High sensitivity C-reactive protein and dyslipidemia as a marker for the risk for cardiovascular disease

Arun Pandeya (1)
Naveen Kumar Shreevastva (2)
Lal Chandra (3)
Vishwajeet Rohil (4)
Prahlad Karki (5)
Madhab Lamsal (6)

(1) Assistant Professor, Department of Biochemistry, Kathmandu Medical College, Basic Science Complex, Duwakot, Bhaktapur, Nepal.
(2) Assistant Professor, Department of Biochemistry, Faculty of Animal Science, Veterinary Science and Fisheries, Agriculture and Forestry University, Rampur, Chitwan, Nepal.
(3) Professor, Department of Biochemistry, Maulana Azad Medical College, New Delhi, India.
(4) Professor, Department of Clinical Biochemistry, Vallabhbhai Patel Chest Institute, University of Delhi, India.
(5) Professor, Department of Internal Medicine, BP Koirala Institute of Health Sciences, Dharan, Nepal
(6) Professor, Department of Biochemistry, BP Koirala Institute of Health Sciences, Dharan, Nepal.

Corresponding author:
Arun Pandeya,
Assistant Professor of Biochemistry,
Kathmandu Medical College, Basic Science Complex,
Duwakot, Bhaktapur, Nepal.
Email: arnpandey@gmail.com

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Abstract

Background: High sensitivity C-reactive protein (hs-CRP), a sensitive marker of inflammation and tissue damage is an acute phase reactant. It is raised in hypertension and predicts cardiovascular outcome. Moreover elevated levels of inflammatory markers such as hs-CRP and altered lipid profile are commonly seen in hypertension which may develop cardiovascular events, hence, hs-CRP, lipid profile and nitric oxide (NO) have been incorporated in the study. The aims of this study were to find out a relationship of serum hs-CRP and dyslipidemia in hypertensives and to find out an association of serum hs-CRP with the risk for Cardiovascular disease (CVD).

Methods: A case-control study was done among the patients visiting the outpatient department (OPD) of BP Koirala Institute of Health Sciences, Dharan, Nepal in which forty seven newly diagnosed hypertensives as cases and fifty age and sex matched healthy normotensives as controls, were enrolled in the study with the prior informed consent. hs-CRP, nitric oxide (NO) and lipid profile were estimated in both the cases and controls.

Results: Hypertensives have significantly raised levels of hs-CRP, non-high density lipoprotein cholesterol (non-HDL-C) and NO compared to that in controls ($P < 0.05$). hs-CRP has a significant positive correlation with systolic as well as diastolic blood pressure, BMI, and with triglyceride (TG) ($P < 0.05$). However, the correlation of hs-CRP with NO is negative but statistically significant (0.000).

Conclusion: The level of hs-CRP, which is thought to be a marker of inflammation, is significantly raised in hypertensives. Moreover, the majority of hypertensives are dyslipidemic suggesting hypertensives to be at an increased risk for the development of CVD.

Key words: Cardiovascular diseases, dyslipidemia, hs-CRP, hypertension, inflammation.

Introduction

C-reactive protein (CRP), is an acute phase immunity protein which is mostly produced by hepatocytes and is also expressed in a variety of organs including heart, skeletal muscle, neurons, artherosclerotic plaques, monocytes and lymphocytes during inflammation (1, 2). Production of CRP is increased in response to stimulation from interleukin-6 (IL-6) and tumor necrosis factor (TNF), hence CRP is considered a biomarker of systemic inflammation (3). Studies have shown a positive association between hypertension and levels of CRP (4,5). CRP also results in significant reduction in mRNA and protein for endothelial nitric oxide synthase (eNOS) thus resulting in decreased production of NO and hence supporting its role in atherogenesis (6). The level of hs-CRP is associated with cardiovascular disease (CVD) and increased levels of hs-CRP in patients indicate a higher risk of suffering from acute myocardial infarction (7).

Both the elevated levels of CRP (>3mg/L) and increasing categories of blood pressure (BP) are independent determinants of future cardiovascular events (8). Hypertension frequently co-exists with dyslipidemia, known as dyslipidemic hypertension which includes derangement in any component of lipid parameters, either increased total cholesterol (TC) or low density lipoprotein cholesterol (LDL-C) or triglycerides (TG) or decreased high density lipoprotein cholesterol (HDL-C) (9). In dyslipidemic hypertension, the risk of CVD is more multiplicative than the sum of the individual risk factors (10). Hypertension is associated with upregulation of lipid oxidizing enzymes (11). In the meantime, when plasma cholesterol, especially LDL-C is high, it becomes trapped in an artery, that can undergo progressive oxidation forming oxidized LDL (ox-LDL) (12). Since, ox-LDL has phosphocholine epitopes, because of which uptake of oxidized LDL is promoted by CRP, this induces atherogenesis (13).

Very limited studies on hs-CRP in hypertension and its association with the risk of cardiovascular disease have been conducted in our setting. In this study, serum levels of hs-CRP were estimated by high sensitive ELISA method with the objective to find out the relationship of serum hs-CRP, BP and dyslipidemia among the subjects of Eastern Nepal and also to establish an association of serum hs-CRP with the risk for CVD.

Material and Methods

Study design

This was a cross-sectional, case-control study encompassing the patients visiting the outpatient department (OPD) of BP Koirala Institute of Health Sciences, Dharan Nepal, in which forty seven newly diagnosed hypertensives as cases and fifty age and sex matched healthy normotensives as controls, with their prior informed consent, were enrolled. Hypertension was clinically diagnosed according to the JNC 7 criteria (14). This study was approved by Institutional Ethical Review Board (IERB) of BP Koirala Institute of Health Sciences, Dharan, Nepal.

Participants

Newly diagnosed hypertensive patients were included in the study, however patients with chronic inflammatory diseases like rheumatoid arthritis (RA), osteoarthritis (OA), autoimmune diseases, tuberculosis and any previous history of diabetes or stroke were excluded from the study. The age and sex matched healthy individuals without any history of hypertension, diabetes mellitus and chronic inflammatory diseases were enrolled as controls.

Data collections and outcomes

Blood pressure (BP) was recorded, height and weight was measured and body mass index (BMI) was calculated in both the cases and controls. Fasting blood sample was withdrawn and serum was separated on which lipid parameters were estimated by enzymatic methods on spectro-photometer. Non-high density lipoprotein cholesterol (Non-HDL-C) was calculated by subtracting HDL-C from TC. Serum Nitrite was estimated by Griess Reaction Method where sulphanilic acid is converted to diazonium salt by nitrite which on coupling with N-napthylethylene diamine forms an azo dye that was quantitated spectrophotometrically at 545 nm (15).

The hs-CRP in the serum samples was estimated by using a high sensitivity ELISA method (CALBIOTECH INC, High sensitivity CRP Elisa) based on the principle of a solid phase enzyme linked immunosorbent assay. The assay system utilizes the mouse monoclonal anti-CRP antibody on microtiter well. A goat anti-CRP antibody was in the antibody enzyme conjugated solution. During reaction the CRP molecule is sandwiched between the solid phase and enzyme linked antibodies. Finally the color intensity was measured spectrophotometrically at 450 nm.

Data were analyzed using SPSS for Windows version 15. The group association was determined by Chi-square test, correlation was tested by Pearson correlation coefficient and P value of less than 0.05 ($P<0.05$) was considered to be significant.

Results

A total of 97 subjects were recruited for the study purpose of which 47 were newly diagnosed hypertensives as cases and the rest were age and sex matched healthy normotensives as controls. The mean values of the various parameters in cases and controls are shown in Table 1. Since, hypertensives were enrolled as cases and normotensives as controls, there was a significant rise in systolic blood pressure (SBP) as well as diastolic blood pressure (DBP) in hypertensives. Similarly, BMI and the levels of hs-CRP, TC, LDL-C and non-HDL-C were significantly increased in cases compared to controls ($P < 0.05$). However, the rise in TG and decrease in HDL-C and NO were statistically not significant in cases compared to that in controls as shown in Table 1.

According to the grades of BMI, 34.0% and 8.5% of the individuals among cases were overweight and obese respectively, although, the majority of the individuals (51.1%) had normal weight. Similarly, among the controls, a huge number of individuals, (76%) had normal weight, 20% were overweight and none was found to be obese which is shown in Table 2.

According to the levels of hs-CRP (considering hs-CRP ≥ 1 mg/L as risk group population), 72.3% of the cases and only 44.0% of the controls were categorized as risk group) which is statistically significant. Similarly, according to the lipid levels, the majority of the individuals of the cases, 59.6% are LDL-C dyslipidemic, followed by 55.3% as TG dyslipidemic and were categorized as a risk group. However, a very few number of controls, 20% were LDL-C dyslipidemic and 32% were TG dyslipidemic, categorized as a risk group for CVD and was statistically significant (P< 0.05) which is shown in Table 3.

Furthermore, hs-CRP as well as non-HDL-C had a positive correlation with SBP, DBP, BMI and TG and was statistically significant (P< 0.05). However, both the hs-CRP and non-HDL-C were negatively correlated with NO and was statistically significant (P< 0.05) as shown in Table 4.

Table 1. Comparison of different parameters between cases and controls
(Student's t test) [p<0.05 is significant]

Parameters	Cases (n=47) Mean±SD	Controls (n=50) Mean±SD	P value
SBP	155.34±18.17	114.00±6.38	0.000
DBP	102.51±9.38	78.50±4.31	0.000
BMI	24.60±3.72	22.55±2.59	0.040
hs-CRP	3.21±3.03	1.35±1.27	0.000
TC	178.27±37.14	146.28±26.31	0.021
HDL-C	41.53±4.05	42.16±3.23	0.150
Triglyceride	159.80±83.15	138.14±76.97	0.838
LDL-C	108.46±38.33	82.42±20.41	0.005
Non-HDL-C	136.74±35.58	104.12±26.02	0.034
Nitric oxide	21.08±7.97	29.88±10.48	0.230

Table 2. Distribution of cases and controls according to different grades of BMI

Different grades of BMI	Cases n=47 (%)	Controls n=50 (%)
Underweight	3 (6.4)	2 (4)
Normal weight	24 (51.1)	38 (76)
Overweight	16 (34)	10 (20)
Obese	4 (8.5)	0 (0)

Table 3. Risk group according to Lipid parameters and hs-CRP [Chi-square test]

Parameters	Group	Case n=47 (%)	Control n=50 (%)	X^2	P value
hs-CRP	Risk	34 (72.3)	22 (44.0)	7.97	0.005
	Non-risk	13 (27.7)	28 (56.0)		
TC	Risk	13 (27.7)	2 (4.0)	10.37	0.001
	Non-risk	34 (72.3)	48 (96.0)		
HDL-C	Risk	16 (34.0)	8 (16.0)	4.23	0.040
	Non-risk	31 (66.0)	42 (84.0)		
Triglyceride	Risk	26 (55.3)	16 (32.0)	5.36	0.021
	Non-risk	21 (44.7)	34 (68.0)		
LDL-C	Risk	28 (59.6)	10 (20.0)	15.92	0.000
	Non-risk	19 (40.4)	40 (80.0)		

Table 4. Correlation of hs-CRP and non-HDL-C with other variables in the total study population [Pearson's correlation] [p< 0.05 is significant]

Variables	hs-CRP r (P)	non-HDL-C r (P)
SBP	0. 289 (0.004)	0.529 (0.000)
DBP	0.376 (0.000)	0.469 (0.000)
BMI	0.471 (0.000)	0.251 (0.013)
TC	0.134 (0.192)	0.995 (0.000)
HDL-C	-0.131 (0.201)	0.152 (0.136)
TG	0.238 (0.019)	0.345 (0.001)
LDL-C	0.103 (0.316)	0.757 (0.000)
Nitric oxide	-0.481 (0.000)	-0.316 (0.002)
hs-CRP	----------	0.150 (0.142)

Discussion

This study intended to evaluate the relationship of high BP with dyslipidemia, NO and the markers of inflammation such as hs-CRP in hypertension. In the present study, statistically significantly raised levels of hs-CRP and BMI as well as an altered lipid profile were found in cases compared to that in controls. A study conducted in Thailand showed statistically raised levels of hs-CRP and BMI as well as deranged lipid profile even in prehypertensives when compared to normotensives (16). The present study has demonstrated significantly raised levels of hs-CRP in cases compared to that in controls (3.21±3.03 vs 1.35±1.27; P <0 .001) which is supported by the study of Cottone S et. al (2.37±0.57 vs 1.6±0.4, P < 0.001) and Shafi Dar M et. al. (3.26±1.37 vs 1.36±0.26, P < 0.001) (17). Similarly, a recent study conducted in Brazil also revealed significantly raised levels of hs-CRP (0.53 ± 0.44 vs 0.38 ± 0.21, P= 0.0118) and BMI (29.99 ± 1.41vs 25.75 ± 3.87 0.0435, P< 0.05) in hypertensives (18). HTN is an inflammatory condition during which the production of an acute phase reactant, the CRP, is increased causing its raised levels in circulation. Even more, CRP damages the endothelial cells, progresses the thickening of vascular intima resulting in peripheral resistance that decreases the speed of blood flow, induces vascular sclerosis and increases the BP (19) and hence, in these days, hs-CRP is believed to be an independent risk factor for hypertension (20).

The American Heart Association and Centre for Disease Control and prevention have recommended CRP as a risk marker for CVD, with CRP levels <1mg/L as a low risk, 1-3 mg/L as an average risk and >3 mg/L as a high risk for CVD (21). A study by Tofano et al. showed a total of 64% of the hypertensives (13.33% as moderate risk and 50.67% as high risk) as the risk population for the CVD in terms of serum levels of hs-CRP (18). Consistent with this, our study has found some higher number of the hypertensives, 72.3% as a risk group population, however, among normotensives, 44% are the risk group population for CVD which is statistically significant (p< 0.05). Showing a high numbers of control group to be an at risk group population in this study may predict the development of hypertension in future even if these people are normotensives now.

Results of the present study indicate a positive correlation of SBP, DBP and BMI with hs-CRP (p= 0.05). Shafi et al. also reported a graded association between BP and hs-CRP elevation in people with hypertension (17). Similarly, a study conducted among T2DM patients in India, showed a significant positive correlation of serum hsCRP with SBP (p < 0.001) and DBP (p < 0.001) in the hypertensives (22). Both HTN and Diabetes mellitus are inflammatory conditions thus showing the raised levels of inflammatory markers such as hs-CRP.

This study found reduced levels of NO in hypertensives. There may be the role of hs-CRP itself for the decreased levels of NO in hypertensives as they have significantly raised levels of hs-CRP which results in inflammation causing endothelial dysfunction and decreases the production of NO by endothelial cells (23). CRP also plays a role in lowering the levels of NO, by significantly reducing mRNA and protein for eNOS (6). NO is an endogenous vasodilator, therefore, decreased production of NO leads to vasoconstriction, arterial stiffness and increased peripheral resistance which finally results in high BP.

The present study showed significantly high BMI in hypertensives compared to that of controls (24.60±3.72 vs 22.55±2.59; p < 0.05). Besides, among the hypertensives 34 % and 8.5% of the individuals were overweight and obese respectively whereas among controls 20% of the individuals were overweight but none were obese. A study by Tofano et al. also found significantly raised BMI in hypertensives compared to that in controls (18). Similarly, a study by Ghomari et al. also established an association between BMI and markers of inflammation, such as CRP and dyslipidemia (24). In the individuals having high BMI, there may be the deposition of fatty tissues which increase the vascular resistance resulting in high BP. In addition, an increase in BMI leads to increased inflammation, insulin resistance, and catecholamine levels inducing other hormonal changes resulting in significant changes in gene expression and increased BP(25).

In the present study, hypertensives being dyslipidemic with statistically significantly high levels of TC, LDL-C and non-HDL-C, were found to be at increased risk for the development of CVD. However, our study found statistically insignificant rise in TG and decrease in HDL-C as well as NO in cases compared to that in controls. Some studies have suggested the co-existence of hypertension and dyslipidemia. According to Dutro et al. 49.7% of the hypertensive patients were dyslipidemic, (26) and in such populations the risk for CVD was more multiplicative than the sum of the individual risk factors (10, 11). Consistent with our findings, a study conducted by Sudjaroen, et al. in Thailand showed existence of dyslipidemia even in prehypertensives (16). A possible elucidation for these relationships is that hypertension and dyslipidemia share common pathophysiological etiologies, such as obesity and the resulting dysregulation of adipocytokine release from adipose tissue (27). Furthermore, dyslipidemia adversely affects functional and structural arterial properties which may impair BP regulation, which, in turn, predisposes individuals with dyslipidemia to the development of hypertension (28). In the present study, lipid parameters, except HDL-C, were positively correlated with hs-CRP. Correlation of NO with hs-CRP was negative and statistically significant (p= 0.000). A similar type of study conducted in Mongolia, also revealed a significant association of hs-CRP with the components of dyslipidemia (29). In general, individuals with dyslipidemia are in a pro-inflammatory state, characterized by elevated levels of inflammatory molecules such as hs-CRP and Interleukin-6 (Il-6). Besides, hypertensives have an ongoing inflammation in the artery and upregulation of lipid oxidizing enzymes which produces ox-LDL, the retention of which in sub-endothelium initiates early atherosclerosis (11, 30).

Therefore, hypertension, dyslipidemia and endothelial functioning are inter-related. The derangement of lipid parameters and significantly raised hs-CRP levels among hypertensives suggest inflammation in the body which indicates development of cardiovascular events in them. Moreover, hypertensives had higher BMI which was associated with markers of inflammation and dyslipidemia. So, early monitoring of markers of cardiovascular disease such as hs-CRP and lipid profile may lead to better quality of life and life expectancy. So, early estimation of markers of inflammation and identification of the patient at risk may prevent CVD events in the patients suffering from hypertension.

Conclusion

CRP, is an acute phase protein, the production of which is induced in response to inflammatory conditions, such as in hypertension which may result in the progression of cardiovascular diseases. Hypertensives have high BMI which is associated with markers of inflammation and dyslipidemia. So, early monitoring of markers of cardiovascular disease such as hs-CRP and lipid profile may lead to better quality of life and life expectancy.

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