

Original Article

Relation of interleukin-17 and high-sensitivity C-reactive proteins with sympathetic reactivity in pre-hypertensive young adult

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ABSTRACT

Objectives: Recent studies have shown that both innate and adaptive immunity response contributes to vascular dysfunction by vascular remodelling and later hypertension. Furthermore, the sympathetic activity mediates the vascular dysfunction through pro-inflammatory activity of immune system. In context to insidious onset hypertension, the study was planned to observe the association of immunity with the increased sympathetic activity in pre-hypertensive adults.

Materials and Methods: Thirty healthy pre-hypertensive (as per JNC VII) non-smokers, non-alcoholic and non-obese male adults volunteers were recruited from the study area. Equal numbers of normotensive controls were taken for comparison. On reporting day, they were subjected to the recording of demographic and anthropometric measurements, hand grip dynamometry and later investigated for serum levels of interleukin-17 (IL-17) and high-sensitivity C-reactive proteins (hsCRP) after written informed consent. The data collected were analysed for differences in mean and association of immune and inflammatory markers with sympathetic activity by statistical tests.

Results: Significantly higher values of weight, BMI, % BF, visceral fat, resting heart rate and IL-17 and a lower sympathetic reactivity was observed in pre-hypertensive subjects. Values of hsCRP was higher in prehypertensive but was not statistically significant. IL-17 was a positive significant predictor with 4.7 times ($P = 0.02$) increase in odds of being pre-hypertensive, whereas sympathetic reactivity was a significant negative predictor ($OR = 0.75$; $P = 0.001$). SBP and DBP are both related negatively and significantly ($P < 0.05$) to the sympathetic reactivity suggesting that blood pressure is related to sympathetic nervous system. Furthermore, the hsCRP is observed to be related positively to the % BF and to only SBP and RHR, complimenting link of adiposity as an inflammatory process to blood pressure. IL-17 levels in blood are observed to be positively and significantly related to DBP.

Conclusion: Elevated IL-17 levels are significant predictor of pre-hypertension along with lower sympathetic reactivity. No direct association was observed between IL-17 and sympathetic system except with raised DBP. Immune mechanism is part of pathogenesis of increased blood pressure in pre-hypertensive with enhanced baseline sympathetic activity.

Keywords: Pre-hypertensive, Interleukin-17, high-sensitivity C-reactive proteins, Sympathetic reactivity

INTRODUCTION

Pathophysiology of hypertension involves the infiltration of the vascular adventitia and perivascular adipose tissue by inflammatory immune cells. Recent studies have shown that

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both innate and adaptive immunity response contributes to vascular dysfunction by vascular remodelling and later hypertension.^[1,2]

Early animal studies have observed the infiltration of T lymphocytes in kidney of hypertensive animals and their low number or absence is associated with lower blood pressure.^[3] Further evidence showed that although there is almost always presence of T lymphocytes in hypertensive animals, their absence is not associated with vascular dysfunctions. Furthermore, adaptive transfer of T cells and not B cells restored the hypertensive response and vascular abnormalities in these animals.^[4] Since polarisation of T cells is dependent on the activation of macrophages and dendritic cells which are the parts of innate immune system, it may be linked to immune and inflammatory disorders.

Autoimmune and inflammatory disorders development have been linked to the subset of T helper cells that secrete the interleukins 17, (for their actions), levels of which found to be raised in (being) several of the autoimmune and inflammatory disorders such as rheumatoid arthritis, psoriasis multiple sclerosis and inflammatory bowel disease.^[5] Recent evidence also suggests the involvement of interleukin-17 (IL-17) in cardiovascular diseases including coronary atherosclerosis and hypertension when compared to those with BP <120/80 mmHg.^[6]

Sympathetic overactivity can activate adaptive immune cells through β 2-adrenergic receptors (ARs) that are expressed especially on T cells^[7] and cytokines released from activated immune cells serve as messengers to the brain, to provide immune system functional information that is utilised by the sympathetic nervous system (SNS) to coordinate all the systems required for an appropriate immune response.^[8] Pre-clinical studies provide evidence indicating that the production of cytokines, including interleukin-17, contributes to high blood pressure, likely through the effects on both the kidney and vasculature. IL17 peripherally causes a pro-inflammatory milieu in smooth muscle upregulating several genes of inflammation^[2] to induce phosphorylation of the endothelial NO synthase impairing the endothelium- dependent vasodilatation.^[9]

Since IL-17 plays a critical role in hypertension and has been found raised in pre-hypertension,^[7,10] it was hypothesised that along with other factors, IL-17 might contribute to the vascular inflammation in pre-hypertension. Furthermore, the cardiovascular damage caused by excessive stimulation of the SNS and their receptors (α - and β -adrenergic receptors) is mediated through a pro-inflammatory activation of the immune system.^[11]

With multiple studies^[12,13] having demonstrated an increased sympathetic activity in pre-hypertensive subjects the study was proposed to investigate serum levels of IL-17 in pre-hypertensive and to evaluate the relationship of IL-17 with

inflammatory and sympathetic activity in pre-hypertension in young adult population.

MATERIALS AND METHODS

This observational analytical study was conducted in the Department of Physiology, Himalayan Institute of Medical Sciences, Swami Ram Nagar, Dehradun, over a period of 12 months. The study subjects were recruited from a representative group of residents, employees and students of Swami Ram Himalayan University, Dehradun, to complete the sample size for each group.

A sample size of 26 in each group was obtained using the sampling size formula for the differences of means for serum IL-17 between normotensive and pre-hypertensive^[10] of 1.9 at 80% of power and an α error of 0.05 with population variance of 6. To improve the strength of the study and considering dropouts of participants of 10%, a sample size of 30 in each group was reached.

Inclusion criteria for pre-hypertensive group ($n=30$) were apparently healthy subjects with the blood pressure – systolic 120–139 mmHg and/or a diastolic 80–89 mmHg and for normotensive group ($n = 30$) were apparently healthy subjects with blood pressure systolic < 120 mmHg and diastolic < 80 mmHg as per the JNC VII criteria.^[11,14]

Exclusion criteria were common for normotensive and pre-hypertensive groups and consisted of history of any chronic disease such as DM and hypertension, history of smoking/ alcohol consumption/active infection and those with BMI ≥ 30 kg/m².

The recruited subjects were asked to report to the department of physiology in the morning hours after a good night's rest and following a light breakfast. Volunteers were asked to avoid caffeine and any kind of physical exercise in the past 24 h. They were subjected to the following investigation after written informed consent.

Medical history

- Relevant medical history (based on exclusion criteria) was taken, including history of present illness, past illness, personal history, drug history, family history and history of allergic reactions
- Clinical examination was done to rule out active and chronic infection.

Baseline characteristics

- Demographic indices and basal physiologic parameters were recorded that included name, age, gender, address, occupation, basal systolic and diastolic blood pressure and resting heart rate (RHR).

Obesity indices measurement

- Body weight, percentage body fat, BMI and visceral fat were measured using an impedance body composition analyser. The instrument works on a patented foot to foot pressure contact electrode bioelectrical impedance analysis technique. The subjects after emptying bladder were asked to stand barefoot and with minimal clothing on the foot pad of the instrument. They were told to stand there till the reading was displayed on the panel
- Sympathetic reactivity by sustained hand grip (SHG) method.

Baseline BP and HR were recorded in sitting position. The subject was asked to hold the dynamometer in the non-dominant hand, with the arm by the side of the body, with the pointer on the dial adjusted at zero and the base rested on the palm. Before the test, maximum voluntary contraction (MVC) was recorded. The subject was instructed to squeeze the dynamometer with maximum isometric effort for at least 5 s and the result was recorded, no other body movement was allowed. After this, the subject was asked to press hand grip dynamometer at 30% of MVC for 3 min.^[15] The alteration in the BP and HR just before the release of hand grip was taken as the index of response to hand grip test. The relative consistency of the hemodynamic changes which occur during the isometric handgrip exercise test indicates that it is a simple and a reliable method for studying the cardiovascular response to stress.^[16]

Immunological and inflammatory markers

Blood sampling for serum IL17 and high-sensitivity C-reactive proteins (hsCRP) was done under basal conditions and after taking aseptic precautions. The samples were collected from cubital vein in a plain yellow top Vacutainer for the estimation of IL17 and hsCRP estimation at NABL certified immunology laboratory of hospital. The freshly collected samples were centrifuged for 15 min and serum stored at -80°C until further analysis. Serum samples were thawed and quantitative measurements of IL17 and

hsCRP will be performed by immunoassay method using a commercially procured kit.

RESULTS

The study was conducted on 30 pre-hypertensive volunteers with equal number of controls. Descriptive analysis of baseline parameters of demographic, anthropometry and cardiovascular parameters observed that the two groups were homogenous with age, height and weight. Indices of obesity including BMI, % body fat (%BF) and five of visceral fat (VF) were significantly different between the two groups with pre-hypertensive having a higher value for the variables than normotensive. Significantly higher values of RHR were also observed in pre-hypertensive group. As would be expected, the groups were different for the mean arterial pressure (MAP) with pre-hypertensive subjects having a higher MAP as compared to normotensive [Table 1].

On analysis of sympathetic reactivity and blood inflammatory markers, it was observed that IL-17 was higher in pre-hypertensive in comparison to normotensive and the difference was significant. Sympathetic reactivity assessed by change in DBP following isometric exercise was significantly lower in pre-hypertensive than in normotensive [Table 2].

Binary logistic regression analysis was applied to determine the independent role played by significantly different independent variables with pre-hypertensive. Model for prediction of being pre-hypertensive was statistically significant and could explain only 83.6% variability of the odds of prehypertension. It was observed that IL-17 value is positive and significant ($b = 1.56$; $P = 0.02$; $\text{OR} = 4.79$) predictor of probability of odds of pre-hypertensive with the OR indicating that for every one unit increases on this predictor the odds of pre-hypertensive change by a factor of 4.7 (the odds are increasing) with higher value of IL-17 more likely in pre-hypertensive than in normotensive. Sympathetic reactivity is negative and significant ($b = -0.28$; $P = 0.001$; $\text{OR} = 0.75$ [CI 0.63–0.89]) predictor of probability of odds of pre-hypertensive and decreasing value is more likely to

Table 1: Demographic, anthropometric, cardiovascular variable (parameters) and inflammatory markers among normotensive and pre-hypertensive.

Parameters	Normotensive (n=30)	Pre-hypertensive (n=30)	P-value
Age (years)	30.39±7.1	31.07±7.2	0.714
Height (cm)	169.70±6.96	169.58±4.97	0.935
Weight (kg)	68.0±11.5	72.6±9.51	0.097
BMI (kg/m ²)	23.49±3.25	25.21±2.36	0.022
%BF	21.2±6.50	23.91±3.2	0.049
VF%	7.59±3.9	9.60±3.0	0.029
RHR (beats/min)	68.16±5.5	74.37±8.9	0.002
MAP (mmHg)	85.72±4.5	97.96±4.2	0.001

VF: Visceral fat, WC: Waist circumference, RHR: Resting heart rate, MAP: Mean arterial pressure

Table 2: Sympathetic reactivity (change in DBP) and inflammatory markers among normotensive and pre-hypertensive.

Parameters	Normotensive (n=33)	Pre-hypertensive (n=33)	P-value
Change in DBP (mmHg)	27±10.9	15.5±11.5	0.001
*hsCRP (ng/ml)	876.93 (451.5–2270.9)	2189.8 (551.48–3481)	0.051
*IL-17 (pg/ml)	2.96 (0.2–4.5)	3.67 (2.1–5.7)	0.039

*Mann-Whitney U-test used for values in median (min-max)

be pre-hypertensive than normotensive and the difference is statistically significant ($P = 0.020$) [Table 3].

[Table 4] shows correlation of significantly different risk factors and inflammatory markers with SBP and DBP ($n=60$).

SBP is positively but insignificantly related with obesity indices (BMI, %BF and VF) and hsCRP in normotensive but obesity markers are positively % significantly related with hsCRP as well as with sympathetic reactivity [Figure 1]. SBP although was significantly and positively related to obesity markers (BMI, %BF and VF) and hsCRP in pre-hypertensive [Figure 2].

DISCUSSION

Inflammation of the vasculature, with an infiltration of immune cells, is a known and important pathological mechanism in the development of cardiovascular diseases, especially hypertension.^[17] Recently, evidences also indicate that chronic low-grade inflammation is an important contributing factor in the development of pre-hypertension.^[18,19] Along significant contribution from the immune system, an increase in SNS activity is also known to contribute in pathophysiology of pre-hypertension. Our study examined the levels of inflammatory (hs-CRP) and immune markers (IL-17) and investigated their association with the activity of SNS in pre-hypertensive young adults.

A total of 30 pre-hypertensive subjects from 20 to 40 years of age and equal number of age- and height- matched normotensive were investigated. Obesity indices BMI, % BF and %VF were found to be significantly higher in pre-hypertensive subjects but were in non-obese levels and correlated well with the previous studies.^[20,21] RHR was significantly increased in pre-hypertensive subjects in our study which can be attributed to higher basal sympathetic tone. High sympathetic drive is one of the major factors in the development of high blood pressure^[22] as evidenced by higher RHR in our study population. Evidence suggests that elevated blood pressure is initiated and maintained by increased sympathetic tone, generated by rostral ventrolateral medulla, which is influenced by cortical and hypothalamic impulses, blood-borne gases and chemicals including cytokines.^[23] Contrary to our finding, study on African young pre-hypertensive adults observed a lower RHR than normotensive though not significant and in females.^[24]

Table 3: Binary logistic regression of significant anthropometric and inflammatory predictors to pre-hypertension model predicting 83.6% probability of odds of prehypertension.

	β	P-value	Odds ratio (CI)
BMI	0.284	0.673	1.329 (0.39–4.9)
% body fat	0.087	0.610	1.090 (0.78–1.52)
VF %	-0.287	0.475	0.751 (0.34–1.6)
Sympathetic reactivity	-0.281	0.001	0.755 (0.63–0.89)
IL-17 (pg/dl)	1.568	0.020	4.799 (1.2–17.6)

Change in DBP during SHG test^[25] was used to assess the impaired sympathetic response. Significant difference in values of change in DBP was observed between normotensive and pre-hypertensive groups with the pre-hypertensive showing a lesser increase in the diastolic blood pressure following SHG test, which signifies increase in basal sympathetic tone and elevated basal DBP in pre-hypertensive subjects.^[21,26] Both lesser rise in DBP, following SHG test^[25] and raised RHR indicated (toward) an imbalance in sympathetic response in pre-hypertensive subjects.^[27]

It has been postulated that the pressure response to the isometric exercise is reflex in origin, which serves to increase the perfusion pressure to the active muscles, in which the blood flow is impeded by the sustained muscular contraction.^[28] This may be the reason for the increase in the peripheral resistance and, consequently, that in the diastolic pressure in our study. Significantly increased vascular resistance in pre-hypertensive young adults was also observed by Bond *et al.* in female African pre-hypertensive adults. Contrary to our finding, larger change in DBP of 40 mmHg versus 6 mmHg was observed in six pre-hypertensive females following SHG test $P < 0.001$ in comparison to normotensive.^[24]

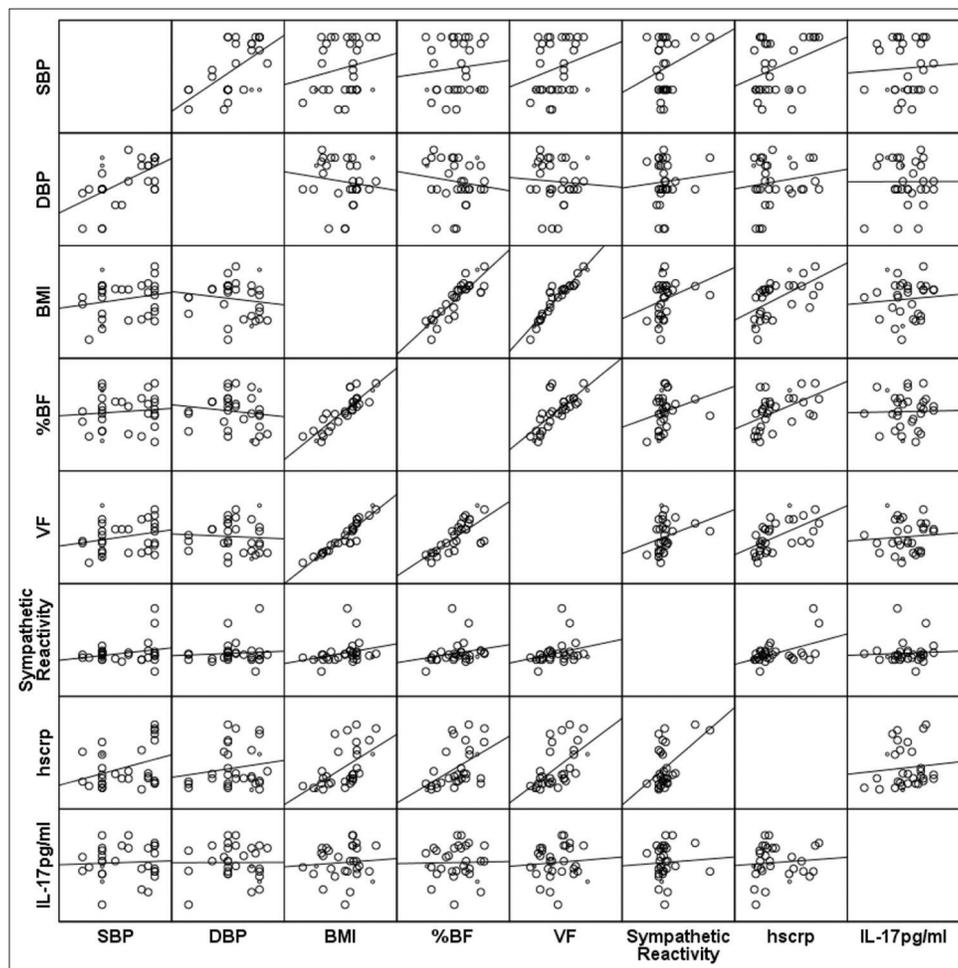
The present study, observed higher mean value of inflammatory marker hs-CRP though insignificant and a significantly higher immune marker IL-17 levels in pre-hypertensive as compared to normotensive, [$P < 0.05$ Table 2]. Corroborating to our finding study done by Wei Yao *et al.*^[10] also observed a significant increase in the values of immune marker IL-17 in pre-hypertensive in the age group of >40–70 years comparison to normotensive subjects and also observed a significant higher levels of hsCRP in them. This suggests that immune dysfunction and vascular inflammation may already exist in pre-hypertensive

Table 4: Correlation of blood pressure with anthropometric, sympathetic reactivity and inflammatory markers.

	SBP	DBP	RHR	MAP	BMI	%BF	VF	Sympathetic reactivity	hsCRP ng/ml	IL-17 pg/ml
SBP (mmHg)	1	0.717**	0.394**	0.886**	0.317*	0.265*	0.324*	-0.331**	0.340**	0.175
DBP (mmHg)		1	0.306*	0.958**	0.148	0.071	0.190	-0.428**	0.045	0.267*
RHR			1	0.365**	0.134	0.163	0.106	-0.107	0.265*	0.034
MAP				1	0.228	0.156	0.260*	-0.420**	0.169	0.249
BMI (Kg/m ²)					1	0.791**	0.936**	0.094	0.250	0.171
%BF						1	0.700**	.0032	0.385**	0.096
VF							1	0.066	0.384**	0.113
Sympathetic reactivity								1	0.101	-0.071
hsCRP (ng/ml)									1	-0.038
IL-17 (pg/ml)										1

SBP and DBP are both related negatively and significantly ($P < 0.05$) to the sympathetic reactivity suggesting that blood pressure is related to SNS.

Furthermore, the hsCRP is observed to be related positively to the % BF ($P = 0.001$), VF ($P = 0.001$), SBP ($P = 0.002$) and RHR ($P = 0.019$), complementing link of adiposity as an inflammatory process to blood pressure. IL-17 levels in blood are observed to be positively and significantly related to DBP [Table 4]

**Figure 1:** Correlation matrix of blood pressure with obesity indices, sympathetic reactivity and inflammatory markers in normotensive.

individuals. The levels of IL-17 in our study were less than those reported in hypertensives. The insignificant difference in hsCRP levels between pre-hypertensive and normotensive

observed in our study can be attributed to small sample size. Establishing the risk predictor for prehypertension, it was observed that only sympathetic reactivity (OR = 0.75) and

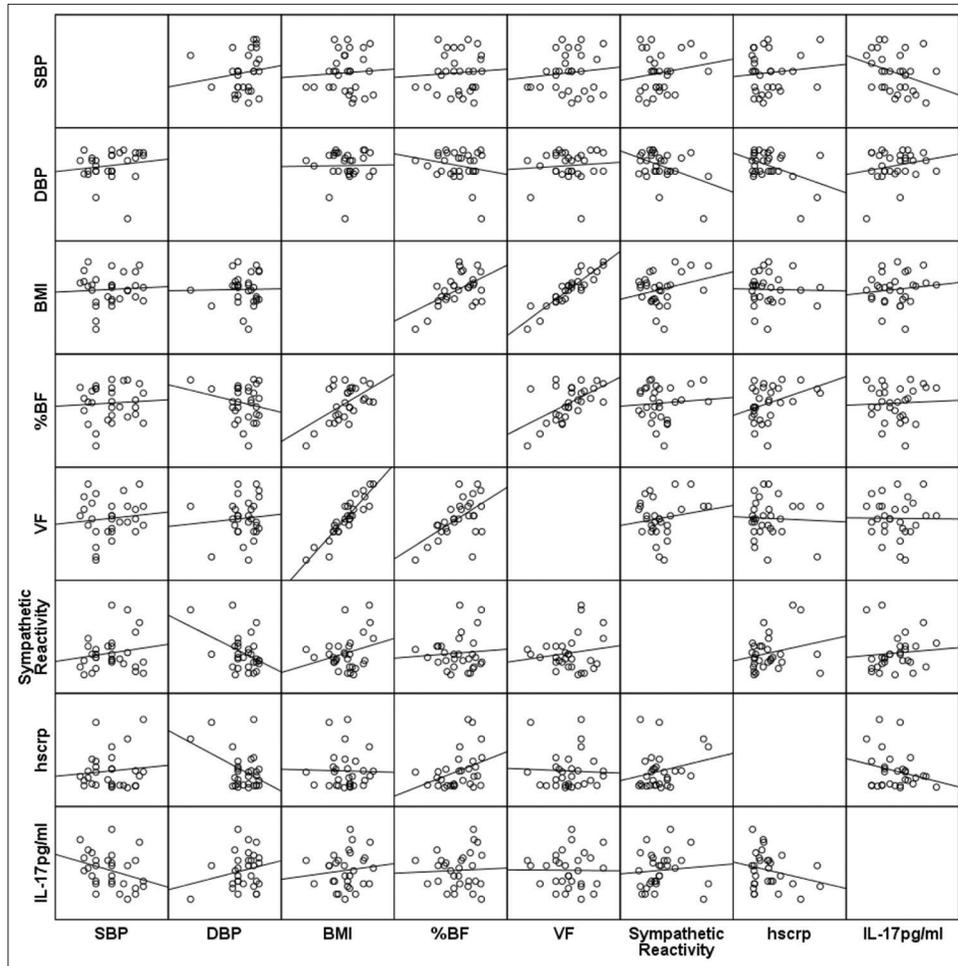


Figure 2: Correction matrix of blood pressure with obesity indices, sympathetic reactivity and inflammatory markers in pre-hypertensive.

IL-17 level (OR = 4.7) were able to increase the probability of odds of being pre-hypertensive. Significant direct relation of IL-17 with pre-hypertension independent of age, sex and BMI was also observed by Yao *et al.*^[10] which also observed a linear relation of IL17 levels with SBP contrary to our finding. Contrary to several other studies,^[29,30] no association of hsCRP could be observed with pre-hypertension.

Significant positive correlation of hs-CRP and % body fat in our study was also observed by several studies^[31,32] indicating low-grade inflammation pathology in increasing body fat. A significant positive correlation between hs-CRP and SBP and RHR may reflect in increased basal sympathetic tone in subjects with low-grade inflammation^[24] as sympathetic stimulation directly influencing bone marrow activity resulting in increase in pro-inflammatory cells (increase inflammation) and decrease in vascular repair.^[11]

On the other hand, significant positive correlation of IL-17 to DBP strengthens the involvement of immune system and sympathetic drive of the body strengthens the existing evidence of cardiovascular damage caused by excessive

stimulation of the sympathetic and reticular activating system and their receptors (α - and β -adrenergic and angiotensin II AT1 receptors) are mediated through a pro-inflammatory activation of the immune system.^[33]

CONCLUSION

Elevated IL-17 levels are significant predictor of pre-hypertension along with lower sympathetic reactivity. Inflammatory marker hsCRP is raised is associated % BF in pre-hypertensive. Study fortifies the inflammation and immune mechanism in the pathogenesis of increased blood pressure in pre-hypertensive in addition to dampen sympathetic reactivity. However, further research on a bigger sample is required to establish linking of immune mechanism to sympathetic over drive in high blood pressure pathology.

Limitation

The study was conducted using only one test to assess the sympathetic reactivity which could result in variability in the

response. Studies on a bigger sample size and with battery of test for sympathetic system activity are required to obtain more conclusive results.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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