Interplay of Serum Leptin, Tumor Necrosis Factor Alpha, and Testosterone in Overweight-Related Hypertensive Men

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Article

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Abstract: Hypertension (HT) is a very common risk factor and a frequent cause of morbidity and mortality worldwide mainly due to much increase in overweight (OW) and obesity that manifests in various forms of cardiovascular disease (CVD). There are a number of factors that may cause overweight hypertension (OHT). However, we planned to conduct the present work to study the HT and OHT men for finding the variation, interrelationship and association of important cytokines mainly serum leptin (Lep) and tumor necrosis factor-alpha (TNF-α), serum testosterone (ST), total cholesterol (TC) and inflammatory status by measuring interleukin-6 (IL-6). Three groups of subjects, the normal controls (NC; n:98; age range: 51-60 years), HT (n: 97; age range: 51-60 years) subjects, and OHT (n: 97; age range: 51-60 years) subjects were studied. Comparisons for Lep, ST, TNF-α, IL-6 and TC levels for the subject groups showed significant variations. The ST indicated significant difference only for NC vs. OHT. The IL-6 gave significant difference for NC vs. OHT and HT vs. OHT. The one-way ANOVA showed significant difference among groups for BMI, TC, IL-6, TNF-α, ST and Lep levels. Significant positive linear correlation for all groups among Lep, TNF-α, IL-6 and TC were found. The ST against TC for HT and OHT groups presented non-significant negative linear correlations. The ST showed significant negative linear correlation with other variables. Conclusively, the present study uncovers the interactive impact of serum leptin, TNF-α, testosterone, total cholesterol and IL-6 in hypertensive and overweight-related hypertensive men.

Keywords: hypertension; overweight-related hypertension; serum leptin; TNF-α; testosterone; total cholesterol; IL-6

1. Introduction

Hypertension (HT) is a very common risk factor and a frequent cause of morbidity and mortality worldwide **[1]** mainly due to much increase in overweight (OW) and obesity **[2]** that manifests in various forms of cardiovascular disease (CVD). It was revealed that there is a significant association between body weight (BW) and HT **[3–5]**.

It was found that high levels of body mass index (BMI) (in either OW or obese subjects) is the main factor leading to several chronic disorders e.g., CVD, diabetes mellitus (DM) and HT **[6].** Furthermore, both normal weight (NW) and OW subjects showed an association between blood pressure (BP) and BMI **[7–9]**. The OW status increases the risk of the development of high BP. It is

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well studied in the Framingham Study that high BP or HT **[10]** and OW **[11]** (are independent risk factors for CVD **[12,13]**. It is documented that the occurrence of HT could increase the BMI **[14]**. The data of all age groups show that the obese subjects with HT ranged 60%-77% with increasing BMI and that was significantly higher as compared to 34% in NW subjects **[15]**.

The tendency in general public of having gradual increase in BP with increase in BW/ BMI was also noted **[16]**, over the life course including late in life **[17]**. Although the various BP range levels have been classified into three grades of HP on the basis of systolic blood pressure (SBP)/ diastolic blood pressure (DBP) in mmHg as: grade-1, 140-159/ 90-99; grade 2, 160-179/ 100-109; and grade 3, ≥ 180/ ≥ 110, management with proper lifestyle and medication is essentially required regardless of any grade **[18]**.

The BP is found higher in OW/obese people than in non-obese people and the lifestyle changes decrease the BP in OW and obese men **[19]**. In view of the interactive effects and association of BW (OW/obesity) and HT, it is highly recommended to have the combined management for both of these risk factors, even in non-hypertensive (NHT) subjects **[20]**. The patients with HP and OW/obesity require proper management especially including the change in lifestyle **[21]**. Furthermore, Reducing the BW decreases the risk of HT for those who were never OW or obese **[21]**.

There are various studies documenting the association of serum leptin (Lep) with other variables including serum tumor necrosis factor-alpha (TNF-α), serum testosterone (ST) and interleukin-6 (IL-6) in HT **[22–28]** and OW-related HT **[29–32]**. However, there are reports that contradict these findings **[33,34]**. No clearly known interactive role of these factors are yet known, that requires further studies to be conducted for exploring the interactive role of serum Lep, TNF-α, ST, total cholesterol (TC), inflammatory status, OW and HT. Therefore, the purpose of present research work was to study and investigate the involvement of the mentioned factors in hypertension and overweight-related hypertension.

2. Materials and Methods

2.1. Study Design, Participants and Data Collection

The design and detailed proposal for the present study was prepared and submitted to the Ethical Approval Committee of the Faculty of Medicine, Umm Al-Qura University. With the issuance of the ethical approval (Approval No: HAPO-02-K-012-2021-02-124), the research work was commenced.

The participants in the present study were informed in their first visit that that the data of subjective information and the blood samples will be collected, and other tests will be carried out considering their personal consent whether they decide or not to take part in the present study. After the selection of each subject for the present study, the detailed interview and assessment was conducted. For this purpose, proper diagnostic procedures were employed and subjects/ patients were characterized for the current study.

Present study comprised three groups of participants, the normal controls (NC; n:98; age range: 51-60 years), hypertensive (HT; n: 97; age range: 51-60 years) subjects, and overweight hypertensive (OHT; n: 97; age range: 51-60 years) subjects. The NC were normotensive (NT) male subjects with NW at BMI 23-24.9 kg/m^2. The HT were hypertensive male subjects with NW at BMI 23-24.9 kg/m^2. Whereas, the OHT were hypertensive male subjects with OW at BMI 28-29.9 kg/m^2.

The NC and HT were those subjects having high normal weight (HNW) BMI, and OHT were considered the subjects with high overweight (HOW) BMI. Subjects having lower and higher levels of BMI other than the mentioned for NC, HT and OHT were not included in the present study.

Furthermore, the NT subjects had SBP/ DBP) as <120/<80 mmHg, and the HT subjects in the range of 140-159/ 90-99 (grade 1-HT) **[18]**. The subjects with lower and higher values of SBP/DBP for HT and OHT groups were not included in the current study. Moreover, subjects having grade 2-HT (SBP/DBP: 160-179/ 100-109) and grade 3-HT (SBP/DBP: ≥ 180/ ≥ 110) **[18]**. were also not entertained for the present work.

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Sample size calculator was used for assessing the required number of samples for the present study. General features of the subjects and history of patients were obtained and recorded in the Questionnaire. The research work was conducted in the Umm Al-Qura University affiliated hospitals in Makkah, Saudi Arabia from June 2021 till Dec 2022. Some of the data in our pilot studies collected and assessed before and after our recent publication **[35]** emphasized to collect the data for other variables besides serum Lep, including TNF-α, testosterone and inflammatory status. Hence, these variables were included in the study design for collecting the data.

2.2. Measurements and Methods

Routine kit methods and enzymatic colorimetric method was employed for the determination of TC. The BMI levels were assessed by dividing the BW (kilograms) with the square of body height (meters) **[36,37]**. The levels of HNW related BMI and HOW related BMI were followed for the Saudi population **[38]**. However, the subjects having low normal weight (LNW) and medium normal weight (MNW) related BMI and low overweight (LOW) and medium overweight (MOW) related BMI were not included in the present study.

The BP (SBP and DBP) levels determined by routine methods **[39]** in the NT subjects were in normal range and in HT subjects were in the HT range **[40,41]**. However, the subjects only with grade-1 HT in the range of 140-159/ 90-99 **[18]** were included. The measurement of BP was carried out using a mercury sphygmomanometer (MS-S1500 Mercury Sphygmomanometer, Medical Sources Co., Limited, Nanjing, Jiangsu). Blood samples of NC, HT and OHT groups were taken, serum separated, and analyzed using ELISA (enzyme-linked immunosorbent assay) kits for serum Lep, TNF-α, ST, and IL-6.

2.3. Data Analysis

The data analysis was performed using the Statistical Package for Social Sciences (version 24.0) for Windows (SPSS Inc., Chicago, IL, USA). The GraphPad Prism (version 6.0) software, San Diego, CA, USA, was used. The values of the analyzed data were obtained as mean ± standard deviation (SD). Distribution of the quantitative characteristics of the present data corresponded to the normal one. The two tailed P-value was obtained by applying the Student t-test (unpaired two samples t–test). The one-way analysis of variance (ANOVA) was employed for comparing the data of three groups of the subjects. The results obtained by Student t-test were further confirmed by the Tukey's Kramer post hoc test. For the determination of positive or negative correlations, linear regression lines were plotted. The values of coefficient of determination (R^2) were obtained that showed the level of significance. The value of significance (P) was obtained considering the biostatistical applications **[42]**. The significance level was considered as $P \leq 0.05$.

3. Results

Age of NC, HT and OHT subject groups respectively was 55.37±2.86, 55.35±2.82 and 55.36±2.78 having no significant difference (Table 1). The BMI in range and mean±SD of these subject groups is given in Table 1. The Tukey-Kramer test for BMI indicated significant difference for NC vs. OHT and HT vs. OHT.

3.1. Variations among Serum Leptin, TNF-α, Testosterone and Other Variables in Hypertensive and Overweight-related Hypertensive Men

All three comparisons for Lep, TNF-α, and TC showed significant results. The ST indicated significant difference for NC vs. OHT, but did not show significant variation for NC vs. HT and HT vs. OHT. The IL-6 gave significant difference for NC vs. OHT and HT vs. OHT, but not for NC vs. HT. The one-way ANOVA showed significant difference among groups for BMI, TC, IL-6, TNF-α, ST and Lep levels.

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Table 1. Characteristic features and related parameters in subjects with hypertension and overweight-related hypertensive men.

Variables	Normal Weight, Hypertensive and Overweight hypertensive Subjects (n: 292)			P-value®
	NC	HT	OHT	
Number of subjects (n)	98	97	97	-
Sex (male)	98	97	97	-
Age (years)	55.37±2.86	55.35±2.82	55.36±2.78	NS
Age range (years)	51-60	51-60	51-60	-
BMI (kg/m²)	24.04±0.60	24.03±0.61	29.06±0.58^3, $3	<0.001
BMI range (kg/m²)	23-24.9	23-24.9	28-29.9	-
TC (mg/dl)	177.06±9.49	189.32±13.65#3	194.16±12.37^3, $1	<0.001
IL-6 ((pg/ml)	6.46±6.23	7.88±6.03	10.90±8.63^3, $1	<0.001
TNF-α (pg/ml)	4.69±2.10	8.25±3.57#3	11.71±5.07^3, $3	<0.001
ST (mg/dl)	417.96±175.28	378.09±179.41	345.36±155.80^1	<0.05
Leptin (ng/mL)	5.75±2.27	10.02±6.35$3	13.13±7.26^3, $2	<0.001

NC: normal control (normotensive with normal weight BMI 23-24.9 kg/m²); HT: hypertensive (hypertensive with normal weight BMI 23-24.9 kg/m²);OHT: overweight hypertensive (hypertensive with overweight BMI 23-24.9 kg/m²); BMI: body mass index; TC: total cholesterol; IL-6: interleukin-6; TNF- α: tumor necrosis factor alpha; ST: serum testosterone; Lep: leptin; values are: mean± standard deviation (SD); two tailed P-value was obtained by applying unpaired two samples t–test; #P-value: HT vs. NC, ^P-value: (OHT vs. NC, $P-value: OHT vs. HT; #, ^, $: P-value ≤0.05; #1, ^1; $1 : P-value ≤0.01; #2, ^2; $2 : P-value ≤0.001; #3, ^3, $3 : P-value ≤0.0001; ®: P-values for one-way ANOVA (analysis of variance); statistical analysis done by using the Statistical Package for Social Sciences (SPSS), version 24.0 for Windows.

3.2. Association of Serum Leptin with Other Variables in Hypertensive and Overweight-related Hypertensive Men

The results for association of serum Lep with other variables in HT and OHT men are given in Table 2. Serum Lep plotted against TNF-α presented highly significant positive linear correlation for NC, HT and OHT subject groups. Similar results in the extent of significance were obtained for association of Lep with ST in NC, HT and OHT subject groups, though the correlations between Lep and other parameters were negative linear. Serum Lep and IL-6 associated significantly with positive linear correlation for all NC, HT and OHT subject groups.

Table 2. Association of serum leptin with other parameters in hypertensive and overweight-related hypertensive men.

Variables	Coefficient of Determination (R^2) for the Correlation of Serum Leptin with Other Variables		
	NC (n: 98)	HT (n:97)	OHT (n:97)
TNF-α	0.62	0.69	0.91
ST	0.34	0.27	0.34
IL-6	0.37	0.72	0.73
TC	0.07	0.09	0.12

NC: normal control (normotensive with normal weight BMI 23-24.9 kg/m²); HT: hypertensive (hypertensive with normal weight BMI 23-24.9 kg/m²); OHT: overweight hypertensive (hypertensive with overweight BMI 23-24.9 kg/m²); BMI: body mass index; TC: total cholesterol; IL-6: interleukin-6; TNF- α: tumor necrosis factor alpha; ST: serum testosterone; all associations showed significant results, regression lines were plotted for obtaining the values of R^2 and the values of significance (P) were obtained; statistical analysis was done by using the Statistical Package for Social Sciences (SPSS), version 24.0 for Windows.

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3.3. Association of Serum TNF-alpha with Other Variables in Hypertensive and Overweight-related Hypertensive Men

Results for the association of serum TNF-alpha with other variables in HT and OHT men are shown in Table 3. Correlation of serum TNF-alpha with ST was found to be negatively linear and significant for all comparisons. Its association with IL-6 and TC was also significant with linear correlation in NC, HT and OHT subject groups.

The results for the plot of TNF-α and Lep are given and described in Table 2.

Table 3. Association of serum TNF-alpha with other parameters in hypertensive and overweight hypertensive men.

Variables	Coefficient of Determination (R2) for the Correlation of Serum TNF-alpha with Other Variables		
	NC	HT	OHT
ST	0.39	0.48	0.37
IL-6	0.38	0.50	0.63
TC	0.12	0.13	0.11

NC: normal control (normotensive with normal weight BMI 23-24.9 kg/m^2); HT: hypertensive (hypertensive with normal weight BMI 23-24.9 kg/m^2); OHT: overweight hypertensive (hypertensive with overweight BMI 23-24.9 kg/m^2); BMI: body mass index; TC: total cholesterol; IL-6: interleukin-6; TNF- α: tumor necrosis factor alpha; ST: serum testosterone; all associations showed significant results, regression lines were plotted for obtaining the values of R^2 and the values of significance (P) were obtained; statistical analysis was done by using the Statistical Package for Social Sciences (SPSS), version 24.0 for Windows.

3.4. Association of Serum Testosterone with Other Variables in Hypertensive and Overweight-related Hypertensive Men

The association of serum testosterone (ST) with other variables in HT and OHT men are shown in Table 4. The ST gave negative linear and significant correlation with IL-6 for all subject groups (NC, HT and OHT). However, negative linear but non-significant correlation of TS with TC was noted in all subject groups except NC subject group that showed significant (P<0.003) negative linear correlation

The results for the plot of ST against Lep and TNF-α are given and described in Tables 2 and 3.

Table 4. Association of serum testosterone with other parameters in hypertensive and overweight-related hypertensive men.

Variables	Coefficient of Determination (R2) for the Correlation of Serum Testosterone (ST) with Other Variables		
	NC	HT	OHT
IL-6	0.11	0.21	0.18
TC	0.09	0.010	0.01

NC: normal control (normotensive with normal weight BMI 23-24.9 kg/m^2); HT: hypertensive (hypertensive with normal weight BMI 23-24.9 kg/m^2); OHT: overweight hypertensive (hypertensive with overweight BMI 23-24.9 kg/m^2); BMI: body mass index; TC: total cholesterol; IL-6: interleukin-6; all associations for ST against IL-6 showed negative linear and significant correlations; all associations for ST against TC showed non-significant negative linear correlations except for NC subject group that showed significant (P<0.003) negative linear correlation; regression lines were plotted for obtaining the values of R^2 and the values of significance (P) were obtained; statistical analysis was done by using the Statistical Package for Social Sciences (SPSS), version 24.0 for Windows.

3.5. Association of Serum Interleukin-6 with Total Cholesterol in Hypertensive and Overweight-related Hypertensive Men

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The association of serum interleukin-6 with total cholesterol in hypertensive and overweight hypertensive men (Table 4) showed positive and significant linear correlation for NC, HT and OHT subject groups.

Table 5. Association of serum interleukin-6 with total cholesterol in hypertensive and overweight-related hypertensive men.

Variable	Coefficient of Determination (R2) for Correlation		
	Serum IL-6		
	NC	HT	OHT
TC	0.13	0.11	0.07

NC: normal control (normotensive with normal weight BMI 23-24.9 kg/m^2); HT: hypertensive (hypertensive with normal weight BMI 23-24.9 kg/m^2); OHT: overweight hypertensive (hypertensive with overweight BMI 23-24.9 kg/m^2); BMI: body mass index; TC: total cholesterol; IL-6: interleukin-6; all associations showed positive linear and significant results, regression lines were plotted for obtaining the values of R^2 and the values of significance (P) were obtained; statistical analysis was done by using the Statistical Package for Social Sciences (SPSS), version 24.0 for Windows.

Results for the associations for IL-6 against Lep, TNF-α, and TS respectively are shown and described in Tables 2, 3 and 4.

4. Discussion

The purpose of the present report was to assess the interacted role of serum Lep with various factors in the occurrence of OW-related HT. Our previous study **[35]** in NW and OW male subjects provided us information of the significant variation and positive linear correlation among serum Lep, BMI and BP, and various other cytokines and inflammatory factors though that study was conducted in 18-20 years old male university students and was quite descriptive involving various low, medium and high BMI levels of NW and OW subjects. However, the aim of this present study is quite different. We are more interested to explore the changes or associations at a specific level of BMI and BP. We selected the subjects in the present study at a specific BMI level of 23-24.9 kg/m^2 for NC and HT and 28-29.9 kg/m^2 for OHT. Similarly, we specified the level of NT and HT, and even only grade-1 HT subjects were included in the present study. This is the main reason that we compared the values and assessed the associations among various variables in three groups rather than determining their associations with BMI or SBP/ DBP. Hence, the actual purpose of our present study was to explore the interactive role of various variables to understand their associated impact in the occurrence of HT and OW-related HT.

We found significant difference of serum Lep for OHT subject group and HT group both against NC subject group. A similar positive correlation was found between serum Lep with OW status **[43–45]**. Furthermore, Lep was revealed having important role in the pathophysiology of OW-related HT **[45]**.

It was investigated that it is the Lep, having influencing role in the OW-related HT **[44]**. The HT and endothelial dysfunction partly relate to serum levels of Lep, and other adipokines **[46,47]**. Inflammation caused by the cytokines causes inflammation dependent aortic stiffening that may lead to ventricular stiffness **[48]**. These observations identify the impact of Lep via inflammatory processes in the progressive development of HT. Furthermore, OW and obesity can lead to dysfunction of perivascular adipose tissue (PVAT) that releases Lep, and other cytokines/ chemokines to the vascular wall **[49–53]** and causes endothelial dysfunction and inflammation **[50]**. These reports are in accordance with the changes found in the present study for IL-6 and TNF-α in HT and OHT subjects compared to NC subjects.

The OW and obesity status increases the production of contractile factors and incorporate increased arterial vasoconstriction and greater vessel tone, producing different effects on the control of vascular tone **[50,54]**. The PVAT derived contractile factors e.g., Lep cause vasoconstriction. It was found that anticontractile activity is decreased in patients with HT **[51]**.

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Arterial stiffness via promoting vascular smooth muscle cell proliferation as well as migration associated with HP has been suggested to be due to Lep receptors located in vessels especially in aorta **[55]**, tunica media, and adventitia in arteries and also in atherosclerotic plaques **[56]**. Furthermore, the function of Lep in promoting the angiogenesis, activating the immune system, increasing the platelet aggregation, producing radical oxygen species (ROS) **[57]**, inducing endothelial oxidative stress and ROS in experimental human cell models **[58]** interactively present a mechanism whereby risk of the development of HT increases. Adiponectin having protective effects on arteries associates negatively with Lep, and hence hypoadiponectinemia associates with increased Lep levels **[59]**.

Another mechanism explaining our present results is that, an increased activity of sympathetic nervous system in OW/ obese subjects has been revealed in several studies **[60–64]**, and it was further found that increased BW associated with HT stimulates the sympathetic stimulation causing increased occurrence of HT with the increase in Lep levels in association with increase in pro-inflammatory cytokines, and hence increased HT condition **[60–62]**.

The second important factor that we investigated in the present work is the increased level of TNF-α in OW and HT subjects. This investigation can be explained with the help of several related reports. The cross-link between the concept of immune system–adiposity–inflammation–blood pressure¸ makes a set of vicious events **[65]** having a major role in HT **[66]**. The TNF-α is an important and effective pro-inflammatory adipocytokine that is involved in causing the low-grade inflammation and influencing the CVD involving OW/ obesity, atherosclerosis and other disorders **[67,68]**. The OW and inflammation in HT men showed significant role of TNF-α **[31]**.

The low-grade inflammation related to the adipose tissue and excess fats **[25]** associates with the immune complications leading to HT and other disorders **[25,26]**. There are a variety of immune factors involved in regulating the immune processes in vascular pathologies caused by adipose tissue derived and a most notorious pro-inflammatory cytokine TNF-α and other adipokines **[69,70]**. Probable immune-related inflammatory changes in newly-diagnosed HT with higher BMI showed higher levels of (TNF)-α, and other factors better characterizing the CV risk in HT patients **[71]**.

The immune mechanisms related to immune system activation explains our observations in the current clinical study. Inflammatory processes are involved in the pathogenesis and continuation of CVD complications **[72–75]**, and the inflammatory markers may serve as emergent therapeutic targets **[73,76,77]**. Increased levels of IL-6 and TNF-α in HT and OHT groups in the present study fit nicely in the proposed mechanism of inflammatory processes leading to CVD complications. The inflammatory status facilitated by the CV risk factors **[78]** is then regulated by the mechanisms related to immune system activation **[71,79,80]**.

Significantly decreased levels of ST in HT and OHT men in the present investigation can be described with the help of other reports. Though the mechanism whereby testosterone decreases in response to HT and OW status, it has been reported that serum levels of ST associate with the incidence of the morbidity and mortality of CVD diseases in men **[81]**. There are studies that show the effect of ST on CVD processes **[82–84]**.

It has been shown in male patients with coronary heart disease (CHD) that acute intracoronary administration of ST brings coronary artery dilation and hence, increases the blood flow and improved coronary activities **[82]**. The long-term administration of normal ST doses decreases the symptoms of angina and cardiac ischemia in men **[83–85]**. The ST is low in men with OW and obese status than in the NW people **[86]**. On contrary, the lifestyle changes bring the ST to increased level in men with OW and obesity **[87]**. The low levels of ST in men in obesity/ OW increases BP that leads to CVD complications, though it is not known, how does ST bring this change.

The OW and obesity are associated with the decrease in ST **[88,89]**. High increase in BW accompanies elevated levels of aromatase from fat that decreases the hypothalamic-pituitary-testis pathway and hence causes decrease in testosterone production by Leydig cells in testes **[90,91]**.

Testosterone deficiency occurs in OW/ obesity leading to changes in blood vessels and vice versa **[28,30,92,93]**. However, it has not been studied thoroughly to have clear idea of the role of

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testosterone in OW subjects. Therefore, an association between BW change and ST variations is not simple **[28]**.

There are reports showing the occurrence of hypogonadism due to decreased levels of ST associated with BW changes **[30,92,93]**. Hence, it seems reasonable to think that the manipulations for decreasing the BW can bring increase in ST **[30]**.

The subjects with increased levels of BMI associated with the occurrence of vascular dysfunctions, decreased ST and increased inflammation **[27]**. This investigation is quite similar to our observation of decreased ST and increased inflammation (IL-6 and TNF-α). On the basis of these observations, it was suggested for manipulating the procedures leading to weight loss, and involving testosterone and anti-inflammatory agents may prevent from vascular dysfunction **[27]**. The ST was found decreased in subjects with high BMI compared to that in low BMI **[27]**.

On the other hand, decreased levels of ST stimulates the fat formation in viscera leading to chain of events causing more decrease in the levels of ST **[94]**. The Lep levels increase in OW and obesity and have negative effect on luteinizing hormone (LH) and the production of human chorionic gonadotropin (hCG)-stimulated testicular androgen **[95]**.

The adipose tissue, fat formation, endocrine events of testosterone homeostasis, and OW/ obesity are associated with the inflammatory processes through release of pro-inflammatory and anti-inflammatory factors **[96]**, and decreased blood supply to adipocytes that causes hypoxia **[97]**. It then becomes a cascade causing further inflammation by releasing TNF-α and IL-6 **[98,99]** decreasing nitric oxide (NO) in blood vessels and vascular dysfunction **[29]**. This interactive set of investigations is a landmark in our present study.

It is not only the testosterone, other sex hormones including estradiol have shown cardioprotective actions in association with the vascular physiology **[82,84]**, though we could not measure the other sex hormones. Suppressing the activity of androgens was found to increase the BP in male subjects **[100]** that verifies the effect of testosterone decreasing BP in men i.e., ST and BP are negatively associated. This indicates that any manipulation to increase the ST could bring decrease in BP in OW and obese men **[87]**. The low levels of ST associates with the morbidity and mortality of cardiovascular disorders in men **[81]**. These reports verify our present results.

There are other studies that did not find change in BP in response to lifestyle changes for decreasing body weight **[33,34]**. They found little change in body weight. The present study comprises the NW subjects with HT and OW subjects with HT and hence changes occurred accordingly. Therefore, we could find progressive increase in various variables with increased BMI in OHT compared to that in HT and NC.

Cardiovascular events in HT increase the morbidity and mortality. The pharmacological interventions, exercise and diet plans including various forms of therapeutic patient education (TPE) help in reducing the morbidity and mortality due to cardiovascular involvements. Such aspects have not frequently been studied considering with the well-organized and personalized approaches.

Conclusively, the present study uncovers the interactive impact of serum leptin, TNF-α, testosterone, total cholesterol and IL-6 in hypertensive and overweight-related hypertensive men. The physiological approach of assessing the anthropometric and biochemical parameters including these and a variety of other factors may further help understanding the cardiovascular events and the influencing factors in hypertension and overweight related hypertension.

5. Limitations

We found wide difference in the age and gender-based levels of serum Lep and other variables in our pilot studies. Furthermore, we were highly interested to investigate the role of testosterone in association with Lep and other factors in men with HT and OHT. Hence, we carried out the present study in men of a specified age-51-60 years. However, to understand the clear evidence of the general role of Lep, ST, TNF-α, inflammatory status and lipid profile in HT and OHT, it is essentially required to have the record of wide age range in both men and women.

We measured the levels of ST but could not determine the levels of other gonadal/ steroid hormones and gonadotrophic hormones for understanding the interplay of endocrine changes in hypertension and overweight-related hypertension.

There is a need to assess the interactive role of leptin with other adipokines especially adiponectin for investigating the overweight-related hypertension. It could not be done mainly due to limited funding available for the proposal related to the current report.

Indeed, another group of subjects comprising obese hypertensives is a highly important group of subjects that we could not investigate in the present study, since our proposal was not related to obese or obese hypertensive subjects. However, we wish to overcome this limitation by carrying out further studies in near future for another proposal in obese and obese hypertensive patients.

Moreover, the data of several diseases including mainly the CHD, DM, renal ischemia/ failure and other kidney disorders, cerebral ischemia/ stroke, and liver diseases was excluded in the present study though these diseases are prevalent in overweight/ obese subjects with/ without hypertension.

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List of Abbreviations

ANOVA:	Analysis of variance
BMI:	Body mass index
BP:	Blood pressure
BW:	Body weight
CHD:	Coronary heart disease
CVD:	Cardiovascular disease
DBP:	Diastolic blood pressure
DM:	Diabetes mellitus
ELISA:	Enzyme-linked immunosorbent assay
hCG:	Human chorionic gonadotropin
HNW:	High normal weight
HOW:	High overweight
HT:	Hypertension/ hypertensive
IL-6:	Interleukin-6
Lep:	Leptin
LH:	Luteinizing hormone
LNW:	Low normal weight
LOW:	Low overweight
MNW:	Medium normal weight
MOW:	Medium overweight

n:	Number of subjects/samples
NC:	Normal control/controls
NHT:	Non-hypertensive
NO:	Nitric oxide
NT:	Normotensive/ normotensives
NW:	Normal weight
OHT:	Overweight hypertensive/ hypertensives
OW:	Overweight
PVAT:	Perivascular adipose tissue
ROS:	Radical oxygen species
SBP:	Systolic blood pressure
SD:	Standard deviation
ST:	Serum testosterone
TC:	Total cholesterol
TNF-α:	Tumor necrosis factor-alpha
TPE:	Therapeutic patient education

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