Atrial Natriuretic Peptide and Leptin in Obesity-associated Hypertension in Middle-aged Egyptian Women

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ABSTRACT

Obesity is a world-wide health problem, whose incidence and prevalence are rising steadily; it may be combined with hypertension, diabetes, dyslipidemia, atherosclerosis, and/or chronic renal failure. Among these, hypertension has been observed in roughly 50% of obese individuals, which has led researchers to consider obesity as one of the most common causes of hypertension. The mechanisms linking obesity to hypertension have not been fully cleared. The present study aimed to clarify the interaction of leptin, soluble leptin receptors and the atrial natriuretic peptide in obese hypertensive patients. The study was performed on seventy five female subjects who were classified into three groups: group I (n=15) healthy lean controls, group II (n=30) obese normotensive patients, and group III (n=30) obese hypertensive patients. All participants were subjected to a thorough clinical assessment, and estimation of serum levels of glucose, creatinine, urea, cholesterol, leptin, soluble leptin receptors (sLR), and atrial natriuretic peptide (ANP). The serum levels of leptin and ANP were significantly higher in obese hypertensive and obese normotensive patients than in the controls, also, these levels were significantly higher in obese hypertensive patients when compared to obese normotensive patients. The serum sLR level in obese hypertensive and obese normotensive patients was significantly lower than in the controls, while its level in obese hypertensive patients was significantly lower than in obese normotensive patients. In the whole studied groups, the serum leptin and ANP levels were positively correlated, significantly, with BMI, diastolic blood pressure, and systolic blood pressure, but their levels were negatively correlated significantly with sLR. The serum sLR level was, significantly, negatively correlated with BMI, diastolic blood pressure, systolic blood pressure, leptin and ANP.

Keywords: *Atrial natriuretic peptide, leptin, soluble leptin receptor, obesity, hypertension.*

INTRODUCTION

With increasing the rate of obesity among adults and children, authorities view it as a serious public health problem. Between 1980 and 2000, obesity incidence among adults has more than doubled; and obesity among adolescents has tripled. In the USA, obesity is the second-leading

cause of preventable death after smoking [(1)]. In Egypt, It has been reported that the prevalence of obesity in adults is very high, particularly among women, and that the prevalence of diabetes and hypertension parallels that of obesity[(2)].

Understanding of neuro-endocrinal mechanisms regulating appetite metabolism and adiposity is revised since the discovery of leptin[(3)]. Leptin is an adipocyte-derived hormone that acts on the hypothalamus to regulate appetite, energy expenditure, and sympathetic outflow. Leptin promotes weight loss by reducing appetite and by increasing energy expenditure through stimulation of sympathetic nerve activity [(4)]. The excitement that followed leptin discovery was soon modulated by the realization that obesity is associated with hyperleptinemia, defining a state of "leptin resistance"[(5)].

Leptin plays its role by interaction with the specific leptin receptor. The leptin receptor exists in several isoforms. A soluble form of leptin receptor (sLR) represents the main leptin-binding activity in human blood. Circulating sLR is derived from ectodomain shedding of membrane-bound receptors and/or by alternative splicing of leptin receptor mRNA. It modulates steady-state leptin levels by modifying circulating free leptin to protect the hormone from degradation and clearance. Binding of leptin with soluble leptin receptor has been suggested to increase the bioavailability of leptin in plasma as well as to decrease binding of leptin to membrane specific receptors[(6)]. When sLR is incubated with free leptin, the leptin-sLR complex is incapable of activating membrane-bound receptors, although it does not inhibit the action of free leptin [(7)].

The risk of hypertension is five-times higher in the obese subjects as compared to those of normal weigh[(8)]. The mechanisms linking obesity to the development of hypertension have not been well-identified [(9)].

Atrial natriuretic peptide (ANP) is a circulating neurotransmitter regulating salt and water homeostasis and vascular tone that control blood pressure. It is cardiac in origin and is secreted mainly in response to increased intra-atrial pressure [(10)]. **Abdel Hafez et al.** [(11)] reported rise in plasma ANP in obesity, which became more elevated if the obesity was associated with hypertension.

The present work was planned to study the interaction of leptin and atrial natriuretic peptide in pathogenesis of hypertension in middle-aged obese females.

SUBJECTS & METHODS

Seventy-five female subjects were enrolled in this study. They were divided according to body mass index (BMI) and blood pressure (BP) into the following groups:

Group 1: Healthy lean controls (n =15), with age ranged between 22-47 years, BMI ≤25 kg/ m^2 and BP ≤120/80 mmHg.

Group II: Obese normotensive patients (n =30), with age ranged between 20-47 years, BMI ≥30 kg/m^2 and BP ≤120/80 mmHg.

Group III: Obese hypertensive patients (n =30), with age ranged between 21-48 years, BMI ≥30 kg/m^2 and BP ≥ 140/90 mmHg. They presented with never-treated, uncomplicated essential (primary) hypertension.

All patients were recruited from the Outpatients' Clinic of Internal Medicine Section, Kasr Al-Aini Hospital, Cairo University. The control volunteers were females from the working staff. All participants gave their informed consent before participation in the study, and the Ethics Committee of Kasr Al-Aini Hospital approved the protocol of the study.

For all subjects, arterial blood pressure was measured in the right arm by mercury sphygmomanometer three times while subjects were in a complete physical and mental rest (i.e. sitting or supine for at least 5.0 minutes before measurement) in a quite room at ambient temperature. Average values were calculated for diastolic and systolic pressures, large cuff sizes were used in obese subjects. BP values ≤120/80 mmHg were considered normotensive, while values ≥ 140/90 mmHg were considered hypertensive [(12)].

Detailed history taking, physical examination and laboratory investigations were done to exclude acute illness, cardiac, hepatic, renal, gastrointestinal, endocrinal, or malignant disease that might affect the parameters under investigation. None of the patients was receiving drugs known to affect the investigated parameters.

To minimize the effect of sex and age on the results of this work, all subjects were females aged 20-47 years old and not receiving contraceptive or hormonal therapy. Blood sampling was performed early in the follicular phase of the menstrual period (within the first week of the cycle).

Analytic procedures:

Following an overnight fast (12 hours), 10 ml blood was collected from the antecubital vein, and serum was kept frozen, in aliquots, at -20°C until used. The following laboratory investigations were performed for each subject: fasting blood glucose[(13)], serum creatinine[(14)], serum urea[(15)], total cholesterol[(16)], serum leptin by RIA technique (LINCO Research, Missouri, USA)[(17)], serum soluble leptin receptors (sLR) by ELISA method (R&D Systems, Minneapolis, USA) [(18)], and serum atrial natriuretic peptide (ANP) by RIA technique (Phoenix Pharmaceuticals Inc., Burlingame, California, USA) [(19)].

Statistical Methods:

The results were analyzed using Statistical Package for Social Science (SPSS) program version 10 (Chicago-IL, USA) [(20)]. Data were presented as mean ± S.D. Student t-test was used for analysis of two quantitative data. Differences among the three groups were compared by one-way ANOVA followed by post-hoc test. Simple linear correlation (Pearson's correlation for quantitative data and Spearman correlation for qualitative data) was done to detect the relation between leptin, sLR and ANP with all other demographic and laboratory data.

RESULTS

The clinical characteristics and anthropometric measurements (mean ± SD) in healthy control (Group I), obese normotensive (Group II) and obese hypertensive subjects (Group III) are shown in **table (I)**.

Table (I): Clinical characteristics and anthropometric measurements of the studied groups (mean ± SD)

	Group I	*Group II*	*Group III*	*P- value*
Age (years)	33.40 ± 13.6	35.43 ± 8.88	38.00 ± 7.49	>0.05
BMI (Kg/m^2)	23.25 ± 1.10	43.04 ± 9.54[a]	43.46 ± 5.73[a]	<0.001
Diastolic BP (mmHg)	74.00 ± 5.07	74.66 ± 5.07	92.66 ± 3.82[ab]	<0.001
Systolic BP (mmHg)	116.00 ± 5.07	116.33 ± 6.14	146.00 ± 7.78[ab]	<0.001

BP: Blood pressur, BMI: Body mass index, p<0.05 was considered significant, (a) Significant difference versus control subjects (b) Significant difference versus obese normotensive patients

The serum levels of creatinine, leptin and ANP were significantly higher in groups II and III versus group I. Also, these levels were significantly higher in group III when compared to group II **(Table II)**.

The serum sLR level in groups II and III was significantly lower than group I. Serum sLR level in group III was significantly lower than its level in group II **(Table II)**.

Table (II): Laboratory data of the studied groups (mean ± SD)

	Group I	*Group II*	*Group III*	*p-value*
F. Glucose (mmol/l)	4.19 ± 0.19	4.98± 0.46[a]	5.07 ± 0.73[a]	<0.005
Urea (mmol/l)	4.53 ± 0.73	6.96 ± 0.96[a]	7.49 ± 0.85[a]	<0.005
Creatinine (µmol/l)	96.8 ± 28.1	118.8 ± 20.2[a]	141.7 ± 28.1[ab]	<0.005
Cholesterol (mmol/l)	4.11 ± 0.13	5.08 ± 0.25[a]	4.85 ± 0.41[a]	<0.001
Leptin (ng/ml)	6.22 ± 1.64	31.03 ± 8.13[a]	49.00 ± 12.2[ab]	<0.001
sLR (ng/ml)	37.26 ± 6.69	26.93 ± 6.94[a]	20.8 ± 4.17[ab]	<0.001
ANP (pg/ml)	53.7 ± 11.98	136.3 ± 35.69[a]	250.6 ± 94.75[ab]	<0.001

p<0.05 was considered significant, (a) Significant difference versus control subjects (b) Significant difference versus obese normotensive patients

Serum leptin levels in the studied groups were positively correlated significantly (P<0.001) with BMI **(Figure 1)** (r=0.680), diastolic blood pressure (r=0.612), systolic blood pressure (r=0.614), cholesterol (r=0.380), urea (r=0.608), creatinine (r=0.390) and ANP (r=0.714) **(Figure 2)**. While it was negatively correlated significantly with sLR (r= -0.817) **(Figure 3)**.

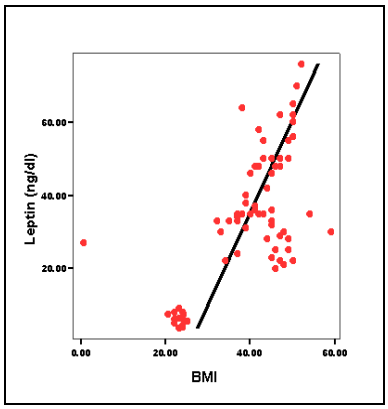

Figure 1: Scatterplot showing correlation between serum Leptin and BMI in the studied groups (r=0.680, p<0.001)

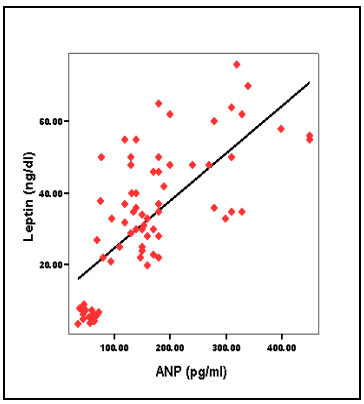

Figure 2: Scatterplot showing correlation between serum leptin and ANP in the studied groups (r=0.714, p<0.001)

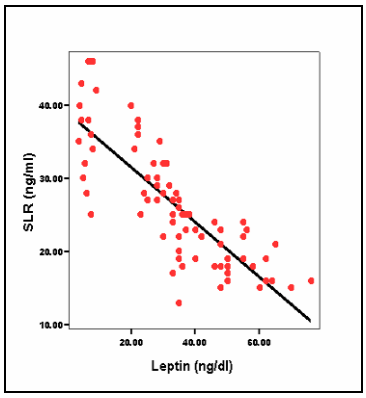

Figure 3: Scatterplot showing correlation between serum Leptin and sLR in the studied groups (r=-0.817, p<0.001)

The serum sLR was negatively correlated significantly (P<0.001) with BMI (r= -0.540) **(Figure 4)**, diastolic blood pressure (r= -0.554), systolic blood pressure (r= -0.557), cholesterol (r= -0.347), urea (r= -0.540), creatinine (r= -0.345), leptin (r=- 0.817) **(Figure 3)** and ANP (r= -0.550).

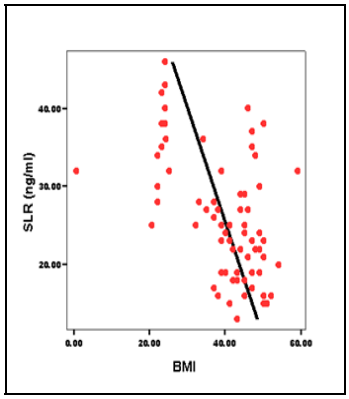

Figure 4: Scatterplot showing correlation between serum sLR and BMI in all studied groups (r=-540, p<0.001)

Serum ANP levels of the investigated groups were, significantly (P<0.001) positively correlated with BMI (r=0.525) **(Figure 5)**, diastolic blood pressure (r=0.561), systolic blood pressure (r=0.570), cholesterol (r=0.256), urea (r=0.536), creatinine (r=0.431) and leptin (r=0.714) **(Figure 1)**. While it was significantly negatively correlated with sLR (r= -0.550, P<0.001).

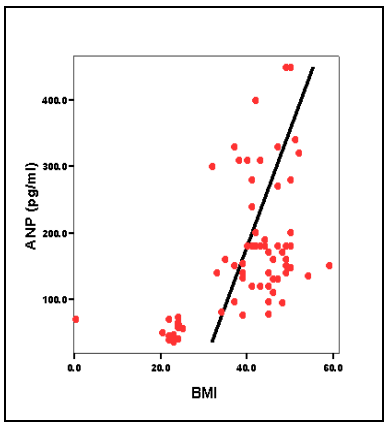

Figure 5: Scatterplot showing correlation between serum ANP and BMI in the studied groups (r=0.525, p<0.001)

DISCUSSION

Leptin, as adipocytokiune is derived from adipose tissue, it is significantly elevated in obese groups versus lean control group, with significant positive correlation between serum leptin concentration and BMI in all studied groups.

Mackintosh and Hirsch [21] reported that females with increased fat mass are associated with higher baseline leptin levels and endogenous production rates. Several other studies demonstrated that increased adiposity is correlated with increased serum leptin levels secondary to increased production rate and decreased elimination[22,23]. In addition, **Hafeezullah**[24] confirmed increased production rate through reporting higher concentration of leptin mRNA in fat from obese compared to thin subjects. The latter finding suggests that leptin gene is expressed more in adipose tissue of obese than from lean subjects. The underlined mechanism affecting the rate of gene expression is not clear.

In the present study the serum levels of leptin were significantly higher in group III than in groups II and I. Also, a significant positive correlation was detected between serum leptin and both systolic and diastolic blood pressures in all studied groups. This suggests that blood pressure might be affected by circulating leptin, or a common effector on leptin level and blood pressure is playing a role. **Al-Hazimi and Syiamic**[25] suggested that serum leptin and angiotensin II levels were strong predictors of elevated blood pressure in obese women.

El-Gharbawy and co-workers [26] found that leptin levels were higher in hypertensive than in normotensive African Americans, but once these individuals were adjusted for obesity, no significant relationship was further observed between leptin and blood pressure. Other investigators, **Shankar and Xiao** [27], reported higher plasma leptin that was positively correlated with hypertension, even after adjusting for other factors. Reduction in serum

leptin levels with administration of angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers suggest a potential interaction between leptin and the renin-angiotensin-aldosterone system for hemodynamic regulation in obesity[28]. Hyperleptinemia enhances vascular smooth muscle cell proliferation[29]. Leptin increases the accumulation of reactive oxygen species (ROS) in endothelial cells and thereby might play a major role in initiation of an inflammation process and genesis of vasoconstriction and atherosclerosis [30]. Leptin may function as a pressure and volume-regulating factor in health and obesity-linked hyperleptinemia, resulting in development of hypertension [31].

Leptin activates the sympathetic nervous system by both local peripheral actions as well as through centrally mediated effects on the hypothalamus [32,33]. The "selective leptin resistance" theory is feasible to explain why hyperleptinemia contributes to increased sympathetic activity and arterial pressure in obesity, in spite of resistance to the metabolic (satiety and weight-reducing) actions of leptin [34].

Besides sympathetic activation, leptin decreases renal vascular nitric oxide (NO) production resulting in systemic vasoconstriction along with sodium retention [35]. Serum creatinine and urea in our obese groups are higher than the lean group suggesting decrease renal efficiency in obesity. Lack of NO and abnormal renal Na^+ handling may contribute to leptin-induced hypertension[36,37]. Hyperinsulinemia characterizing obesity may be a contributing factor in development of sodium retention [38]. Conclusively, the interaction among the vasoconstricting, vasodilatory, and natriuretic effects of leptin to achieve volume and pressure homeostasis in normal conditions may be disrupted during chronic hyperleptinemia, and this effect could lead to hypertension and possible cardiac and renal dysfunction [39,40].

In the present study the sLR serum levels were significantly lower in obese hypertensive and obese normotensive patients compared to the control group. Similar results were obtained by[41,42,43]. The relationship of sLR with the degree of adiposity suggests that high sLR levels may enhance leptin action in lean subjects more than in obese subjects [44], and in lean subjects leptin circulates mainly in the bound form, whereas in obese subjects the majority of leptin circulates in the free form [6].

In the present study, there was a significant negative correlation between serum sLR and both BMI and leptin in the whole studied population. Circulating sLR expresses how leptin receptors are bioactive. In obesity, characterized by hyperleptinemia and leptin resistance, there may be down-regulation of leptin receptors, resulting in reduced circulating sLR[45]. **Huang et al.**[42] and **Gajewska et al.**[6] had reported that the sLR showed a significant inverse correlation with leptin and percentage of body fat.

Because the natriuretic peptide system plays a key role in the regulation of renal handling of sodium and water, it has been speculated that obese individuals may have an

impaired natriuretic peptide response. In a study in our laboratory, raised serum ANP was observed in obese subjects with and without hypertension [11].

In the present study, ANP levels of obese hypertensive and obese normotensive subjects had significantly higher serum ANP level than that of the lean control subjects. Also, the mean serum ANP level of obese hypertensive subjects was significantly higher than ANP level of obese normotensive. There was a significant positive correlation between serum ANP level and systolic BP, diastolic BP and BMI in the whole studied population.

Numerous studies reported high concentrations of ANP in patients with arterial hypertension regardless of body weight [46,47,48].

Rise of serum ANP in obesity may be a pathophysiologic mechanism to protect against the hemodynamic changes that are associated with expanded blood volume in obesity and hypertension [11]. ANP is known to be vasodilator and an inhibitor to rennin-angiotensin-aldosterone axis, besides its diuretic and natriuretic effects [49].

In the study of **Wang and co-workers**[50], plasma natriuretic peptide levels were, variably, higher in hypertensive compared with normotensive individuals. However, in contradiction to our results they reported that overweight and obese individuals with hypertension still had lower plasma ANP level compared with normotensive individuals with normal BMI. Natriuretic peptides, in obese patients with hypertension may protect against further elevation of blood pressure rather than contribute to the pathogenesis of hypertension by guarding against fluid volume expansion.

In this study, a significant positive correlation was detected between serum ANP level and leptin, while a significant negative correlation was found between serum ANP level and sLR in the whole studied groups. Such correlation suggests that ANP may influence leptin receptor activity. Both leptin and ANP enhance sympathetic over-activity [51].

Atrial natriuretic peptide has been shown to promote adipose tissue lipolysis through cGMP-mediated hormone-sensitive lipase activation[52,53]. **Nielsen et al.**[54] suggested that the increased release of free fatty acids (FFA) into the portal vein from lipolysis in visceral fat depots of obese subjects could explain the strong association between visceral obesity and increased sympathetic nerve outflow and blood pressure. Obesity-associated hyperinsulinemia may be a crucial pathophysiologic feature of promoted lipolysis in visceral adipose tissue[55] Fatty acid binding protein-2 may undergo mutation in metabolic syndrome, this impaired fatty acid utilization may ensue resulting in enhanced sympathetic activity [56].

In addition, **Mascareno et al.** [57], investigated the molecular mechanism(s) that play a role in leptin signaling during the development of left ventricular hypertrophy due to pressure overload (i.e. hypertension), and they observed that leptin plays a role in modulating the transcriptional activity of nuclear factor activated T

cell 4 which is the promoter of the ANP gene, followed by an increase in the expression of the ANP gene. Increased ANP in patients with idiopathic hypertension might indicate left ventricular hypertrophy, in which the increased left ventricular mass may significantly enhance the ventricular contribution of circulating ANP [(58)].

Thus, it seems that an interaction between leptin and ANP in development of hypertension in obese subjects may exist. The interaction may aim at reduction of the circulating plasma volume besides adapting for energy homeostasis.

Serum glucose in obese groups is significantly higher than the lean control group. Insulin has a sustained antinatriuretic action that is triggered by increased glucose, and it is powerful enough to completely block the natriuresis caused by hyperglycemia [(38)]. This action of insulin may be an etiological factor of sodium retention in obesity with subsequent rise of blood pressure.

To summarize, many hormonal factors are interplaying to cause rise of blood pressure in obesity; leptin through enhancing sympathetic activity and affection of the renal functions. Leptin, also, promotes release of ANP from ventricles to modulate plasma volume, vascular tone, renal water and sodium homeostasis. Both promote lipolysis from visceral adipose tissue. The latter effect is enhanced by hyperinsulinemia characterizing obesity. ANP, along with leptin and FFA activates sympathetic functions.

REFERENCES

1- **Barness A, Opitz M and Gilbert E. (2007):** Obesity: genetic, molecular, and environmental aspects. Am. J. Med. Genet., 143: 3016–3034.

2- **Galal M. (2002):** The nutrition transition in Egypt: under nutrition and the food consumption context. Public health nutrition, 5: 141–148.

3- **Flier S. (2004):** Obesity wars: molecular progress confronts an expanding epidemic. Cell, 116: 337–350.

4- **Haynes G, Morgan A, Walsh A, Mark L and Sivitz I. (1997):** Receptor mediated regional sympathetic nerve activation by leptin. J. Clin. Invest., 100: 270–278.

5- **Rahmouni K, Morgan A, Morgan M, Mark L and Haynes G. (2005):** Role of selective leptin resistance in diet-induced obesity-hypertension. Diabetes 54: 2012–2018.

6- **Gajewska J, Weker H, Ambroszkiewicz J, Chełchowska M, Dyląg H, Ołtarzewski M and Laskowska-Klita T. (2009):** Can leptin and soluble leptin receptor concentrations be used in assessing the efficacy of weight reduction programme in prepubertal obese children? Gastroenterology 13: 237-243.

7- **Yang G, Ge H, Boucher A, Yu X and Li C. (2004):** Modulation of direct leptin signaling by soluble leptin receptor. Mole. Endocrinol., 18: 1354-1362.

8- **Haslam W and James P. (2005):** Obesity. Lancet 366: 1197–1209.

9- **Stenvikel P, Lonnqvist F and Schalling M. (1999):** Molecular studies of leptin: Implication of renal disease. Nephrol. Dial. Transplant., 14: 1103–1112.

10- **Hender T, Hender J, Anderson B, Persson B and Petersson A. (1987):** ANF-a cardiac hormone and putative central neurotransmitter. Eur. Hert. J. B., 8: 87–98.

11- **Abdel Hafez M, Nasr S, El-Ghazaly S, Abdel-Ghany N, Okasha S and El-Molla B. (1994):** Plasma atrial natriuretic factor in obesity: Correlation to echocardiography. J. Clin. Biochem. Nutr., 16: 59-63.

12- **National Heart, Lung and Blood Institute (2003):** Release new high blood pressure guidelines for American family physician. J. Am Academy, 228-231.

13- **Caraway T. (1976):** In Fundamentals of Clinical Chemistry. 2nd edition, Philadelphia, pp. 242–245.

14- **Heinegard D and Tiderstrom K. (1973):** Determination of serum creatinine by direct colorimetric method. Clin. Chem. Acta., 43: 305 –310.

15- **Tabacco M. (1975):** Clinical diagnosis and measurement by laboratory methods. Clinical Chemistry, 25: 36–39.

16- **Flegg M. (1973):** investigation of the determination of serum cholesterol by an enzymatic method. Ann. Clin. Biochem., 10: 79 –84.

17- **Pelleymounter A. (1995):** Effects of the obese gene product on body weight regulation ob/ob mice. Science, 269: 540–547.

18- **Sahu A. (2004):** A hypothalamic role in energy balance with special emphasis on leptin. Endocrinology, 145: 2613–2620.

19- **Wang N, Chou J, Chang K, Avila C and Romero R. (1990):** Endothelin-1 in Human Plasma and Amniotic Fluid. In Endothelin-derived contracting factors. edited by Rubanyi G. and Vanchoutte P., Karger, Basel, pp.143

20- **Norusis MJ. (1997):** SPSS 7.5 guide to data analysis, Simon and Schuster Company, Upper Saddle River. New Jersey.

21- **Mackintosh M and Hirsch J. (2001):** The effects of leptin administration in non-obese human subjects. Obes. Res., 9: 462– 469.

22- **Farooqi S, Matarese G, Lord G, Keogh J, Lawrence E, Agwu C et al. (2002):** Beneficial effect of leptin on obesity ,T cell hyporesponsiveness and neuroendocrine / metabolic dysfunction of human congenital leptin deficiency. J. Clin. Invest., 110: 1093–1103.

23- **Banks A. (2004):** The many lives of leptin. Peptides, 25: 331–338.

24- **Hafeezullah M. (2006):** Leptin: fights against obesity! Pak. J. Physiol., 2: 153-159.

25- **Al-Hazimi A and Syiamic A. (2004):** Relationship between plasma angiotensin II, leptin and arterial blood pressure. Saudi Med. J., 25: 1193–1198.

26- El-Gharbawy A, Kotchen J, Grim C et al. (2003): Gender-specific correlates of leptin with hypertension-related phenotypes in African Americans. Am. J. Hypertens., 15: 989–993.

27- Shankar A and Xiao J. (2010): Positive relationship between plasma leptin level and hypertension. Hypertension 56:623-635.

28- Santos L, Picoli Souza K, Silva D et al. (2009): Long term treatment with ACE inhibitor enalapril decreases body weight gain and increases life span in rats. Biochemical Pharmacology 78:951–958.

29- Huang F, Xiong X, Wang H, You S and Zeng H. (2010): Leptin-induced vascular smooth muscle cell proliferation via regulating cell cycle, activating ERK1/2 and NF-*κ*B. Acta Biochimica et Biophysica Sinica 42(5):325–331.

30- Bouloumié A, Marumo T, Lafontan M and Busse R. (1999): Leptin induces oxidative stress in human endothelial cells. The FASEB Journal 13: 1231-1238.

31- Kshatriya S, Reams P, Spear M, Freeman H, Dietz R and Villarreal D. (2010): Obesity hypertension: the emerging role of leptin in renal and cardiovascular dyshomeostasis. Curr. Opin. Nephrol. Hypertens., 19: 72-78.

32- Correia M and Haynes W. (2008): Does selective leptin resistance cause obesity-related hypertension? Rev. Bras. Hypertens., 15:189-194.

33- Mark L, Agassandian K, Morgan A, Liu X, Cassell D and Rahmouni K. (2009): Leptin signaling in the nucleus tractus solitarii increases sympathetic nerve activity to the kidney. Hypertension 53: 375–380.

34- Mark L and Sivitz I. (2002): Uncoupling metabolism and coupling leptin to cardiovascular disease. Arterioscl. Thromb. Vasc. Biol., 22: 881–883.

35- Bravo P, Morse S, Borne D, Aguilar E and Reisin E. (2006): Leptin and hypertension in obesity. Vasc. Health Risk Manag., 2: 163–169.

36- Beltowski J, Wójcicka G, Marciniak A and Jamroz A. (2004): Oxidative stress, nitric oxid production, and renal sodium handling in leptin-induced hypertension. Life Sciences 74: 2987-3000.

37- Bełtowski J, Wójcicka G, Jamroz A and Marciniak A. (2009): Resistance to acute NO-mimetic and EDHF-mimetic effects of leptin in the metabolic syndrome. Life Sciences 85: 557–567.

38- Manhiani M, Cormican T and Brands W. (2011): Chronic sodium- retaining action of insulin in diabetic dogs. Am. J. Physiol. Renal Physiol., 300(4): 957-965.

39- Marchi-Alves L, Nogueira M, Mendes I and Godoy S. (2010): Leptin, obesity and hypertension: importance of nursing actions. Acta Paulista de Enfermagem 23: 286-290.

40- Kshatriya S, Liu K, Salah A, Szombathy T, Freeman H, Reams P, Spear M and Villarreal D. (2011): Obesity Hypertension: The Regulatory Role of Leptin. Int. J. Hypertens., 1: 46-53.

41- Rosika M, Krek M, Matoulek M,Jarkovska Z, Marek V, Justova V et al. (2003): Serum ghrelin levels in obese patients: The Relationship to serum leptin levels and soluble leptin receptors levels. Physiol. Res., 52: 61–66.

42- Huang X, Fan Y, Zhang H, Wang P, Yuan J, Li M and Zhan X. (2008): Serum leptin and soluble leptin receptor in non-alcoholic fatty liver disease. World J. Gastroenterol., 14: 2888-2893.

43- Thomopoulos C, Papadopoulos P, Papazachou O, Bratsas A, Massias S, Anastasiadis G, Perrea D and Makris T. (2009): Free leptin is associated with masked hypertension in nonobese subjects. Hypertension 53: 965-972.

44- Papadopoulos P, Makris K, Poulakou M, Papazachou G, Hatzizacharias N, Perrea N et al. (2006): Human soluble leptin receptor concentration in healthy offspring of hypertensive parents. J. Clin. Hypertens., 8: 797–802.

45- El-Sherbini S, Gattas L, Mohamed H, Moaty M, Tapozada S and Hanna L. (2009): Circulating concentrations of leptin hormone, soluble leptin receptor and free leptin index in obese Egyptian women before and after therapy. J. Med. Sci., 9: 219-226.

46- Abdel Hafez M, Abdel Ghany N, Sharaf M, El-Eshmawy K and Beltagi R. (1989a): Atrial natriuretic peptide, aldosterone, and plasma rennin activity in essential hypertension. Bull. Egypt. Soc. Physiol .Sci., 9: 213-219.

47- Abdel Hafez M, El-Dally A, Iman S, Abdel Ghany N and Makin B. (1989b): Atrial natriuretic peptide in hypertensive pregnancy; relation to other factors. Bull. Egypt. Soc. Physiol. Sci., 9: 305-317.

48- Mussalo H, Vanninen E, Ikheimo R and Hartikainen J. (2003): NT-pro-ANP and BNP in Renovascular and in severe and mild essential hypertension. Kidney Blood Pres. Res., 26: 34–41.

49- Levin E, Gardner D and Samson W. (1998): Natriuretic peptides. N. Engl. J. Med., 339: 321– 328.

50- - Wang TJ, Larson G, Levy D, Benjamin J, Leip P, Wilson W et al. (2004): Impact of obesity on plasma natriuretic peptide levels. Circulation 109: 594–600.

51- Birkenfeld L, Boschmann M, Moro C, Adams F, Heusser K, Tank J et al. (2006): Beta-adrenergic and atrial natriuretic peptide interactions on human cardiovascular and metabolic regulation. J. Clin. Endocrinol. Metab., 91: 5069 –5075.

52- Moro C and Smith R. (2009): Diabetes. Natriuretic Peptides: New Players in Energy Homeostasis. Diabetes 58: 2726–2728.

53- Miyashita K, Itoh H, Tsujimoto H and et al., (2009): Natriuretic peptides/cGMP-dependent protein kinase cascades promote muscle mitochondrial biogenesis and prevent obesity. Diabetes 58: 2880–2892.

54- Nielsen S, Guo Z, Johnson M, Hensrud D and Jensen D. (2004): Splanchnic lipolysis in human obesity. J. Clin . Inv., 113: 1582–1588.

55- Kahn B and Flier S. (2000): Obesity and insulin resistance. J. Clin. Invest., 106: 473-481.

56- De Luis D, Sagrado G, Aller R, Izaola O and Conde R. (2011): Metabolic syndrome and ALA54THR polymorphism of fatty acid–binding protein 2 in obese patients . Metabolism, 60 (5): 664-668.

57- Mascareno E, Beckles D, Dhar-Mascareno M and Siddiqui M. (2009): Enhanced hypertrophy in ob/ob mice due to an impairment in expression of atrial natriuretic peptide. Vasc. Pharmacol., 51: 198-204.

58- Irzmanski R, Barylski M, Maciei B, Mariusz P, Jan K, Cierniewski C et al. (2007): The concentration of atrial and brain natriuretic peptide in patients with idiopathic hypertension. Med. Sci. Monit., 13: 449-456.

الببتيد الأذيني المدر للصوديوم والليبتين في حالات ارتفاع ضغط الدم المصاحب للبدانة في السيدات المصريات متوسطات العمر

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البدانة مشكلة صحية في جميع أنحاء العالم، حيث أن حدوثها وانتشارها يتزايد باطراد، وهي من الممكن أن تجتمع مع ارتفاع ضغط الدم، مرض البوال السكري، اختلال دهون الدم، تصلب الشرايين و/ أو الفشل الكلوي المزمن. من بين هؤلاء، لوحظ أن ارتفاع ضغط الدم يوجد في حوالي ٥٠٪ من الأفراد البدينين، مما قاد الباحثون لاعتبار البدانة من أكثر الأسباب شيوعا للتسبب في ارتفاع ضغط الدم. إن الآليات التي تربط البدانة بارتفاع ضغط الدم لم يتم إيضاحها بالكامل. تهدف الدراسة الحالية إلى توضيح التفاعل بين الليبتين، مستقبلات الليبتين القابلة للذوبان والببتيد الأذيني المدر للصوديوم في مرضى البدانة وارتفاع ضغط الدم.

تم تنفيذ الدراسة على ٧٥ سيدة، حيث تم تصنيفهم إلى ثلاث مجموعات: المجموعة الأولى (عدد ١٥) مجموعة ضابطة، المجموعة الثانية (عدد ٣٠) بدينات ذوات ضغط دم طبيعي، المجموعة الثالثة (عدد ٣٠) بدينات ذوات ضغط دم مرتفع. كل المشاركات في الدراسة أجري لهن تقييم إكلينيكي شامل وتقدير مستويات مصل الدم لكل من: سكر الجلوكوز، الكرياتينين، البولينا، الكوليستيرول، الليبتين، مستقبلات الليبتين القابلة للذوبان والببتيد الأذيني المدر للصوديوم.

وجد أن مستويات مصل الدم لكل من الليبتين والببتيد الأذيني المدر للصوديوم قد أوضحت زيادة ذات دلالة إحصائية في مجموعتي البدانة وضغط الدم الطبيعي والبدنة وضغط الدم المرتفع مقارنة بالمجموعة الضابطة، كما كانت هناك زيادة ذات دلالة إحصائية في مجموعة البدانة وضغط الدم المرتفع مقارنة بمجموعة البدانة وضغط الدم الطبيعي، أما مستويات مستقبلات الليبتين القابلة للذوبان في مصل الدم في مجموعتي البدانة وضغط الدم الطبيعي والبدانة وضغط الدم المرتفع فقد أوضحت انخفاض ذو دلالة إحصائية مقارنة بالمجموعة الضابطة.

في كل المجموعات التي تمت دراستها، وجد أن مستويات الليبتين والببتيد الأذيني المدر للصوديوم في مصل الدم أوضحت علاقة ذات دلالة إحصائية إيجابية مع كل من معامل كتلة الجسم، ضغط الدم الإنبساطي وضغط الدم الإنقباضي، لكن مستوياتهما أوضحت علاقة ذات دلالة إحصائية عكسية مع مستقبلات الليبتين القابلة للذوبان.

أما عن مستوى مستقبلات الليبتين القابلة للذوبان في مصل الدم فقد وجدت علاقة ذات دلالة إحصائية عكسية مع كل من معامل كتلة الجسم، ضغط الدم الإنبساطي، ضغط الدم الإنقباضي، الليبتين والببتيد الأذيني المدر للصوديوم.

إن الليبتين والببتيد الأذيني المدر للصوديوم قد يؤثران على عملية نضح الكلى وبالتالي يؤديان إلى احتباس الماء والصوديوم. كما أنهما هرمونان قد ينشطان الجهاز السمبثاوي وجهاز الرينين- أنجيوتنسين مما قد يساهم في ارتفاع ضغط الدم في حالات البدانة.