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Proinflammatory Mediators in Normal Weight Hypertensive Women of Reproductive Age

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Abstract

Background: Based on age- and gender-specific studies, it has been revealed that hypertension (HTN) is an independent risk factor in the development and progression of cardiovascular diseases (CVDs). Therefore, the present study was designed to investigate the distinct impact of proinflammatory mediators -interleukin (IL-6), leptin (Lep), tumor necrosis factor-alpha (TNF-α), and homocysteine (Hcy) in normal weight (NW) normotensive (NTN) and HTN women of reproductive age with grade-1 HTN.
Methods and Results: The participants in the present study were NW women with NTN (n=200, age: 20-29 years) and HTN (n=198, age: 20-29 years) of reproductive age. The enzyme-linked immunosorbent assay (ELISA) kits were used to determine serum levels of pro-inflammatory mediators. Highly significant increases in serum levels ($p<0.001$) and significant positive linear correlations ($p<0.001$) for Lep, IL-6, and TNF-α in HTN compared to NTN women were investigated.
Conclusion: Results obtained in the present study in patients with HTN, independent of the influence of BW, indicate the pathophysiological significance of the interactive role of the inflammatory mediators (Lep, IL-6, and TNF-α) that would hopefully help further understanding of the mechanism of the development and progression of HTN and therapeutic implications for HTN. **(International Journal of Biomedicine. 2026;16(4):499-504.)**

Keywords: leptin, Interleukin-6, tumor necrosis factor-alpha, normal weight, hypertension, reproductive-age women

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Abbreviations

BMI, body mass index; **BP,** blood pressure; **BW,** body weight; **CVDs,** cardiovascular diseases; **DBP,** diastolic blood pressure; **DM,** diabetes mellitus; **ELISA,** enzyme linked immunosorbent assay; **Hb,** hemoglobin; **Hcy,** homocysteine; **HTN,** hypertension; **IL-6,** interleukin-6; **Lep,** leptin; **MCL,** menstrual cycle length; **MPD,** menstrual phase duration; **NTN,** normotension; **NW,** normal weight; **OW,** overweight; **PVAT,** perivascular adipose tissue; **R2,** coefficient of determination; **ROS,** radical oxygen species; **SBP,** systolic blood pressure; **SPSS,** Statistical Package for Social Sciences; **TNF-α,** tumor necrosis factor-alpha; **UQU,** Umm Al-Qura University.

Introduction

Based on age- and gender-specific studies, hypertension (HTN) is prevalent worldwide and is one of the major health problems requiring immediate attention.[1] It has been revealed that high blood pressure (BP) or HTN is an independent risk factor in the development and progression of cardiovascular diseases (CVDs).[2] Therefore, it is essential to study HTN thoroughly, considering various perspectives and screening, prevention, and therapeutic procedures.[1]

Considering systolic blood pressure (SBP) and diastolic blood pressure (DBP) levels irrespective of lifestyle and therapeutic criteria, HTN has been classified into three grades: grade 1 (SBP: 140-159 mmHg, DBP: 90-99 mmHg), grade 2 (SBP: 160-179 mmHg, DBP: 100-109 mmHg), and grade 3 (SBP: ≥180, DBP: ≥110).[3] Effective treatment of HTN and various other CVDs in women requires a better understanding of the sex-related differences that lead to a higher prevalence in women than men in view of more frequent female-related interactions,[4] e.g., heightened vasodilation in microvasculature and aortic stiffness due to small-sized coronary arteries in women.

The HTN-based information provides strong evidence of BP's influence on the development/progression of HTN.[5] Despite that, further clarification is required in view of controversial results due to different approaches/criteria employed for studying HTN patients.[5-7]

There are a variety of factors, including pro-inflammatory mediators-interleukin-6 (IL-6), leptin (Lep), tumor necrosis factor-alpha (TNF-α), and homocysteine (Hcy) that may

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affect HTN and other vascular disorders.[8-16] However, no clear consensus exists on the interactive impact of various factors in understanding the mechanism of HTN, despite exploring the involvement of these factors,[17] though they have been studied in other CVDs, stroke, diabetes, and other disorders.[18-21] Therefore, the present study was designed to investigate the distinct impact of proinflammatory mediators in NW women of reproductive age with grade 1 HTN.

Materials and Methods

The present case-control study (HTN compared to NTN women) was carried out from January 2024 to January 2026 at the hospitals in Makkah (Saudi Arabia) collaborating with Umm Al-Qura University (UQU). Ethical approval for the current study (Approval No. HAPO-02-K-012-2022-01-1069) was obtained from the Faculty of Medicine, UQU. The methods, procedures, and techniques were employed in accordance with the instructions of the committee for institutional ethics on human experimentation and the Declaration of Helsinki (revised in 2013).

The sample size for the present work was calculated by: n=z2 *p* (1-p)/e2 (z, e and p respectively are: confidence level, margin of error/ confidence interval and proportion (p=0.5). The number of samples obtained using the formula was 385, and we planned to collect 420 samples for the present study. However, required patient/subject history and/or blood samples could not be properly managed for 22 participants (10 NTN and 12 HTN). Therefore, the sample size in the present study is 398 participants (200 NTN (Group 1) and 198 HTN (Group 2) with an age range of 20-29 years in both groups.

The subjects collected for both groups were well matched by age (20-29 years), sex (female subjects), and BW and, hence, body mass index (BMI) (≥18.5 and ≤24.9 kg/m²). Furthermore, all subjects in Group 2 (HTN) had grade-1 HTN (data for grade-2 and grade-3 HTN patients were not included). The participants in Group 1 (NTN) were healthy women without HTN, other cardiovascular disorders, or other disorders. The SBP and DBP were ≤120 and ≤80 mmHg, respectively, in NTN participants, and 140–159 and 90–99 mmHg, respectively, in HTN patients (grade 1). The BP measurements were taken by a manual mercury sphygmomanometer (MS-S1500-Mercury-Sphygmomanometer, Medical Sources Company Limited, Nanjing, Jiangsu, China).

Data from both groups were collected during the ovulatory cycle with the participants' permission/consent. The female individuals in both groups were of childbearing age (reproductive age) and free of anemia. Furthermore, they were not taking vitamin B, folic acid, or other supplements. They were all non-smokers, non-obese, non-pregnant, and non-diabetic. Those who were breastfeeding were not included in the present study.

The general features and patient/subject history were recorded and entered into a special questionnaire. The screening of the required participants was based on sex, age range, BW, and BP. The records of their menstrual cycle length (MCL in days) and 7 menstrual phase duration (MPD in days) were recorded. Their hemoglobin (Hb) levels were determined using a hematology analyzer, Sysmex XN 100i (Sysmex Europe SE, Norderstedt, Germany). The concentration of serum IL-6 was determined using a human interleukin-6 (IL-6) enzyme-linked immunosorbent assay (ELISA) kit. Serum homocysteine (Hcy) was measured using the Human-Hcy ELISA Kit. Serum Lep estimation was carried out using Lep human ELISA kit (ab100581)-Abcam's leptin human ELISA (Cambridge, UK), whereas serum TNF-α was measured by ELISA assay (catalog. STA00C, Quantikine ELISA, R&D Systems Inc., Minneapolis, MN, USA).

General biostatistical tests for the analysis of variation were performed using mean ± Standard Deviation (SD), and an unpaired t-test with two-tailed p-values was used to compare the HTN and NTN groups.[22] Whereas, to analyze and obtain the correlation between each pair of variables in both groups, the significance (p-value) was determined using the Statistical Package for the Social Sciences (SPSS), version 24.0 for Windows, and the coefficient of determination (R^2) was obtained. A p-value < 0.05 indicated significant variation or correlation between the two parameters.

Results

The present report in NW reproductive age women investigates the impact of serum proinflammatory mediators, IL-6, TNF-α, Hcy and Lep in NTN group (n=200, age: 25.05±2.95 years, MPD: 5.34±1.23 days, MCL: 28.37±1.39 days) and HTN group 8 (n=198, age: 25.00±2.96 years, MPD: 5.24±1.27 days, MCL: 28.45±1.40 days). Some of the general characteristics and variables studied in the current study are presented in Table 1.

Table 1.

General characteristics and variables of normal weight normotensive and hypertensive women of reproductive age.

Variables	Characteristics and variables in normal-weight normotensive and hypertensive women of reproductive age			
	NTN (n=200)	HTN (n=198)	Significance level	
			t-value	p-value
Number of subjects (n)	200	198	-	-
Age (years)	25.05±2.95	25.00±2.96	0.15	0.88
MPD (days)	5.34±1.23	5.24±1.27	0.80	0.42
MCL (days)	28.37±1.39	28.45±1.40	0.64	0.52
Hb (g/dL)	13.64±1.08	13.53±1.02	1.04	0.30
IL-6 (pg/mL)	3.83±1.82	6.39±2.72	11.03	<0.001
TNF-α (pg/ml)	4.20±2.28	6.35±2.69	8.63	<0.001
Hcy (µmol/L)	4.60±1.01	4.61±1.00	0.11	0.91
Lep (ng/mL)	4.65±1.86	9.16±3.24	17.04	<0.001

NTN: normotensive, HTN: hypertensive, MPD: menstrual phase duration, MCL: menstrual cycle length, Hb: hemoglobin, IL-6: interleukin-6, TNF- α: tumor necrosis factor alpha, Hcy: homocysteine, Lep: leptin.

Highly significant increases in serum levels of Lep, IL-6, and TNF-α were observed in HTN women compared

with NTN women (p<0.001; Table 1). The characteristics and variables in HTN women that did not show significant differences compared with NTN women were age, MPD, MCL, Hb, and Hcy (p>0.05; Table 1).

Serum Lep levels were plotted against other variables in both NTN and HTN groups of women. Significant positive linear correlations of serum Lep with IL-6 and TNF-α were observed in HTN women (p<0.001; Table 2). Serum Lep levels did not show a significant correlation with the remaining parameters (age, Hb, and Hcy) in HTN women (p>0.05, Table 2). All variables in the NTN group of women showed no significant correlation with serum Lep (p>0.05, Table 2).

Table 2.

Correlation of serum leptin levels with other variables in normal-weight hypertensive women of reproductive age.

Variables	R^2 and p-value for serum leptin against other variables in normal-weight normotensive and hypertensive women of reproductive age			
	NTN		HTN	
	R^2	p	R^2	p
Age	0.002	0.509	0.006	0.266
Hb	0.002	0.509	0.003	0.434
IL-6	0.001	0.590	0.560	<0.001
Hcy	0.001	0.590	0.000	0.895
TNF-α	0.003	0.475	0.290	<0.001

NTN: normotensive, HTN: hypertensive, Hb: hemoglobin, IL-6: interleukin-6, Hcy: homocysteine, TNF- α: tumor necrosis factor alpha.

A plot of serum IL-6 against Lep and TNF-α in HTN women showed a significant positive linear correlation (p<0.001; Table 3). Whereas age, Hb and serum Hcy showed non-significant correlation with serum levels of IL-6 (p>0.05, Table 3). Serum IL-6 did not show significant correlation with any of the parameters in NTN women (p>0.05, Table 3).

Table 3.

Correlation of serum IL-6 levels with other variables in normal-weight hypertensive women of reproductive age.

Variables	R^2 and p-value for serum IL-6 against other variables in normal-weight normotensive and hypertensive women of reproductive age			
	NTN		HTN	
	R^2	p	R^2	p
Age	0.006	0.286	0.001	0.733
Hb	0.012	0.110	0.006	0.281
Lep	0.001	0.590	0.560	<0.001
Hcy	0.001	0.590	0.001	0.590
TNF-α	0.001	0.594	0.190	<0.001

IL-6: interleukin-6, NTN: normotensive, HTN: hypertensive, Hb: hemoglobin, Lep: leptin, Hcy: homocysteine, TNF- α: tumor necrosis factor alpha.

Table 4 presents the results of the correlation between serum TNF-α levels and other variables in NW reproductive-age women with HTN. A significant positive linear correlation between TNF-α levels and each of Lep and IL-6 levels was found in the HTN group of women (p<0.001, Table 4). The other parameters, age, Hb, and serum Hcy, did not show a significant correlation with serum TNF-α levels (p>0.05, Table 4). Serum TNF-α levels showed no significant correlation with any parameter in NTN women (p>0.05, Table 4).

Table 4.

Correlation of serum TNF-α levels with other variables in normal-weight hypertensive women of reproductive age.

Variables	R^2 and p-value for serum TNF-α against other variables in normal-weight normotensive and hypertensive women of reproductive age			
	NTN		HTN	
	R^2	p	R^2	p
Age	0.000	0.976	0.009	0.178
Hb	0.001	0.706	0.002	0.559
Lep	0.003	0.475	0.290	<0.001
Hcy	0.001	0.649	0.001	0.665
IL-6	0.003	0.475	0.290	<0.001

TNF- α: tumor necrosis factor alpha, NTN: normotensive, HTN: hypertensive, Hb: hemoglobin, Lep: leptin, Hcy: homocysteine, IL-6: interleukin-6.

Discussion

Important findings in the present report are the highly significant increases in serum levels and significant positive linear correlations for Lep, IL-6, and TNF-α in HTN women of reproductive age with NW compared to NTN women of reproductive age with NW. The present work, comprising HTN grade-1 participants compared with NTN participants, is a well-controlled study considering sex, age, and BP status. Therefore, it is valuable to compare with already published reports and to interpret the results in light of the existing literature to understand the pathophysiological mechanisms and management of HTN.

Serum Lep-related studies provide evidence for our present findings on the impact of Lep in the progressive development of HTN[23,24] via endothelial dysfunction[25] and inflammation-related aortic stiffening, particularly in women, leading to ventricular stiffness.[26]

Other Lep-related mechanisms justifying the leading role of Lep in HTN in our present study are: enhanced sympathetic activity increasing BP and causing HTN,[24,27,28] Lep receptors in various blood vessels and atherosclerotic plaques causing arterial stiffness and HTN,[29] Lep-related increased immune activation, angiogenesis, increased platelet aggregation/production of radical oxygen species (ROS),[30] induction of endothelial related oxidative stress and the ROS,[31] and PVAT (perivascular adipose tissue)-derived contractile activity of Lep leading to decrease in vascular relaxation and development of HTN.[32]

Significantly increased levels of the most notorious pro-inflammatory cytokine, TNF-α, in women with HTN compared to women with NTN in the current study can be explained by previously published reports describing a vicious cycle[33] that links adiposity, inflammation, the immune system, and BP,

leading to HTN.[34] TNF-α causes low-grade inflammation and induces HTN, atherosclerosis, and other CVD dysfunctions.[35] IL-6 is another important risk factor in the present investigation that increases with increasing BP and, along with other important pro-inflammatory markers, is associated with immune system activation leading to HTN and other CVDs.[35-38] Serum Hcy and Hb in the current report did not show a significant difference between HTN and NTN subjects, consistent with earlier reports for HTN vs. NTN subjects.[39]

A study previously conducted in the Saudi Arabian population provides general information relevant to the present work.[40] However, our currently collected data did not correspond to the wide range of body weight/BMI investigated in that study.

The current investigation has merits as well as demerits/limitations. Since the participants in both groups (HTN and NTN) were non-obese, non-smoking, non-diabetic, non-pregnant, and non-anemic, and had similar ages and normal body weight within the reproductive age range, the present study is well-controlled and well-matched. Furthermore, women in the HTN group had grade 1 HTN.

The limitations or demerits in the present study are a narrow range of age, BW, and hence BMI, and BP, and the exclusion of male participants and overweight (OW), obese, anemic, and smoking female subjects, as well as women with HTN of grade 2 and grade 3. Furthermore, other pro-inflammatory and anti-inflammatory markers, along with other variables, need to be assessed in both groups to gain a clear idea of the role of inflammation in patients with HTN. Another limitation is that HTN women patients having comorbidities, including mainly other CHDs, diabetes mellitus, kidney diseases, stroke, and renal ischemia/failure, could not be consulted. However, these and other disorders are prevalent in HTN patients. It would be interesting and valuable to study HTN patients with various other medical comorbidities. Despite that, the present investigation provides a platform to carry out further studies to explore the pathophysiological mechanisms underlying the development of HTN in reproductive-age women and to provide insightful information for the management of patients with HTN.

Conclusion

The present study provides evidence of significant variation and correlation in Lep, TNF-α, and IL-6 among NW women with HTN compared to NTN women participants within the same age range, BW, and reproductive age status. The increased serum levels of Lep, TNF-α, and IL-6 in NW women with HTN compared to NW women with NTN indicate the pathophysiological significance of the interactive role of these inflammatory mediators independent of the influence of BW, which would hopefully help further understanding of the mechanism of the development and progression of HTN and therapeutic implications for HTN.

Ethical Considerations

The present study was approved by the Ethics Committee of the Faculty of Medicine, Umm Al-Qura University (UQU) (Approval Number: HAPO-02-K-012-2022-01-1069). All methods, procedures, and techniques used were in accordance with the Declaration of Helsinki of 1964, as revised in 2013. Written informed consent was obtained from all subjects who participated in the current study.

Author Contributions

Zahir Hussain contributed to supervision, conceptualization, investigation, data curation, formal analysis, writing the original draft, review and editing, and final approval of the article.

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Conflicts of Interest

The author declares that there are no competing interests/conflicts of interest.

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