International Journal of Biotechnology and Biochemistry
ISSN 0973-2691 Volume 13, Number 4 (2017) pp. 413-421

http://www.ripublication.com

Study of HS-CRP, Insulin Resistance and Dyslipidemia as Predictive Markers in Pre-Hpertension"

Dr. Srikrishna R.[1] , Dr. Akshatha L.N.[2]*, Dr. Virupaksha L.[3] and Dr Vinay Kumar K.[4]

[1]Professor, Department of Biochemistry,
[2]Assistant Professor, Department of Biochemistry,
[3]Associate Professor, Department of Medicine,
[4]Associate Professor, Department of Dentistry,
Shridevi Institute of Medical sciences and Research Hospital,Tumkur, Karnataka
*(*Corresponding Author)*

Abstract:

Background: Pre-hypertension is defined as systolic blood pressure of 120 to 139 mm of Hg and diastolic pressure of 80 to 89 mm of Hg. Pre-hypertension is highly prevalent among the population in the developing countries including India. Pre-hypertension can progress to overt hypertension and is considered as an important risk factor for cardiovascular diseases and cerebrovascular diseases. C-reactive protein (CRP), a marker of inflammation predicts coronary heart disease incidence in healthy subjects and has been associated with decreased endothelium-dependent relaxation, a potential risk factor for hypertension. Elevated hs-CRP levels, increased insulin resistance and dyslipedemia have been reported as predictive markers in pre-hypertension and hypertension in several studies.

Aim: The aim of the present study was to evaluate the hs-CRP levels, insulin resistance and lipid profile in Pre-hypertension patients in comparison with normotensive controls.

Materials and Methods: 62 Pre-hypertensive subjects and 61 age and sex matched normotensive controls were included in the study as per the guidelines of Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of blood pressure (JNC 7). Hs-CRP, insulin levels, homeostasis of minimal assessment of insulin resistance (HOMA-IR) and lipid profile were analyzed in both pre-hypertensive group

and normotensive controls. Statistical analyses were carried out by using independent't' test between the groups and Pearson correlation analyses were carried out between various parameters with systolic blood pressure(SBP) and diastolic blood pressure(DBP).

Results: hs-CRP levels, insulin resistance by HOMA-IR, total cholesterol, triacyl glycerol and LDL-cholesterol levels were significantly higher (p□0.05) in pre-hypertensive group compared to normotensive control group. HDL-cholesterol levels were significantly lower (p□0.05) in pre-hypertensive group than the normotensive control group.

Conclusion: The present study concludes that the established cardiovascular risk factors such as hs-CRP, Insulin resistance and dyslipidemia, which have roles in the etiopathogenesis of hypertension were elevated in pre-hypertensive subjects in comparison with normotensive controls. Thus the early detection of these modifiable risk factors could help the population at risk delay or prevent the onset of overt hypertension and other cardiovascular and cerebrovascular complications.

Key words: Pre-hypertension, hs-CRP, insulin resistance, hyperlipidemia.

INTRODUCTION

Prehypertension is defined as a systolic blood pressure of 120–139 mmHg and/or a diastolic blood pressure of 80–89 mmHg. The concept of prehypertension 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[1]. Prehypertension is a precursor of clinical hypertension and is closely related with the increased incidence of cardiovascular disease[2-4]. Patients with Prehypertension (120–139/80–89 mmHg) have an increased risk of cardiovascular morbidity and mortality compared with patients who have normal blood pressure (<120/80 mmHg).

Prehypertension remains an important public health challenge all over the world. The overall prevalence of prehypertension was 31% all over the world and in India it was found to be in the range of 35-45% as reported by many studies[3,5]. Pre-hypertension is often associated with traditional cardiovascular risk factors like obesity, insulin resistance and dyslipidemia.

C-reactive protein is a marker of systemic inflammation that has been associated with an increased risk of myocardial infarction and stroke. It is normally present as a trace constituent. Hs-CRP measures the CRP values as low as 0.3mg/L and therefore it has been used commonly as a marker of inflammation. The Centers for Disease Control and Prevention/American Heart Association (CDC/AHA) statement suggested that

when CRP < 1 mg/L, there is low cardiovascular risk; when it is 1-3 mg/L, intermediate (average) cardiovascular risk; when it is >3 mg/L, high cardiovascular risk; and when >10 mg/L, the infected part or the acute coronary syndrome should be detected. Insulin resistance is a well-established entity in several cardiovascular disorders including hypertension. Recent reports have indicated the existence of insulin resistance in prehypertension. Dyslipidemia is a common risk factor found in prehypertension and hypertension. Even though many studies from across the world have reported association between hs-CRP, insulin resistance and dyslipidemia in pre-hypertension, only few studies have been done on this subject in India. Therefore we designed this case control study to know the association of hs-CRP, insulin resistance and dyslipidemia in pre-hypertension.

MATERIALS AND METHODS:

This case control study was conducted at Shridevi Institute of Medical Sciences and Research Hospital, Tumkur during the period of January to November 2016. The study group included 62 subjects with pre-hypertension and 60 normotensive age and sex matched controls. The prehypertensive subjects and normotensive controls were selected from the persons attending the outpatient department of Medicine as per the recommendations of the Joint National Committee 7 report. Patients with history of diabetes, renal disease, endocrine dysfunction, coronary heart disease, infections, chronic smoking, alcohol intake, and those who are on any kind of medications were excluded from the study. Subjects with BMI□30 were also excluded from the study.

Informed consent was taken from each subject and the study was approved by the ethical committee of the Institute.

Measurement of BP : Blood pressure was measured using sphygmomanometer (Diamond, India) with subjects in sitting position, leg uncrossed and after five minutes of rest. Blood pressure was measured on both arms and higher of the two was taken into consideration. Blood pressure was measured three times after a rest interval of five minutes in between the measurements. The average of three values was used for study**.** The body mass index (BMI) of each subject was measured by using the formula BMI = weight (kg)/height^2 (m^2).

6 ml of venous blood was drawn under aseptic conditions from each subject in the fasting state. Serum was separated by centrifuging the sample at 5000 rpm for 6-8 minutes and the serum was analyzed for the following parameters.

Fasting blood glucose by Glucose oxidase (GOD) method, lipid profile by standard enzymatic methods and hs-CRP by immunoturbidimetric method was measured in ERBA Chem 7 semiautoanalyzer using ERBA reagents. Fasting insulin was measured by electrochemiluminescence method in Roche's COBAS e 411 fully automated

analyzer. Insulin resistance, in the form of Homeostasis of minimal assessment of insulin resistance (HOMA-IR) was calculated using the Mathew's formula HOMA-IR = Fasting glucose (mmol/L) x Fasting insulin (μU/mL) / 22.5 [2].

Statistical Analysis: The Parameters were expressed as mean values i.e. mean±SD and analyzed by one-way ANOVA test using SPSS software version 16 with p value 0.05 as significant. Pearson correlation was used to correlation of systolic and diastolic blood pressure with hs-CRP, HOMA-IR and other parameters.

RESULTS:

The general demographic characteristic features of controls and Pre-hypertensive cases are shown in table- 1. The study included 61 healthy controls and 62 pre-hypertensive subjects. Of the 61 controls, 30 were males and 31 were females and their mean age was 34.91±8.01 years. Of the 62 pre-hypertensive cases, 36 were males and 26 were females and their mean age was 35.06±7.87 years. The mean value of BMI in Normotensive controls and Pre-hypertensive cases was 22.58±2.69 and 24.39±2.90 respectively.

Table: 1 General characteristic of Controls and Pre-Hypertension Subjects

Parameter	**Normotensive Controls n= 61**	**Pre-Hypertension Cases n=62**
Age (Yrs)	**34.91±8.01**	**35.06±7.87**
Sex	**Males=30 Females=31**	**Males=36 Females=26**
BMI (Kg/m^2)	**22.58±2.69**	**24.39±2.90**

The table-2 shows the comparison of mean values of fasting blood glucose (FBS), Fasting Insulin, Systolic and Diastolic blood pressure between controls and Pre-hypertension cases.

Table: 2 Comparison of mean values of FBS, Fasting Insulin Systolic and Diastolic blood pressure between controls and Pre-hypertension cases

Parameter	**Normotensive Controls n= 61**	**Pre-Hypertension Cases n=62**	**P value (<0.05=Significant)**
FBS (mg/dl)	**89.98±12.16**	**91.53±9.36**	**0.430 (Not significant)**
Fasting Insulin (μU/mL)	**9.87±1.18**	**15.29±1.76**	**0.000**
S. BP(mmHg)	**114.23±4.44**	**131.82±4.39**	**0.000**
D. BP(mmHg)	**74.85±4.12**	**85.85±2.32**	**0.000**

The mean values of fasting insulin levels, Systolic blood pressure (S.BP) and Diastolic blood pressure(D.BP) were significantly higher (p=0.00) in pre-hypertensive cases when compared to Normotensive controls . However there was no statistical significance (p= 0.430) in fasting blood glucose levels (FBS) between the groups.

The comparison of mean values of Hs-CRP, Insulin Resistance (HOMA-IR) and Lipid Profile between Controls and Pre-Hypertension Subjects is shown in Table no 3.

Table 3: Comparison of mean values of Hs-CRP, Insulin Resistance (HOMA-IR) and Lipid Profile between Controls and Pre-Hypertension Subjects

Parameter	**Normotensive Controls**	**Pre-Hypertension Cases**	**P Value (<0.05= Significant)**
Hs-CRP (mg/l)	**1.25±0.36**	**4.77±1.02**	**0.000**
HOMA-IR	**2.19±0.43**	**3.45±0.61**	**0.000**
TC (mg/dl)	**178.16±13.78**	**207.44±17.53**	**0.000**
HDLC (mg/dl)	**43.68±6.27**	**37.42±4.87**	**0.000**
LDLC (mg/dl)	**100.66±13.78**	**133.84±16.78**	**0.000**
VLDL (mg/dl)	**33.80±3.56**	**36.00±4.06**	**0.002**
TAG (mg/dl)	**169.03±17.84**	**180.08±20.09**	**0.001**

The mean values of hs-CRP, Insulin Resistance (HOMA-IR), Total Cholesterol(TC), LDL-cholesterol(LDL-C), VLDL Cholesterol(VLDL-C) and Triacyl Glycerol (TAG) were significantly (P<0.05) higher in pre-hypertensive subjects when compared to Normotensive healthy controls. The mean values of HDL Cholesterol (HDL-C) were significantly lower in pre-hypertensive controls in comparison to Normotensive controls and was statistically significant (P<0.05).

There was a positive correlation (Pearson Correlation) between systolic blood pressure and diastolic blood pressure with hs-CRP levels and HOMA-IR.

DISCUSSION:

Prehypertension is the new term introduced by JNC-7 refers to the Systolic blood pressure in the range of 120-139 mm Hg and diastolic blood pressure in the range of 80-89 mm Hg.Several studies have demonstrated that the presence of predictive risk factors like Insulin resistance, Dyslipidemia and Inflammation and its influence on the

clinical occurrence of cardiovascular disease in subjects with elevated blood pressure[6-9]

In our prospective case –control study, the hs-CRP levels were significantly (p□0.05) elevated in Pre-hypertensive subjects compared to Normotensive controls. There was also a positive association between hs-CRP with that of Systolic and Diastolic blood pressure. C-reactive protein, an acute phase protein and marker of low grade systemic inflammation predicts cardiovascular mortality and morbidity in patients with pre-existing CVD and in apparently healthy subjects[10]. Hs-CRP which is the measurable form of CRP in very minimum concentrations has been postulated to be elevated prior to the elevation of blood pressure[10].

The elevated hs-CRP levels in Prehypertension cases than in normotensive controls as shown in our study is in agreement with several other studies which reported similar results such as Talikoti P et.al[11],Shafi Dar M et.al[12] and so on.

The C-reactive protein (CRP) is a marker of systemic inflammation that has been associated with an increased risk of incident myocardial infarction and stroke[13-15]. The probable cause for increased hs-CRP levels in Prehypertension is that inflammation is an important factor in the development of hypertension, and cross-sectional evidence demonstrates higher C-reactive protein levels among those individuals with elevated blood pressure (BP). Higher levels of C-reactive protein may increase BP by reducing nitric oxide production in endothelial cells, resulting in vasoconstriction and increased production of endothelin1.C-reactive protein may also function as a proatherosclerotic factor by up-regulating angiotensin type 1 receptor expression[16-17].

In our study the serum total Cholesterol, LDL-Cholesterol, VLDL-Cholesterol and Triacylglycerol levels were significantly higher in Prehypertension subjects than in Normotensive controls. HDL-Cholesterol levels were significantly lower in Prehypertension cases when compared to normotensive controls. This type of dyslipidemia has also been reported by several studies which further substantiate our findings[18-20].

Increased Total Cholesterol (hypercholesterolemia), increased LDL-C levels and decreased HDL-C levels are known risk factors for development of atherosclerosis and subsequent cardiovascular diseases. Hence our findings suggest that dyslipidemia is found in prehypertensive subjects and therefore they are at higher risk of developing coronary artery diseases than the normotensive subjects. By screening the patients of Prehypertension with lipid parameters we could reduce the risk of developing hypertension and cardiovascular diseases[20].

Insulin resistance in our study was measured as HOMA-IR(Homeostasis of minimal assessment of insulin resistance) and was found to be significantly higher in Prehypertensive subjects than in Normotensive controls. Similar results have been reported by many studies[21,22].

In our study, Body mass index (BMI), a measure of obesity was significantly higher in prehypertensive subjects when compared to normotensive controls. This shows that Prehypertension is more prevalent in people who are overweight. Studies have shown that insulin resistance is commonly associated with obesity and its severity is directly proportional to the value of body mass index[21]. Moreover, triad of hypertriglyceridemia, obesity and Low HDL-C levels are considered to be surrogate markers of insulin resistance[21].

CONCLUSION:

The present study concludes that the established cardiovascular risk factors such as hs-CRP, Insulin resistance and dyslipidemia, which have roles in the etiopathogenesis of hypertension were elevated in pre-hypertensive subjects in comparison with normotensive controls. Thus the early detection of these modifiable risk factors could help the population at risk delay or prevent the onset of overt hypertension and other cardiovascular and cerebrovascular complications.

LIMITATIONS OF THE STUDY:

The main limitation of our study is the selection of a small group of subjects which may not reflect the Prehypertension profile of large populations.

The other limitation of our study is that, we have not followed up the prehypertensive subjects, whether they developed overt Hypertension and or cardiovascular manifestations in the subsequent period.

Conflicts of interest: None

References:

[1] A. V. Chobanian, G. L. Bakris, H. R. Black et al., "Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure," *Hypertension*, 2003; 42(6) 1206–1252.

[2] Mathews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetolgia*. 1985;28(7):412–19.

[3] Chaudhry K, Diwan S K et al. (2012). Prehypertension in young females, where do they stand?, *Indian Heart Journal*, vol 6403(2012), 280–283.

[4] Wenwen Zhang and Ninghua Li, "Prevalence, Risk Factors, and Management of Prehypertension,"*International Journal of Hypertension*, vol. 2011, 6

pages, 2011.

[5] M. Lanord Stanley J , D. Elantamilan ,T. S. Kumaravel Prevalence of Prehypertension and its Correlation with Indian Diabetic Risk Score in Rural Population, *Indian Journal of Science and Technology*,vol 6(8)august 2013 5163-66.

[6] Sundström J, Sullivan L, D'Agostino RB, Jacques PF, Selhub J, Rosenberg IH, et al. Plasma homocysteine, hypertension incidence, and blood pressure tracking: the Framingham Heart Study.*Hypertension*. 2003;42(6):1100–05.

[7] Chrysohoou C, Pitsavos C, Panagiotakos DB, Skoumas J, Stefanadis C. Association between prehypertension status and inflammatory markers related to atherosclerotic disease: The ATTICA Study. *Am J Hypertens*. 2004;17(7):568–73.

[8] Sesso HD, Buring JE, Rifai N, Blake GJ, Gaziano JM, Ridker PM. C-reactive protein and the risk of developing hypertension. *JAMA.* 2003;290(22):2945–51.

[9] King, D. E., Egan, B. M., Mainous, A. G. and Geesey, M. E. (2004), Elevation of C-Reactive Protein in People With Prehypertension. *The Journal of Clinical Hypertension*, 6: 562–568.

[10] Danesh J, Wheeler JG, Hirschfield GM, Eda S, Eiriksdottir G, Rumley A, et al. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. *N Engl JMed*.2004;350:1387–97.

[11] Talikoti P, Bobby Z, Hamide A. Hyperhomocysteinemia, Insulin Resistance and High HS- CRP Levels in Prehypertension. *Journal of Clinical and Diagnostic Research□: JCDR*. 2014;8(8):CC07-CC09.

[12] Shafi Dar M, Pandith AA, Sameer AS, Sultan M, Yousuf A, Mudassar S. hs-CRP: A potential marker for hypertension in Kashmiri population. *Indian Journal of Clinical Biochemistry*. 2010;25(2):208-212.

[13] Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med.*1997;336:973-979.

[14] Koenig W, Sund M, Frohlich M.et al.C-reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from theMonitoring Trends and Determinants in Cardiovascular Disease, Augsburg Cohort Study, 1984 to1992.*Circulation.*1999;99:237-242.

[15] Tracy RP, Lemaitre RN, Psaty BM. et al. Relationship of C-reactive protein to risk of cardiovascular disease in the elderly: results from the Cardiovascular

Health Study and the Rural Health Promotion Project. *Arterioscler Thromb Vasc Biol.*1997;17:1121-1127.

[16] Yamada S, Gotoh T, Nakashima Y. et al. Distribution of serum C-reactive protein and its association with atherosclerotic risk factors in a Japanese population: Jichi Medical School Cohort Study. *Am J Epidemiol.*2001;153:1183-1190.

[17] Bautista LE, Lopez-Jaramillo P, Vera LM. et al. Is C-reactive protein an independent risk factor for essential hypertension? *J Hypertens.*2001;19:857-861.

[18] Bharath T, Manjula P. Lipid profile but not highly sensitive C-reactive protein helps distinguish prehypertensives from normal subjects. *Journal of Natural Science, Biology, and Medicine*. 2015;6(2):347-350.

[19] Hitesh A. Jani1, Priti C. Bhanderi , Chandankumar Sharma ,Maulik Padalia. Comparative study of serum lipid profile between prehypertensive and normotensive. *Int J Res Med Sci.* 2014 Nov;2(4):1648-1651.

[20] Bharath T, Manjula P. Lipid profile but not highly sensitive C-reactive protein helps distinguish prehypertensives from normal subjects. *Journal of Natural Science, Biology, and Medicine*. 2015;6(2):347-350.

[21] Ryuichi Kawamoto, Katsuhiko Kohara, Yasuharu Tabara, Masanori Abe, Tomo Kusunoki and Tetsuro Miki. "Insulin resistance and prevalence of prehypertension and hypertension among community-dwelling persons." *Journal of atherosclerosis and thrombosis* 17 2 (2010): 148-55.

[22] Player MS, Mainous AG , Diaz VA, Everett CJ. "Prehypertension and insulin resistance in a nationally representative adult population". *J Clin Hypertens*. 2007 Jun;9(6):424-9.