A Proposed Inflammatory Score of Circulating Cytokines/ Adipokines Associated with Resistant Hypertension, but Dependent on Obesity Parameters

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Abstract

Background: **There is evidence that subclinical systemic inflammation is present in resistant hypertension (RHTN).**

Objective: **The aim of the study was to develop an integrated measure of circulating cytokines/adipokines involved in the pathophysiology of RHTN.**

Methods: **RHTN (n = 112) and mild to moderate hypertensive (HTN) subjects (n=112) were studied in a cross-sectional design. Plasma cytokines/adipokines (TNF-alpha, interleukins [IL]-6, -8, -10, leptin and adiponectin) values were divided into tertiles, to which a score ranging from 1 (lowest tertile) to 3 (highest tertile) was assigned. The inflammatory score (IS) of each subject was the sum of each pro-inflammatory cytokine scores from which anti-inflammatory cytokines (adiponectin and IL-10) scores were subtracted. The level of significance accepted was alpha = 0.05.**

Results: **IS was higher in RHTN subjects compared with HTN subjects [4 (2-6) vs. 3 (2-5); p = 0.02, respectively]. IS positively correlated with body fat parameters, such as body mass index (r = 0.40; p < 0.001), waist circumference (r = 0.30; p < 0.001) and fat mass assessed by bioelectrical impedance analysis (r = 0.31; p < 0.001) in all hypertensive subjects. Logistic regression analyses revealed that IS was an independent predictor of RHTN (OR = 1.20; p = 0.02), independent of age, gender and race, although it did not remain significant after adjustment for body fat parameters.**

Conclusion: **A state of subclinical inflammation defined by an IS including TNF-alpha, IL-6, IL-8, IL-10, leptin and adiponectin is associated with obese RHTN. In addition, this score correlates with obesity parameters, independently of hypertensive status. The IS may be used for the evaluation of conditions involving low-grade inflammation, such as obesity-related RHTN. Indeed, it also highlights the strong relationship between obesity and inflammatory process. (Arq Bras Cardiol. 2019; 112(4):383-389)**

Keywords: **Hypertension/physiopathology; Obesity; Inflammation; Cytokines; Adipokines; Probability; Risk Factors**

Introduction

Inflammation is an important pathophysiological factor underlying hypertension, obesity, and metabolic syndrome. Overweight and obese status include a higher prevalence of hypertension and maladaptive consequences including cardiorenal and metabolic disorders. Excess visceral fat is a source of cytokines, that creates an inflammatory-oxidative stress cascade contributing to insulin resistance (IR), endothelial dysfunction, vascular stiffening, and sodium retention in the kidney.[1,2] The combined presence of obesity and IR also contributes to overactivation of both sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system.[3] Ultimately, these disarrangements can lead to the occurrence of resistance to antihypertensive treatment.[4]

Our research group have explored inflammatory cytokines – the anti-inflammatory adiponectin and interleukin 10 and the pro-inflammatory leptin, tumor necrosis factor-alpha (TNF-α), and interleukins 6 (IL-6) – in resistant hypertension (RHTN) associating them to the lack of blood pressure (BP) control and vascular-renal damage.[5-7] In addition, low-grade chronic inflammation, estimated by high C-reactive protein levels, was able to predict major fatal and nonfatal cardiovascular outcomes, and cardiac remodeling in this high-risk population.[8-10]

Adiponectin has an anti-inflammatory role and directly stimulates the production of nitric oxide (NO) in endothelial cells via phosphorylation of endothelial

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NO synthase.[10] It down regulates TNF-α production from macrophage by inhibiting nuclear transcription factor NF-kappa B.[11,12] On the other hand, IL-6 inhibits adiponectin expression and secretion in 3T3-L1 adipocytes *in vitro*.[13] Additionally TNF-α increases the secretion of leptin,[14] which in turn stimulates the SNS.[15] Since cytokines and adipokines have interconnected roles, we aimed with this study (1) to develop an integrated measure of several circulating cytokines/adipokines among subjects with RHTN and mild to moderate hypertension (HTN), and (2) to assess the potential impact of this inflammatory score (IS) on resistance to antihypertensive treatment.

Population and methods

A convenience sample of 112 subjects diagnosed with RHTN attending the Specialized Outpatient Clinic in RHTN of the University of Campinas (UNICAMP, Campinas, Brazil) and 112 HTN attending the Hypertension Clinic of Valinhos (Valinhos, Brazil) were consecutively enrolled in this cross-sectional study. RHTN was defined according to American Heart Association Statement as either (1) the subjects whose BP levels remain above goal (≥ 140/90 mmHg) despite concurrent use of three or more antihypertensive drugs of different classes, or (2) those with controlled BP levels using four or more antihypertensive medication. Ideally, one of the agents should be a diuretic, and all agents should be prescribed at optimal doses.[16] Patients with controlled BP using three or less antihypertensive drugs, or not yet controlled using two or less of these medications were classified as having HTN (grade 1 and grade 2 hypertension).[17]

A 6-month period follow-up for screening and exclusion of secondary causes of hypertension was performed to guarantee a precise diagnosis for HTN and "true" RHTN. The exclusion criteria were compounded with renal artery stenosis, coarctation of the aorta, pheochromocytoma, primary hyperaldosteronism (aldosterone to renin ratio > 20 $ng.dL^{-1}$ per $ng.mL^{-1}.h^{-1}$), Cushing syndrome, obstructive sleep apnea-hypopnea syndrome (patients with previous polysomnographic diagnosis, or classified as high risk by the Berlin questionnaire). This period also included pill count to exclude the lack of BP control due to poor medication adherence,[18] and ambulatory BP monitoring (ABPM) to exclude white coat hypertension. We also excluded patients with symptomatic ischemic heart disease, impaired renal function, chronic kidney disease (creatinine clearance < 30 mL/min/1.73m^2) and liver disease (medical history, and platelet and transaminase levels). Inclusion criterion was age over 18 years old.

Blood pressure measurements

Office systolic BP (SBP) and diastolic BP (DBP) were assessed by a trained health professional according to the European Society of Hypertension guidelines for the management of arterial hypertension.[17] We used a validated digital sphygmomanometer (HEM-907XL, OMRON Healthcare Inc., Bannockburn, IL, USA). Ambulatory BP measurement was performed using an automatic oscillometric monitor (Spacelabs90207, SpacelabsInc, Redmon, WA, USA). Patients were instructed to maintain normal daily activities and record their 24-hour activities in a personal diary.

Body composition

The body composition was determined by the Bioimpedance Analyser 450 device (Biodynamics Corporation, Seattle, WA, USA) to assess fat-free mass and fat mass (FM). Briefly, the method is based on tetrapolar bioelectrical impedance (electrodes on feet and hands) to estimate mass and fluid compartments of the body. The measurements were performed after an 8-hour fast, and patients were instructed to avoid physical activity and smoking prior to the exam.

Biochemical tests

Blood samples were collected at morning after an 8-hour fast from patients in the sitting position. Plasma levels of aldosterone and renin were measured by radioimmunoassay (Immunotech SAS, Marseille, France), while the cytokines and adipokines – TNF-alpha, IL-6, IL-8, IL-10, leptin and adiponectin – were measured using enzyme-linked immunosorbent assay (ELISA) (R&D Systems, Inc., Minneapolis, USA), according to the manufacturer's instructions. Creatinine clearance was calculated from 24h-urine creatinine level, urine flow rate, and plasma creatinine concentration as the removal rate per minute divided by plasma creatinine concentration.

Statistical analyses

Continuous variables were expressed as mean and standard deviation or median (1st and 3rd quartiles), according to data distribution assessed by the Kolmogorov–Smirnov test. Unpaired Student's t-test or the Mann Whitney test was applied to compare continuous data between the RHTN and HT. Categorical variables were presented in frequencies and percentages compared by chi-square or Fisher's exact test. Pearson or Spearman tests was used to assess correlation of continuous data. Multiple logistic regression analyses were performed to evaluate the association of IS with resistance to antihypertensive treatment, adjusting for potential confounders.

For IS calculation, the values of plasma cytokine/adipokine (TNF-alpha, IL-6, -8, -10, leptin and adiponectin) were divided into tertiles, and a score ranging from 1 (lowest tertile) to 3 (highest tertile) was assigned to them. The IS was considered as the sum of each pro-inflammatory cytokine score (TNF-alpha, IL-6, IL-8 and leptin) from which adiponectin and IL-10 – both anti-inflammatory cytokines – scores were subtracted for each subject.

The analyses were performed using the software SigmaPlot (version 12, Systat Software, Inc., San Jose, CA USA, www.systatsoftware.com) and GraphPad Prism (version 7.00 for Windows, GraphPad Software, La Jolla, CA, USA, www.graphpad.com). The level of significance accepted was alpha 0.05.

Results

General characteristics of both hypertensive groups are described in Table 1. Body fat parameters (body mass index - BMI, waist circumference - WC and FM) revealed to be increased in the RHTN subjects, as well as lipid profile, glycated hemoglobin and aldosterone levels compared to their counterparts. Compared with HTN, RHTN individuals used

Table 1 – Clinical and biochemical characteristics of patients with mild-to-moderate hypertension (HTN) and patients with resistant hypertension (RHTN)

	HTN (n = 112)	RHTN (n = 112)	p-value
Age (years)	66 ± 10	58 ± 10	< 0.001
Female, n (%)	63 (56)	78 (70)	0.27
Black, n (%)	13 (12)	55 (49)	< 0.001
BMI (Kg/m^2)	27(25-31)	31(27-35)	< 0.001
WC (cm)	94 ± 12	101 ± 14	0.003
FFM (Kg)	53 (46-62)	55 (49-64)	0.11
FM (Kg)	20 (15-27)	26 (20-35)	< 0.001
Office SBP (mmHg)	139 (131-149)	149 (134-163)	< 0.001
Office DBP (mmHg)	82 (77-85)	85 (78-92)	0.03
ABPM SBP (mmHg)	126 (118-134)	130 (118-144)	0.03
ABPM DBP (mmHg)	75 (70-81)	75 (70-86)	0.22
HR (bpm)	67 (61-75)	67 (58-75)	0.35
Glucose (mg/dL)	97 (90-107)	101 (90-126)	0.09
HbA1C (%)	6.0 (5.7-6.4)	6.3 (5.9-7.3)	0.03
Cholesterol (mg/dL)	165 (136-187)	181 (150-209)	0.001
LDL-c (mg/dL)	88 (64-109)	97 (77-125)	0.004
HDL-c (mg/dL)	48 (41-56)	46 (38-54)	0.31
Triglycerides (mg/dL)	108 (80-150)	126 (93-185)	0.02
Urea (mg/dL)	34 (27-43)	35 (27-44)	0.52
Creatinine (mg/dL)	0.95 (0.79-1.10)	0.94 (0.80-1.18)	0.19
Renin (pg/mL)	29 (14-73)	25 (12-72)	0.39
Aldosterone (pg/mL)	68 (41-111)	92 (56-176)	0.006
Creat. Clear (mL/min/1.73m^2)	75 (58-93)	81 (61-97)	0.89

Values are expressed as mean ± standard deviation or median (1st, 3rd quartiles), according to data distribution. BMI: body mass index; WC: waist circumference; FFM: fat-free mass; FM: fat mass; SBP: systolic blood pressure; DBP: diastolic blood pressure; ABPM: ambulatory blood pressure monitoring; HR: heart rate; HbA1C: glycated hemoglobin; LDL: low-density lipoprotein; HDL: high-density lipoprotein; Creat Clear: creatinine clearance.

a greater number of antiplatelet drugs and almost all classes of antihypertensive agents, except for angiotensin II receptor blockers (ARBs). On the other hand, a greater number of HTN subjects were taking statins (Table 2).

IS was higher in the RHTN compared to HTN group [4 (2-6) *vs.* 3 (2-5); p = 0.02, respectively – Figure 1]. Curiously, IS positively correlated with BMI (r = 0.40; p < 0.001), WC (r = 0.30; p < 0.001) and FM (r = 0.31; p < 0.001) in all hypertensive subjects.

Finally, the independent logistic regression models revealed that IS was associated with the presence of RHTN (Odds ratio (OR) = 1.20; p = 0.02), independently of age, gender and race, although it was no longer significant after the adjustments for the body fat parameters studied (Table 3).

Discussion

Our study revealed that the integrated measure of pro-inflammatory and anti-inflammatory cytokines/adipokines scores was associated with the occurrence of RHTN. The IS arises as a strong factor related to body fat parameters, suggesting the relevance of subclinical inflammation in obesity condition regardless of the hypertension degree.

Recent findings from our group have suggested that inflammatory process underlies the pathophysiology of RHTN and its related comorbidities like diabetes, obesity and metabolic syndrome. Altered levels of cytokines and adipokines, such as IL-10, IL-1 beta, adiponectin and leptin, were found in RHTN subjects compared to their controls.[5,7,19] Hyperleptinemia and hypoadiponectinemia were associated with the lack of BP control,[5,19] as well as target organ damage – arterial stiffness and microalbuminuria – in this high-risk population.[6] Obese diabetic RHTN subjects showed lower levels of adiponectin combined with a greater autonomic dysfunction (characterized by a hyperactive sympathetic system and a hypoactive parasympathetic system) than non-diabetic patients.[20]

Recently, we have found a huge prevalence of metabolic syndrome in these RHTN subjects (73%), which may explain the high IS. Interestingly, the HTN group also showed a considerable prevalence of the syndrome (60%),[21] which might justify the worsening of their score in our present study.

Table 2 – Medications used by subjects with mild-to-moderate hypertension (HTN) and subjects with resistant hypertension (RHTN)

	HTN (n = 112)	RHTN (n = 112)	p-value
Antihypertensive drugs			
Number of classes	2 (2-3)	4 (4-5)	< 0.001
Diuretics, n (%)	70 (63)	108 (96)	0.02
ACEIs, n (%)	20 (18)	43 (38)	0.02
ARBs, n (%)	81 (72)	61 (54)	0.01
CCBs, n (%)	53 (47)	94 (84)	< 0.001
Beta-blockers, n (%)	14 (13)	79 (71)	< 0.001
Central α-agonists, n (%)	01 (01)	31 (28)	< 0.001
Statins, n (%)	84 (75)	60 (54)	0.001
Glucose-lowering drugs, n (%)	42 (38)	57 (51)	0.06
Antiplateletdrugs, n (%)	20 (18)	65 (58)	< 0.001

ACEIs: angiotensin-converting enzyme inhibitors; ARBs: angiotensin receptor blockers; CCBs: calcium channel blockers.

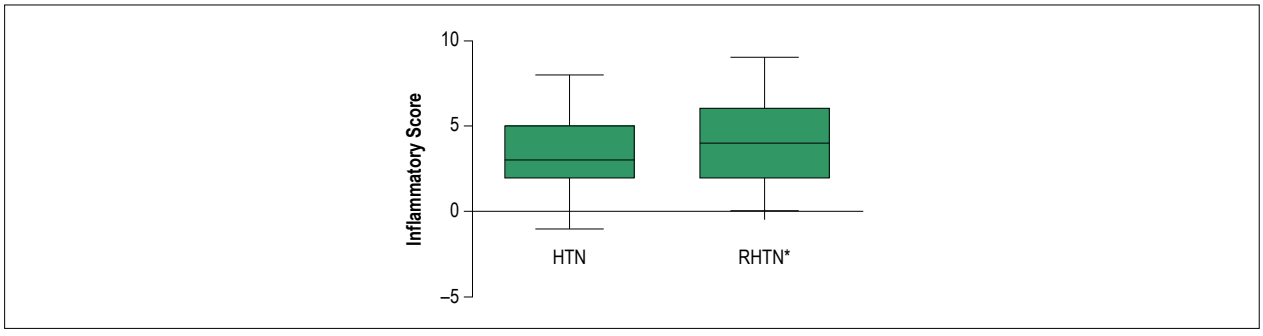

Figure 1 – *Inflammatory score calculated between subjects with mild-to-moderate hypertension (HTN) and resistant hypertension (RHTN) (3 [2-5] vs. 4 [2-6], p = 0.02, respectively). IS of each subject was the sum of each pro-inflammatory cytokine score (TNF-alpha, interleukins (IL) -6, -8, -10) from which the scores of anti-inflammatory cytokines (adiponectin and IL-10) were subtracted; *p < 0.05 vs. HTN*

In addition, the HTN group was older than the RHTN group, and hence an increased IS could be attributed to age.[22]

Experimental studies share similar findings of the role of inflammation on hypertension. Researchers have investigated changes in the systolic pressure of spontaneously hypertensive rats (SHR) treated with infliximab – a TNF-alpha-neutralizing agent.[23] This study revealed cardiovascular benefits of inhibiting this cytokine in SHR with the reduction of both systolic BP and cardiac remodeling. The authors suggested a vasodilation dependent-mechanism in which the infliximab effect is able to induce the NO synthesis.[23] Interestingly, a recent study[24] described a new pathway of hypertension linked to an immune-inflammatory-oxidative stress cascade. Kirabo et al.[24] demonstrated that an angiotensin II–infused mice model increased reactive oxygen species in dendritic cells releasing pro-inflammatory cytokines (IL-6, IL-1 beta, and IL-23), which in turn promoted T cell proliferation featuring a pro-inflammatory phenotype. Ultimately, these mechanisms led to hypertension, suggesting new potential targets to treat hypertension.[24] Our results revealed that the IS – already investigated in type 2 diabetes[25] – was able to address in a single measure a great variety of mechanistically aligned cytokines/adipokines, involved in the pathophysiology of RHTN. Therefore, this approach could enhance estimation of the relation between the low-grade inflammation and high-risk populations such as the obese subjects with RHTN studied in this work.

It is well recognized that obesity, characterized by chronic activation of the immune system and inflammatory pathways, is a critical factor contributing to IR and type 2 diabetes, both comorbidities quite often presented in subjects with RHTN. In this context, many studies have supported this relationship. Esposito et al.[26] found that weight loss and lifestyle changes decreased vascular inflammatory markers, such as IL-6, IL-18, and C-reactive protein, whereas adiponectin levels increased significantly in obese women. Similar effects of reducing levels of TNF-alpha were found in response to these interventions.[27] Overweight and obesity have been suggested to cause microvascular dysfunction characterized by (1) impaired insulin sensitivity, (2) SNS activation and (3) increased vascular peripheral resistance. Along with this, changes in adipokines secretion leading to increased levels of free fatty acids and inflammatory mediators have also

Table 3 – Independent multiple logistic regressions to evaluate the association of the inflammatory score with the presence of resistant hypertension

	OR (95%CI)	p-value
Model 1		
IS	1.20 (1.02-1.38)	0.02
Model 2		
IS	1.10 (0.92-1.28)	0.35
BMI (Kg/m^2)	1.12 (1.05-1.20)	< 0.01
Model 3		
IS	0.97 (0.80-1.18)	0.73
WC (cm)	1.04 (1.01-1.07)	0.01
Model 4		
IS	1.00 (0.84-1.19)	0.96
FM (Kg)	1.08 (1.04-1.13)	<0.01

All models were adjusted for age, gender and race. IS: inflammatory score; BMI: body mass index; WC: waist circumference; FM: fat mass.

been suggested to be involved.[28-30] Interestingly, impaired microvascular function in obese subjects was normalized one year after a gastric bypass surgery, and it was also associated with BP reduction.[31] Elevated levels of free fatty acids lead to endothelial dysfunction by reducing the production of NO, and increasing endothelin-1 vasoconstrictor tone and the release of pro-inflammatory cytokines[32] – which is an early hypertension-related factor associated with future cardiovascular events.[33,34]

Our findings showed that the association of IS and RHTN was abolished when the influence of body fat parameters was considered. Moreover, the IS was no longer significant after exclusion of obese subjects from both groups (data not shown). Our proposed score revealed its high dependence on obesity in the RHTN population, although this is expected since it is well-known these subjects are predominantly obese/overweight, as we found in our study – prevalence of 88%. Accordingly, the IS may reflect the inflammatory process underlying RHTN in an obesity-dependent manner, with the potential to be a clinical prognosis tool providing cardiovascular risk stratification in these obese subjects. On the other hand, we recognized that the design of this study is not sufficient to infer a temporal or cause-effect relationships. We also suggest that once obesity is established and hypertension is manifested, high BP may also contribute to further activation of inflammatory process. Thus, a vicious circle is created with both conditions – hypertension and obesity – that reinforces each other through inflammatory pathways.

Pharmacological or non-pharmacological treatments may affect inflammatory cytokines/adipokines. Studies have indicated that simvastatin reduces plasma levels of TNF-alpha and IL-6.[35,36] Antihypertensive drugs such as candesartan,[37] enalapril,[38] and mineralocorticoid receptor antagonist have also been shown to reverse proinflammatory cytokines.[39] Indeed, exercise and lifestyle modification reduced IL-8 levels in subjects with the metabolic syndrome,[40] while significantly increased adiponectin levels in obese patients.[26] Nevertheless, although these potential sources of variability may be present, they probably did not affect our findings since RHTN subjects had a high IS even though they used a greater number of antihypertensive agents. The use of individualized care also justifies the lack of standard therapy, and due to ethical issues, our subjects could not be assessed withdrawing the drugs. Finally, in a perspective of therapy approach, anti-inflammatory drugs or anticytokine molecules targeting the immune system, such as minocycline, can be attractive and of great interest in clinical setting to treat hypertension and prevent its cardiovascular complications, as supported by previous works.[41-43]

Some limitations should be mentioned. Since the population studied in this study is a convenience sample, with no sample size calculation, we recognize that our findings may not reflect the characteristics of the general population. Bias may also be present by comparing populations from different centers. It is worth mentioning that inflammatory process is quite complex and to measure its mediators is even more challenging since (i) it presents high costs, (ii) is still unavailable in clinical practice, and (iii) cutoff values may have heterogeneous profiles, which make the reproducibility more difficult. Even though, testing specificity and sensitivity in different populations are mandatory in order to guarantee a reliable score. Finally, this proposed score may change if the number of pro-inflammatory cytokines and/or anti-inflammatory cytokines changes.

Conclusion

In conclusion, our findings suggest that the IS, addressing many circulating cytokines/adipokines, may provide clinically important information to complement cardiovascular risk stratification in obese RHTN subjects. Moreover, our proposed score seems to be highly dependent on obesity-related hypertension. It is necessary to validate this score in larger populations in order to allow its use safely in clinical practice.

Author contributions

Conception and design of the research and writing of the manuscript: de Faria AP; acquisition of data: de Faria AP, Ritter AMV; analysis and interpretation of the data and critical

revision of the manuscript for intellectual content: de Faria AP, Ritter AMV, Gasparetti CS, Corrêa NB, Brunelli V, Almeida A, Pires NF, Modolo R, Moreno Junior H; statistical analysis: de Faria AP, Modolo R; obtaining funding: de Faria AP, Ritter AMV, Moreno Junior H.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Faculdade de Ciências Médicas da Universidade Estadual de Campinas under the protocol number 188.161/2013; CAAE: 11189712.8.0000.5404. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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