Relationship between plasma angiotensinII, leptin and arterial blood pressure

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ABSTRACT

Objective: Obesity and hypertension are 2 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) and serum leptin levels and to investigate the relation between serum AGII and leptin. This study also aimed to rule out if there is a difference in serum AGII and leptin levels between lean and obese hypertensive females.

Methods: 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 preexisting cardiovascular disease, were non pregnant, had no previous history of ill health or smoking and were not on antihypertensive therapy. This study was performed in King Abdul-Aziz University Hospital, Jeddah, Kingdom of Saudi Arabia from January 2002 through to January 2003

Results: In lean groups, there were a significant increase in BMI and 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 arterial blood pressure (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 and OH) or obese females (ON and OH) were analyzed (P=0.000 and 0.04). However, in lean females (LN and LH) there was no relation between serum AGII and serum leptin.

Conclusion: When obesity is present, both serum AGII and 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 and 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 ABP has to be carried out.

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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/m^2. Anything above or below that range will increase certain risk of morbidity and mortality. In general, a BMI 28 kg/m^2 increases 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

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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, adipsin, 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 BMI in different human populations. Circulating AGII 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 AGII 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 claim 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 remolding, which are all involved in the regulation of arterial blood pressure (ABP).[22] Thus, RAS and leptin may act together in the pathogenesis of essential hypertension in obese persons.

The aim of this study was to identify the relationship between ABP and BMI, serum leptin and serum AGII levels. As well as to address if there is relation between serum AGII and serum leptin level. Furthermore, we tried to figure out if there is a difference in BMI, serum AGII and serum leptin exists between lean normotensive subjects (LN), lean hypertensive subjects (LH), obese normotensive subjects (ON) and obese hypertensive subjects (OH). The findings of this study may help us to understand the pathophysiological role of AGII and leptin in obesity-related hypertension.

Methods. ***Subjects.*** Four groups of female subject (same sex) who were carefully matched for age and body mass index (BMI) were studied (**Table 1**). They were classified as Group one 16 lean normotensive female LN (mean age 24.5 ± 4.72 years, mean BMI 19.88 ± 0.81 kg/m^2, and blood pressure (BP) 92.00 ± 6.00 mm Hg). Group 2 25 obese normotensive (ON) female ON (mean age 26.12 ± 4.05 years, mean BMI 32.44 ± 2.65 kg/m^2 and mean BP 95.5 ± 7.4mm Hg). Group 3 12 lean essential hypertensive female (LH) (mean age 28 ± 3.36 years, mean BMI 21.8 ± 1.11 kg/m^2, mean BP 115.83 ± 2.72 mm Hg). Group 4 25 obese essential hypertensive female OH (mean age 28.16 ± 2.10, mean BMI 37.72 ± 6.12 kg/m^2, mean BP 122.88 ± 8.31mm Hg). All subjects had no evidence of preexisting cardiovascular disease, were non pregnant, had no previous history of ill health or smoking and were taking no regular medication.

Measurements. Supine BP was initially measured 3 times with a mercury sphygmomanometer; the first and fifth Korotokoff sounds were taken as systolic and diastolic values, and mean arterial BP was calculated. Studied subjects were classified as normotensive if BP was <140 mm Hg systolic or <90 mm Hg diastolic or hypertensive if BP was ≥140 mm Hg systolic or, ≥90 mm Hg 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. Body height in meters was measured, body weight in kilograms was measured, BMI (body weight in kilograms divided by the square of the height in meters) kg/m^2 was measured. Studied subjects were considered obese if there BMI was > 27 kg/m^2, lean if the BMI was <25 kg/m^2 and overweight if the BMI was 25-27 kg/m^2.[23] Fasting serum AGII[24] and leptin[25] levels were assessed the same day of the study using ELISA procedure on a blood sample that was taken from a cannula placed in an antecubital vein of the contralateral to that used for BP 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 ≤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 and lean subjects separately. Similarly, regression analysis performed to describe the relationship between serum AGII level as a dependant variable and serum leptin level as an independent variable in all studied subjects as well as obese and 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. Body mass index 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

Table 1 - Base line age, body mass index. Arterial blood pressure serum angiotensinII and serum leptin data for lean normotensive, obese normotensive, lean hypertensive and obese hypertensive subjects.

Variable	Lean normotensive females (n=16)	Obese normotensive females (n=25)	Lean hypertensive females (n=12)	Obese hypertensive females (n=25)
Age (years) mean ± SD	24.5 ± 3.72	26.12 ± 4.05	28.0 ± 3.36	28.16 ± 2.10
BMI (kg/m^2) mean ± SD	20.00 ± 0.81	32.44 ± 2.65	21.83 ± 1.11	37.10 6 ± 6.12
P*		0.000		
P**			0.000	
ABP (mm Hg) mean ± SD	92.00 ± 6.00	95.5 ± 7.4	115.83 ± 2.72	122.88 ± 8.31
P***				0.001
Serum AGII (ng/ml) mean ± SD	0.18 ± 0.14	0.28 ± 0.33	0.80 ± 0.37	1.60 ± 1.01
P	NS			
P*		0.000		
P**			0.000	
P***				0.001
Serum leptin (ng/ml) mean ± SD	8.36 ± 5.43	23.15 ± 6.73	11.5 ± 6.07	43.36 ± 6.12
P	0.000			
P*		NS		
P**			0.000	
P***				0.001

NS - not significant
P Shows significance between normotensive groups (lean and obese)
P* Shows significance between lean groups (normotensive and hypertensive subjects)
P** Shows significance between obese groups (normotensive and hypertensive subjects)
P*** Shows significance between hypertensive groups (obese and lean subjects)

Table 2 - Liner regression analysis for all studied females (LN, LH, ON, OH), obese females (ON and OH) and lean females (LN and LH). Mean ABP was used as dependant variable and serum AGII and serum leptin are used as independent variables.

Dependent variable mean ABP (mm Hg)	Serum AGII (ng/ml)	BMI (kg/m2)	Serum leptin (ng/ml)
All studied females (LN, LH, ON, OH)*	0.70	0.52	0.40
R			
R^2	0.50	0.30	0.32
P	0.000	0.000	0.000
Obese females (ON, OH)	0.67	0.69	0.67
R			
R^2	0.45	0.47	0.45
P	0.000	0.000	0.000
Lean females (LN, LH)	0.76	0.74	0.23
R			
R^2	0.45	0.54	0.05
P	0.000	0.000	NS

NS - not significant, * LN - lean normotensive, LH - lean hypertensive, ON - obese normotensive, OH - obese hypertensive, ABP - arterial blood pressure, AGII - angiotensinII BMI - body mass index

Table 3 - Liner regression analysis for all studied females (LN, LH, ON, OH), obese females (ON and OH) and lean females (LN and LH). Serum AGII is used as dependent variable and serum leptin is used as independent variables.

Dependent variable mean ABP (mm Hg)	Serum leptin ng/ml in all studied females (LN, LH, ON, OH)*	Serum leptin ng/ml in obese females (ON, OH)	Serum leptin ng/ml in lean females (LN, LH)
R	0.45	0.4	0.035
R^2	0.2	0.2	0.001
P	0.000	0.004	NS

LN - lean normotensive, LH - lean hypertensive, ON - obese normotensive, OH - obese hypertensive, AGII - angiotensinII, ABP - arterial blood pressure

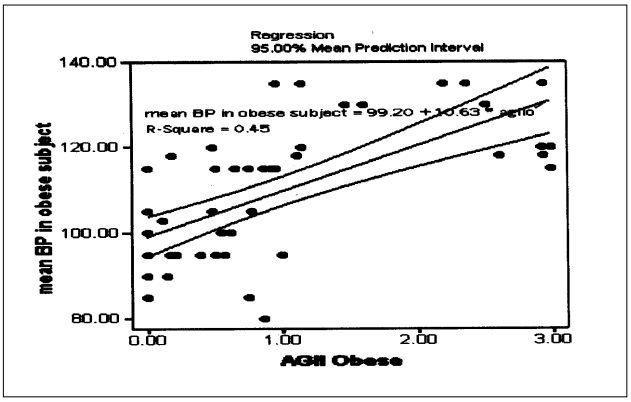

Figure 1 - Shows that mean ABP is significantly related to serum AGII in obese females (ON and OH). ABP - arterial blood pressure, AGII - angiotensinII, ON - obese normotensive, OH - obese hypertensive.

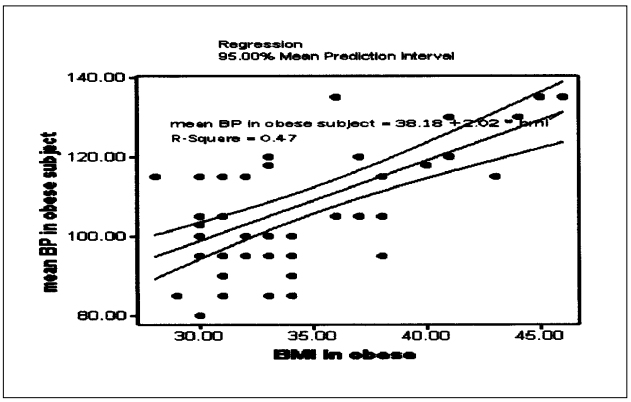

Figure 2 - Shows that mean ABP is significantly related to BMI in obese females (ON and OH). ABP - arterial blood pressure, BMI - body mass index, ON - obese normotensive, OH - obese hypertensive.

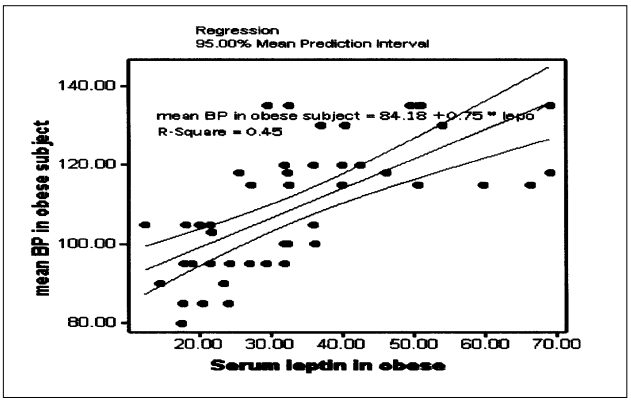

Figure 3 - Shows that mean ABP is significantly related to serum lepton in obese subjects (ON and OH). ATP - arterial blood pressure, ON - obese normotensive, OH - obese hypertensive.

normotensive groups to which they were comparable. In obese hypertensive group, ABP, serum leptin and serum AGII were significantly greater than in lean hypertensive group *P*= 0.001, 0.000 and 0.001, **Table 1**. In lean groups (normotensive and hypertensive), there were a significant increase in BMI and serum AGII in lean hypertensive group when compared with lean normotensive group (*P*=0.000) 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 and hypertensive) showed significant increase in all parameters (serum AGII, BMI and serum leptin) (*P*=0.000) in obese hypertensive than in ON 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 **(Table 2)**. Linear regression analysis performed separately for obese groups (ON and OH together), and lean groups (LN and LH together), showed that in obese and lean groups, ABP was strongly related to BMI, serum AGII and serum leptin, except for the lean groups where the ABP showed insignificant relation to the serum leptin level **(Table 2) (Figures 1, 2 & 3)**. A significant correlation was found between serum AGII and serum leptin if all studied females (LN, LH, ON and OH) or obese females (ON and OH) were analyzed. But in lean females (LN and LH) there was no relation between serum AGII and serum lepton **(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 reapportion, reports of paracrine and hormonal factors derived from adipose tissue have promoted speculations regarding the role of adipose tissue in the pathophysiology of obesity induced hypertension.[26] The present study determined that the serum AGII and 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 OH females, serum AGII and serum leptin showed a further increase, even when compared with LH females. 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 and serum leptin were significant

independent predictors of BP level, when all females (LN, ON, LH and OH) together were tested and when obese females (ON and OH) and lean females (LN and LH) were tested separately. Except in lean females in whom the serum leptin was not a 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] and humans.[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 depressor 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 antinatriuriesis.[38] Our results do not agree with those of Wang et al[39] who did not find a relation between serum leptin and BP. However, it should be emphasized that the subjects studied by Wang et al[39] had an elevation in blood pressure that was similar but an elevation in body weight that was much less than that displayed by our studied females. Beside the relation between leptin and 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, anigotensin converting enzyme (ACE) and 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 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 and OH together) and in obese female groups (ON and OH together). While in lean female groups (LN and 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 and 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 OH subjects may favor sympathetic and AGII effects on the heart, such as left ventricular hypertrophy, and vascular lesions, such as those associated with atherosclerosis. However, 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] From this study, we may suggest that the elevation of serum AGII and serum leptin levels when associated with increased BMI may contribute to the pathophysiology of obesity induced hypertension. When obesity is present, both serum AGII and serum leptin were strong predictors of BP, which is not the case in lean females in whom only serum AGII is a predictor of BP. In OH patients, the use of the drugs that reduce the sympathetic activity induced by high serum leptin is appropriate for achieving BP control and for organ protection.

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