ORIGINAL ARTICLE

The Role of High-sensitivity C-reactive Protein as a Cardiovascular Risk Marker in Essential Hypertension

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ABSTRACT

Background: Hypertension is a common and independent risk factor of cardiovascular disease, especially the coronary artery disease. The primary or essential hypertension can be classified further, based on the blood pressure measurements, done during initial assessment and diagnosis. The risk of complications does not correlate with the stage of hypertension as per the results of many studies done earlier. Hence, it is imperative to look for some way of assessing the risk of future cardiovascular complications in subjects (overt hypertensives as well as pre-hypertensives) to reduce the morbidity associated. The researchers all around the world are currently studying the role of various inflammatory markers as risk assessment tools in hypertension. High-sensitivity C-reactive protein (hs-CRP) is the most studied of all. This study is done with the aim to assess the cardiovascular risk in subjects diagnosed with essential hypertension, comparing their stage of hypertension and hs-CRP levels.

Materials and Methods: A total of 150 subjects were selected in this study: 50 as controls, 50 as newly diagnosed/untreated patient group, and 50 as treated patient group. The hs-CRP was assayed using standard immunoturbidimetric assay and using a fully automated analyzer, and values compared statistically. There was a significant increase in the hs-CRP levels in the untreated patient group (3.93 ± 1.01) when compared to the control group (1.07 ± 0.39). Furthermore, the comparison between the hs-CRP levels in the untreated patient group versus treated patient group and showed a significant drop in levels of hs-CRP in the treated group (1.26 ± 0.54). Both of these above findings suggest that hs-CRP, which marks the level of subclinical inflammation, could be used to assess the risk of morbid events and also can be used as a tool to assess the response of patients to treatment offered.

Conclusion: Thus, it is concluded that hs-CRP levels are significantly increased in untreated hypertensive subjects and the levels significantly drop the following treatment.

KEY WORDS: Blood pressure, cardiovascular, high-sensitivity C-reactive protein, hypertension, inflammation.

Introduction

Globally, the prevalence of hypertension is rising.[1] At which point of measurement of blood pressure (BP), is the term hypertension used? Most data that are available during this present time indicate that there is no such sharp dividing point.[2] Actually, physicians are compelled to treat people who fall in the pre-hypertension levels of BP measurements.

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Now, is there any guiding tool to help physicians begin the medical management for hypertension, other than the BP measurements alone? The usual risk factor evaluations do not always, accurately identify patients at risk of the atherothrombotic events. About half of all strokes and myocardial infarctions occur in patients with normal cholesterol levels as shown statistically. Hence, lipid profile may not be considered as risk assessment tool independently.

Inflammatory markers, such as interleukin-1 (IL-1) and IL-6, have less clinical utility because the assays, required for their assessment, are either inappropriate for routine clinical use or the protein of interest has too short a half-life for clinical evaluation.[3] The novel cardiac risk assessment tool,

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hs-CRP is gaining more recognition as a biomarker in essential hypertension to predict the degree of vascular pathology.[4] CRP is a pentraxin,[5] which means five berries (Greek word-Penta means five and Ragos mean Berries).

Inflammation after its onset leads to expression of pro-inflammatory cytokines, especially IL-1, which in turn expresses IL-6, which leads to increased expression of CRP gene, thereby the production of CRP is increased.[6] Many studies have said that CRP is not only a marker of inflammation in atherosclerosis but also an actual participant in the disease process. Actually, CRP binds to the phospholipid residues with high affinity and also with a large number of other autologous and extrinsic ligands. Thus, damaged endothelial membrane phospholipids also acts as ligands.

It also activates the complement, sustaining inflammation, and induces the monocytes to produce IL-6 that in turn induces C-reactive protein (CRP) production. Thus, CRP once formed can activate its own synthesis.[7]

It is shown that CRP enhances the expression of local endothelial cell surface adhesion molecules, monocyte chemotactic protein 1, endothelin 1, plasmalogen activator inhibitor-1 and reduces the endothelial nitric oxide (NO) bioactivity and also increases the tissue uptake of modified low-density lipoprotein.

Furthermore, studies say that the increased CRP levels are linked with a decrease in endothelium-dependent relaxation, and this endothelial dysfunction may progress, leading to vessel wall lesions and later on to atherosclerotic plaques.

In this way, CRP has proved to be having a causal role in the pathogenesis of hypertension and it is already a proved risk assessment tool for future stroke and coronary heart disease.[8]

The levels of hs-CRP indicate the risk, i.e., a level of <1 mg/L is low risk, 1-3 mg/L is moderate risk, and >3 mg/L is high risk.[9]

Materials and Methods

This study is a cross-sectional study among subjects attending the hypertension clinic, master health checkups, and Outpatient Department in Government Stanley Hospital. All study participants provided written, informed consent, and the study protocol was reviewed and approved by the institutional ethical committee review board.

Inclusion criteria

Those subjects who were healthy with average BP within normal limit were included as:

- Control Group 1
- Patients with new onset hypertension (untreated) were included as study Group 2
- Patients, who were already taking regular treatment for hypertension, were included as study Group 3 (treated).

Exclusion criteria

1. Smoking
2. Alcoholism
3. Chronic inflammatory conditions
4. Tuberculosis
5. Autoimmune diseases such as rheumatoid arthritis
6. Diabetes mellitus
7. Stroke
8. Hepatic diseases
9. Renal diseases
10. Acute infections/sepsis
11. Recent history of trauma
12. Drug therapies such as lipid lowering agents and probenecid
13. Gout
14. Critically ill patients.

Study participants were included in this study following a detailed self-reported questionnaire and basic preliminary lab tests. The total number of subjects included in the study was 150. Out of this, 50 were new onset hypertensives (untreated patients), 50 were hypertensives on regular treatment (treated), and 50 were normotensive subjects (controls).

The sample size was calculated using the formula given below:[10]

$$n = \frac{2 \times (Z\alpha + Z1 - \beta)^2 \delta^2}{\Delta^2}$$

Where, "n" is sample size, Z is constant, $Z\alpha$ is constant set according to the α error allowed, $Z\,1-\beta$ denotes constant set according to the power of the study, δ denotes the estimated standard deviation (SD), and Δ denotes the estimated effect size.

Our study was set with an allowed error of 0.05, confidence interval 95%, SD 1.01, effect size of 0.5, and so, the minimum sample size as per the formula given above comes around 50.[10]

After getting a written, informed consent from the selected subjects, a thorough general examination was done, and 2 BP recordings were taken ½ h apart. The average of the BP recordings was taken.

The sample from selected subjects was assayed for all the routine blood parameters such as glucose, urea, creatinine, liver function test, lipid profile using the usual kit methods using a fully automated analyzer.

Standard assays for CRP typically have a lower detection limit of 3-8 mg/L. Therefore, these assays lack the sensitivity within the lower-normal range and so cannot be used for atherosclerotic risk prediction. However, there are newer assay systems available in the market which are highly sensitive and can assay even lower levels of CRP. Many such "high-sensitivity (Hs)" or "ultra-sensitive" assays for CRP are now commercially available ("hs" in hs-CRP refers to "high sensitivity" assay).[11] Hs-CRP was also assayed by latex immunoturbidimetric assay (using diazyme assay kit) in the fully automated analyzer(Beckman Coulter AU 400 series).

Results and Statistics

The results, which were got in the present study, are given in the Tables 1-4 along with the relevant statistical correlation.

Table 2 shows that the mean age of the control group (Group 1) is 36.24 ± 5.157, untreated patients (Group 2) is 49.16 ± 7.046, and for the treated patients (Group 3) is 59.62 ± 7.540. The age between groups was tested using Chi-square test, and there is a significant difference between groups inferring age as an independent factor influencing the onset of hypertension.

About 92% of the control group (without any disease-normotensives) are in ages 31-40, whereas only 16% of the untreated (newly diagnosed hypertensives) and 1% of the treated (known hypertensives on regular treatment) are between 31 and 40 years. Most of the untreated newly diagnosed hypertensives are between ages 51 and 60 years. In the case of the treated known hypertensives, the majority are between 51 and 70 years.

Thus, we can understand that the onset and diagnosis of hypertension are usually around 50 years, and the treatment for hypertension has to be continued once started.

It has been said in the literature that there are mild increases of hs-CRP in female subjects as compared to the males, and hence, Chi-square test was performed to compare the sex distribution among various groups. However, no significant difference is noted.

The mean hs-CRP of the control group was 1.0798 ± 0.39625, and it was significantly increased in untreated patients (mean is 3.9322 ± 1.01456).

It is known that the serum hs-CRP value <1 mg/L signifies low risk, 1-3 mg/L intermediate risk, and >3 mg/L high risk of developing atherosclerosis.

Hence, the untreated patients have a high risk for future atherothrombotic events as compared with the control.

Furthermore, the mean hs-CRP levels are low in treated patients as compared with the untreated group signifying the decrease in the inflammatory process following treatment.

Discussion

The 7th report of the Joint National Committee on prevention, detection, evaluation, and treatment of high BP says that the people with systolic BP ≥120 mm Hg or diastolic BP ≥80 mm Hg are at

Table 1: The distribution of age of participants and the hs-CRP levels in each of the three groups

Items	Control				Untreated				Treated			
	N	Min	Max	Mean±SD	*N*	Min	Max	Mean±SD	*N*	Min	Max	Mean±SD
Age	50	31	54	36.24±5.157	50	36	65	49.16±7.046	50	38	79	59.62±7.540
Hs-CRP	50	0.09	2.10	1.0798±0.39625	50	1.20	6.70	3.9322±1.01456	50	0.06	2.40	1.2616±0.54613

Hs-CRP: High-sensitivity C-reactive protein, SD: Standard deviation

Table 2: The Chi-square test employed to test the significance of age distribution

Age (years)	*N*=50 (%)			Significance
	Control	Untreated	Treated	
31-40	46 (92)	8 (16)	1 (2)	χ^2=136.492 df=8 0.000<0.05 Significant
41-50	1 (2)	18 (36)	6 (12)	
51-60	3 (6)	23 (46)	22 (44)	
61-70	0	1 (2)	17 (34)	
71 and above	0	0	4 (8)	

Table 3: The Chi-square test employed to test the gender distribution among the groups

Gender	*N*=50 (%)			Significance
	Control	Untreated	Treated	
Male	34 (68)	26 (52)	26 (52)	χ^2=3.488 df=2 0.175>0.05 Not significant
Female	16 (32)	24 (48)	24 (48)	

Table 4: The "unpaired Student's *t*-test" employed for comparing the different groups

Comparison of hs-CRP between groups	Mean±SD	Statistical inference
Hs-CRP (*N*=50)		
Control	1.0798±0.39625	*t*=−18.518 0.000<0.05 Significant
Untreated	3.9322±1.01456	
Hs-CRP (*N*=50)		
Untreated	3.9322±1.01456	*t*=16.389 0.000<0.05 Significant
Treated	1.2616±0.54613	
Hs-CRP (*N*=50)		
Control	1.0798±0.39625	*t*=−1.905 0.060<0.05 Significant
Treated	1.2616±0.54613	

Hs-CRP: High-sensitivity C-reactive protein, SD: Standard deviation

increased risk of progressing to overt hypertension and need regular follow-ups. However, there is considerable variation in the rate of progression to overt hypertension. Physicians face the challenge of identifying people falling in this category of pre-hypertension who have a high risk of atherothrombotic events and are compelled to start intensive interventions even before the onset of overt hypertension with increase in BP readings.[12]

Of all the available markers, hs-CRP is the one most studied and also standard assays are available in the market at reasonable cost.

CRP, at concentrations known to predict adverse vascular events, by causing a decrease in activity of NO, in turn, inhibits vasodilatation, an important compensatory mechanism in chronic ischemia. Through this decrease in NO biosynthesis, it may lead to many diverse cardiovascular diseases. Risk reduction strategies designed to lower plasma CRP may be effective by improving NO bioavailability.[13]

Many large-scale cohort studies have shown that the levels of hs-CRP are an independent and strong predictor of future risk of myocardial infarction, stroke, peripheral arterial disease, and vascular death among individuals without known cardiovascular disease.[14-22]

In our present study, we have found that there is a significant association of increase levels of hs-CRP and hypertension and the degree of inflammation as attributed by the stage of hypertension and treatment history is also clearly associated with levels of hs-CRP.

Shafi Dar *et al*. have discussed the association between the BP and serum hs-CRP levels in their study conducted, in 2010, in a set of Kashmiri Indians. According to their study, individuals with pre-hypertension are more likely to have significantly increased levels of serum hs-CRP levels as compared to the normotensive control subjects, and they conclude that the difference in the elevation levels of hs-CRP was also found to be duration dependent. Patients with shorter duration of the hypertensive history of <1 year had significantly elevated levels of hs-CRP as compared to patients with longer duration of hypertensive history (5 years).[23]

Similarly, Xu *et al*. have concluded that of a total of 767 hypertensives and 762 non-hypertensives people aged 30 or more who were selected as participants for their study and after the adjustments for the covariate factors, high level of CRP (≥2.54) was significantly associated with hypertension and the odds ratio being 1.337.[24]

With all the above-mentioned studies proving the causal link between hs-CRP and hypertension,

there are still more recent studies, which prove the association of high hs-CRP levels in pre-hypertensive people leading to early onset of morbid cardiovascular events.

One such study was done by Sesso *et al*. which investigated 20,525 women aged 45 or above and followed up for average 7.8 years, and the results of their cohort study show that higher level of CRP was associated with one and half times increased risk of hypertension compared to lower level of CRP, which in turn says that there would be inflammatory pathologic process in development of hypertension and inflammatory reaction might be direct cause of hypertension.[25]

There are also several other studies done in the past few years having the same conclusions, showing a significant positive association of elevated hs-CRP levels, and the increased risk of future athero thrombotic events.[26,27]

Hommels *et al*. in their study have proved that that the hs-CRP levels were significantly raised in the 57 patients with confirmed atherosclerosis of the aorta (4.6 mg/L; $P < 0.005$) as compared to the 26 patients without any angiographic lesions (1.7 mg/L; $P < 0.005$). Moreover, in those with renal artery stenosis, levels of hs-CRP were more when the degree of stenosis was more than 50%.[26]

To conclude, serum hs-CRP levels are significantly elevated in newly diagnosed untreated hypertensive subjects as compared to the normotensive controls and treated hypertensives, putting them into a substantially increased risk of developing future atherothrombotic events, and hence, it is wise to begin treatment strategies in people with high hs-CRP levels even if their BP measurements is not markedly elevated.

Finally, the limitations of our study are:

1. It is a cross-sectional study, and hence, the relationship between the study parameters and hypertension cannot be deemed causal in nature
2. Residual confounding is of concern
3. Single baseline measurement of the parameters was only done
4. Subjects with diabetes mellitus were excluded, but those with latent diabetes were not ruled out.

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