



Association of TNF-alpha with Blood Pressure Levels in Prehypertensive Adults in Makurdi, Nigeria

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Authors' contributions

This work was carried out in collaboration between both authors. Author AA designed the study and wrote the protocol. Authors AA and SJG wrote the first draft of the manuscript and performed the statistical analysis. Author AA managed the analyses of the study. Authors AA and SJG managed the literature searches. Both authors read and approved the final manuscript.

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ABSTRACT

Background: Previous studies have reported vascular inflammation in hypertension, which mediates its complications. However, studies' regarding vascular inflammation in prehypertensives has been neglected.

Aim: Our study aims at investigating vascular inflammation using tumour necrosis factor-alpha (TNF- α) in prehypertensive individuals.

Materials and Methods: This case-control study comprised of 70 randomly selected male and female patients aged 18-55 years, who were attending general health, check up at a tertiary hospital. The biochemical and anthropometric parameters of 35 prehypertensives were compared with 35 normotensive control group.

Results: Prehypertensives (systolic blood pressure [SBP] 130.91 ± 8.70 ; diastolic BP 83.17 ± 5.86) had significant ($P < 0.002$), elevated TNF- α level compared to anthropometrically matched normotensives (SBP 111.03 ± 6.89 ; DBP 70.40 ± 3.87). No significant difference ($P > 0.05$) was observed in the levels of lipids between the two study groups. A significant positive correlation was

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observed between; TNF- α and SBP ($r=.387$, $P=.022$), TNF- α and DBP ($r=.381$, $P=.024$) in the prehypertensive group. There was no significant correlation ($P>0.05$) between; TNF- α and plasma lipids, TNF- α and body mass index, TNF- α and waist circumference in the prehypertensive group.

Conclusion: Our study observes a positive association of TNF- α with blood pressure in prehypertensives. It is indicative that prehypertension predisposes individuals to mild chronic inflammation.

Keywords: Prehypertension, tumour necrosis factor-alpha, inflammation, blood pressure.

1. INTRODUCTION

High blood pressure is among the risk factors of cardiovascular and renal diseases. A limited knowledge of high blood pressure (HBP) risk factors has exposed individuals to HBP [1]. The concept prehypertension (PreHTN) was introduced as a guideline for the management of blood pressure by the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment (JNC-7) of HBP [2]. Prehypertension was defined as a systolic blood pressure of 120–139 mmHg and/or a diastolic blood pressure of 80–89 mmHg. The JNC-7 classified individuals consistently having SBP of ≥ 140 and DBP ≥ 89 mmHg as hypertensives. Recently, the American College of Cardiology (ACC) and American Heart Association (AHA) proposed a new classification of high blood pressure [3]. This new guideline sub-divides the widely acceptable JNC-7 prehypertension into; raised blood pressure (as persons with systolic BP between 120-129 mmHg and diastolic BP less than 80 mmHg) and Stage 1- hypertension (systolic between 130-139 or diastolic between 80-89). Hypertension defined by JNC-7 is renamed stage 2 hypertension (systolic BP of at least 140 or diastolic BP of at least 90 mm Hg) by the ACC/AHA [3]. Both JNC-7 and ACC/AHA maintains normotensives as individuals with systolic BP of ≤ 120 and/or diastolic BP of ≤ 80 mmHg [2,3].

A statistical analysis of disease-free (apparently healthy) National Health and Nutrition Examination Survey (NHANES) adult participants conducted from 1999 to 2006 found the overall prevalence of PreHTN in apparently healthy adults to be 36.3% [4]. A cross-sectional analysis of 5553 prehypertensives from a population-based national cohort study, showed a 62.9% prevalence of prehypertension in the black race compared to 54.1% in whites [5]. Patients with PreHTN (120–139/80–89 mmHg) have an increased risk of cardiovascular morbidity and mortality compared with normotensive ($<120/80$ mmHg) individuals [6]. Prehypertensive

individuals are not usually placed on antihypertensive drug therapy, but rather advised to modify their lifestyle to lower their blood pressure to normal values targeted at reducing the risk of developing hypertension [7].

Vascular inflammation has been reported to play key roles in the pathogenesis and progression of hypertension [8]. Published data suggest that chronic inflammation could be an independent risk factor for high blood pressure [9]. Tumour necrosis factor-alpha (TNF- α) is a known marker of mild chronic inflammation, synthesized by various cell types under the stimulatory action of cell stressors [10]. The major stimulants of TNF- α gene transcription in these cells include microbial lipopolysaccharides and other macrophage activating agents [10]. Most cardiovascular risk factors are recognized promoters of inflammation [11-13]. Specifically, arterial hypertension is reported an independent correlate of circulating inflammatory markers [14-16]. The inflammatory roles of TNF- α include; enhancement of cell differentiation, proliferation and apoptosis [17].

Over the years, researchers paid more attention to the existence of generalized endothelial dysfunction in essential hypertension than preHTN. However, the relationship between preHTN and inflammation has not been thoroughly investigated. Most previous studies regarding inflammation in hypertensives failed to control for other risk factors of chronic inflammation and high blood pressure. This study aimed at determining the relationship between preHTN and inflammation, devoid of confounding effects.

2. MATERIALS AND METHODS

2.1 Study Design

The case-control study compared the anthropometric and biochemical parameters of prehypertensives with normotensive controls.

2.2 Study Area and Population

A sample of male and female participants aged 18-55 years, was randomly drawn from patients attending general health checkup at the Federal Medical Centre Makurdi, from December 2015 to February 2016.

2.3 Sample Size

The sample size was determined using the formula for case-control studies that compare two group means [18]; $n=1+2C(s/d)^2$, where s , is the standard deviation (an estimate of the population standard deviation of blood pressure), d the effect size (the estimated mean difference of the blood pressure of prehypertensives and normotensives) and C a constant dependent on the level of significance and statistical power. At a significance level of 5%, and statistical power of 90%, C is 10.51. The calculated sample size was 32.4, which was approximated to 35 for each group.

2.4 Selection Criteria

The inclusion criteria took into cognizance, the impact of infectious organisms/other conditions that stimulate TNF production, and as such excluded patients with infections from the study. Other confounding factors of raised blood pressure were as well considered. Individuals were eligible to participate in the study if they: (a) were 18 to 55 years of age; (b) had no history of hypertension and were not using antihypertensive medications; (c) had no history of cardiovascular disease (coronary disease, stroke, peripheral vascular disease) and were not dyslipidemic nor using lipid-lowering drugs; (d) were free of any other major systemic illnesses (e.g. cancer, diabetes mellitus); (e) were nonsmokers; (f) were not pregnant. All subjects provided written informed consent, and the study was approved by the institutional ethical committee.

2.5 Data Collection

Participants on a 12 hour overnight fast, arrived during morning hours in a fasting state. Self-reported information on demographic characteristics (age, sex, financial status, and education), detailed medical history, dietary and lifestyle habits, such as smoking status, and physical activity were obtained.

2.5.1 Blood pressure

The health checkup examination required 2 visits, 1 week apart. All participants rested for an acclimation period of at least 30-minutes, each time they visit the clinic. Blood pressure measurement during each visit was taken using an aneroid sphygmomanometer (ELKA aneroid sphygmomanometer; Von Schlieben Co., Berlin, Germany), three times 5 minutes apart with the right arm relaxed and well supported by a table, at an angle of 45-degree from the trunk. The systolic BP level was determined by the first perception of sound. The diastolic BP level was determined by phase V when the repetitive sounds become fully disappeared. The average of the second and third measurements was taken as the participant's BP during each visit. The average BP of the two visits was used in this analysis. Patients whose average BP levels were greater or equal to 140/90 mmHg or were taking antihypertensive medication or had a physician tell them that they have hypertension but were untreated were classified as hypertensives. Participants who had mean systolic/diastolic BPs within the range of 120 to 139/80 to 89 mmHg and never told that they had high BP levels were defined as prehypertensives, according to JNC-7 [2] guidelines. Normotensives were also defined according to JNC-7 criteria.

2.5.2 Body mass index and waist circumference

Body weight to the nearest 0.1 kg and height to the nearest centimetre were measured with the subjects barefoot and in light clothing and BMI was calculated as weight (kilograms)/height (meters squared). Waist circumference (WC) was measured horizontally at the level of the natural waist, which was identified as the level at the hollow moulding of the trunk when the trunk was laterally concave.

2.5.3 Blood sample collection

Blood samples were collected between 8 and 10 AM from fasting participants. Subjects were supine for 10 min before blood collection. Blood was collected into a plain glass vacutainer tube for serum lipids and TNF- α determination. All samples were collected without occlusion. The tubes were kept on ice until centrifuged at 3000 rpm for 10 min within 2 h of blood collection. Serum was extracted aseptically and stored at -70°C for estimation of TNF- α . Biochemical evaluation using fresh serum was carried out in

the laboratory of the institution following the criteria of the World Health Organization reference laboratories.

2.6 Laboratory Methods

The E-max microplate reader (Molecular Devices, Sunnyvale, USA) was used for immunoassay of TNF- α , whereas a spectrophotometer OPTIMA SP 300 (OPTIMA Inc., Tokyo, Japan) was used for analysis of fasting plasma total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides (TGs).

2.6.1 Determination of serum tumour necrosis factor-alpha

The TNF- α immunoassay kit (DRG international California, USA), was used for the assay of TNF- α . The determination of TNF- α in serum was based on the enzyme-linked immunosorbent assay sandwich principle. At a sample detection limit of 0.7 pg/ml given by the manufacturer, the results of 30 serum samples from apparently healthy persons ranged between 4.6 and 12.4 pg/ml.

2.6.2 Determination of serum lipids

The reagent kits for the determination of total cholesterol, HDL-C, and TGs were obtained from Randox laboratories Limited, United Kingdom. Total cholesterol was determined by the cholesterol esterase method. The HDL-C was determined by the cholesterol esterase method after fractional separation from other lipids. Triglycerides were determined using the lipase method. LDL-C and VLDL-C were estimated using the Friedewald equation [19].

2.7 Statistical Analysis

Continuous variables were presented as mean values \pm standard deviation. Comparisons between continuous variables of prehypertensive and normotensive groups were performed by the student's t-test. Pearson's correlation coefficient was used in testing relationships between TNF- α and systolic BP, diastolic BP, total cholesterol, HDL-C, LDL-C, VLDL-C and TGs. All reported *P* values were based on two-sided tests and compared to a significance level of 5% (0.05). SPSS version 21 (Statistical Package for Social Sciences; IBM Armonk, New York, United States) software was used for all the statistical calculations.

3. RESULTS

The comparison of serum TNF- α level, total cholesterol, HDL-C, LDL-C, VLDL-C, TGs between prehypertensives and anthropometrically matched normotensives is presented in Table 1. Prehypertensives had significant ($P<0.002$), elevated TNF- α level compared to normotensives, with no significant difference ($P>0.05$) observed in the levels of lipids between the two study groups.

Figs. 1 and 2 respectively present the relationships between TNF- α and systolic BP, TNF- α and diastolic BP in prehypertensive subjects. A significant positive correlation was observed between; TNF- α and systolic BP ($r=0.387$, $P=0.022$), TNF- α and diastolic BP ($r=0.381$, $P=0.024$) in prehypertensive subjects.

Fig. 3 presents the relationship between TNF- α and systolic BP, in normotensive subjects. A significant positive correlation was observed between; TNF- α and systolic BP ($r=0.816$, $P=0.000$) in normotensives.

Figs. 4 and 5 respectively present the relationships between TNF- α and systolic BP, diastolic BP in all the apparently healthy subjects studied. In the overall subjects studied, TNF- α level was shown to significantly correlate positively with both systolic BP ($r=0.473$, $P=0.000$), and diastolic BP ($r=0.467$, $P=0.000$).

Table 2 presents the relationships of TNF- α , blood pressure with lipids, age, BMI, WC in prehypertensive subjects. There was a significant ($r=0.414$, $P=0.013$) relationship between TNF- α and age, where as no significant correlation ($P>0.05$) was observed between; TNF- α and lipids (total cholesterol, HDL-C, LDL-C, VLDL-C, TGs), TNF- α and BMI, TNF- α and WC in prehypertensive subjects. There was no significant correlation ($P>0.05$) between; blood pressure (systolic & diastolic) and lipids (total cholesterol, LDL-C, VLDL-C, TGs), blood pressure and age, blood pressure and BMI, blood pressure and WC in prehypertensive subjects.

The relationships of TNF- α , blood pressure and lipids, age, BMI, WC in normotensive subjects studied is presented in Table 3. A significant correlation of DBP was observed with age($r=0.372$, $P=0.028$), BMI($r=0.523$, $P=0.001$), WC($r=0.338$, $P=0.047$), VLDL-C($r=0.368$, $P=0.03$), and TGs($r=0.371$, $P=0.028$). No significant correlation was observed between TNF- α and DBP($r=0.225$, $P=0.193$).

The relationships of TNF- α , blood pressure and lipids, age, BMI, WC in the overall subjects studied are presented in Table 4. Whereas a significant ($r=0.326$, $P=0.006$) correlation existed between TNF- α and age, a non-significant correlation ($P>0.05$) was observed between; TNF- α and lipids (total cholesterol, HDL-C, LDL-C, VLDL-C, TGs), TNF- α and BMI, TNF- α and WC in all the apparently healthy subjects. No significant correlation ($P>0.05$) was observed between; blood pressure (systolic & diastolic) and lipids (total cholesterol, LDL-C, VLDL-C, TGs), blood pressure and age, blood pressure and BMI, blood pressure and WC in all the apparently healthy subjects.

4. DISCUSSION

Prehypertension is a precursor of clinical hypertension. Hypertension is a well known major injurious risk factor that promotes cardiovascular diseases like atherosclerosis. Vascular inflammation is the hallmark in the

pathogenesis and progression of hypertension and atherosclerosis. Our study determined to circulate TNF- α as a biomarker of mild chronic inflammation in prehypertensives. Previous reports exist on the association of inflammation with hypertension. Scant literature in this regard is available in prehypertensives. It is in this light that our study sought to investigate the relationship between mild chronic inflammation and preHTN independent of confounding factors of raised TNF- α and blood pressure. Abnormal high levels of serum TNF- α is reported in septic shock, graft rejection, infections, cancer, obesity, immunological diseases, diabetes mellitus, cardiovascular diseases, advanced age [10,11,12,13,17]. To obtain homogenous results devoid of interferences from these confounding factors, participants were carefully selected by excluding those with infectious diseases (viral, parasitic and bacterial), immunological diseases, cancer, abnormal body composition, diabetes, dyslipidemia, advanced age, hypertension and other disease conditions. Participants in the

Table 1. Blood pressure, age, BMI, waist circumference, TNF- α , Lipids in prehypertensive and normotensive control subjects

Parameters	PreHTN (n=35)	Control (n=35)	Calc. t- value	P-value
SBP (mmHg)	130.91 \pm 8.70	111.03 \pm 6.89	10.60	0.000*
DBP (mmHg)	83.17 \pm 5.86	70.40 \pm 3.87	10.80	0.000*
Age (years)	35.57 \pm 10.73	33.63 \pm 9.10	0.82	0.417
BMI (Kg/m ²)	24.72 \pm 3.39	24.40 \pm 3.51	1.81	0.072
WC (cm)	69.17 \pm 8.04	68.20 \pm 5.96	0.40	0.694
TNF- α (pg/mL)	52.85 \pm 90.69	4.59 \pm 5.08	3.14	0.002*
T.Chol (mmol/L)	4.28 \pm 0.63	4.18 \pm 0.58	0.71	0.483
HDL-C (mmol/L)	1.61 \pm 0.37	1.59 \pm 0.37	0.19	0.848
LDL-C (mmol/L)	2.21 \pm 0.70	2.14 \pm 0.70	0.45	0.658
VLDL-C (mmol/L)	0.49 \pm 0.22	0.45 \pm 0.13	1.10	0.274
TG (mmol/l)	1.00 \pm 0.38	0.94 \pm 0.30	0.77	0.445

mean \pm standard deviation, critical $t = 1.99$, *significant, SBP- systolic blood pressure, DBP- diastolic blood pressure, WC- waist

circumference, BMI- body mass index, T.Chol.-total cholesterol, HDL-C- high-density lipoprotein cholesterol, LDL-C- low density

lipoprotein cholesterol, VLDL-C- very low-density lipoprotein cholesterol, TG- triglyceride

Table 2. Pearson's correlation coefficients of blood pressure and TNF-alpha with other variables in prehypertensive subjects

Parameters	Age	BMI	WC	TC	HDL	LDL	VLDL	TG
SBP	0.224	-0.033	-0.065	-0.077	0.441*	-0.261	0.038	-0.145
DBP	0.128	0.162	-0.027	0.142	0.412*	-0.045	-0.055	-0.144
TNF- α	0.414*	0.115	-0.167	0.297	0.260	0.065	0.170	0.221

* Correlation is significant at the 0.05 level (2-tailed). SBP- systolic blood pressure, DBP- diastolic blood pressure, WC- waist

circumference, BMI- body mass index, TC.-total cholesterol, HDL- high-density lipoprotein cholesterol, LDL- low-density lipoprotein cholesterol, VLDL- very low-density lipoprotein cholesterol, TG- triglyceride

Table 3. Pearson's correlation coefficients of blood pressure and TNF-alpha with other variables in normotensives

Parameters	Age	BMI	WC	TC	HDL	LDL	VLDL	TG
SBP	-0.055	-0.013	-0.136	-0.191	-0.047	-0.154	0.103	0.046
DBP	0.372*	0.523**	0.338*	0.054	-0.142	0.052	0.368*	0.371*
TNF-α	-0.077	-0.150	-0.230	-0.141	0.045	-0.157	0.083	0.029

**Correlation is significant at the 0.01 level (2-tailed), * Correlation is significant at the 0.05 level (2-tailed). SBP- systolic blood pressure, DBP- diastolic blood pressure, WC- waist circumference, BMI- body mass index, T.Chol.- total cholesterol, HDL-C- high-density lipoprotein cholesterol, LDL-C- low-density lipoprotein cholesterol, VLDL-C- very low-density lipoprotein cholesterol, TG- triglyceride

Table 4. Pearson's correlation coefficients of blood pressure and TNF-alpha with other variables in overall apparently healthy subjects

Parameters	Age	BMI	WC	TC	HDL	LDL	VLDL	TG
SBP	0.146	0.023	-0.001	-0.009	0.157	-0.088	0.109	0.030
DBP	0.208	0.221	0.111	0.133	0.134	0.039	0.143	0.093
TNF-α	0.326**	0.086	-0.107	0.229	0.182	0.056	0.185	0.195

**Correlation is significant at the 0.01 level (2-tailed), SBP- systolic blood pressure, DBP- diastolic blood pressure, WC- waist circumference, BMI- body mass index, T.Chol.-total cholesterol, HDL-C- high-density lipoprotein cholesterol, LDL-C- low-density lipoprotein cholesterol, VLDL-C- very low-density lipoprotein cholesterol, TG- triglyceride

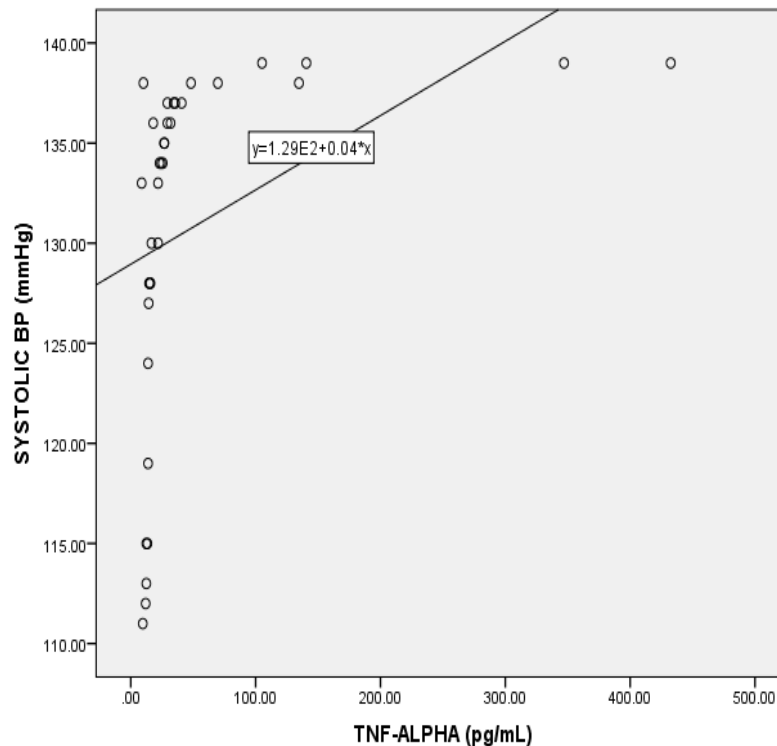


Fig. 1. Correlation of TNF-alpha with systolic blood pressure in prehypertensive subjects

$r=0.387$, $n=35$, $p=0.022$, BP- blood pressure, TNF-tumor necrosis factor

prehypertensive group were also carefully anthropometrically matched with normotensive controls.

Our study compared TNF-α level, lipids in anthropometrically matched prehypertensive and normotensive apparently healthy subjects. In this

study, while lipid levels remained the same, TNF- α level was observed to be higher in the prehypertensive than normotensive individuals. This study found a positive correlation of TNF- α with blood pressure (systolic and diastolic) separately in prehypertensives and overall apparently healthy participants. In normotensives, diastolic blood pressure and not SBP correlated positively with TNF- α . Diastolic BP of normotensives also correlated positively with age, BMI, WC, VLDL-C and TGs. Blood pressure (systolic and diastolic) did not correlate with lipids or physical variables in prehypertensives and the overall participants of our study. In all the 3 groups studied TNF- α levels did not correlate with lipids or physical variables. Our findings show that the relationship observed between TNF- α and blood pressure in the prehypertensive group was not influenced by physical parameters and lipids.

This study is consistent with other studies in hypertensives. Increased plasma concentration of proinflammatory cytokines, in hypertensive individuals, have been confirmed in such studies [20-23]. A previous study conducted in different

grades of blood pressure in essential hypertensive patients showed that TNF- α levels were consistently elevated in both stage 1 and 2 of hypertension [24]. Daytime diastolic blood pressure has been shown to be independently associated with TNF- α in hypertensive patients [1,25]. In apparently healthy Japanese women, Ito et al. found an association of serum TNF- α with LDL-C and blood pressure [26]. Chae et al. reported a significant association between inflammatory markers and elevated BP in apparently healthy patients [27]. Abramson et al. demonstrated a positive association between TNF- α and daytime diastolic BP in healthy, normotensive adults [28]. Chrysohoou et al. studied the association between prehypertension status and inflammatory markers related to atherosclerotic disease and observed a higher increase in TNF- α level, in prehypertensive subjects compared to normotensive subjects [29].

The studies of Sheu et al. and Mendall et al. in human subjects did not agree with the positive association between TNF- α level and blood pressure found in our study and other studies [30,31].

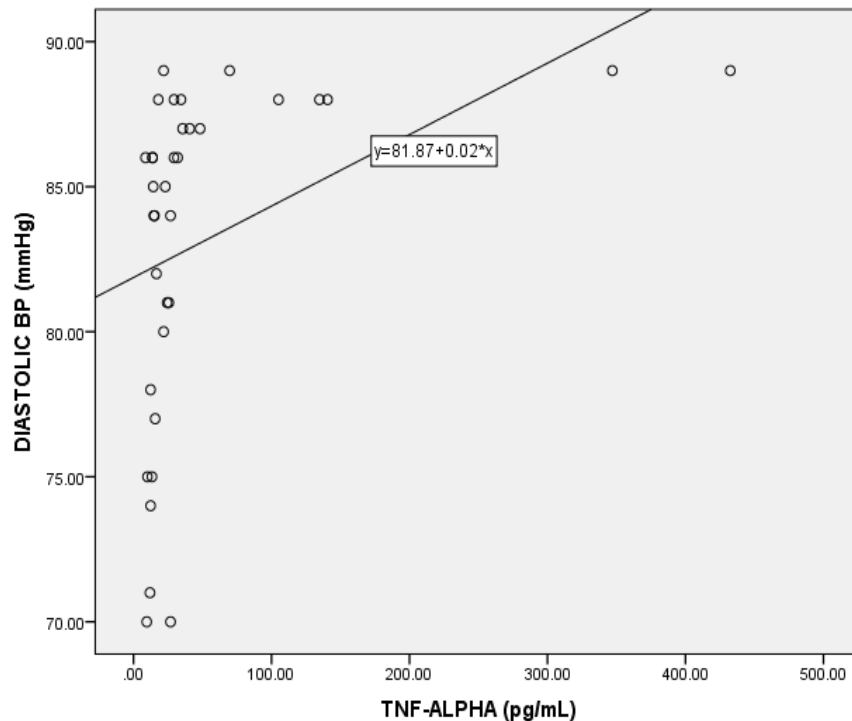


Fig. 2. Correlation of TNF-alpha with diastolic blood pressure in prehypertensive subjects
 $r=0.381$, $n=35$, $p=0.024$, BP- blood pressure, TNF-tumor necrosis factor

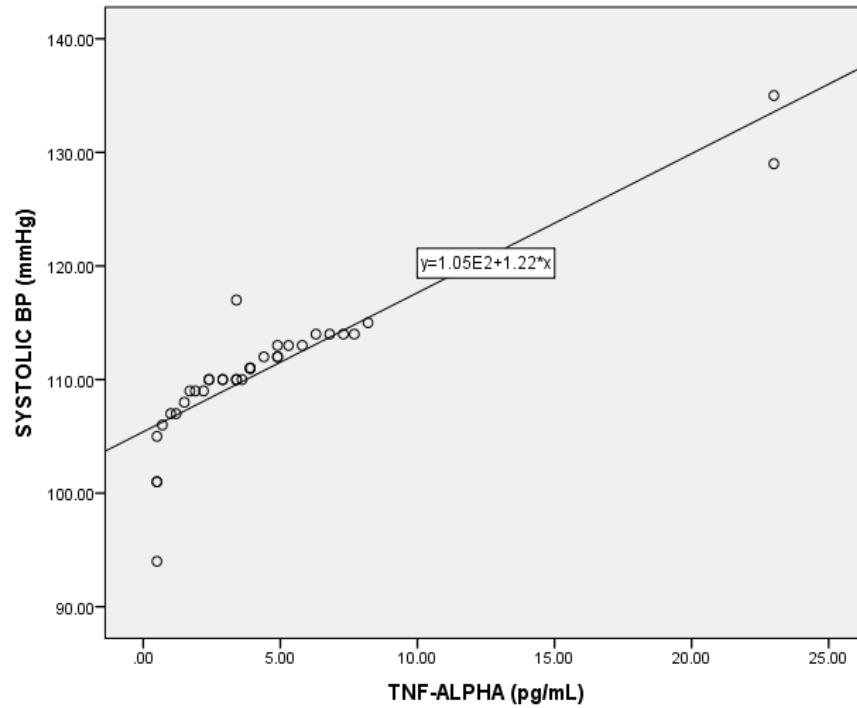


Fig. 3. Correlation of TNF-alpha with systolic blood pressure in normotensive subjects
r=0.816, n=35, p=0.000, BP- blood pressure, TNF-tumor necrosis factor

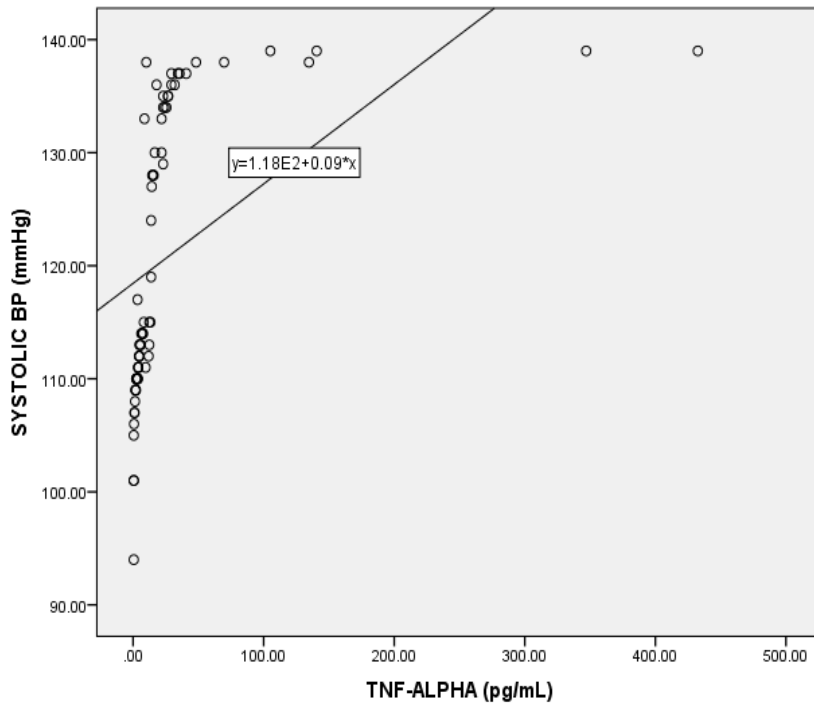


Fig. 4. Correlation of TNF-alpha with systolic blood pressure in all apparently healthy subjects
r=0.473, n=70, p=0.000, BP- blood pressure, TNF-tumor necrosis factor

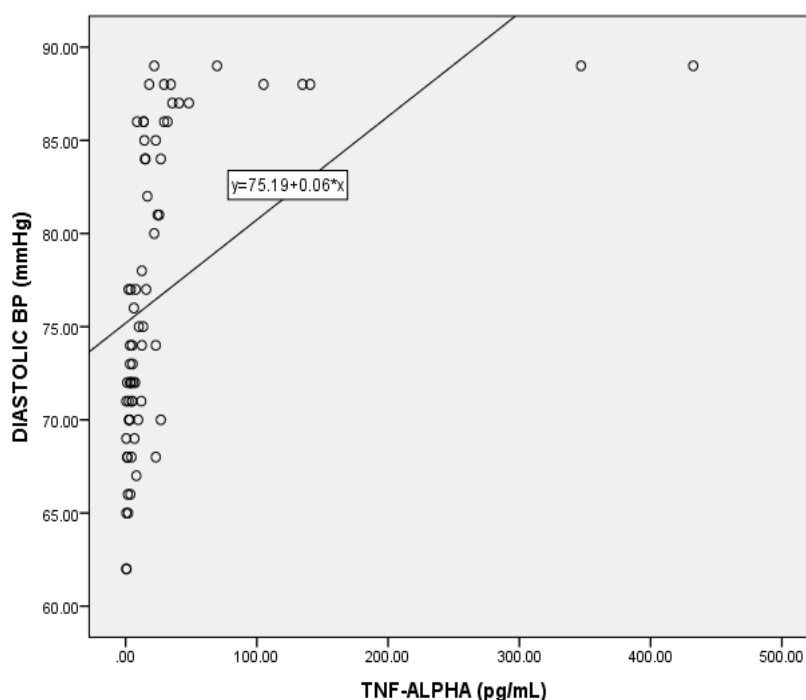


Fig. 5. Correlation of TNF-alpha with diastolic blood pressure in all apparently healthy subjects
 $r=0.467$, $n=70$, $p=0.000$, BP- blood pressure, TNF-tumor necrosis factor

Essential hypertension is characterized by increased peripheral vascular resistance to blood flow [32]. This resistance induces stress on the vascular endothelium contributing to complications of hypertension [33]. In hypertension, resistance arteries undergo a process of inflammatory remodelling involving extracellular matrix deposition and chronic vasoconstriction [33,34]. Experimental data suggest that elevated blood pressure may stimulate pro-inflammatory responses, resulting in endothelial inflammation in the arterial walls and subsequently to hypertension [35,36]. Experimental evidence suggests that elevated BP specifically stimulate endothelial expression of cytokines that promote inflammation in hypertension [27,37]. An experimental study conducted by Fernandez-Real et al. showed that the degree of activation of the TNF- α system was positively and significantly associated with systolic and diastolic BP in type 2 diabetics [38]. TNF- α has been shown to decrease endothelial nitric oxide synthase mRNA level by shortening its half-life [39]. This decreases bioavailable nitric oxide leading to endothelial dysfunction, followed by chronic vasoconstriction and elevated blood pressure. Also, a polymorphism in the promoter region of the TNF- α gene has been associated with increased TNF- α and

systolic BP [40]. It is possible that elevated TNF- α , initiates the development of high blood pressure, or enhances the progression of hypertension through stages to complications.

The limitations of our study must be considered. The number of subjects in our study groups was small due to the selection criteria aimed at eliminating confounding factors of the measured variables. A battery of inflammatory markers other than TNF- α can be measured. Since TNF- α was measured at the same point in time as BP, it is not possible to know whether one precedes the other or vice versa. A follow-up study on participants is required to determine the direction of the cause-effect relationship between blood pressure and TNF- α .

5. CONCLUSION

Our study observes an association of blood pressure with TNF- α in prehypertensives. The cause and effect relationship between blood pressure and TNF- α could be bidirectional. A moderate rise in blood pressure could serve as a stress inducer of TNF- α production in initiating vascular inflammation. The mild chronic inflammation in the prehypertensives could further enhance the progression of moderately

elevated blood pressure to hypertension and its complications. We recommend the adoption of healthy lifestyles geared towards maintenance of normal blood pressure levels.

CONSENT

The patient's written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

Ethical approval for this study was obtained from the ethics committee of Federal Medical Centre, Makurdi, Nigeria.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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