ABSTRACT

Obesity and hypertension are two closely associated conditions and obesity probably predisposed to hypertension. The mechanism of the association between obesity and hypertension is not clear. The aim of the present study was to clarify the relationship between blood pressure (BP), body mass index (BMI), serum angiotensinII (AGII) & serum leptin levels and to investigate the relation between serum AGII & Leptin. This study also aimed to rule out if there is a difference in serum AGII & leptin levels between lean and obese hypertensive females.

We measured fasting serum AGII and leptin levels in 16 normotensive lean (LN) females, 25 obese normotensive (ON) females, 12 lean hypertensive (LH) females and 25 obese hypertensive (OH) females. All subjects had no evidence of pre-existing cardiovascular disease, were non pregnant, had no previous history of ill health or smoking and were not on antihypertensive therapy.

In lean groups there were a significant increase in BMI & Serum AGII in hypertensive group compared to normotensive group while the serum leptin level was insignificantly higher in hypertensive group than in normotensive group. On the other hand there was a significant increase in serum AGII, BMI and serum leptin for obese hypertensive compared to obese normotensive group.

The mean ABP was significantly correlated to serum AGII, serum leptin and BMI in all groups. A significant correlation was found between serum AGII and serum leptin if all studied females (LN, LH, ON & OH) or obese females (ON& OH) were analyzed (P = 0.000 & 0.04). But in lean females (LN& LH) there was no relation between serum AGII & serum leptin.

In CONCLUSION

When obesity is present, both serum AGII & serum leptin were strong predictor of BP, which is not the case in lean females in whom only serum AGII is a predictor of BP. Elevation of serum AGII & serum leptin levels when associated with increased BMI may contribute to the pathophysiology of obesity-induced hypertension.

Further study on leptin resistance in obese persons and its relation to increased arterial blood pressure has to be done.

KEYWORDS: Blood pressure, Obesity, Leptin, Hypertension
INTRODUCTION

Obesity is a steady increasing health problem that is defined as increased mass of adipose tissue (1). It causes complications such as cancer (endometrium, breast and colon), diabetes mellitus, hypertension, stroke, coronary heart disease, cardiomyopathy, non-alcoholic steatohepatitis, osteoarthritis, reproductive problems, sleep apnea, and gall bladder disease (2).

An ideal body mass index (BMI) (weight in kilogram divided by the height in square meter) is 20-24 kg/m². Anything above or below that range will increase certain risk of morbidity and mortality. In general, a BMI 28 kg/m² increasing the risk for morbidity (3).

It is now obvious that obesity is a disease rather than a social problem, and it is associated with many disorders that lead to life threatening problems (4).

One of these diseases is hypertension. Although obesity is believed to be the major cause of human essential hypertension (5,6), the mechanisms responsible for weight-related increase in blood pressure are poorly understood (7). The adipose tissue participates in the regulation of a variety of homeostatic processes as an endocrine organ that secretes many biologically active molecules such as free fatty acid, adipin, angiotensinogen and leptin (8).

A prevailing concept has been that obesity induced hypertension is secondary to insulin resistance and hyperinsulinemia (9), despite the fact that experimental studies in humans (10) and dogs (11) have challenged this concept. Recently interest has focused in the role of kidney and renal sympathetic nerves in obesity induced hypertension (12,13).

It is further interesting to note that some studies found positive correlation between plasma angiotensinogen levels (14-16), renin activity (17-18) and plasma angiotensin converting enzyme activity (14) and body mass index in different human populations. Circulating angiotensin II is unique in that it is formed in the blood by the interaction of circulating proteins. There is in addition local rennin angiotensin system in tissues in which angiotensin II is apparently secreted by various types of cell (19). It is secreted by white fat and brown fat and it may play a role in the induced hypertension in obese patients (20).

Since the discovery of leptin (fat melting hormone secreted from the adipocytes) (21), researchers tried to investigate its role in obesity induced hypertension they claimed that leptin has sympathetic, vascular and renal actions that can influence blood pressure (8).

Both leptin and renin-angiotensin system (RAS) can influence the activity of the sympathetic nervous system, water and electrolyte metabolism as well as vascular remodeling, which are all involved in the regulation of arterial blood pressure (22). Thus RAS and leptin may act together in the pathogenesis of essential hypertension in obese persons.

The aim of this study was to answer the following questions:
1. Does an interrelationship exist between arterial blood pressure and BMI, serum leptin and serum angiotensin II levels?
2. Does an interrelationship exist between serum AGII & serum leptin level?
3. Is there a difference in BMI, serum AGII & serum leptin exists between lean normotensive subjects (LN), lean hypertensive subjects (LH), obese normotensive subjects (ON) and obese hypertensive subjects (OH)?

The answers may help us to understand the pathophysiological role of AGII and leptin in obesity-related hypertension.
METHODS OF STUDY

Subjects
Four groups of female subject (same sex) who were carefully matched for age and body mass index were studied (table 1). They were classified as:

- **Group 1**: sixteen lean normotensive female LN (mean age 24.5 ± 4.72 years, mean body mass index 19.88 ± 0.81 Kg/m², and blood pressure BP 92.00 ± 6.00mm Hg).
- **Group 2**: twenty five obese normotensive female ON (mean age 26.12 ± 4.05 years, mean body mass index 32.44 ± 2.65 Kg/m² and mean BP 95.5 ± 7.4mm Hg).
- **Group 3**: twelve lean essential hypertensive female LH (mean age 28 ± 3.36 years, mean body mass index 21.8 ± 1.11 Kg/m², mean BP 115.83 ± 2.72 mm Hg).
- **Group 4**: twenty five obese essential hypertensive female OH (mean age 28.16 ± 2.10, mean body mass index 37.72 ± 6.12 Kg/m², mean BP 122.88 ± 8.31mmHg).

All subjects had no evidence of pre-existing cardiovascular disease, were non pregnant, had no previous history of ill health or smoking and were taking no regular medication.

Measurements:
- Supine blood pressure (BP) was initially measured 3 times with a mercury sphygmomanometer; the first & fifth Korotokoff sounds were taken as systolic & diastolic values, respectively and mean arterial BP was calculated. Studied subjects were classified as normotensive if (BP) was < 140 mmHg systolic or < 90 mmHg diastolic or hypertensive if BP was ≥ 140 mmHg systolic or, ≥ 90 mmHg diastolic (23), and standard cuff and a tight cuff (bladder, 150 X 330 mm and 150 X 360 mm) were used in lean and obese subjects, respectively.
- Body height in meters was measured
- Body weight in kilograms was measured
- Body mass index (BMI, body weight in kilograms divided by the square of the height in meters) Kg/m² was measured. Studied subjects were considered obese if there BMI was > 27 Kg/m², lean if the BMI was <25 Kg/m² and overweight if the BMI was 25-27 Kg/m² (23).
- Fasting serum angiotensin II(24) & leptin(25) levels were assessed the same day of the study using ELISA procedure on a blood sample that was taken from a canula placed in an antecubital vein of the contralateral to that used for blood pressure measurements.

Statistical analysis
All values were reported as mean ± SD. Means were compared by independent-sample T test to locate between-group differences.

A P value < or equals 0.05 was considered to be statistically significant.

Regression analysis was used to describe the relationship between ABP as a dependant variable and BMI, serum leptin level and serum AGII level as independent variables, in all studied subjects, as well as obese & lean subjects separately. Similarly, regression analysis performed to describe the relationship between serum AGII level as a dependant variable & serum leptin level as an independent variable in all studied subjects as well as obese & lean subjects.

RESULTS
All subjects completed the study protocol. As shown in table 1, the 4 groups of females were matched for age, and they were all females. BMI were similarly elevated in normotensive and hypertensive obese groups compared with normotensive and hypertensive lean groups to which they were comparable. The mean BP was similarly elevated in obese and lean hypertensive groups compared to obese and lean normotensive groups to which they were comparable.
In obese hypertensive group, ABP, serum leptin & serum AGII were significantly greater than in lean hypertensive group P= 0.001,0.001 & 0.001 respectively table 1. 

In lean groups (normotensive & hypertensive), there were a significant increase in BMI & Serum AGII in lean hypertensive group when compared with lean normotensive group (P = 0.001) while the serum leptin level was insignificantly higher in lean hypertensive group than in lean normotensive group (table 1). 

On the other hand the obese groups (normotensive & hypertensive) showed significant increase in all parameters (serum AGII, BMI & serum leptin) (P=0.000) in obese hypertensive than in obese normotensive group (table 1) 

Using the linear regression analysis, in all studied subjects (LN, LH, ON, OH), revealed that mean ABP was significantly related to serum AGII, serum leptin and BMI (figure 1,2 and 3) & table 2. 

Linear regression analysis performed separately for obese groups (ON & OH together), and lean groups (LN & LH together), showed that in obese and lean groups, ABP was strongly related to BMI, serum AGII & serum Leptin, except for the lean groups where the ABP showed insignificant relation to the serum leptin level (table 2) figure 4,5,6,7,8 and 9.

A significant correlation was found between serum AGII and serum leptin if all studied females (LN, LH, ON & OH) or obese females (ON& OH) were analyzed. But in lean females (LN& LH) there was no relation between serum AGII & serum leptin (table 3).

**DISCUSSION**

Hypertension develops in almost 60% of obese individual. Apart from the recent observation of obesity associated structural changes in kidney that may lead to enhanced tubular sodium reabsorption, reports of paracrine and hormonal factors derived from adipose tissue have promoted speculations about the role of adipose tissue in the pathophysiology of obesity-induced hypertension (26).

The present study determined that the serum AGII & serum leptin were significantly greater in obese normotensive and lean hypertensive females than in lean normotensive control females, except for, serum AGII which was insignificantly greater in normotensive obese than in normotensive lean control subjects. However, the striking finding of the present study is that in obese hypertensive females (OH), serum AGII & serum leptin showed a further increase, even when compared with hypertensive lean females (LH). Which was so marked as to make the increase of BP by only obesity, and explain why the BP in OH was significantly higher than in LH females.

This study also provides data that may explain the mechanism of obesity-induced hypertension. Confirming previous findings, (27-32) this study showed that, BMI, serum AGII & serum leptin were significant independent predictor of BP level, when all females (LN, ON, LH & OH) together were tested & when obese females (ON & OH) and lean females (LN & LH) were tested separately. Except in lean females in whom the serum leptin was not significant independent predictor of BP level.

There are several possible explanations for this increase dependence of arterial BP on leptin in obese person. First, hyperleptinemia increases norepinephrine turnover in adipose tissue and increases sympathetic activity, which contributes to blood pressure elevation (33). This explanation is supported by other studies on animal (7,34) & human (35). Who found that leptin increases the sympathetic activity in obese subjects, which is mediated primary via the central nervous system (35 &36).

The second possibility is that leptin posses both depresser and presser effects, but the chronic effect of leptin appears to be presser (37).
Third possible explanation for the increased dependence of BP on leptin in obese subjects is that leptin could promote antinatriuresis (38).

Our results do not agree with those of Wang et al, (39) who did not find a relation between serum leptin & BP. However it should be emphasized that the subjects studied by Wang et al had an elevation in blood pressure that was similar but an elevation in body weight that was much less than that displayed by our study subjects. The relation between leptin & obesity -induced hypertension, the elevated serum AGII could contribute in the pathogenesis of obesity-induced hypertension this may be due to increase AGII production by adipocytes, (34) and the increased sensitivity of the pressor effects of AGII in obese subjects (39).

There are evidence that adipose tissue is an important source of angiotensinogen as well as the renin, angiotensin converting enzyme (ACE) & AGII (40-42). This may explain the significant elevation of AGII in OH females in our study than in LH females. This finding is supported by Massiera F et al, (41) who reported that angiotensinogen produced by adipose tissue plays a role in both local adipose tissue development and in endocrine system, which supports a role of adipose angiotensinogen in hypertensive obese patients. Other investigators,(22) found that obesity may alter the levels of ACE and angiotensinogen, and provide a potential pathway through which obesity leads to elevation of blood pressure.

Other finding of the present study deserve to be discussed, we found that the serum leptin was a strongly predictor variable of serum AGII in all studied female groups (LN, LH, ON & OH together) & in obese female groups (ON & OH together). While in lean female groups (LN & LH) there was no significant relation between them.

This may explain why we found that, serum AGII was significantly higher in obese hypertensive females than in lean hypertensive females. The elevated serum AGII can be explained by the leptin levels in this study and not only by the secreted AGII production by the adipocytes. This finding is supported by other studies, (22,43) who found a relation between hyperleptinemia & AGII.

This is of important clinical implications. For example, given the direct effect of leptin on increased sympathetic activity and AGII production, the marked leptin production seen in obese hypertensive subjects may favor sympathetic & AGII effects on the heart, such as left ventricular hypertrophy, and vascular lesions, such as those associated with atherosclerosis.

Furthermore, the increased sympathetic activation induced by leptin may also be responsible, at least in part, for the greater incidence of sudden death reported in obese hypertensive patients (44).

ACKNOWLEDGMENT

We are grateful to the sisters in the Records Department, King AbdulAziz University Hospital, for help with tracing case files.

CONCLUSION

The elevation of serum AGII & serum leptin levels when associated with increased BMI may contribute to the pathophysiology of obesity-induced hypertension. When obesity is present, both serum AGII & serum leptin were strong predictor of BP, which is not the case in lean females in whom only serum AGII is a predictor of BP.

In obese hypertensive patients, the use of the drugs that reduce the sympathetic activity induced by high serum leptin is appropriate for achieving blood pressure control and for organ protection.
Table 1: Base line Age, body mass index (BMI). Arterial blood pressure (ABP), Serum serum angiotensinII (AGII) & Serum Leptin Data for Lean normotensive, obese normotensive, Lean hypertensive, and obese hypertensive subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lean normotensive females (n=16)</th>
<th>Obese normotensive females (n=25)</th>
<th>Lean hypertensive females (n=12)</th>
<th>Obese hypertensive females (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) mean ± SD</td>
<td>24.5 ± 3.72</td>
<td>26.12 ± 4.05</td>
<td>28.0 ± 3.36</td>
<td>28.16 ± 2.10</td>
</tr>
<tr>
<td>BMI (Kg/m²) mean ± SD</td>
<td>20.00 ± 0.81</td>
<td>32.44 ± 2.65</td>
<td>21.83 ± 1.11</td>
<td>37.72 ± 6.12</td>
</tr>
<tr>
<td>ABP(mmHg) mean ± SD</td>
<td>92.00 ± 6.00</td>
<td>95.5 ± 7.4</td>
<td>115.83 ± 2.72</td>
<td>122.88 ± 8.31</td>
</tr>
<tr>
<td>Serum AGII (ng/ml) mean ± SD</td>
<td>0.18 ± 0.14</td>
<td>0.28 ± 0.33</td>
<td>0.80 ± 0.37</td>
<td>1.60 ± 1.01</td>
</tr>
<tr>
<td>Serum leptin (ng/ml) mean ± SD</td>
<td>8.36 ± 5.43</td>
<td>23.15 ± 6.73</td>
<td>11.56 ± 6.07</td>
<td>43.36 ± 6.12</td>
</tr>
<tr>
<td>P</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
</tr>
</tbody>
</table>

P Shows significance between normotensive groups (Lean & obese).
P*: Shows significance between lean groups (normotensive & hypertensive subjects).
P**: Shows significance between obese groups (normotensive & hypertensive subjects).
P***: Shows significance between hypertensive groups (obese & lean subjects).

Table 2: Linear regression analysis for all studied females (LN, LH, ON, OH), obese females (ON &OH) and leans females (LN&LH). Mean ABP was used as dependant variable &Serum AGII, BMI & Serum Leptin are used as independent variables.

<table>
<thead>
<tr>
<th>Dependent variable mean ABP (mmHg)</th>
<th>Serum AGII (ng/ml)</th>
<th>BMI(Kg/m²)</th>
<th>Serum Leptin (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All studied females (LN, LH, ON, OH)*R</td>
<td>0.70</td>
<td>0.52</td>
<td>0.40</td>
</tr>
<tr>
<td>R²</td>
<td>0.50</td>
<td>0.30</td>
<td>0.32</td>
</tr>
<tr>
<td>P</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Obese females (ON,OH)R</td>
<td>0.67</td>
<td>0.69</td>
<td>0.67</td>
</tr>
<tr>
<td>R²</td>
<td>0.45</td>
<td>0.47</td>
<td>0.45</td>
</tr>
<tr>
<td>P</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Lean females (LN, LH)R</td>
<td>0.76</td>
<td>0.74</td>
<td>0.23</td>
</tr>
<tr>
<td>R²</td>
<td>0.45</td>
<td>0.54</td>
<td>0.05</td>
</tr>
<tr>
<td>P</td>
<td>0.001</td>
<td>0.001</td>
<td>NS</td>
</tr>
</tbody>
</table>

*LN; lean normotensive, LH; lean hypertensive, ON; obese normotensive, OH; obese hypertensive
pertensive.

Table 3: Linear regression analysis for all studied females (LN, LH, ON, OH), obese females (ON & OH) and lean females (LN & LH). Serum AGII is used as dependent variable & Serum Leptin is used as independent variables.

<table>
<thead>
<tr>
<th>Dependant variable mean ABP (mmHg)</th>
<th>Serum leptin ng/ml in all studied females (LN, LH, ON, OH)*</th>
<th>Serum leptin ng/ml in obese females (ON, OH)</th>
<th>Serum leptin ng/ml in lean females (LN, LH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>0.45</td>
<td>0.4</td>
<td>0.035</td>
</tr>
<tr>
<td>R2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.001</td>
</tr>
<tr>
<td>P</td>
<td>0.001</td>
<td>0.004</td>
<td>NS</td>
</tr>
</tbody>
</table>

*LN; lean normotensive, LH; lean hypertensive, ON; obese normotensive, OH; obese hypertensive.

Figure 1: Shows that mean ABP is significantly related to serum AGII in all studied females (LN, LH, ON & OH).
**Figure 2:** Shows that mean ABP is significantly related to BMI in all studied females (LN, LH, ON & OH).

**Figure 3:** Shows that mean ABP is significantly related to serum leptin in all studied females (LN, LH, ON & OH).
Figure 4: Shows that mean ABP is significantly related to serum AGII in obese females (ON & OH).

Figure 5: Shows that mean ABP is significantly related to BMI in obese females (ON & OH).
Figure 6: Shows that mean ABP is significantly related to serum leptin in obese subjects (ON & OH).

Figure 7: Shows that mean ABP is significantly related to serum AGII in lean females (LN & LH).
Figure 8: Shows that mean ABP is significantly related to BMI in lean females (LN, LH).

Regression
95.00% Mean Prediction Interval

\[
abp_l = -43.50 + 3.03 \times bmi_l
\]
\[
R^2 = 0.24
\]

Figure 9: Shows that mean ABP is significantly related to serum leptin in lean females (LN, LH).

Regression
95.00% Mean Prediction Interval

\[
abp_l = 97.14 + 0.52 \times lept_l
\]
\[
R^2 = 0.06
\]
REFERENCE

المقدمة:

السمنة وارتفاع ضغط الدم الشرياني حالتان مرتبطتان ارتباطاً وثيقاً كما أن السمنة تزيد في احتمال ارتفاع ضغط الدم. ولكن كيفية هذا الارتباط بين السمنة وارتفاع ضغط الدم مازالت غير واضحة.

الهدف من البحث:

كان الهدف من إجراء هذه الدراسة هو إيضاح العلاقة بين ضغط الدم الشرياني وكلاً من معامل كتلة الجسم ومستوى الليبرتين والأنجيوتينسين 2 في بلازما الدم وكذلك بحث العلاقة بين الليبرتين والأنجيوتينسين 2 في البلازما وكم تهدف هذه الدراسة أيضاً إلى قياس الفرق بين مستوى الأنجيوتينسين 2 والليبرتين في قد السيدة السمن صوبة ذات ضغط الدم المرتفع ومستواها في قد السيدات النحافة ذات ضغط الدم المرتفع.

طريقة الدراسة:

تم قياس المستوى الصائم في البلازما لكل من الأنجيوتينسين 2 والليبرتين في 16 سيدة نحيفة ذات ضغط دم طبيعي و 25 سيدة سمنة ذات ضغط دم مرتفع و 25 سيدة سمنة ذات ضغط دم مرتفع. ولم يكن هناك أي دليل على إصابة أي من السيدات بأي مرض في القلب كما أنهم كانوا من غير المدخنين.

وكانوا أيضاً من غير الحوامل ولم يستخدموا أدوية مخفضة لضغط الدم المرتفع.

نتائج البحث:

أظهرت نتائج السيدات النحيفات زيادة في قيمة أخصائيه في معامل كتلة الجسم ومستوى الأنجيوتينسين 2 في البلازما في مجموعة السيدات ذات ضغط الدم المرتفع عند مقارنة هذه النتائج عند السيدات ذات ضغط الدم الطبيعي. كما أظهرت نتائج نفس المقارنة زيادة في مستوى الليبرتين في البلازما في مجموعة السيدات ذات ضغط الدم المرتفع ولكن هذه الزيادة لم يكن لها مغزى إحصائياً.

ومن ناحية أخرى دلت النتائج على وجود زيادة في قيمة إحصائية في مستوى الأنجيوتينسين 2 والليبرتين وعمران كلاً من السيدات النحيفة في معامل كتلة الجسم في البلازما ذات ضغط الدم الطبيعي.

وكما أظهرت نتائج البحث أيضاً أن متوسط ضغط الدم الشرياني لعلاقة ذو قيمة إحصائية من كل من الأنجيوتينسين 2 والليبرتين ومعامل كتلة الجسم في كل مجموعة التي تم دراستها في هذا البحث.

الخلاصة:

شكل مستوى الأنجيوتينسين 2 والليبرتين في الدم مؤشراً لمستوى ضغط الدم الشرياني في حالات السيدات المصابة بالسمنة بينما كان الأنجيوتينسين 2 فقط هو المؤشر لضغط الدم في السيدات النحيفات. لذلك فإن مستوى الأنجيوتينسين 2 والليبرتين في الدم المصχوب يزيد في معامل كتلة الجسم قد يكون أحد الطرق البيوانسيولوجية لارتفاع ضغط الدم الشرياني المصاحب للسمنة.