180-193.

10. Organisation WH. "Waist circumference and waist -hip ratio: report of WHO expert consultation". Geneva (2008): 8-11.

11. Guzik TJ., *et al*. "Role of the T cell in the genesis of angiotensin II induced hypertension and vascular dysfunction". *Journal of Experimental Medicine* 204 (2007): 2449-2460.

12. Pruijm M., *et al*. "Inflammatory markers and blood pressure: sex differences and the effect of fat mass in the CoLaus Study". *Journal of Human Hypertension* 27 (2013): 169-175.

13. Sesso HD., *et al*. "C-reactive protein and the risk of developing hypertension". *Journal of American Medicine Association* 290 (2003): 2945-2951.

14. Grundy SM. "Inflammation, hypertension, and the metabolic syndrome". *Journal of American Medicine Assocaition* 290.22 (2003): 3000-3002.

15. Smith GD., *et al*. "Association of C-reactive protein with blood pressure and hypertension: life course confounding and mendelian randomization tests of causality". *Arteriosclerosis, Thrombosis, and Vascular Biology* 25 (2005): 1051-1056.

16. Kjeldsen SE., *et al.* "Increased prevalence of metabolic syndrome in uncontrolled hypertension across Europe: the global cardiometabolic risk profile in patients with hypertension disease survey". *Journal of Hypertension* 26 (2008): 2064-2070.

17. Jani Y., *et al*. "Control of Arterial Hypertension among type-2 Diabetics". *International Journal of Biomedicine* 3.4 (2013): 232-239.

18. Arcucci O. *et al*. "Association of suboptimal blood pressure control with body size and metabolic abnormalities". *Journal of Hypertension* 25 (2007): 2296-2300.

19. Garcia VP., *et al*. "Sex differences in High Sensitive C-Reactive Protein in subjects with Risk Factors of Metabolic Syndrome". *Arqquivos Brasileiros Cardiologia* 106.3 (2016): 182-187.

20. Ridker PM., *et al*. "Should C-reactive protein be added to metabolic syndrome and to assessment of global cardiovascular risk?". *Circulation* 109 (2004): 2818-2825.

21. Sandhu HS., *et al*. "A Study of Correlation between Lipid Profile and Body Mass Index (BMI) in Patients with Diabetes Mellitus". *Journal of Human Ecology* 24 (2008): 227-229.

22. Matsuda M and Shimomura I. "Increased oxidative stress in obesity: Implications for metabolic syndrome, diabetes, hypertension, dyslipidemia, atherosclerosis, and cancer". *Obesity Research and Clinical Practice* 7 (2013): E330-E341.