DOI:10.24041/ejmr2018.75

HIGHLY SENSITIVE C - REACTIVE PROTEIN IN HYPERTENSION, AS A POTENTIAL MARKER OF CARDIOVASCULAR EVENTS A CASE-CONTROL HOSPITAL-BASED STUDY

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Received on : 11-10-2018
Accepted on : 22-12-2018

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ABSTRACT

As inflammation had a role in every stage of atherogenesis and hypertension, in turn leading to Cardiovascular Disease. Hs-CRP level estimation can be an important screening method for assessing the risk. Thus, this study to evaluate the effect of essential hypertension on hs-CRP levels in Indian adult population. As well as clustering of other cardiovascular risk factors in comparison with a control group in a population.

Acase-control study was carried out in of Era's Lucknow Medical College & Hospital, Lucknow, and Uttar Pradesh. All patients coming in out-patient department were screened for inclusion & exclusion criteria. Those selected were subjected to screening of risk factors of cardiovascular diseases & serum hs CRP estimation.Significant CAD risk factors in our cases came out to be: higher weight (p-value: 0.0470), raised BMI (>25) (p-value: 0.005), higher waist circumference (p-value: 0.0010) & smoking (p-value: 0.008). Average hs-CRP values in the hypertensive group (cases) was higher (2.85 ± 2.4 mg/L) than in normotensive group (control) (2.36 ± 2.08 mg/L). No significant difference in values among the controlled & uncontrolled group of previously diagnosed hypertensives was observed but a significant difference was found between newly diagnosed Stage I & Stage II hypertensives.Also, though not significant a rising trend was noted in hs-CRP values with an increase in the risk category. On CAD risk stratification according to hs CRP values cases hada significantly higher prevalence of hs-CRP levels than controls. Conclusion: The study did not reveal any significant difference in hs CRP values in hypertensives than from the normotensive population. But the significant difference between Stage I & Stage II of hypertension was observed in hs-CRP values.

KEYWORDS: C - reactive protein, Cardiovascular , Atherogenesis, Hypertension.

INTRODUCTION

Chronic vascular diseases account for over a quarter (26%) of all deaths due to non-communicable diseases globally (1-2). The fifth of cardiovascular deaths globally is accounted by Indian population.

High blood pressure is reported to be a strong, consistent and independent risk factor for cardiovascular and renal disease (3). Hypertension also called as silent killer directly responsible for 57% of all stroke deaths & 24 % of all coronary heart deaths in India.

As inflammation had a role in every stage of atherogenesis and hypertension, in turn leading to Chronic Heart Disease or Cerebrovascular disease particularly in presence of other risk factors (4).

Highly sensitive C - reactive protein is now considered as one of the most reliable markers of inflammation (5).The values show the greatest change from very low to very high levels and is closely related to the degree of inflammation. Thus considered as a potential marker of atherosclerotic risk as it promotes the atherosclerotic process (6). Recently, hs-CRP has been identified as an independent marker of the cardiovascular risk factor independent of several other risk factors (7).

The benefit of hs-CRP lies in its analytical and assay characteristics most conducive to use in clinical practice (8). The present-day studies employ CRP determination by ELISA and this quantitative estimation is called hs-CRP. By hs-CRP assays, so obtained constant ratio as low as 0.15mh/L can be measured.

It has time and again proven that addition of hs- CRP to

screening based on standard lipid levels have shown to improve the prediction of risk for stroke and Myocardial Infarction. But, not many studies are done in Indian population to depict the effect of this novel inflammatory marker. Since Indians are facing a double burden of diseases; communicable diseases are still not under control and non-communicable diseases prevalence is increasing.

The purpose of this study was to evaluate the association of Serum hs-CRP levels with different stages of hypertension. The clustering of other cardiovascular risk factors and serum hs-CRP levels in Indian population.

MATERIALS AND METHODS

It was a hospital-basedun-matched case-control study.

Sample

After obtaining clearance from the institutional ethics committee. All the patients attending Medicine OPD, Urban Health Training Centre of the Hospital were screened for inclusion or exclusion criteria for cases and controls. The study was conducted in Era's Lucknow Medical College, Lucknow Uttar Pradesh in the Department of Medicine under the scholarship of Short Term Studentship programme of Indian Council of Medical Research.

Inclusion Criteria Of Cases:

1. Diagnosed cases of Hypertension, whether or not on antihypertensive drugs, irrespective of whether the blood pressure is under control or uncontrolled in the age group of 30-55 years.
2. Newly diagnosed hypertensive i.e. elevated blood pressure readings in the same environment (>139mmHg Systolic blood pressure or > 90 mmHg Diastolic Blood Pressure) on more than two occasions at least an interval of one week or average elevated BP readings on home-based blood pressure monitoring; in the age group of 30-55 years of age.

Inclusion Criteria For Controls:

1. Allnormotensive individuals (defined as systolic blood pressure < 140 mm Hg and Diastolic BP < 90 mm Hg) aged 30 -55 years of age.

Exclusion Criteria (for cases and controls):

1. Any acute illness or with the history of any acute trauma. (illness of duration less than three months)
2. Patients suffering from fever or an obvious inflammatory process (any injury in past 03 months, rheumatic arthritis, auto-immune disorders, a recent history of vaccination, evidence of acute and chronic inflammation in Total Leucocyte Count, Differential Leucocyte Count, Erythrocyte Sedimentation Rate).
3. Patients with serious chronic illnesses or debilitating disease. (As hemiplegia, Chronic Kidney Disease, Paraplegia, Chronic liver disease, and Chronic skin diseases etc.)
4. Diabetic patients, Cancer patients.
5. Pregnant and breastfeeding mothers or a history of abortion in the past 03 months.
6. Showing evidence of infection in laboratory examination.
7. Failure to obtain an informed written consent.

Sample Size

The sample size was calculated used open epi software for calculating sample size. With the assumptions of Observational study, Power 80%, taking 1:1 ratio of cases to controls, hypothetical proportions of controls with exposure taking as 40. The sample size came out to be 133 each of cases and controls, total sample size came out to be 266.

Sampling Procedure

After obtaining written consent from each enrolled subject (case or control). Using a standard questionnaire, a complete history and necessary information with the emphasis on cardiovascular risk evaluation obtained from both case and controls. It was followed by a detailed physical examination. All subjects were investigated for Haemoglobin, Total Leucocyte Count, Differential Leucocyte Count, Erythrocyte Sedimentation Rate, Fasting Blood Sugar & Post Prandial Blood Sugar, Fasting Serum Lipid Profile, Blood Urea, Serum Creatinine, Serum Electrolytes, Serum Bilirubin, Serum Liver Enzymes, urine routine & microscopy, Electro Cardiograph. Blood for analysis of Serum Hs CRP was drawn simultaneously at the time of investigation on the same day of all evaluation in both cases and controls. The blood samples so obtained for assessing Hs-CRP levels were stored in labelled vials in a Deep freezer at -20^{0}C. Cardiovascular risk factors evaluated were: gender, smoking, chronic alcohol intake, obesity, dyslipidemia.

Criteria And Investigations

Cases were classified into:

Low risk – Absence of any cardiovascular risk factor.

Moderate risk – Presence of 1-2 risk factors.

High Risk - > 3 risk factors or presence of target organ damage as evidenced by clinical cardiac, cerebrovascular, renal involvement or retinopathy.

Risk Factors Being

Non-modifiable: Family history of (Hypertension, CAD, type –II DM, dyslipidaemia), Ethnicity (South Asian, African or Caribbean), Male sex, > 30 years of age, low socio-economic class);

Modifiable: Obesity (Body Mass Index > 25, smoking, chronic alcohol intake, hypertension, type-II Diabetes Mellitus) (9).

Dyslipidaemia by presence of any one of the following: Serum Cholesterol > 200mg/dL, Serum Low Density Lipoprotein> 160 mg/dL, Serum Triglyceride > 200mg/dL, Serum High Density Lipoprotein< 35 mg/dL.

Obesity: By Body Mass Index > 25; waist circumference: Men ≥ 90 cm and women ≥ 80 cm.

Electro Cardio Graph: Evidence of left ventricular hypertrophy, ischemia or old infarction.

Renal involvement: Raised Serum Creatinine level and albuminuria.

Known Coronary Artery Disease: Episode of angina or myocardial infarction in life.

Hypertensive: Blood pressure measurement by mercury sphygmomanometer as > 139 mm of Hg systolic or diastolic as > 89 mm of mercury in left arm at the level of heart in sitting position. Two separate readings were taken 30 minutes apart. Categorized further as per JNC VII: Stage I: 140-159/ 90-99 mm of Hg; Stage II: ≥ 160/ 99 mm of Hg. (no pre-hypertensives were included since the comparison was to between diagnosed hypertensives and non-hypertensives).

Controlled Hypertensive's: Known cases of hypertension and controlled on current medication.

Known hypertensives: Irrespective whether controlled or not; or on antihypertensive treatment or not.

Hs- CRP:

Quantitative CRP estimation was done by ELISA using the kit supplied by Bio Check, Inc. 837 Cowan Rd. Burlingame, CA 94010. The kit was specified as "High sensitivity C- Reactive Protein Enzyme Immunoassay Test Kit" Catalogue number: BC -1119 (hs-CRP ELISA).

Hs-CRP interpretation:

Average hs CRP levels were determined in all hypertensives across the classification of hypertension and in all the three risk categories and in the target organ damage group. Values of Hs –CRP > 10 mg/L were excluded. Hs-CRP risk categorization: low risk (<1.0 mg/l), average risk (1.0 to 3.0 mg/l), and high risk (> 3.0 mg/L (10).

The collected data were tabulated on the computer using Windows XP operating system on Microsoft Office 2000, Excel package and the statistical analysis (unpaired, unequal variance, two-tailed unpaired Student's t-test for comparing 02 means, ANOVA when comparing means of 3 or more groups) was done on the same. Rejection criteria for null hypothesis were taken as $p < 0.05$.

RESULTS

A total of 159 cases and 141 controls were subjected to inclusion and exclusion criteria. Out of which only 138 cases and 130 controls fulfilled the criteria. Due to lack of availability of sufficient funds randomly samples were picked for the screening of Hs-CRP levels, thus 100 cases and 100 controls using computer-generated random numbers.

76% of the cases were already diagnosed as hypertensives while 24% freshly diagnosed cases as per JNC VII criteria were included in the study. There was no diabetic included in the study.

Clinical Characteristics	Cases (n=100)	Controls (n=100)	P value
Age (years)	48.36 ± 8.59	44.12 ± 7.9	40.000
Male to female ratio	0.96:1	0.76:1	0.0630
Weight (Kg)	64.19±13.29	60.57±11.98	0.0470
Height (cm)	159.62±9.56	159.26±9.79	0.7980
Waist Circumference (cm)	91.26±13.19	85.25±11.78	0.0010
Hip Circumference (cm)	97.18±11.43	95.56±8.43	0.2740
Systolic Blood Pressure (mm of Hg)	140.47±18.72	122.30±10.85	<0.0001
Diastolic Blood Pressure (mm of Hg)	86.81±10.37	79.87±6.89	<0.0001

Table 1: Clinical Characteristics of the participants.

Risk factors	Cases (n=100)	Controls (n=100)	P value
Male Sex	49	36	0.060
Increased waist circumference	80	50	0.001
Obesity (BMI = 25)	51	31	0.005
Alcohol intake (> 60 ml in most days of the week)	03	04	0.510
Smoking (> 3 cigarette/bidi per day for > 1 year)	21	06	0.008
Family History of CVD	23	20	0.632
Dyslipidemia (raised S.TG, S.LDL, S. Cholesterol or decreased S. HDL)	56	48	0.080

Table 2: Prevalence Of Cardiovascular Risk Factors In Cases And Control Group In Our Study

Table I describes the demographic characteristics, anthropometric details in study participants. Waist circumference in centimeters and weight in kilograms were raised significantly (p-value: 0.001 & 0.047 respectively in cases as compared to controls.

TableII outlines the important cardiovascular risk factors in the cases and controls. Smoking was found to be highly prevalent among cases (p-value: 0.005). As well as other risk factors obesity, raised waist circumference and dyslipidaemia was significantly more prevalent in cases in comparison to controls (p-value < 0.05).

Average hs-CRP values in the hypertensive group (cases) was 2.85 ± 2.4 mg/L (n=66) and in normotensive group (control) was 2.36 ± 2.08 mg/L (n=72). However, 34% of cases and 28% of controls had very high hs-CRP levels 9.10mg/L). Thus cases and controls having hs-CRP values > 9.9mg/L were excluded further in the analysis.

On assessing the average hs-CRP according to various risk categories of CAD. Though not significant a rising trend was noted in hs-CRP values with increase in a risk category. (p-value > 0.05)

Table III depicts the average hs-CRP values in the hypertensive population according to a different group of hypertension whether stage I or Stage II of newly diagnosed or known hypertensive who are either controlled or uncontrolled. However, the hs-CRP values did not differ significantly in all the groups. But the significant difference was found between newly diagnosed stage I & Stage II hypertensives. (p-value < 0.05)

Table IV demonstrates Hs-CRP level categorization as "Low risk", "Moderate risk" and "High risk" of developing CAD. After excluding the hs-CRP values ≥10mg/L (n=34 in cases and n=28 in controls), the number of evaluable hs-CRP in cases, controls came to be 66 & 72 respectively. Therefore, among 34.8% were at low risk while 40.9% were at high risk in cases. In controls, 43.1% were at low risk and 30.6% in the high-risk category. But statistically insignificant when Extended Mantel-Haenszel chi-square for linear trend was applied and p-value > 0.05.

DISCUSSION

Cardiovascular Diseases are the most dreaded complication of hypertension occurs in India at a younger age, as they are more severe and extensive following a malignant course.

The average age of the cases was 48.36 years while that of the control group was 44.12 years. An equal proportion of either sex in the hypertensive population. Similarly, the significantly higher weight and waist circumference in the hypertensive population can be explained. Firstly, obesity and moreover, central adiposity is highly prevalent in Indian population (11-13). Besides, there is a tendency to clustering of cardiovascular risk factors in our population (14-15). Also, since 76% of our cases were known hypertensives and 50% of which were uncontrolled only suggests that these hypertensives were not careful about reducing their risk profile and hence a trend towards central adiposity. This is corroborated by the fact that over one-fifth of the hypertensives consumed tobacco. Obesity, dyslipidaemia, and smoking were the three most common modifiable cardiovascular risk factors noticed in the hypertensive population of our study vis-à-vis healthy controls. This has been also projected by authors in healthy as well as CAD patients and across ages from premature CAD to septuagenarian CAD (16).

Although there is no conclusive evidence to believe that hypertension has elevated Hs-CRP levels, unlike the hard-core evidence that exists for diabetes and coronary artery diseases. However, hypertension is believed to be a continuum of atherosclerosis, a part of the spectrum to which diabetes and coronary artery diseases also belong. In continuum to detect early signs of cardiovascular damage and thus timely initiation of therapy novel markers of inflammation are being searched my medical fraternity. Hs-CRP is one of the novel markers which is being studied. Though recently American Heart Association in its recommendations on hs-CRP. It stated that CRP concentration has continuous associations with the risk of coronary heart disease, ischemic stroke, vascular mortality, and death from several cancers and lung disease that are each of broadly similar size. The relevance of CRP to these range of disorders is unclear. Associations with ischemic vascular disease depend considerably on conventional risk factors and other markers of inflammation (17).

The Sensitivity of the hs-CRP assay- The minimum detectable concentration of CRP ELISA assay as measured by 2 SD of the mean of a zero standard is estimated to be 0.1 mg/L. Additionally, the functional sensitivity was determined to be 0.1 mg/L (as determined by inter-assay %CV <20%). The lower limit of Hs –CRP ELISA 0.1mg/L and upper limit = 10 mg/L.

This study also attempted to study the average Hs-CRP levels in different stages of hypertension viz. Stage I and Stage II. A significant difference was found between newly diagnosed Stage I & Stage II cases of hypertension but no significant difference was delineated between controlled and uncontrolled

hypertension. Another noteworthy finding is a high frequency of hs-CRP values ≥ 10 mg/dL in both the controls (28%) and the cases (34%) despite adopting rigorous inclusion and exclusion criteria in the study.

Average hs-CRP values in cases and controls were comparable implying that hypertensives probably are similar to normotensive as regards the chronic inflammatory process of atherosclerosis is concerned. However, this appears intriguing since high blood pressure has been reported to be associated with elevated C-reactive protein, a marker of chronic mild inflammation (18-19). But Hs-CRP has shown to have higher values in hypertensives in comparison to normotensive (20-22). In Indian context results of raised hs-CRP values in hypertensives have been demonstrated in the Indian Kashmiri population (23).

But at the same time, there was a significant difference between Stage I & Stage II newly diagnosed hypertensives. It may owe due to lifestyle management and drug effect on known hypertensives which this study has not evaluated.

Interestingly, when hypertensive cases were classified into risk categories depending upon the presence of associated cardiovascular risk factors, average hs-CRP values increased with the number of risk factors. Since obesity, smoking and dyslipidemia all can contribute to some extent in elevated hs-CRP levels; it is understandable that the clustering of risk factors in this study is associated with raised hs-CRP levels (24). This is endorsed by a study wherein, microalbuminuria accompanied by elevated hs-CRP strongly correlated with metabolic abnormalities in essential hypertension and identified a patient subset at very high cardiovascular risk (25). Although dyslipidaemia is not known to elevate Hs-CRP levels insulin resistance and the metabolic-syndrome related with elevated Hs-CRP levels. Dyslipidemia is very well a part and parcel of metabolic syndrome. Besides, statins and fibrates are known to reduce Hs-CRP levels partly by improving endothelial dysfunction and stabilizing plaque or by improvement in dyslipidemia also contribute to the reduction of hs-CRP levels (26-27).

When the cases, as well as controls, were classified into different risk categories based solely on the Hs-CRP levels. Of the total 41%, hypertensives came in high risk as against 30% of normotensive.

CONCLUSION

Evaluation of Hs-CRP levels in hypertension did not reveal any significant difference from the normotensive population in our study; nor did hs-CRP values in hypertensives showed an increasing trend with increasing clustering of risk factors. Besides average Hs-CRP levels were higher in newly diagnosed Stage II hypertensives in comparison to Stage I hypertensives.

Limitations

Firstly, it was an unmatched case and control were selected from the Out Patient Department of the tertiary health care center. As it is hospital-based study, it is non-representative of the community. Secondly, the sample was stored for 02 months before analyzing for hs-CRP may have caused inflammatory markers to change their course. Lastly, due to time constraint (had to be carried out in 02 months duration) and funding constraints target of calculated sample size could not be achieved. During the design of the protocol, we failed to make another group of treatment compliance and non-compliant patients.

We premise that occult infections viz. chronic sinusitis, undiagnosed and asymptomatic inflammatory processes, certain health conditions which to date are not known to cause elevation of hs-CRP may be playing a role in this aberrancy. This may also be confounding factor and we propose that a more stringent inclusion of cases be adopted in any further study like this.

ACKNOWLEDGMENT

The authors acknowledge the scholarship by Indian Council Medical Research under Short Term Studentship scheme for carrying out this research.

1. To Management of Era's Lucknow Medical College, Lucknow, UP for providing with the necessary logistics.
2. To Short Term Studentship by ICMR.
3. Dr. Kalpana Baghel, Dr. Ashwini Singh, Dr. Anshu Aggarwal, Dr. Tahseen Azim (MBBS students in year 2005 of ELMC, Lucknow UP.)

To Biochemistry & Medicine Department of Era's Lucknow Medical College, Lucknow, Uttar Pradesh.

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How to cite this article: Dogra E, Prakash A, Nigam A, Kumar S. A, Highly Sensitive C - Reactive Protein In Hypertension, As A Potential Marker Of Cardiovascular Events A Case-control Hospital-based Study. EJMR. 2018; 5(2):109-115.