ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

High Sensitive C – Reactive Protein in Hypertension and Metabolic Syndrome.

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ABSTRACT

C-reactive protein has repeatedly been associated with blood pressure and prevalent and incident hypertension. In hypertensive individuals, C-reactive protein levels associate with vascular stiffness, atherosclerosis and the development of end-organ damage and cardiovascular events. It shows the generation of pro-inflammatory cytokine and is widely accepted as an independent cardiovascular risk marker. The metabolic syndrome is characterized by low-grade inflammation. C-reactive protein, the best characterized biomarker of inflammation, is an independent predictor of future cardiovascular events and also a strong risk factor for cardiovascular disease. Recent reports have provided provocative evidence that high sensitive C-reactive protein (hsCRP) may impair insulin signaling. Accumulating evidence suggests a close association of CRP and the pathogenesis of metabolic syndrome. 200 Hypertension and 200 metabolic syndrome and 200 controls peripheral venous blood sample was collected into a plain (5mL) and fluoride vials from the study subjects. High-sensitive CRP, Malondialdehyde and ferric reducing ability of plasma were assessed. C-reactive protein levels have been shown to be stable with little or no diurnal variation, making C-reactive protein the most commonly used and best standardized inflammatory marker of cardiovascular and metabolic disorders. A positive association between high blood pressure and elevated high sensitive C-reactive protein was noted in our study.

Keywords: Hypertension, C-reactive protein, Metabolic syndrome, Malondialdehyde

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ISSN: 0975-8585

INTRODUCTION

Essential hypertension is a heterogeneous disorder, with different patients having different causal factors that lead to high blood pressure. Oxidative stress is described as a condition in which cellular antioxidant defenses are inadequate to completely inactivate the reactive oxygen species (ROS) and reactive nitrogen species (RNS) generated because of their excessive production, loss of antioxidant defenses, or both [1].Vascular oxidative stress has been demonstrated in spontaneous (genetic) and experimental models of hypertension [2-3]. Free radicals have diverse roles in the vascular redox systems in the patients of hypertension, thus the complexity of the redox signaling in the distinct spatial spectrums should be considered for a better understanding of the hypertension.

Thus oxidative stress promotes vascular smooth cell proliferation and hypertrophy and collagen deposition leading to thickening of vascular media and narrowing of vascular lumen. Oxygen radicals may also induce endothelial permeability with extravasation of plasma protein and macromolecules and recruitment of inflammatory proteins and cells, which could further impair endothelial function and aggravate vascular damage. All these effects on vasculature may explain in hypertension and metabolic syndrome(MetS) how oxidative stress leads to inflammation and it leads to endothelial dysfunction (ED) [4-9].

C-reactive protein (CRP) is a marker of low grade chronic systemic inflammation. CRP is a positive acute phase protein that is increased in inflammation. Inflammatory stimuli cause the release of cytokines like interleukin (IL-1), IL-6 and tumor necrosis factor-a (TNFα), and these cytokines increase the synthesis and release of CRP. CRP is released by the liver following stimulation by interleukin-6, and is also locally produced in atheromatous lesions. Although most studies relied on a single measurement of CRP, this is not expected to affect the results, as CRP levels have been shown to be stable with little or no diurnal variation, making CRP the most commonly used and best standardized inflammatory marker of cardiovascular and metabolic disorders [10].

The present study was designed to study the relationship of CRP with the components of metabolic syndrome and also studied comparison of levels in hypertension and metabolic syndrome.

MATERIAL AND METHODS

In all subjects, anthropometric measurements, including height, weight and waist circumference measurements; systolic and diastolic blood pressure were recorded. After overnight fasting, peripheral venous blood sample was collected into a plain (5mL) and fluoride vials from the study subjects. The samples were then centrifuged at 3000 rpm for 15 minutes. The separated serum (plain vial) and plasma (fluoride vial) were stored at -50^0 C until further analysis. High sensitive C-reactive (hsCRP) protein done on Turbidometric method, Malondialdehyde (MDA) was analyzed as thiobarbituric acid reactive substances (TBARS). Total antioxidant capacity was determined by ferric reducing ability of plasma (FRAP) method in which a colorless ferric tripyridyltriazine complex at low pH is reduced to a blue ferrous complex by the antioxidants in the plasma.

Statistical analysis

All values were expressed as mean ± standard error of mean (SEM) Independent samples 't' test was used to test the significance of difference in means between study group and controls. For men and women, a student t-test or Mann-Whitney nonparametric test was used to compare between control and MetS participants normal or non-normal distribution, respectively. A P-value less than 0.05 were considered statistically significant. Correlation of oxidative stress parameters with components of metabolic syndrome was assessed by Spearman's rank correlation analysis. Statistical analysis was done by using Microsoft Excel and SPSS for windows version 11.5 (SPSS, Inc., Chicago).

ISSN: 0975-8585

RESULTS

Table 1: Shows Comparison of the components of hypertension, metabolic syndrome, and control group

S.No.	Parameters	Hypertension(n-200) Mean±SE	MetS(n-200) Mean±SE	Controls(n-200)	p Value
1	MDA	6.73± 0.87	5.73± 0.98	0.07± 0.01	p<0.001
2	TAC (FRAP)	0.62± 0.08	0.42 ± 0.09	1.32± 0.14	p<0.001
3	hsCRP	3.92±2.61	3.81±2.57	1.64±1.43	P<0.0001
4	SBP(mmHg)	132.1 ±4.1	136.2±4.4	124.2±2.1	P<0.006
5	DBP(mmHg)	82.7 ±1.3	84.9±1.6	74±1.3	P<0.001
6	Waist circumstances(cm)	121.3±5.6	111.9±5.9	85.1±1.1	p<0.019

All data are expressed as Mean±SE, FRAP-Ferric reducing ability of plasma, TAC-Total Antioxidant capacity, MDA-Malondialdehyde, SBP- Systolic blood pressure, DBP-Diastolic blood pressure, FBS-Fasting blood sugar.

DISCUSSION

Hypertension is a cause as well as effect of oxidative stress [10]. Hypertension as a result of reduced bioavailability of nitric oxide, causes converting of nitric oxide to peroxynitrite. Also, endothelial nitric oxide synthase (eNOS) can undergo uncoupling in the presence of peroxynitrite which is diverted towards lipid peroxidation [11]. C-reactive protein (CRP) is a marker of low grade chronic systemic inflammation. Normal high-sensitivity CRP (hs- CRP) varies from 0 - 5 mg/L in healthy young adults [12] and is significantly associated with the metabolic syndrome and its components. Higher CRP levels provide additional prognostic information on cardiovascular risk in patients with metabolic syndrome [13]. Our analysis revealed that there was a significant association between hs-CRP and the components of the metabolic syndrome. A positive association between high blood pressure and elevated hs-CRP was noted in some studies [14-16] , but our study correlate with their study, we found a significant association between hypertension and elevated hs-CRP level.

More recently it was considered that measurement of CRP should be added in the metabolic syndrome components as it was closely related with other components of the syndrome [17]. The treatment of several components of metabolic syndrome may have beneficial effects in preventing cardiovascular disease. Therefore, if subclinical inflammation is indeed another aspect of metabolic syndrome. A positive correlation was found between hs-CRP and the components of metabolic syndrome. There was a linear increase in hs-CRP with increasing number of metabolic syndrome components. Hence hs-CRP can probably be used as a surrogate marker of chronic inflammation in patients with metabolic syndrome. Serum, hs-CRP levels has been shown to predict myocardial infarction, stroke, peripheral arterial disease and sudden cardiac deaths [18]. [In the present study hs-CRP levels showed positive associated with HTN in univariate logistic regression analysis OR: 2.35, 95% CI: 2.4-2.65; P<0.001]

By these results, our study suggests that hs-CRP may act as a rise factor independent of lipid levels in predicting the risk of CAD in HTN patients. Thus our findings suggest that higher levels of hs –CRP are independently associated with an increased risk of CAD [17]. Elevated CRP was associated with nearly 2-fold increased odds of prediabetes or diabetes, a 2-fold increased odds of MetS only, and nearly 5-fold increased odds of MetS plus prediabetes or diabetes after multivariable adjustment [13].Our findings are consistent with other studies that have reported a significant association between elevated CRP in diabetes and MetS. The mechanisms responsible for increased cardiovascular morbidity and mortality in individuals with diabetes and MetS, are not fully explained by traditional risk factors and may be partially explained by inflammation and endothelial dysfunction [13-15]. Visceral adiposity is associated with increased production of proinflammatory cytokines and hepatic CRP and also associated with visceral adiposity and may be upregulated by the increased production of pro inflammatory cytokines. Inflammation may promote development of diabetes by triggering beta cell dysfunction, apoptosis and impaired insulin signaling or development of hypertension by influencing platelet adhesion and aggregation, production of oxidants and induction of renal vasoconstriction [15].

The median level of CRP in our study participants was higher than reported in other studies with Asian populations and may be due to analytic or pre analytic sources of variability such as a lack of standardized reference material for CRP measurement. This study, it is not possible to establish temporality or determine if elevated biomarkers lead to development of the diabetes and MetS or if development of the individual

components of the MetS lead to inflammation and endothelial dysfunction [13-15] Oxidative stress is a consequence of low level inflammation one of the mechanisms by which inflammation causes atherogenesis [17].

The results from our study indicated a strong association between elevated biomarkers of inflammation and endothelial dysfunction with increased diabetes and the MetS among adults in south Indian population. Strategies to reduce inflammation may be important therapeutic targets for people at risk of developing diabetes and MetS.

CONCLUSION

CRP is released by the liver following stimulation by interleukin-6, and is also locally produced in atheromatous lesions. Although most studies relied on a single measurement of CRP, this is not expected to affect the results, as CRP levels have been shown to be stable with little or no diurnal variation, making CRP the most commonly used and best standardized inflammatory marker of cardiovascular and metabolic disorders. A positive association between high blood pressure and elevated hs-CRP was noted in our study. A positive correlation was found between hs-CRP and the components of metabolic syndrome and Hypertension. Hence hs-CRP can probably be used as a surrogate marker of chronic inflammation in patients with Hypertension and metabolic syndrome. Further studies are required to better understand the complex oxidative equilibrium under physiological pathological conditions leads to inflammation and finally it leads to ED.

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