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Inflammatory markers and cardiovascular risk factors in prehypertensive subjects – a hospital based study from Lucknow, Uttar Pradesh, India

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Abstract

Background

Hypertension is likely the most common disease in the world and has been recognized as a major risk factor for several cardiovascular diseases (CVD). Prehypertension refers to borderline blood pressure levels, between 120 and 139 mmHg systolic or 80 and 89 mmHg diastolic. Increased risk of CVD among prehypertensive subjects has been variably documented in literature.

Methods

A number of total 60 patients were divided into three groups; hypertension, prehypertension and normotensives, twenty in each. BMI, B.P, Lipid Profile, IL-6 and TNF α, carotid intima media thickness were measured. Statistical Package for the Social Sciences (SPPS) for Windows Version 16.0 (SPSS Inc.; Chicago, IL, USA), was used to analyze the results.

Results

BMI was maximum amongst the prehypertensives, along with increased level of cholesterol, Triglyceride and VLDL. Mean levels of IL-6 and TNF- α were significantly higher in prehypertensives than normotensives. A significant correlation was also found between BMI(r=0.237) and SBP (r = 0.241), While TNF- α was significantly associated with IL-6 (r = 0.639) and DBP (r = 0.255).

Conclusion

An association was found between the prehypertension status and inflammatory markers in cardiovascular disease. Prehypertension might be a proinflammatory condition. Early detection may help to take necessary interventions.

Keywords

Cardiovascular disease, blood pressure, inflammatory cytokines, inflammatory markers, prehypertension

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Background

Hypertension is likely the most common disease in the world and has been recognized as a major risk factor for several cardiovascular diseases (CVD) [1]. Prehypertension refers to borderline blood pressure levels, between 120 and 139 mmHg systolic or 80 and 89 mmHg diastolic [2]. Increased risk of CVD among prehypertensive subjects has been variably documented in literature with some studies strongly supporting it [3,4]. This clinical condition modestly increases the risk of CVD when it is associated with some other additional risk factors [5].Chronic low grade inflammation in hypertension is integral to the development and progression of atherosclerotic process. Apart from the deleterious effects on heart, hypertension is considered as a premier risk factor for several other diseases affecting brain, and kidneys[6].Prevalence of hypertension depends on genetic background, environmental factors, and level of economic development[1].

According to a report of WHO, in the year 2008, worldwide overall prevalence of raised blood pressure among adults (age≥25 years) was around 40%. Factors like population growth and ageing is an added risk for this deadly situation, for which uncontrolled hypertension rose from 600 million in1980 to nearly 1 billion in 2008 [7].Developing countries are the most vulnerable in this context and hypertension is one of the leading causes of death and disability[8].Hypertension is considered as the fourth contributor to premature death in developed countries and the seventh in developing countries [9].

Several studies in Southeast Asia show that prevalence of hypertension in Bangladesh: 17.9%, Nepal: 33.8%, Pakistan: 33% (above the age of 45) [10-12]. In Sri Lanka it was found that nearly one-third of the adult population is hypertensive [13]. Gupta reported that 57% of all stroke deaths and 24% of all coronary heart disease (CHD) deaths in India is due to hypertension [14]. By the year 2025, rates for HTN may overshoot 22.9% for Indian men and 23.6% women. Prevalence in urban areas is more comparing rural areas, 25% and 10% respectively [14-17]**.** According to the WHO 2008 estimates, the prevalence of raised BP in Indians was 32.5% (33.2% in men and 31.7% in women) [18]. Although higher prevalence rate, fortunately, due to availability of a wide variety of pharmacological and herbal treatment choices for lowering blood pressure, has reduced the disease burden [6,19].

A number of diagnostic tests like lipid Profile, Interleukin-6 (IL-6) and Tumor necrosis factor-alpha (TNF-α), Carotid Intima Media Thickness (CIMT) became extremely popular. Advanced vascular disease in the peripheral and coronary circulation can be identified by measuring the Intima-media thickness of carotid arteries is well established. It is also helpful to observe the response to therapy [20].A number of peer reviewed biomedical literatures documented that among the hypertensive subjects carotid intima media thickness increased as compared with normotensive subjects [21, 22].Another marker for the hypertension is TNF-alpha, which plays a major role on salt appetite and blood pressure, a contributory factor to cardiac hypertrophy. TNF-α is a multifunctional cytokine plays a key factor in different pathophysiological processes, like inflammation, survival of cell, growth, cellular differentiation, and apoptosis [23].As inflammation is a key factor for the progression of hypertension and other CVS disorders, so the interaction between TNF-α and other factor like Angiotensin II (Ang II) plays an important role in the modulation of hypertensive response.

Although several cross-sectional works has been done in hypertensive patients, however the association between prehypertensive state inflammation and cardiovascular risk factors requires more insight. The purpose of this study was to investigate whether a relationship exists between the prehypertension status in subjects free of cardiovascular disease and the inflammatory markers that can be directly linked to the atherosclerotic process.

Material and Methods

Study Period

This study was conducted between 16.11.2012 to 15.11.2013.

Study design, participants and the collection of data

Known hypertensive attending outdoor of Medicine Department of Era's Lucknow Medical College and Hospital, Lucknow, were recruited. A number of total 60 patients were divided into three groups; hypertension, prehypertension and normotension, twenty in each.

Gp I: Normotensive,
Gp II: Prehypertensive subjects (BP 121-139 / 81-89)
Gp III: Known Hypertensives

Data collection

Study was carried out in the Department of Biochemistry, in collaboration with Department of Medicine and Department of Radiology of Era's Lucknow Medical College, Lucknow, Uttar Pradesh, India. Detailed history of patients attending for outdoor treatment in Medicine department and also of normal healthy subjects were recorded on the "Proforma". Both males and females between 30-70 years of age were included in this study.Unique study identification number was used in this study to maintain the confidentiality and to avoid biasness.

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Measurement of Body mass index (BMI)
Health Scale was used to measure weight and height. Body mass index (BMI) was determined by dividing weight (wt) in kilograms by height (height) in meters square (BMI = kg/m2).

Measurement of blood pressure (B.P)
Blood pressure was measured, after at least 5 minutes of rest, with subjects in seating posture. A mercury sphygmomanometer with an appropriate sized cuff covering two third of the upper arm, was used. The onset of the first tapping sound was considered for the indication of the systolic blood pressure, whereas the point of complete disappearance of the sound (Korotkoff V) was considered to indicate diastolic blood pressure. The mean of three readings were recorded. Hypertensive was defined as a systolic BP>140mm Hg and or a diastolic BP > 90mm Hg or current treatment with antihypertensive medication.

Selection of subjects
Blood pressure levels more then 145-150 / 90-95mmHg (when measured on at least two occasions) were considered as adult hypertensives. Participants who had mean systolic/diastolic BPs within the range of 121 to 139mm Hg /81 to 89mm Hg and never told that they had high BP levels were defined as prehypertensives, as it has recently been suggested by the American Heart Association [2].The remainders of the participant were defined as normotensives.

Blood Collection
Blood samples were collected by venipuncture in the morning after a 12hr overnight fast, in Ethylenediaminetetraacetic acid, (EDTA) coated vials. This was centrifuged at 3000rpm for 10minutes at 4^{o}C within 2hr of blood collection. The plasma was aspirated out and used for further estimations.

Estimation of lipid profile
Total Cholesterol (TC), triglycerides (TG) and high-density lipoprotein (HDL) were measured in plasma by colorimetric methods using commercially available biomedical kits for human subjects (TransasiaBiomedicals Ltd., Germany).Low-density lipoprotein (LDL) and very low-densitylipoprotein (VLDL) was calculated according to Frieldwald formula.VLDL-cholesterol = Plasma TG/5, LDL-cholesterol = Plasma TC-(HDL chol + VLDL chol). All the values are in mg/dl plasma.

Estimation of IL-6 and TNF α
Stored plasma samples were tested for levels of IL-6 and TNF- α. High sensitivity Enzyme linked immune sorbant assay (ELISA) were conducted for these parameters in duplicate using the BIORAD analyzer and kits (GEN-PROBE, Diaclone, France).

Assessment of CIMT
To measure carotid intima media thickness, ultrasonography of the common carotid artery, carotid bifurcation, and internal carotid artery (left and right) was performed with a 11-MHz linear-array transducer (LOGIQ 5-GE). On a longitudinal, two-dimensional ultrasound image of the carotid artery, the anterior (near) and posterior (far) walls of the carotid artery are displayed as two bright white lines separated by a hypoechogenic space. The distance between the leading edge of the first bright line of the far wall and the leading edge of the second bright line indicates the intima–media thickness.

Inclusion criteria
All subjects visited Department of Medicine (normotensives, prehypertensives and hypertensives) willing to participate voluntarily were enrolled for this research work.

Exclusion criteria
Few patients were excluded for the following reasons like history of diabetes mellitus, chronic renal, liver and others endocrine diseases. Subjects under steroidal and non-steroidal anti-inflammatory therapies, hormonal substitutive or contraceptive therapy, thyroid dysfunctions, drugs or alcohol abuse, smoking and mental disability, psychiatric illnesses and other critical illnesses were excluded. People who refused to complete the questionnaire with sociodemographic and other details were also excluded. Electrocardiographic evidence of heart block, ischemia, or prior coronary events were also excluded.

Ethical committee approval
Standard format “Informed consent form” were filled up by the patients/parents or guardian. The study protocol and informed consent were approved by the Institutional Ethics Committee of Era’s Lucknow Medical College and Hospital. Study, was conducted according to the guidelines for human experimentation established by the Declaration of Helsinki.

Outcome variable
BMI, SBP, DBP, lipid profile, CIMT, IL-6, TNF- α were considered as outcome variable.

Explanatory variables
The demographic factors age, gender were set as explanatory variables.

Sample size calculation
In a pilot study with 5 patients showed CIMT(R)Standard deviation in group I [Pre hypertension] = 0.05, CIMT(R) Standard deviation in group [Normotensive] II = 0.04, Mean difference = 0.07, Effect size = 1.56, with Alpha Error(%) = 5, Power(%)= 80, sided = 2. Required sample size per group was7[24, 25].

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Data management and statistical analysis

Differences in the means and prevalence of study variables between the groups were compared using Student's 't' test. Regression analysis was used to test significant determinants of prehypertension status. Data were expressed as the mean ± SD. Statistical analyses were performed using software Statistical Package for the Social Sciences – SPSS (Licensed Version 16).Statistical significance was indicated by $p < 0.05$.

Results

Table - 1shows that as the age progressesboth the systolic and diastolic blood pressure increased. BMI was maximum amongst the prehypertensives, followed by hypertensive and normotensive individuals.

Pre and post values of Cholesterol, Triglyceride, HDL Cholesterol, LDL Cholesterol and VLDL Cholesterol as well as inflammatory markers likeIL-6 and TNF-α of three different study groups were compared. Prehypertensive subjects showed increased level of cholesterol, Triglyceride and VLDL cholesterol as compared to normotensive and hypertensives by 19.25% and 5.01%, 49.67% and 17.84%, 48.92% and 17.1% respectively. Mean levels of IL-6 and TNF- α were significantly higher in prehypertensives than normotensives (Table - 2).

In regression analysis, body mass index, blood pressure, CIMT were the independent risk factors. Plasma levels of IL-6 were strongly associated with CIMT [right (r=0.362) and CIMT left (r = 0.334)], and with TNF- α (r =0.639).

A significant correlation was also found between BMI(r=0.237) and SBP (r = 0.241), While TNF- α was significantly associated with IL-6 (r = 0.639) and DBP (r = 0.255) (Table – 3).

The metabolic parameters like cholesterol was significantly associated with BMI (r = 0.234), SBP (r = 0.286), DBP (r = 0.274), triglyceride (r = 0.532), HDL-cholesterol (r =0.503), LDL-cholesterol (r = 0.928), and VLDL- cholesterol (r = 0.541). Likewise LDL- cholesterol was also significantly associated with BMI (r =0.238), SBP (r = 0.283) and DBP (r = 0.272). No correlation was found between triglyceride and BMI, SBP and DBP. Same pattern was observed with HDL cholesterol, while VLDL was associated only with DBP (r = 0.230).

Table – 3Association between different variables and inflammatory markers (regression analysis)

Variables	IL-6	TNF- α
BMI	0.237[x]	---
SBP	0.241[x]	---
DBP	-	0.255[†]
CIMT (R)	-0.362[†]	---
CIMT (L)	-0.334[†]	---
IL-6	---	0.639[†]
TNF-α	0.639[†]	---

[x]P>0.05 statistically not significant
[†]P<0.01 statistically significant

Table – 1 Blood pressure and BMI in hypertension status (Mean±SD)

Variable	Normotension	Prehypertension	Hypertension	Total(n=60)	P value
Age (years)	39.75±11.58	42.89±12.40	47.57±12.18	36.82±15.81	0.001[†]
Systolic BP	116.0±5.0	137.74±5.00	162.86±16.45	139.28±22.13	0.001[†]
Diastolic BP	74.50±5.10	89.21±2.57	101.24±8.02	88.52±12.51	0.001[†]
BMI,(Kg/m^2)	21.67±2.58	26.05±4.23	23.09±5.24	23.56±4.50	0.006[†]

[†]P<0.01 statistically significant

Table – 2 CIMT and metabolic parameters in study group (Mean±SD)

Variable	Normotension	Prehypertension	Hypertension	Total (n=60)	p value
CIMT (R)	0.62±0.04	0.69±0.05	0.69±0.06	0.66±0.06	0.001[†]
CIMT (L)	0.66±0.05	0.69±0.03	0.73±0.07	0.69±0.06	0.001[†]
Cholesterol (mg/dl)	163.35±19.11	194.80±54.21	185.50±34.91	181.22±40.42	0.045[x]
LDL cholesterol (mg/dl)	93.70±16.54	110.87±44.71	111.14±30.87	105.24±33.27	0.073[x]
HDL cholesterol (mg/dl)	44.82±8.40	44.12±6.35	42.60±6.80	43.85±7.18	0.723[x]
Triglycerides (mg/dl)	123.10±23.96	184.25±62.05	156.35±57.41	154.57±55.87	0.004[†]
VLDL cholesterol (mg/dl)	24.59±4.79	36.62±12.58	31.27±11.48	30.83±11.20	0.005[†]
IL-6 (pg/ml)	6.4±1.4	9.8±7.7	5.3±6.6	5.2±6.9	0.001[†]
TNF- α (pg/ml)	1.8±8.4	2.9±1.4	2.5±2.5	2.3±1.7	0.202[x]

[x]P>0.05 statistically not significant
[†]P<0.01 statistically significant

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Discussion

Ample evidences suggest the global prevalence of hypertension affects the morphology of cardiovascular system and related disorders. Early detection may save lives of millions worldwide. Prehypertension was initially categorized in 2003 by Joint National Commitee-7 in order to classify those at high risk of the future development of hypertension [26]. The syndrome was recognized as a major health concern that was growing in frequency, however only lifestyle modifications such as weight loss and exercise were recommended as treatment [27]. The prevalence of prehypertension, at ~30%, is greater than that of hypertension and such subjects already had an intermediate risk of cardiovascular disease and mortality compared with normotensives and hypertensives [28]. Hypertension, hypercholesterolemia, hyperinsulinemia, and diabetes mellitus have been recognized to stimulate the secretion of leukocyte soluble adhesion molecules and hemostatic factors, encouraging the atherosclerotic process [29].They have also been related to increased plasma concentration of inflammatory markers [30,31].

Cardiovascular risk factors in hypertension status

Previous reports showed that progression of age is a crucial factor for hypertension, which reflects in the blood pressure of the subjects. In the present study, when we selected the samples same pattern was observed in our study population. Maximum blood pressure (both the systolic and diastolic) was observed in the hypertensives in accordance with other studies in the Southeast Asia region [32]. BMI was maximum amongst the prehypertensives, followed by hypertensive and normotensive individuals.

CIMT and Metabolic Parameters in study Group

The present study demonstrates that lipid profile was elevated in prehypertensive subjects when compared to normotensive controls. This is constraint with previous research [33].Carotid intima media thickness (R and L) was more in our study among the prehypertensives and hypertensives, when compared with normotensives. Earlier works supports these findings [20-22]. This may be due to the fact that high blood pressure is the major contributory factor for the initiation and pathologic progression of carotid wall hypertrophy. Hemodynamic factors - such as local distending pressure, pulsatile load, and shear stress are responsible for intrinsic changes in the wall of artery which results in intimal/medial thickening [34-36].

Changes in inflammatory markers

In our study, prehypertensive subjects showed a higher level of IL-6, which has been independently associated with CHD mortality, inflammatory markers and metabolic syndrome [37,38]. Our results supports many earlier epidemiologic studies correlated the higher level of inflammatory markers - IL-6 [32], IL-1β and TNF-α - to the elevated blood pressure level or hypertensive status [39- 41].So our study confirms a clear association between hypertension and inflammatory markers. This supports previous human experimentation by Chamarthi*et al.* amongst hypertensives and normotensives [42]. So this result suggests that the IL-6 marker could be a novel therapeutic target for the management of this devastating disorder [43].

There are several studies to date that have looked into the potential association between increasing TNF- α and hypertension. Few reported a positive association with TNF-α and hypertension [44,45], while some reporting negative results [46]. In the present research, a clear association was observed between the status of hypertension and TNF- α. A study by Chrysohoou*et al* demonstrated an association between elevated TNF- α levels and prehypertension [47]. This increased level is a contributory factor to both the maintenance of a chronic low-grade inflammatory state in obese patients, associated with comorbid conditions like hypertension [48]. These changes have provided an ample scope for the potential targets which include inflammatory cytokines, like TNF-α and IL-6 to measure and identify or monitor the ongoing inflammatory process.

Conclusion

In conclusion, an association was found between the prehypertension status and inflammatory markers in cardiovascular disease. Our findings are clinically important as this suggests that prehypertension might be a proinflammatory condition. Early detection may help to take necessary interventions. More insight is required to confirm this hypothesis of a direct relationship prehypertension condition and the inflammatory process.

Limitations and future scope of the study

The present study involves a small population so it limits the ability to establish causal relationships but the underlying mechanisms remain to be established. Subjects in our research had mild to moderate hypertension. So more understanding is required in case of severe hypertensives. Our subjects were under age 60.Since prehypertension seems to mainly affect middle aged and young adults, included in our study. Subjects from this age group and not elderly individual, where in even age related vascular changes contribute to hypertension.

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Abbreviations

Angeotensin II (Ang II), Body mass index (BMI), cardiovascular diseases (CVD), Carotid Intima Media Thickness (CIMT), coronary heart disease (CHD), Enzyme linked immune sorbant assay (ELISA), Ethylenediaminetetraacetic acid, (EDTA), high-density lipoprotein (HDL), Interleukin-6 (IL-6), Low-density lipoprotein (LDL), Total Cholesterol (TC), triglycerides (TG), Tumor necrosis factor-alpha (TNF-α), very low-density lipoprotein (VLDL), World Health Organization (WHO).

Competing interests

The authors declare that there is no conflict of interest.

Authors' contribution

Dr. Anu Chandra and Dr. Pradyumn Singh designed the study, constructed the questionnaire, performed the experiment, interpreted the data, drafted the manuscript, and revised it. Dr. Tasleem Raza and Dr. Farzana Mahdi conducted the research formulated and analyzed the data. All authors took part in critical revision and finally approved the manuscript.

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