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Research Article

hsCRP in pre-hypertension and hypertension: a prospective study in Southern Asian region

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ABSTRACT

Background: Hypertension is turned into a leading cause of non-communicable disease associated mortality and morbidity in both developing as well as developed world. Hypertension is reported to be the fourth contributor to premature death in developed countries and the seventh in developing countries. In the regard of early diagnosis and better prognosis, the concept of pre-hypertension, defined as a systolic blood pressure of 120-139 mmHg and/or a diastolic blood pressure of 80-89 mmHg was introduced as the new guideline for the management of blood pressure by the seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure (JNC-7). Among various other factors inflammation may be a causative factor for development of Hypertension But the association is not very clear. Accordingly, we have designed our study to find any association of hsCRP with pre-hypertension and hypertension so that early prevention and control can help to avoid or delay the grave outcome and complications of hypertension.
Methods: A total of 37 hypertensives, 30 pre-hypertensives and 31 age and sex matched healthy control subjects were selected for the study, with consent. Two BP readings were taken five minutes apart, on both arms, with a mercury sphygmomanometer. The estimation of serum hsCRP was done on XL-600 automatic analyzer with the kit (Erba Mannheim) based on the measurement of antigen-antibody reaction by the end-point method.
Results: There is significant difference in systemic and diastolic blood pressure and hsCRP in between group study. In pre-hypertensive group hsCRP is correlated with diastolic blood pressure.
Conclusion: Our results suggest a correlation exists between hsCRP and hypertension more significantly with pre-hypertension. So estimation of serum hsCRP can be a good diagnostic as well as prognostic marker in diagnosing pre-hypertensives and prevent the occurance of hypertension and cardio vascular disorders thereby.

Keywords: Hypertension, Pre-hypertension, hsCRP, Systolic blood pressure, Diastolic blood pressure

INTRODUCTION

Hypertension is an important worldwide public-health challenge because of its high frequency and concomitant risks of cardiovascular and kidney disease.[1,2] Industrialization, urbanization, and associated lifestyle changes has led to an epidemiologic transition.[3] As per the World Health Statistics 2012, of the estimated 57 million global deaths in 2008, 36 million (63%) were due to Non-Communicable Diseases (NCDs). The largest proportion of NCD deaths is caused by cardiovascular diseases (48%). In terms of attributable deaths, raised blood pressure is one of the leading behavioral and physiological risk factor to which 13% of global deaths are attributed. Hypertension is reported to be the fourth contributor to premature death in developed countries and the seventh in developing countries.[4] Hypertension is directly responsible for 57% of all stroke deaths and 24% of all coronary heart disease deaths in India.[5] Due to its

high mortality and morbidity early diagnosis and effective prevention is important. In this regard the concept of pre-hypertension, defined as a systolic blood pressure of 120-139 mmHg and/or a diastolic blood pressure of 80-89 mmHg was introduced as the new guideline for the management of blood pressure by the seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure (JNC-7).[6] A statistical analysis conducted by National Health and Nutrition Examination Survey from 1999 to 2006 found the prevalence of pre-hypertension in disease free adults is 36.3% in all over world.[7] Many studies demonstrated that the pre-hypertensives had higher levels of blood glucose, insulin resistance, total cholesterol, low density lipoprotein cholesterol, and triglycerides, higher body mass index, abnormalities of glucose metabolism and lower levels of high-density lipoprotein cholesterol than the normotensive group.[8-10]

There are many established risk factors for development of hypertension which reiterates the importance of an early diagnosis preferably at the stage of pre-hypertension. A growing body of evidences indicates that vascular inflammation may be involved in both the initiation and development of hypertension.[11] This is evident from the elevated levels of inflammatory markers like Tumor Necrosis Factor-α (TNF-α), Interleukin-6 (IL-6) and C-Reactive Protein (CRP) found in people with hypertension.[12]

In healthy individuals C-Reactive Proteins (CRP) is present in plasma in minimal amounts but the concentration increases 100 fold in response to injury, infection or inflammation. CRP is named so for its ability to precipitate the somatic C-polysaccharides of Streptococcus pneumoniae and is the first acute phase protein to be described.[13,14] CRP is primarily synthesized by liver in response to interleukin-6 (IL-6) and interleukin-1ß (IL-1ß). As a good biological marker it is stable, half-life of 19 hours and small variation in values between fresh and frozen forms.[15,16]

The relevance of elevated levels of inflammatory markers in predicting cardiovascular risk is gaining increasing recognition and in that respect CRP has been the most intensively investigated in clinical studies.[11]

In the year 2001, a cross-sectional study was conducted by Bautista et al., for the first time measured CRP in hypertension and found CRP to be an independent risk factor for the development of hypertension.[17]

Although, CRP is an efficient marker for inflammation, it is not detectable at a very low level (i.e. <3 mg/l) by routine lab methods. Specialized techniques can detect hsCRP at a level lower than 3 mg/l and so are more important for detection of the pro-inflammatory state at the earliest.

The association of inflammatory markers with pre-hypertension and hypertension is not very clear. Few studies, however, have explored interrelations between levels of CRP and hypertensive risk factors, and data from these reports have been inconsistent.[18-21] Hence, we hypothesized that the pre-hypertensive condition is associated with a pro-inflammatory condition that can be linked to a significant increase in the levels of hsCRP in plasma.

Accordingly, we have designed our study to find any association of hsCRP with pre-hypertension and hypertension so that early prevention and control can help to avoid or delay the grave outcome and complications of hypertension.

METHODS

Study design

Cross sectional hospital based study.

Study site

The study was carried out at the department of biochemistry, Calcutta National Medical College and Hospital (CNMCH).

Duration of study

The duration of study was six months (01.10.2013 to 31.03.2014).

Selection of cases and controls

A total of 37 hypertensives (19 males and 18 females, aged 40 to 60 years) and 30 pre-hypertensives (16 male and 14 female, aged 40 to 60 years) were selected for the study. Written informed consent was taken from them. Cases were selected from clinically newly diagnosed hypertensive and pre-hypertensive patients attending the medicine outdoor department of Calcutta national medical college. 31 (16 male and 13 female) age and sex matched healthy control subjects were also selected for the study, with consent.

Inclusion criteria

Subjects between the age group of 40 -60 years were selected. Blood samples from cases were collected before institution of anti-hypertensive treatment, the criteria for diagnosis of hypertension were systolic pressure of ≥140 mm of Hg and diastolic pressure of ≥90 mm of Hg, pre-hypertension were systolic pressure of ≥120 mmHg to ≤140 mmHg and diastolic pressure of ≥80 mmHg to ≤90 mmHg. The criteria for the controls were age and sex matched healthy normotensive individuals (systolic pressure ≤ 120 mmHg and diastolic pressure ≤80 mmHg) without any family history of hypertension.

Exclusion criteria

Hypertensive patients who were already on anti-hypertensive treatment were excluded from the study. Study subjects were examined systematically to exclude any disease (Secondary hypertension) or factors known to cause or associated with hypertension.

Subjects with any underlying condition or taking any drugs like steroids, oral contraceptive pills, and thyroxin were excluded from the study.

Similarly, subjects with any underlying condition or taking any drug known to alter serum calcium levels or calcium supplementations have been excluded from the study.

Subjects who are smoker, suffering through any inflammatory conditions and malignancy, obese, pregnant women, excluded from the study.

Ethical clearance

Before commencement of the work, ethical clearance was obtained from the institutional ethics committee, according to the Helsinki declaration. Written informed consent was taken from cases and control subjects.

Methods for analysis of test parameters

Blood pressure measurement[21]

In a quiet and comfortably seated study subject, two BP readings were taken five minutes apart, on both arms, with a mercury sphygmomanometer (cuff size, 12.5 x 40 cm). The SBP and DBP were read to the nearest 2 mm Hg. The first and fifth phases of Korotkoff's sounds were taken as the criteria for SBP and DBP respectively. The average of two consecutive readings was recorded.

Serum hsCRP[23]

For the estimation of serum hsCRP, 2 ml of fasting, venous, non-haemolysed blood sample was withdrawn without the aid of a tourniquet, in a plain sterile bulb. The blood samples were analysed immediately. The estimation of serum hsCRP was done on XL-600 Automatic analyzer with the kit (Erba Mannheim) based on the measurement of antigen-antibody reaction by the end-point method.

RESULTS

One way ANOVA analysis shows there is significant difference in systolic and diastolic blood pressure and hsCRP in between group study.

Table 1: The demographic profile of various study groups.

Parameter	Control (n=31)	Pre-hpertensive (n=30)	Hypertensive (n=37)
(SBP) Systolic blood pressure (mmHg) Mean ± SD	108.9677 ± 4.976504	130.7333 ± 5.668627	160 ± 18.80307
(DBP) Diastolic blood pressure (mmHg) Mean ± SD	74.9 ± 3.718018	84.66667 ± 2.892718	97.67568 ± 7.99324
hsCRP	2.456129 ± 1.355627	7.899667 ± 1.099299	8.458649 ± 0.88101

Table 2: ANOVA analysis between different groups for SBP, DBP, hsCRP.

Parameter	Mean square	F	Sig
SBP			
Between groups Within groups **Total**	22339.073 151.609	147.347	0.000
DBP			
Between groups Within groups **Total**	4445.503 31.131	142.798	0.000
hsCRP			
Between groups Within groups **Total**	353.221 1.243	284.085	0.000

But post hoc Bonferroni analysis showed that the difference of hsCRP is not significant in between pre-hypertensive and hypertensive group whereas it is significant in hypertensive and pre-hypertensive group when compared with control. Regression analysis shows a significant dependence of hsCRP on DBP only in pre-hypertensive group.

According to post hoc Bonferroni SBP and DBP levels are significantly different in all control (grouop-1), pre-hypertensive (group-2), hypertensive (group-3) groups but hsCRP is not significantly different in between pre-hypertensive (group-2), hypertensive (group-3) group.

In Table 4 regression analyses shows significant dependence of hsCRP on DBP in pre-hypertensive group.

Table 3: Post hoc bonferroni shows intergroup significance between various groups.

(I) Group all	(J) Group all	Mean difference (I-J)	Sig.
SBP			
1.00	2.00	-21.76559*	0.000
	3.00	-51.03226*	0.000
2.00	1.00	21.76559*	0.000
	3.00	-29.26667*	0.000
3.00	1.00	51.03226*	0.000
	2.00	29.26667*	0.000
DBP			
1.00	2.00	-9.76344*	0.000
	3.00	-22.77245*	0.000
2.00	1.00	9.76344*	0.000
	3.00	-13.00901*	0.000
3.00	1.00	22.77245*	0.000
	2.00	13.00901*	0.000
hsCRP			
1.00	2.00	-5.44354*	0.000
	3.00	-6.00252*	0.000
2.00	1.00	5.44354*	0.000
	3.00	-0.55898	0.132
3.00	1.00	6.00252*	0.000
	2.00	0.55898	0.132

Table 4: Regression analysis coefficients of SBP and DBP with dependent variable hsCRP in different groups.

Model	Standardized coefficients	t	Sig.
	Beta		
Control			
(Constant)		-1.385	0.177
SBPcon	0.428	2.216	0.035
DBPcon	-0.079	-0.410	0.685
Pre-hypertensive			
(Constant)		-0.169	0.867
SBPpre	-0.368	-2.507	0.018
DBPpre	0.566	3.857	0.001
Hypertensive			
(Constant)		3.431	0.002
SBPhtn	0.128	0.591	0.558
DBPhtn	0.119	0.550	0.586

DISCUSSION

In our study, we find that hsCRP level is increased significantly in pre-hypertensive and hypertensive group than in normotensive control. In pre-hypertensive cases, increase in hsCRP level is positively related with increase in diastolic blood pressure.

CRP is an acute phase protein which is increased in plasma during inflammation. Many cross-sectional studies show increased CRP level in hypertensive people.[24-26] Inflammation may be an underling pathological factor for development of hypertension also.

CRP increases the blood pressure may be by several mechanisms. It decreases the production of nitric oxide by endothelial cells, so indirectly inhibits vasodilatation. On the other hand, it increases leukocyte adhesion, platelet activation, oxidation and thrombosis. CRP upregulates the angiotensin type-1 receptor so mediates the angiotensin-II mediated increase in blood pressure.[27,28] Pulse Wave Velocity and augmentation index, a measure of arterial stiffening was associated with many circulating inflammatory markers in recent studies suggesting that inflammation may play a role in arterial stiffness.[29-31] All these facts indicate CPR has a role in development of hypertension. Ki Chul Sung and workers found hsCRP to be an independent risk factor for development of hypertension in Korean population.[32]

In our study also we get higher level of hsCRP in pre-hypertensive and hypertensive group than control.

Many studies[19-21] do find the same kind of result as ours.

In our study we also find an association between diastolic blood pressure and hsCRP level in pre-hypertensive group but not in control and hypertensive group. Sesso et al. found a positive association between increasing hsCRP and pre-hypertensive.[25] Possible mechanisms for this association being oxidative stress and interaction with adhesion molecules, plasminogen activator inhibitor-1 and low density lipoprotein cholesterol (LDL-C) uptake.[36] Due to its inflammatory pathology in hypertension, other acute phase proteins e.g. Sialic Acid (SA) also increases. Through the development of atherosclerosis, SA can promote hypertension indirectly. Secondly, SA as the main source of vascular endothelial cell surface negative charge; it can influence the vascular endothelial cell function for promoting the development of hypertension. Thirdly, SA can also affect LDL metabolism, inducing vascular smooth muscle damage, and the damaged muscle can promote the development of hypertension.[38] This way, Many hypothesis suggests that in the early stage of hypertension, grade of inflammation determines the level of hypertension.[37] Many studies show the difference in the elevation levels of hs-CRP was also found to be duration dependent Patients with shorter duration of hypertensive history (<1 year) were found to have significantly elevated levels of hs-CRP compared to those with longer duration of hypertensive history (<5 years).[21,36]

Many studies did not find any association between these two groups.[17,19]

Pre-hypertension not only developed in hypertension but it is an increased risk factor for myocardial infraction and coronary artery disease.[33] For each 20 mmHg increase in systolic blood pressure or 10mmHg increase in diastolic

blood pressure over 115/75 mmHg, there was a twofold increase in mortality associated with coronary artery disease and stroke.[34] Longitudinal data from the Framingham heart study indicated that individuals formerly classified as having "normal" and "high-normal" blood pressure (120-139/80-89 mmHg) were at increased risk of developing full-blown hypertension and cardiovascular disease later in life than those with optimal blood pressure of <120/80 mmHg.[35]

CONCLUSION

Pre-hypertension and hypertension both are having an inflammatory pathology. Pre-hypertension not only developed in hypertension but also increases the chances of cardiovascular diseases. Our results suggests a dependence of hsCRP on DBP in pre-hypertension, so estimation of serum hsCRP can be a good diagnostic as well as prognostic marker in diagnosing pre-hypertensives and prevent the occurrence of hypertension and cardio vascular disorders thereby & measuring the hsCRP level proper treatment module can be framed.

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