

Original Research Article

Investigation of selected inflammatory parameters as potential markers and risk factors for hypertension

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Abstract

Purpose: To determine changes in selected inflammatory parameters as potential markers and risk factors for hypertension.

Methods: A case-control design with 150 participants comprising 100 hypertensive patients (study group) and 50 healthy individuals that served as controls was evaluated. The study was carried out from October 2023 to July 2024 in AL Nasiriyah Teaching Hospital, Basra, Iraq. Demographic parameters such as age, gender, family history, smoking status and other sociodemographic information of the patients were documented using questionnaire. Lipid profiles, urea, serum creatinine and other chronic disease inflammatory parameters, including Pro B-type natriuretic peptide (BNP), malondialdehyde (MDA), tumour necrosis factor- α (TNF- α), hydrogen peroxide (H₂O₂), and interleukin-6 (IL-6) were also analyzed.

Results: There were significantly increased levels of IL-6, TNF- α , MDA, H₂O₂, and Pro B-type natriuretic peptide (BNP) in sera of hypertensive patients compared to control group ($p < 0.05$). Hypertensive patients had higher lipid profiles (cholesterol, triglyceride (TG), very low-density lipoprotein (VLDL), and low-density lipoprotein (LDL)) than control group ($p < 0.05$), except for HDL (42.3650 ± 9.24 mg/dL), which was lower. The study group had significantly higher concentrations of urea and serum creatinine when compared with control group ($p < 0.05$).

Conclusion: Inflammatory and metabolic mediators are risk factors for hypertension. As the levels of these variables increase, the likelihood of developing or worsening hypertension also increases. Further studies are needed to validate the findings reported.

Keywords: Inflammatory parameters, Hypertension, Risk factors, Biomarkers, Cardiovascular disease

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INTRODUCTION

Hypertension is often diagnosed when blood pressure regularly exceeds 140 mmHg (Systolic pressure) and 90 mmHg (diastolic pressure). Hypertension increases the risk of other cardiovascular diseases, stroke, and kidney failure, resulting in severe morbidity and mortality [1]. Nearly 1.28 billion people worldwide suffer

from hypertension [2]. Besides advances in knowledge and treatment of hypertension, the roles of metabolic and inflammatory mediators are emerging [3-5]. High blood pressure is linked to low-grade inflammation, since several indicators have been found in hypertensive individuals [3]. Hypertension raises C-reactive protein (CRP), a measure of systemic inflammation. Interleukin-6 (IL-6) and tumour

necrosis factor- α (TNF- α) are pro-inflammatory cytokines involved in immunological responses, and have been reported to be elevated in hypertensive patients [3,4]. The TNF- α causes endothelial dysfunction, vascular inflammation, and increased vascular resistance. It decreases nitric oxide (NO) bioavailability, impairs vasodilation, elevates blood pressure and activates immune cells that worsen vascular inflammation [5].

Immune cells (monocytes) are recruited to inflammatory areas by monocyte chemoattractant protein-1 (MCP-1) which contributes to hypertension and vascular inflammation [6]. The MCP-1 expression increases monocyte penetration through vascular walls, where they become macrophages. This process causes chronic inflammation and remodeling, thus raising blood pressure [6]. Chronic inflammation causes blood vessel remodeling, while increased artery wall thickness and stiffness increase peripheral resistance and blood pressure [7]. Low-grade chronic inflammation may be associated with metabolic dysfunction and hypertension. Pro-inflammatory cytokines increase oxidative stress, vascular inflammation, and endothelial dysfunction, thereby increasing vascular resistance and blood pressure [8]. Hypertensive patients have been reported to exhibit higher systemic inflammation than normotensives [9].

This study, therefore, examines the effect of some metabolic and inflammatory mediators as risk factors for hypertension.

METHODS

Study design

This case-control study involved 150 participants. They were divided into two groups based on their status as 100 hypertensive patients (study group) and 50 healthy subjects (control group). The study was conducted from October 2023 to July 2024. Patients with hypertension were selected from AL Nasiriyah Teaching Hospital, Basra, Iraq, while healthy subjects were volunteers (including staff, students and patients' relatives) around the hospitals who consented to participate in the study. The researchers and supporting Physicians conducted comprehensive clinical history recording and clinical examination, and collected blood samples for relevant laboratory tests from all the subjects using the most recent clinical practice guidelines from the World Health Organization to identify the clinical conditions of hypertension [10].

Inclusion criteria

The following criteria were used to choose the participants: both male and female volunteers between the ages of 25 and 60 with a body mass index (BMI) below 25, with or without hypertension, with no comorbidities, and no history of myocardial infarction (MI) or angina.

Exclusion criteria

Patients with diabetes, those on immunosuppressive therapy like corticosteroids, patients with autoimmune disease, myocardial infarction (MI) or angina, and patients who have had any form of surgery were excluded from the study. Furthermore, patients on other medicines or supplements, pregnant patients, and patients with other chronic disorders were also excluded from the study.

Ethical approval

The protocol for this study was approved by Basrah Pharmacy College Ethical Committee and the Cardiologist Consultant Unit at AL-Hussein Teaching Hospital, Basrah, Iraq (approval no. EC 175) and was conducted following the conditions in the Declaration of Helsinki [11].

Data collection

Records were collected for each subject's age, gender, family history, smoking status, social activities, and eating habits using a pre-tested, validated questionnaire. Patients' medical histories, social activities, and other sociodemographic details were compiled, while lipid profiles, serum creatinine, and urea were determined using appropriate kits.

Specimen collection

Blood sample collection

Blood samples (5 mL) were collected by scientists in the Clinical Chemical Laboratory of Al Hussein Teaching Hospital's outpatient unit and stored in plain heparinized tubes at room temperature for 15 min. The blood samples were centrifuged at 4000g for 10 min to obtain sera. Sera were kept at -20 °C before analysis in order to reduce the number of freezing-thawing cycles.

Assay for lipid profile

High-density lipoprotein (HDL), total cholesterol (TC), triglycerides (TG), very low-density lipoprotein (VLDL), and Low-density lipoprotein

(LDL) were quantified using an automated clinical chemistry analyzer. The equipment utilizes halogen-tungsten lamps with eight wavelengths (340 – 670 nm) and bi-directional Laboratory Information System (LIS) communication. Independent mixing unit, cuvette washing station, inbuilt barcode reader, and optional Ion-Selective Electrode (ISE) module for K⁺, Na⁺, and Cl⁻ measurements were also used.

Urea and creatinine measurement

This was performed using an automated chemical analyzer with the following measuring principles: absorbance photometry (kinetic mode) for urea and absorbance photometry (end-point mode) for serum creatinine (Sr.Cr).

Enzyme-Linked Immunosorbent-Assay (ELISA)

This was used to measure the levels of MDA, H₂O₂, TNF- α , IL-6, and Pro-BNP in the serum of patients and control groups using commercially available kits in line with the manufacturer's instructions.

Statistical analysis

Statistical Package for the Social Sciences (version 16) was used for data processing. Values are recorded as mean $\pm$ standard

deviation (SD). Analysis of variance (ANOVA) and logistic regression analysis were conducted to determine the inferential statistics for potential marker that is expressed in hypertension. A *p*-value less than 0.05 was considered statistically significant.

RESULTS

Demographic distribution

The study group comprised a total of 100 hypertensive patients consisting of 47 males and 53 females with mean age of 56.491 ± 11.57 years and mean BMI of 27.11 ± 4.98 kg/m². Fifty (50) healthy individuals, consisting of 31 males and 19 females with mean age of 55.68 ± 8.96 years and mean BMI of 26.1575 ± 2.214 kg/m², were recruited as control group. Other demographic details of the subjects are shown in Table 1.

Relationship between oxidative stress and hypertension

As shown in Table 2, the levels of metabolic and inflammatory mediators, such as MDA, TNF- α , H₂O₂, IL-6 and Pro BNP were significantly higher in study group when compared with control group (*p* < 0.05).

Table 1: Demographic parameters of patients and controls

Parameter	Control (n=50)	Study (n=100)	P-value
Mean age (years)	55.7±9.0	56.5±11.6	0.495
Gender ratio (Male: female)	31:19	47:53	0.083
Mean BMI (kg/m²)	26.2±2.2	27.1±5.0	0.204
Systolic BP (mmHg)	132.3±9.7	143.2±13.7	0.001*
Diastolic BP (mmHg)	73.2±9.8	84.4±9	0.001*
Marital status			
Married (%)	80	86	0.003*
Unmarried (%)	20	14	
Smoking history			
No (%)	68	72	0.612
Yes (%)	32	28	
Drug allergy	Negative	Negative	0.216

Values are mean $\pm$ SD; **P* < 0.05 vs control group

Table 2: Inflammation and oxidative stress markers in hypertensive patients compared to healthy controls

Parameter	Control (n=50)	Study (n=50)	P-value
MDA (μ mol/L)	1.611 $\pm$ 1.09	2.01 $\pm$ 1.07	0.019*
TNF (ng/L)	18.82 $\pm$ 3.84	20.03 $\pm$ 2.91	0.04*
H ₂ O ₂ (mmol/kg)	18.91 $\pm$ 7.13	22.89 $\pm$ 4.64	0.001*
IL6 (ng/mL)	10.04 $\pm$ 3.39	11.25 $\pm$ 2.84	0.023*
Pro BNP (pg/mL)	85.26 $\pm$ 17.22	98.28 $\pm$ 16.73	0.001

**P* < 0.05 vs control

Relationship between lipid profiles, kidney functions, and hypertension

Table 3 reports the level of lipid profile and kidney function parameters in the two groups. Parameters in the study group were higher than control group, except for HDL, which was lower in study group. Furthermore, study group has higher urea, creatinine levels compared to control group ($p < 0.05$).

Correlation between levels of kidney function parameters and systolic and diastolic blood pressure

Table 4 shows the correlation between kidney function and blood pressure in the study group. There was a positive correlation between levels of kidney function parameters (urea, serum creatinine) and systolic and diastolic blood pressure.

Correlation between oxidative stress markers and blood pressure

A positive correlation between the levels of oxidative stress markers (IL-6, H_2O_2 , TNF, MDA and Pro-BNP) and blood pressure in the study group is revealed in Table 5.

Correlation between inflammatory and oxidative stress markers

Pearson correlation among the study group's inflammatory and oxidative parameters shows a moderate positive correlation between H_2O_2 and TNF- α , with a significant positive correlation between TNF, IL-6 and Pro-BNP. There was a weak positive correlation among other parameters (Table 6).

Relationship between levels of markers and hypertension

Logistic regression analysis for each parameter revealed a significant positive statistical relationship between the levels of TNF, IL-6, MDA, and H_2O_2 and hypertension ($p < 0.05$) as shown in Table 7.

DISCUSSION

Age alters the vascular system and arteries become less elastic, thereby raising blood pressure in susceptible individuals. Even heart-healthy persons who feel well may experience this challenge; hence, many are unaware. Ramezankhani *et al* [9] reported that hypertension was more common among older individuals with mean age of 51 years, which also agrees with the demographic finding of this study.

Previous investigations reported poor management of hypertension among married people regardless of race or age [12]. People living alone have well-controlled blood pressure, according to Shah and Cook [12]. Married people were more than four times the number of unmarried people and were older than the unmarried. This is understandable as all the participants were adults. Pregnancy, birth control medications, and hormonal changes after menopause increase the risk of high blood pressure in women. Nearly 52 % of hypertensive-related deaths have been reported in women [10]. Furthermore, the average systolic and diastolic blood pressures increased with BMI; hence, there was a higher BMI in hypertensive patients than normotensive patients, although they were not significantly different ($p > 0.5$) [11].

Table 3: Comparison of levels of lipid profile and kidney function parameters between hypertensive patients and healthy controls

Parameter	Control (n=50)	Patients (n=100)	P-value
Cholesterol	168.89±26.71	207.26±43.33	0.001
TG	127.94±52.64	189.83±60.00	0.001
HDL	48.15±8.70	42.37±9.24	0.001
VLDL	25.95±10.37	35.35±16.19	0.001
LDL	105.44±17.53	125.22± 37.62	0.001
Urea	24.66±6.04	35.24±10.68	0.001
Sr.Cr	0.71±0.14	1.05±0.52	0.001

Serum creatinine: Sr.Cr

Table 4: Correlation between levels of kidney function parameters and blood pressure

Parameter		Urea	Serum creatinine
Systolic BP	Pearson correlation	0.013	0.066
	P-value	0.889	0.477
Diastolic BP	Pearson correlation	0.098	0.147
	P-value	0.285	0.108

Table 5: Correlation of levels of inflammatory and oxidative stress markers with blood pressure

Parameter		IL6	H ₂ O ₂	TNF- α	MDA	Pro-BNP
Systolic BP	Pearson correlation	0.247	0.202	0.255	0.230	0.215
	P-value	0.013	0.044	0.011	0.021	0.032
Diastolic BP	Pearson correlation	0.196	0.252	0.197	0.211	0.254
	P-value	0.048	0.011	0.049	0.035	0.011

Table 6: Correlation between inflammatory and oxidative stress markers

Parameter		IL6	TNF- α	Pro-BNP	MDA	H ₂ O ₂
IL6	Pearson correlation	1.0	0.055	0.295**	0.061	0.035
	P-value	0.0	0.583	0.003	0.546	0.727
TNF	Pearson correlation	0.055	1.0	0.282**	0.143	0.198*
	P-value	0.583		0.004	0.157	0.048
Pro-BNP	Pearson correlation	0.295**	0.282**	1.0	0.186	0.149
	P-value	0.003	0.004		0.064	0.138
MDA	Pearson correlation	0.061	0.143	0.186	1.0	0.156
	P-value	0.546	0.157	0.064		0.121
H ₂ O ₂	Pearson correlation	0.035	0.198*	0.149	0.156	1.0
	P-value	0.727	0.048	0.138	0.121	

* $P < 0.05$ indicates statistically significant correlation ** $P < 0.001$ indicates highly significant correlation

Table 7: Predictors of hypertension: logistic regression analysis of inflammatory, oxidative stress, and kidney function parameters

Predictor	Regression coefficient (B)	P-value
TNF	0.190	0.021
IL-6	0.171	0.043
MDA	0.412	0.039
H ₂ O ₂	0.124	0.011
Pro BNP	0.026	0.244
Urea	0.008	0.818
Sr.Cr	0.300	0.860

Serum creatinine: Sr.Cr

There were two to three times more non-smokers than smokers and there were fewer smokers among the study (hypertensive) group. This is because previous reports suggest that there is a strong correlation between cigarette smoking and hypertension, resulting in artery damage and increased heart disease risk. This has been responsible for measures that have led to a reduction in the number of smokers in the hypertensive group. Factors such as age, sex, socioeconomic level, and poor education have been reported to influence hypertension [13].

Elevated levels of IL-6, H₂O₂, TNF- α , MDA, and pro-BNP may signal a heightened inflammatory response and oxidative damage, which in turn affect cardiovascular function and blood pressure. These elevated inflammatory markers suggest that they may all be part of a shared pathway involving inflammation and oxidative stress, which could contribute to conditions such as hypertension, cardiovascular disease, and other chronic conditions. Even in normotensives, raised IL-6 levels cause hypertensives to respond to angiotensin II (ACE) infusion, suggesting new therapeutic targets [14]. Multiple studies indicate that proinflammatory

cytokines like TNF- α stimulate ACE synthesis, leading to inflammation-mediated hypertension [14-17]. Another study found that angiotensin II increases levels of reactive oxygen species (ROS), particularly superoxide, by increasing NADH and NADPH oxidase. Therefore, IL-6, triggered by angiotensin II, increases NADH and NADPH synthesis, changing vascular permeability, constriction, fibrosis and raising blood pressure [18].

Considering factors like disease stage, other biomarkers, and the health status of the individual, positive correlations between levels of IL-6, H₂O₂, and pro-BNP with blood pressure suggest that increased inflammation, oxidative stress, and cardiac strain are linked to higher blood pressure. These markers may be useful in understanding the mechanisms that underlie hypertension, as they reflect key processes that contribute to its development and progression.

Interleukin-6 may cause hypertension by affecting vascular inflammation, stiffness, and endothelial dysfunction. It also increases artery wall collagen synthesis and fibrinogenesis. Interestingly, atherosclerotic plaques exhibit

elevated IL-6 [19]. This study is identifying elevated IL-6 and TNF- α levels as well as other inflammatory and metabolic markers as possible risk factors for high blood pressure in healthy individuals. Plasma levels of IL-6 and TNF- α have been linked to coronary endothelial dysfunction in hypertensive patients [20]. Pro-BNP is a 32-amino-acid peptide with vasodilator and natriuretic characteristics. In reaction to chamber stretching, the cardiac ventricles release 108-amino-acid pro-brain natriuretic peptide, which may affect blood pressure. Recently, plasma pro-BNP levels have been studied as hypertension markers, as information about their concentration has been applied for diagnosis, risk assessment and treatments in adults with congestive heart failure and hypertension [23].

Findings from this study confirm previously reported outcomes that plasma pro-BNP levels largely reflect left ventricular myocardial mass, suggesting its use as a diagnostic for left ventricular (LV) hypertrophy in critical hypertensive patients [24]. The pro-BNP levels are often evaluated to direct antihypertensive treatment; while monitoring it allows clinicians to identify hypertensives with subclinical cardiac stress for more aggressive or personalized treatment to avert cardiovascular events [24]. Hypertensive patients in this study had significantly elevated H_2O_2 levels ($p < 0.05$). In particular, agonists like serotonin, phenylephrine, and H_2O_2 increase vasoconstriction while decreasing endothelial relaxation [25]. Changes in vascular smooth muscle membrane potential and Ca^{2+} handling may cause hypertension-induced vasoconstriction and endothelial dysfunction that reduces relaxation [25]. Most of these tests were done in arteries; therefore, it is uncertain if H_2O_2 level increases hypertension through venous reactivity [25]. These findings support the suggestion that increase in H_2O_2 levels causes increased venous tone and arterial resistance and, consequently, hypertension because mean circulatory pressure (an indication of venous tone) is higher in hypertensive than normotensive patients [26]. Another study reveals that elevated H_2O_2 levels enhance splanchnic venoconstriction, which increases cardiac output and blood pressure.

Among lipoproteins and their lipids, TG, VLDL, and LDL cause blood pressure to rise the most. Lipids such as HDL and TG were possible exposure foci. Data from this study suggests that comprehensive lipid profile management may benefit blood pressure control, which is consistent with previous studies that found elevated LDL, VLDL, and TG in hypertensive

patients [27]. Current consensus on comprehensive blood pressure and dyslipidemia therapy focuses solely on major lipids, with LDL-C as the main intervention target. However, systolic and diastolic blood pressures have different susceptibility populations, mechanisms, and prognoses [12].

The causal role of hypertension-associated lipoproteins is reflected by decrease in anti-atherogenic HDL and an increase in atherogenic VLDL, TG, and LDL levels, resulting in changes in arterial stiffness. This affects blood pressure control over time and facilitates the transition from mixed hypertension to isolated systolic hypertension, which is more common. Hypertension may be caused by atherosclerosis, which is characterized by increased cholesterol, TG, VLDL, and LDL levels and inflammation [25].

There were elevated urea and serum creatinine levels in hypertensive individuals, which have several explanations indicated in earlier studies [26-27]. Kidney transplant affects blood pressure, with normotensive recipients of genetically programmed hypertensive kidneys developing hypertension and hypertensive patients with renal failure receiving the kidney of a normotensive donor developing normotension [27]. Renal illness causes hypertension, but there is growing evidence that a genetic predisposition to hypertension enhances the risk of developing hypertension [9]. Parents of children with glomerulonephritis have been reported to have higher blood pressures than matched controls [28]. This also applies to diabetic nephropathy, where parents of type 1 diabetics had higher blood pressure than those without diabetes [1,9]. This study reveals that a positive correlation exists between the levels of urea and serum creatinine and hypertension, but the correlation is not statistically significant ($p > 0.05$). This non-significant result suggests that there is not strong enough evidence to conclude a meaningful or reliable relationship between these variables. Hence, the observed correlation could be due to random variables.

Limitations of this study

The first limitation was the few and variable number of patients in the study group and control group. It was quite challenging to recruit healthy patients as controls for this study. Secondly, the study was conducted in only one institution. There would be need to repeat the study in multiple centers and finally results from single samples were reported. The effect of antihypertensive medications, foods, beverages

and other related substances that could alter overall outcomes of this study was not studied.

CONCLUSION

This study suggests that the inflammatory and metabolic mediators are risk factors for hypertension. As the levels of these variables increase, the likelihood of developing or worsening hypertension also increases. This highlights the interconnected role of inflammation, oxidative stress and kidney function in hypertension. It is important to expand this study to include more patients and larger number of variables.

DECLARATIONS

Acknowledgement/Funding

None.

Ethical approval

None provided.

Use of Artificial intelligence/Large language models

We also declare that we did not use Generative artificial intelligence (AI) and AI-assisted technologies in writing the manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the author(s) named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

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