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Association of anthropometric indices of obesity and white blood cell count with arterial stiffness and blood pressure

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ABSTRACT: *Background:* Obesity induces oxidative stress and inflammation, which may lead to arterial stiffness and hypertension. The relationship of white blood cell count (WBC) and anthropometric indices with arterial stiffness index (ASI) and blood pressure was evaluated in this study.
Methods: Thirty male subjects aged between 35-55 years were selected in each of normotensive, prehypertensive and hypertensive groups. Their weight, height, waist circumference (WC) and hip circumference (HC) were measured according to the WHO guidelines. BMI, waist hip ratio (WHR), waist stature ratio (WSR) and conicity index (CI) were calculated. ASI was calculated from digital volume pulse recorded by photoplethysmography with iWorx-214 physiological interface system. The white blood cell count and differential was done. One way ANOVA followed by Post Hoc Tukey's Test was applied to determine the difference between the groups. Pearson's coefficient was calculated to study the correlation. Statistically, p value < 0.05 was considered significant.
Results: There was statistically significant difference in WHR (0.000), WC (0.003) and ASI (0.000) between the study groups but not BMI (0.223). Amongst the anthropometric measurements, WHR and WC had positive correlation with the systolic and diastolic blood pressure. The WBC and absolute neutrophil count correlated significantly with WHR and WC but not with ASI and blood pressure.
Conclusions: The central obesity is a more robust risk factor for arterial stiffness and blood pressure than BMI. The inflammation may be involved in pathogenesis of visceral obesity and arterial stiffness that may be determined by elevated white blood cell counts.

KEYWORDS: Prehypertension; hypertension; Arterial stiffness index; central obesity; inflammation; neutrophil-lymphocyte ratio; cardiovascular diseases.

1 INTRODUCTION

Hypertension is the boiling issue of the today's world. The prevalence of hypertension has been increasing all over the globe including Pakistan. In the United States, twenty-nine percent of the adults above nineteen years in age have hypertension and approximately thirty-seven percent are pre-hypertensive's [1]. In Pakistan, it has been estimated that one-third of population above forty-five years of age and twenty percent aged above fifteen years have hypertension [2].

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Hypertension is a multifactorial disorder caused by various environmental, physiological and genetic factors. The endothelial dysfunction, vascular stiffness, abnormal sympathetic outflow, alterations in renin-angiotensin system and increased plasma aldosterone levels are involved primarily in the increased arterial pressure [3].

The measurement of arterial stiffness index (ASI) has been proposed to be a useful non invasive tool for the cardiovascular risk assessment because of its ability to identify early target organ damage [4]. The stiffness of the arterial wall determined by analysis of digital volume pulse contour is a simple, reproducible and noninvasive method of assessing arterial stiffness. There has been a strong evidence that the stiffness index score derived by this technique is comparable to the arterial stiffness determined by pulse-wave velocity, which is the gold standard marker [5]. ASI may serve as a noninvasive tool for assessing the patients at risk of stroke, coronary artery disease and heart failure. It has been documented to be more sensitive tool in risk stratification for cardiovascular diseases (CVD) in comparison to plasma glucose, total cholesterol, and waist to hip ratio in apparently healthy population [6].

Obesity and hypertension have become swift growing worldwide epidemics [7]. There has been progressive increase in blood pressure with increasing obesity, which is result of sedentary life styles, urbanization, industrialization and behavioral adaptations. The rise in blood pressure is generally considered as an essential component of aging. However, this rise in blood pressure is by no means inevitable [8].

In various studies body mass index (BMI), waist-hip ratio (WHR), waist circumference (WC), waist-stature ratio (WSR) and Conicity index (CI) have been proposed as markers of obesity. However, it is not yet fully clear which anthropometric index of obesity has the strongest association with blood pressure in our population. Literature survey shows that BMI determines the overall obesity but not the central or visceral obesity, which is more closely associated with blood pressure and cardiovascular diseases [9], [10]. Obesity has been associated with oxidative stress, inflammation, and hypertension [11].

Arterial stiffness is determined by structural and functional intrinsic elastic properties of the vessel wall. The outer adventitial layer is composed of collagen fibers, fibroblasts, adipocytes, lymphocytes, macrophages and dendritic cells [12]. The adventitial cells are generally the first to be activated and recruited in response to the inflammation and oxidative stress leading to alterations in the tone and elasticity of the vessel wall. The cytokines and inflammatory signals from the adventitia play a critical role in alterations in the extracellular matrix (ECM). The modulation of ECM leads to the high elastin to collagen ratio, resulting in increased stiffness of the arterial wall [13]. The long term increased BP results in distension of the arterial wall, leading to greater and greater recruitment of the inelastic collagen fibers and thereby, reduction in its elasticity. The structural changes in the medial layer of the elastic arteries mainly result from the progressive elastic fibre degeneration [14].

Hypertension leads to increased stretch of the vessel wall by raised hydrostatic pressure or cyclic strain, which in turn influences endothelial cell gene expression and function [15]. The expression of intercellular adhesion molecule-1 (sICAM-1) increases in linear fashion in response to progressive rise in cyclic strain. The elevated sICAM-1 results in greater activation of WBCs and adhesion of monocytes to endothelial cells [16]. The activated WBCs release a variety of hydrolytic enzymes, cytokines, and growth factors, which can induce further vascular damage. Moreover, neutrophil aggregate along with platelets, to the vessel wall resulting in its narrowing and stiffening.

The literature review shows that WBC and neutrophil lymphocyte ratio (NLR) may predict inflammatory status in various cardiovascular pathologies. Increased white blood cell (WBC) count is related to cardiovascular disease in patients with type II diabetes mellitus and raised NLR is associated with metabolic syndrome and poor outcome after reperfusion procedures in acute coronary syndrome[17], [18].

In our research project, we evaluated the simplest markers of inflammation i.e. WBC, ANC, NLR and ESR, ASI and anthropometric markers of obesity (BMI, WHR, CI, WSR, WC) in equal number of normotensive, prehypertensive and hypertensive male subjects. Moreover, we have studied the correlation of these simple markers of inflammation and anthropometric indices of obesity with ASI and blood pressure.

2 MATERIAL AND METHODS

The study was carried out at Dept. of Physiology and Clinicopathalogical Lab, Army Medical College in collaboration with Military Hospital Rawalpindi, Pakistan. The duration of study was six months from Dec. 2013 to May 2014. It was case a control study and thirty male subjects aged between 35-55 years were selected in each of normotensive, prehypertensive and hypertensive group by non-probability, convenience sampling. The grouping was done in light of JNC-VII report [19]. Approximately, one thousand subjects were interviewed and subjects having any allergic disease, fever or taking any medications for at least last two weeks were excluded from the study. Those who had diabetes, chronic inflammatory disease or any prolonged illness were also excluded. The study was started after approval from Ethical Review Committee

Army Medical College and Centre for Research in Experimental and Applied Medicine. After informed consent, the subjects' particulars were recorded and detailed medical history was inquired.

2.1 BLOOD PRESSURE MEASUREMENT

Blood pressure was measured by auscultatory method with the mercury sphygmomanometer. First reading was taken at the time of filling the proforma, second during recording of pulse wave contour for recording the stiffness of the vessel wall and third just before drawing the blood. The average systolic (SBP), diastolic (DBP), pulse pressure (PP) and mean arterial pressure [MAP = DBP + 1/3 (SBP – DBP)] were recorded. In order to exclude diabetes mellitus blood sugar was checked by the glucometer.

2.2 ANTHROMETRIC MEASUREMENTS

Weight, height, waist and hip circumference were measured using standard protocols. Weight (Wt) was measured nearest to 0.1 kg with pointer spring balance, without shoes and wearing light clothing. Height (Ht) was recorded to the nearest 0.5 cm. WC was measured using a rubber measuring tape, horizontally halfway between the lower border of the rib cage and the iliac crest. Hip circumference (HC) was measured at the widest part over the buttocks. WC and HC were measured to the nearest 0.5 cm.The WHR was calculated by dividing the WC (cm) by the HC (cm). BMI was determined as weight (kg) divided by height in meters square. Waist-Stature Ratio [WSR=WC/Ht] and Conicity index [CI=WC (m)/$0.109\ \sqrt{\mathrm{Wt\ (kg)/Ht\ (m)}}$] were calculated.

2.3 ARTERIAL STIFFNESS INDEX

It was observed by placing plethesmograph on the volar surface of the distal segment of middle finger and digital volume pulse (DVP) recorded by Human/Animal Physiology interface system iWorx-214. The recorded data was analyzed, using LabScribe software and reflection time was calculated by placing cursor on the two peaks of DVP. The arterial stiffness index was calculated as [ASI = Height (meters)/ Reflection time (seconds)].

2.4 WHITE BLOOD CELL COUNT

The blood cell count and differential leucocytes count (DLC) was done by KX-21 automated hematology analyzer and confirmed by microscopy of Leishman stained peripheral smear in the supervision of hematologist. The DLC was also done by technician of the Clinicopathalogical lab and observer difference was less than 2%. ESR was done by Westergren's method.

2.5 STATISTICAL ANALYSIS

Statistical analysis was performed using, IBM-SPSS version 20. ANOVA was applied followed by Post-Hoc Tukey test to compare the means of obesity indices (BMI, WHR, CI, WSR, and WC), blood pressure variables, blood cell counts (WBC, ANC, NLR, ESR) and arterial stiffness index (ASI) in normotensive, prehypertensive and hypertensive subjects. In order to determine the correlation between different variables; Pearson's correlation coefficient was calculated. The p value <0.05 was considered statistically significant.

3 RESULTS

The comparison of age, blood pressure variables, proposed inflammatory markers and obesity indices by one way ANOVA followed by Post Hoc Tukey's test is given in normotensive, prehypertensive and hypertensive subjects in Table-1 and Table-2. There has been significant difference in WC and WHR (determinants of central obesity) and ASI amongst the three groups.

The Pearson's coefficient was calculated to study the correlation between different variables. There was statistically significant relationship between blood pressure variables and WHR and WC. There was a weak association between CI and WSR. However, the BMI was not related to the blood pressure (Table-3). There has been strong relationship between ASI and blood pressure as Pearson correlation coefficient was 0.808 [p value: 0.0001] and 0.739 [p value 0.0001] for systolic and diastolic blood pressure respectively. Moreover, a significant correlation was seen between ASI, WHR and WC. There was no relationship seen between the proposed markers of inflammation with systolic and diastolic blood pressure. Interestingly, the WBC and ANC were correlated to WC, WHR and CI (Table 3). The correlation orders of anthropometric indices of obesity with SBP and DBP are given in Table-4.

4 DISCUSSION

Years ago in 1967, Framingham Heart Study indicated, that obesity is a principal risk factor in arterial hypertension [20]. In our study, we have taken the equal number of normotensive, prehypertensive and hypertensive male subjects in middle age group (35 to 55 years) to study the correlation of obesity indices and white cell counts (WBC) with arterial stiffness (ASI) and blood pressure. It was found that markers of central obesity (WHR>WC>WSR>CI) are better correlated with hypertension than indices of whole obesity i.e. BMI. These results were similar to the findings by Gus *et al.*(2009) that waist to hip ratio and waist-stature ratio were better predictors of the incidence of hypertension than BMI, especially in male gender [21]. Our results supported the findings of the study by Zhou *et al.*(2003) that in male gender hypertension depends mainly on the visceral/central obesity [22]. Mark *et al.*(1999) found that the prevalence of elevated blood pressure was positively correlated with increasing adipose tissue [23]. It had been proposed that substantial compression of the kidneys by visceral fat deposits and the activation of renin-angiotensin system might be important factors in elevation of blood pressure with increasing body weight [24].

The visceral fat has been proposed to contribute in increasing the blood pressure by enhancing sympathetic activity [25]. The BMI was comparable in three groups in our study, which was similar to the findings of a study conducted in male and female population of Peshawar, Pakistan. It was observed that large percentage of males in the normal BMI category had signs of hypertension [26]. The studies by Sakurai *et al.* (2006) and Mufunda *et al.* (2006) also supported our observation that BMI does not have significant association with blood pressure especialy in male gender [27], [28]. The correlation orders of obesity indices with systolic and diastolic blood pressure in various studies and the present one are given in Table-4.

The white blood cell count, ANC, ESR and NLR were found comparable in normotensive, prehypertensive and hypertensive subjects. These results were similar to the findings of the study conducted by Acar *et al.* (2013) and Julius *et al.* (2014), but contrary to the findings of two other studies (Pusuroglu *et al.*, 2014, Rajkumari *et al.*, 2013). These contrary findings could be due to the difference in the duration of hypertension in subjects who participated in various studies. The hypertension over long period of time has been associated with elastin fiber fatigue and fracture due to continuous stretching of arterial tree which may lead to systemic inflammation in the long standing hypertension [3], [4], [29], [30].

In our study, there was a rise in NLR with increasing ASI but this relationship was not statistically significant. These results were similar to the findings of Blann *et.al*, in patients with stable coronary artery disease. In their study, ASI was strongly related with age and blood pressure but not with the markers of systemic inflammation [31].

When correlation between NLR and ASI was analyzed separately in each group, there was modest positive correlation (r=0.432) in normotensive subjects but no correlation was observed in prehypertensive and hypertensive subjects. It may be inferred from these findings that inflammatory processes play important role in the vascular stiffening in subclinical stage before any other manifestation. Our results supported the findings by Malahfji *et al.* (2014) that WBC and NLR were associated with ASI in asymptomatic individuals free of CVD [32]. In a study, conducted by Park *et al.* (2011) NLR was independently associated with arterial stiffness, irrespective of blood pressure variations which was contrary to our findings [33]. This conflict in the findings of the two studies may be due to the difference in the study design. In that study, the grouping was based on NLR and NLR was studied as a qualitative or categorical variable. The NLR had been divided into four quartiles and it was revealed that the mean blood pressure and arterial stiffness was higher in the highest quartile of NLR and blood pressure was associated with the increasing quartile of NLR. However, in our study, NLR was studied as a numerical or quantitative variable and its association with arterial stiffness index in equal number of normotensive, prehypertensive and hypertensive subjects was investigated. Statistically, the results of co-relational studies are more reliable when both the variables are quantitative while, the categorization of numerical data may yield misleading results [34].

The initial stiffening in the vessel wall may involve inflammatory process and inflammation could precede the development of hypertension. This observation is supported by the findings of various studies, in which elevated WBC count and especially raised neutrophil count were associated with higher incidence of hypertension [3], [35]. However, continuous stretching of the vessel wall over a prolonged period of time due to sustained hypertension may lead to the mechanical injury and inflammation that may be responsible for the strong association of inflammatory cells in hypertensive subjects. Therefore, a vicious cycle develops which leads to further stiffening of the vessel wall. These inflammatory processes may play a pivotal role in cardiovascular complications and end organ damage as a consequence of continuously high blood pressure.

Our study had certain limitations that only one time blood sampling was done and inflammatory markers like high-sensitivity C-reactive protein (hs-CRP), interleukins, adhesion molecules, selectins, TNF-α were not measured to confirm the inflammatory status in the subjects participating in the study. Therefore, further evaluation in a crossectional study with multiple sampling may help in assessing the relevance of NLR with arterial stiffness in cardiovascular diseases.

Table-1: Comparison of anthropometric indices, white cell count and arterial stiffness index amongst the groups.

Variables	Group 1 Normotensive Mean ± SD (n=30)	Group 2 Prehypertensive Mean ± SD (n=30)	Group 3 Hypertensive Mean ± SD (n=30)	p-value (sig.)
Age	40.10 ± 4.29	43.17 ± 5.17	47.90 ± 5.30	**0.000**
SBP	110.17 ± 5.89	129.93 ± 4.46	164.03 ± 11.63	**0.000**
DBP	72.90 ± 5.87	86.20 ± 2.25	104.97 ± 11.17	**0.000**
MAP	37.26 ± 4.88	43.73 ± 4.26	59.07 ± 7.71	**0.000**
PP	85.32 ± 5.40	100.78 ±2.45	124.66 ± 10.73	**0.000**
BMI	25.47 ± 2.78	25.77 ± 3.16	26.76 ± 3.01	0.223
WC	0.90 ± 0.08	0.95 ± 0.09	0.98 ± 0.08	**0.003**
CI	1.28 ± 0.07	1.32 ± 0.08	1.32 ± 0.08	0.051
WHR	0.94 ± 0.56	0.999 ± 0.08	1.03 ±.09	**0.000**
WSR	0.54 ± 0.05	0.54 ± 0.11	0.57 ± 0.05	0.102
WBC (k/µL)	6.86 ± 1.45	7.57 ± 1.64	6.96 ± 1.67	0.185
ANC (k/µL)	3.93 ± 0.83	4.59 ± 1.35	4.17 ± 1.22	0.094
ALC (k/µL)	2.41 ± 0.65	2.43 ± 0.6	2.38 ± 0.7	0.729
NLR	1.72 ± 0.52	1.74 ± 0.37	1.94 ± 0.63	0.161
ASI	6.67 ± 0.52	7.85 ± 0.62	12.19 ± 2.62	**0.000**

All values are expressed as mean plus/minus standard deviation.

[SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; MAP: mean arterial pressure; BMI: body mass index; WC: waist circumference; CI: conicity index; WHR: waist to hip ratio; WSR: waist stature ratio; WBC: white blood cell count; ANC: absolute neutrophil count; ALC: absolute lymphocyte count; NLR: neutrophil-lymphocyte ratio; ASI: arterial stiffness index; Kg: kilogram; m: meters; s: seconds]

Table-2: Comparison of anthropometric indices, white cell count and arterial stiffness index between the groups

Variables	Normotensive vs Prehypertensive	Normotensive vs Hypertensive	Prehypertensive vs hypertensive
Age	**0.048**	**0.0001**	**0.001**
SBP	**0.0001**	**0.0001**	**0.0001**
DBP	**0.0001**	**0.0001**	**0.0001**
MAP	**0.0001**	**0.0001**	**0.0001**
PP	**0.0001**	**0.0001**	**0.0001**
WC	**0.057**	**0.003**	0.523
WHR	**0.011**	**0.0001**	0.371
ASI	**0.014**	**0.0001**	**0.0001**

[SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; MAP: mean arterial pressure; WC: waist circumference; WHR: waist to hip ratio; ASI: arterial stiffness index]

Table-3: Relationship of anthropometric indices and white cell counts with arterial stiffness index and blood pressure variables

VARIABLES		BMI	WC	WHR	CI	WSR	WBC	ANC	ESR	NLR
ASI	R	0.107	**0.218**	**0.269**	0.136	0.098	.041	0.068	0.082	0.183
	P	0.316	**0.038**	**0.010**	0.201	0.357	.703	0.523	0.441	0.085
SBP	R	0.177	**0.323**	**0.372**	0.192	0.167	0.055	0.125	0.157	**0.271**
	P	0.095	**0.002**	**0.0001**	0.070	0.116	0.605	0.239	0.140	**0.010**
DBP	R	0.181	**0.346**	**0.362**	**0.250**	0.186	0.023	0.122	0.082	**0.314**
	P	0.088	**0.001**	**0.0001**	**0.017**	0.080	0.830	0.253	0.440	**0.003**
MAP	R	0.182	**0.341**	**0.372**	**0.228**	0.180	0.038	0.125	0.117	**0.299**
	P	0.086	**0.001**	**0.0001**	**0.031**	0.089	0.724	0.240	0.273	**0.004**
PP	R	0.135	**0.323**	**0.209**	0.070	0.167	0.089	0.105	0.198	0.155
	P	0.204	**0.002**	**0.003**	0.051	0.116	0.405	0.325	0.080	0.144

[BMI: Body Mass Index; WC: waist circumference; WHR: waist to hip ratio; CI: conicity index; WSR: waist stature ratio; WBC: white blood cell count; ANC: absolute neutrophil count; NLR: neutrophil-lymphocyte ratio; ASI: arterial stiffness index; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; PP: pulse pressure]

Table 04: Correlation orders of anthropometric indices with systolic and diastolic blood pressure in various studies.

Studies	Systolic Blood Pressure	Diastolic Blood Pressure
Zhou Z et al. [10] (n 29079)	BMI>WC>WSR>WHR>CI	BMI>WC>WSR>WHR>CI
Yalcin et al.[36] (n 267)	WSR>BMI>WC>WHR>CI	BMI>WC>WSR>WHR>CI
Ghosh & Bandyopadhyay [37] (n180)	WSR>BMI>WC>WHR>CI	BM>WC>WSR>WHR>CI
Ghosh JR, Bandyopadhyay AR[38](n=179)	WC > CI > WSR > BMI (0.01) (0.01) (0.62) (0.70)	WC > CI > WSR > BMI (0.01) (0.01) (0.05) (0.53)
Present study (n 90)	WHR > WC > WSR > CI >BMI (0.000)(0.002)(0.04)(0.07)(0.09)	WHR > WC > CI > WSR >BMI (0.000)(0.001)(0.01)(0.06)(0.09)

[BMI: Body Mass Index; WC: waist circumference; WHR: waist to hip ratio; CI: conicity index; WSR: waist stature ratio].

5 CONCLUSIONS

The central obesity is a more robust risk factor for arterial stiffness and blood pressure. The inflammation may be involved in pathogenesis of visceral obesity and arterial stiffness that may be determined by elevated white blood cell counts. However, the white blood cell count and differential white cell count may not give information about the inflammatory status in hypertension, which may be due to its complex pathophysiology.

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