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Immune-Endocrine crosstalk in hypertensive overweight men: Dysregulation of IL-17 and IL-40-mediated inflammatory pathways

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Abstract

Hypertension belongs to the category of serious health concerns among overweight people that are frequently attributed to chronic low-grade inflammation. The present study investigated the significance of the selected pro-inflammatory cytokines interleukin-17 (IL-17), interleukin-40 (IL-40), and tumor necrosis factor-alpha (TNF- α) as the markers of inflammation in non-smoking overweight men with hypertension. This case control study included 70 adult men (40 hypertensive and 30 age matched controls). Anthropometric parameters, arterial blood pressure, lipid profile, liver enzymes, renal function markers, aldosterone, cortisone, and serum cytokines were investigated. The concentrations of cytokines were determined through the enzyme-linked immunosorbent assay procedures. Body weight, body mass index, systolic and diastolic blood pressure, among hypertensive participants, were significantly higher in the cases than the controls ($p \leq 0.01$). Hypertensive subjects had significantly high serum concentrations of TNF-α, IL-17 and IL-40, which are indicators of a strong pro-inflammatory condition. Also, hypertensive patients were characterized by dyslipidemia and raised liver enzyme activity, raised aldosterone and cortisone levels, and slight but significant rises in serum creatinine. The results indicated that hypertension among overweight non-smoking men is interrelated with immune response, metabolic dysregulation as well as endocrine dysregulation. It is interesting to note that IL-40 was also a candidate novel inflammatory biomarker in addition to the previously known cytokines, TNF- α and IL- 17. The study findings revealed that the inflammatory and immune-endocrine pathways could be a new chance in the early management and detection of obesity-related hypertension.

Keywords: Hypertension, Cytokines, IL-40, TNF-α, Liver enzymes, ELISA.

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Introduction

Hypertension is one of the chronic diseases in which the blood pressure in the arteries remains elevated leading to the development of cardiac workload and vascular resistance. It ranks high among the risk factors of cardiovascular diseases, such as coronary heart disease and stroke. Cardiac output as well as peripheral vascular resistance determines blood pressure.[1] Often termed a “silent killer,”

hypertension commonly progresses without noticeable symptoms, and early manifestations are frequently overlooked. Its development is multifactorial, involving genetic, behavioral, and environmental influences [1]. It was reported that blood pressure in the range of 90/60–120/80 mmHg is considered normal, while readings ≥140/90 mmHg on two separate occasions are diagnostic of hypertension.[2] High blood pressure runs more commonly in overweight or obese people, smokers and those who have ever had myocardial infarction or stroke.[3]

Hypertension is the main pedal pusher for the wheels of cardiovascular morbidity and mortality all over the world. About 9.4 million deaths per year can be attributed to this condition.[4] This renders it a colossal health challenge to the masses due to its significant association with chronic kidney disease and other cardiovascular complications that present huge economic and healthcare costs.[5] Hypertension risk factors are multifactorial and comprise hereditary inclination, old age, sex, obesity, cigarette smoking, high alcohol consumption, psychological stress, excessive intake of sodium in diet, chronic illnesses, including diabetes, and lack of exercise.[1, 4] By raising awareness and knowledge about these risk factors among the population, prevention and control programs will also be improved significantly.

Cytokines are small protein secreted by some cells in the body and especially the immune cells that are used to communicate between the cells. They aid in the management of immune system, inflammation and cell proliferation.[6] Cytokines are divided into pro-inflammatory or anti-inflammatory. They may be further categorized according to T-helper cell functions namely T-helper cell type 1 (Th1) functions that bolster cell-mediated immunity or T-helper cell type 2 that bolster humoral immunity. Cytokines that are involved in such processes include interleukin-40 (IL-4), IL-5, IL-6, and IL-10.[7, 8] The functions of IL-40 in regulating the immune system and maintaining B cell equilibrium suggest that it could be a factor in the development of autoimmune diseases. The protein is a potential contributor to the causes of autoimmune conditions because of its involvement in immunological regulation and the preservation of B cell homeostasis.[9, 10] Human B cells generate IL-40 when stimulated by anti-IgM, and the presence of IL-4 and transforming growth factor (TGF)-b1 enhances this production.[11, 12]

The present study aimed to investigate the dysregulations of selected inflammatory cytokines (IL-17 and IL-40), and the effects of endocrine changes in overweight non-smoking men with hypertension.

Materials and Methods

Study population

This research was conducted during March 2025 to September 2025. This case-control study included 70 male participants (40 hypertensive patients and 30 controls). An expert cardiologist diagnosed the patients based on electrocardiogram changes. Participants were age-matched, with no history of diabetes mellitus, chronic kidney disease, liver disease, autoimmune disorders, or smoking.

Anthropometric and arterial blood pressure measurements

Body weight, height, and body mass index (BMI) were recorded using standard procedures. Arterial blood pressure was measured using a standard sphygmomanometer after the participants were seated at rest for at least 10 minutes. Three consecutive readings were obtained at five-minute intervals, and the mean values of these measurements were recorded for analysis.

Collection of blood samples

Fasting blood samples (5 ml) were collected, in sterilized test tubes, from each study participant for biochemical analysis and cytokine assay. The samples were centrifuged at 1,000 rpm for 15 minutes. Then the obtained sera were used for cytokine assay and biochemical analysis.

Cytokine assay

Serum levels of TNF-α, IL-17, and IL-40 were quantified using the sandwich enzyme linked immunosorbent assay (ELISA) commercial kits

(BOSTER Biological Technology, USA) following the manufacturer's instructions [13, 14].

Biochemical analysis

The obtained sera were analyzed for the assessment of lipid profile (total cholesterol, High-density lipoprotein (HDL) and cholesterol), liver enzymes (aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine, aldosterone, and cortisone using the ELISA system reader (Human, Germany) following the manufacturer's instructions.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, IBM Corp., Armonk, NY, USA). Values are presented as mean ± standard deviation (SD). The means of all measured variables were compared using unpaired Student T test. A *p*-value <0.05 was considered statistically significant.

Results

Table 1 shows the age, body weight and BMI of hypertensive patients and control subjects. There are significant differences regarding the body weight and BMI between hypertensive patients and normal controls ($p \leq 0.01$), while age did not differ significantly between these groups. A 70 % of hypertensive men were overweight (BMI more than 30 Kg/m^2). Both systolic and diastolic blood pressures were significantly higher in hypertensive patients compared to the controls ($p \leq 0.01$).

Table 1. Anthropometric and blood pressure measures in controls and hypertensive patients.

Parameter	Control (n = 30)	Patient (n = 40)	*p* value
Age (years)	50.5 ± 2.1	54.5 ± 3.4	NS
Body weight (Kg)	75.5 ± 4.5	89.5 ± 9.5	≤0.01
BMI (Kg/m^2)	22.8 ± 3.4	29.2 ± 2.5	≤0.01
Systolic Bp (mmHg)	117.0 ± 3.0	153.0 ± 4.0	≤0.01
Diastolic Bp (mmHg)	83.0 ± 2.0	94.0 ± 3.0	≤0.01

$p \leq 0.05$ is significant.

The results in Table 2, revealed that a significant elevation in the concentration of IL-17 (1372.5 ± 211 ng/ml) was observed in the overweight hypertensive patients compared with the normal control participants (683.5 ± 112 ng/ml) ($p \leq 0.01$). A similar trend was also observed with the IL-40. Furthermore, in comparison with the normal control participants (135.5 ± 9.5 pg/ml), a significant rise in the concentration of TNF-α (205.5 ± 16.4 pg/ml) was recorded in the overweight hypertensive patients ($p \leq 0.01$).

Table 2. Level of pro-inflammatory cytokines in overweight hypertensive patients and control participants.

Parameter	Control (n = 30)	Patient (n = 40)	*p* value
TNF-α (pg/ml)	135.5 ± 9.5	205.5 ± 16.4	≤0.01
IL-40 (ng/ml)	8.4 ± 1.6	18.5 ± 2.6	≤0.05
IL-17 ng/ml	683.5 ± 112	1372.5 ± 211	≤0.01

$p \leq 0.05$ is significant.

Analysis of the lipid profile revealed significantly increased total cholesterol and reduced HDL cholesterol in hypertensive patients (Table 3). Additionally, serum AST and ALT activities were elevated, alongside significantly higher aldosterone and cortisone levels (Table 4). Creatinine levels, although within the normal range, were modestly but significantly higher in

hypertensive patients. There is a significant increase in serum AST levels (36.40 ± 3.50 U/L) in overweight hypertensive patients compared to the controls (20.500 ± 2.30 U/L) ($p \leq 0.01$). Also, the level of ALT in the blood was significantly higher in overweight hypertensive patients compared to control participants with values of 33.50 ± 3.40 and 21.500 ± 3.80 U/L, respectively, ($p \leq 0.01$). Also, there was a significant elevation in the concentration of serum aldosterone of the overweight hypertensive patients (106.8 ± 18.2 pg/ml) compared to the normal controls (25.1 ± 7.3 pg/ml) ($p \leq 0.01$). In addition, the level of cortisone in the blood of overweight hypertensive patients was significantly higher (14.3 ± 3.5 ng/ml) compared to the controls (6.44 ± 2.7) ($p \leq 0.01$).

Table 3. Lipid profile of the overweight hypertensive patients and normal controls.

Parameter	Control (n = 30)	Patient (n = 40)	*p*-value
Cholesterol (mg/dl)	191·2 ± 6·8	217·5 ± 8·4	≤0·01
HDL cholesterol (mg/dl)	52·19 ± 12·2	41·3 ± 11.0	≤0·01

$p \leq 0.05$ is significant.

Table 4. Levels of liver enzymes, cortisone, and aldosterone in the blood of people with high blood pressure and normal controls.

Parameter	Control (n = 30)	Patient (n = 40)	*p*-value
AST (U/L)	20.500 ± 2.30	36.40 ± 3.50	≤0.01
ALT (U/l)	21.500 ± 3.80	33.50 ± 3.40	≤0.01
Aldosterone (pg/ml)	25.100 ± 7.30	106.80 ± 18.20	≤0.01
Cortisone (ng/ml)	6.440 ± 2.70	14.30 ± 3.50	≤0.01
Creatinine (mg/dl)	0.398 ± 0.03	0.45 ± 0.05	≤0.01

AST: Aspartate aminotransferase; ALT: Alanine Aminotransferase. $p \leq 0.05$ is significant.

Discussion

The study revealed that individuals with hypertension had significantly higher body weight and BMI compared to controls with normal blood pressure ($p < 0.01$). Researchers have established a correlation between overweight and obesity (BMI of 30 kg/m^2 or higher) and the risk of cardiovascular diseases among men and women [15, 16]. The results of the present research are in line with past reports which indicated that the BMI has a significant predictive value of high blood pressure even when it is adjusted to other factors like occupation, marital status and smoking status.[17]

In the current study, it was established that hypertension among overweight, non-smoking men is related to a strong pro-inflammatory environment, as shown by the high circulatory levels of TNF-α, IL-17, and IL-40. This result reinforces available evidence that links immune activation and inflammation mediated by cytokines in the onset and course of hypertension.[18, 19, 20] TNF-α is a pleiotropic cytokine with varied biological roles that mediate receptor-mediated signaling pathways with the ability to induce apoptotic and necrotic cell death.[21, 22] In hypertension, TNF-α could be involved in endothelial damage, vascular remodeling, and vascular impaired vasodilation, thus maintaining high blood pressure. These findings are in line with earlier reports which point to TNF-α as a major mediator of systemic inflammation and dysfunction of the vascular system in hypertension.[12, 18] Another interesting result of this study is that the IL-40 level was significantly higher among hypertensive patients than normotensive controls ($p \leq 0.01$).

The IL-40 outcome of the present study is in line with previous research findings that indicated that levels of IL-40 were higher in patients with coronary heart disease and that there was a positive relationship between IL-40 and serum cholesterol levels.[23] Mechanistically, IL-40 has been demonstrated to aggravate atherosclerosis through its effects on endothelial inflammation and the arterial smooth muscular cells by triggering vascular inflammation and structural alterations [10, 11]. Such results indicated the possibility of IL-40 involvement in immune dysregulation linked with hypertension.

Also, the levels of circulating IL-17 were found to be considerably greater in people with increased blood pressure, which supports findings in the previous researches.[24, 25] Smokers were not used in this study though it has been indicated that the elevation in IL-17 was reported in smoking hypertensive patients.[26] This implies that the reported elevation was not due to smoking. IL-17 facilitates vascular inflammation, dysfunction of the endothelium, and sodium retention in the kidney, which elevate the vascular resistance and blood pressure.[27] The simultaneous increase of TNF-α, IL-17, and IL-40, in turn, highlight the versatile nature of immune-mediated inflammation in hypertension, and IL-40 can be a potential biomarker or a treatment option.[28]

The current research established a considerable dyslipidemia in patients with high blood pressure with high total cholesterol and low HDL-cholesterol levels than normotensive ones ($p \leq 0.01$). This lipid disorder is aligned with prior evidence that hypertension was associated with poor metabolic and cardiovascular risk phenotypes.[29] Low HDL-cholesterol can worsen reverse cholesterol transportation and antioxidant coverage, which in turn can expose hypertensive patients to endothelial malfunction and atherosclerosis. Simultaneously, the hypertensive patients portrayed much higher serum concentrations of aldosterone, which is associated with previous reports of higher concentrations of aldosterone in hypertension ($p \leq 0.01$).[29]

Aldosterone is becoming increasingly recognized as a contributing factor to the pathophysiology of hypertension and cardiovascular disease.[5, 30] In addition to its classical effects of sodium and water retention, aldosterone stimulates vascular remodeling, oxidative stress, and inflammation which cause cardiac and renal damage despite the absence of hyperaldosteronism.[31, 32, 33] Continuous stimulation of renin-angiotensin-aldosterone system especially in end-stage renal dysfunction develops a vicious cycle between kidney damage, aldosterone overload, and unremitting hypertension.[34, 35] The levels of serum cortisone were also raised significantly in hypertensive subjects ($p \leq 0.01$).

Though different hormones, aldosterone and cortisol have opposite effects on inflammation, their joint increase indicates the regulation of neurohormonal and stress-response systems, including adrenocorticotropic hormone (ACTH) and oxidative stress signals.[36, 37] Taken together, the above findings highlight the effect of aldosterone as a mediator of target-organ injury in the heart, kidney, and brain regardless of blood pressure and sodium retention effects.[38, 39] The interaction of the effect of aldosterone and cortisone underscores the interplay of inflammation and neurohormonal stimulation in maintaining hypertensive pathology.[40]

The current research indicated a considerably high level of mean serum creatinine in hypertensive individuals relative to normotensive controls ($p<0.01$), which is in line with other studies that showed that hypertension is characterized by impaired renal activity.[41, 42] Higher creatinine indicated decreased glomerular filtration and the strong correlation between hypertension and progressive renal injury. This correlation is also justified by the role played by the aldosterone mediated renal damage that adds to the chronic kidney dysfunction and long-term increase in blood pressure. With respect to hepatic functionality, it was showed to often be affected by hepatocellular injury, which is indicated by a rise in the AST and ALT levels in patients treated with pulmonary hypertension.[36, 37] In addition, epidemiological research has documented a close relation between hypertension and progressive nonalcoholic fatty liver disease especially in

obese adults, indicating the metabolic systemic load that comes with hypertensive pathology.[43,44]

Aldosterone has more effects other than the classical effects of conserving sodium. It has vasoactive effects that stimulate vascular inflammation, oxidative stress, and fibrosis by activating the mineralocorticoid receptor pathway, leading to arterial stiffness and end-organ damage despite inhibited renal sodium retention. It is these mechanisms that can be used to explain how it has a growing role in resistant hypertension where aldosterone plays a role in volume expansion and increased rigidity of the arteries.[45] Moreover, autonomous adrenal secretion is currently identified as primary aldosteronism, which is a rather frequent secondary cause of intractable hypertension with the increased cardiovascular risk.[24] Cortisone, the inactive precursor of cortisol, is changed to its active form under the influence of 11-hydroxysteroid dehydrogenase type 1 (11β-HSD1), which is a highly expressed enzyme in liver and adipose tissue. High activity of 11β-HSD1 boosts the local cortisol concentration that encourages sodium retention, improved vascular tone and sensitivity to vasoconstrictors thus contributing to hypertension.[46] The mechanism is illustrated in the excess condition of glucocorticoid, including the Cushing's syndrome, in which arterial high blood pressure is a very common occurrence.

In conclusion, overweight nonsmoking men with hypertension are characterized by a high level of pro-inflammatory cytokines, metabolic (disturbances), hepatic enzyme, and endocrine dysregulation. Cytokines, IL-17 and TNF-α, are proven to have role in hypertensive inflammation, and IL-40 is a potentially promising new inflammatory marker. The fact that it works through immune-endocrine interactions marks a valid intention to target them an important choice in the treatment of hypertension related to obesity.

Author Contributions

RKI; conceived and designed the study, performed data collection and analysis, and drafted the manuscript. HMM; contributed to the methodology, data interpretation, and critical revision of the manuscript. MEM; supervised the research work, contributed to data analysis and interpretation, and reviewed and approved the final version of the manuscript. All authors read and approved the final manuscript.

Declaration of Conflicting Interests

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Ethical approval

The study protocol was reviewed and approved by the Ethical Committee of the University of Northern Technical University (Ref. NTU/REC/2025/1/19; dated January 2025).

Informed consent

A written informed consent was obtained from each study participant before being included in the study.

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