A POSSIBLE RELATIONSHIP BETWEEN ATRIAL NATRIURETIC FACTOR AND SERUM LEPTIN IN OBESITY-ASSOCIATED HYPERTENSION

Thesis

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ABSTRACT

Obesity is considered a world health problem, where its incidence and prevalence are rising steadily, along with several conditions associated with it, such as hypertension, diabetes, dyslipidemia, atherosclerosis, and 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.

Leptin acts as a regulator of adipose-tissue mass and body weight, operates through effects on hypothalamic centers that inhibit food intake and stimulate energy expenditure.

ANP is secreted from atrial granules into the circulation in response to acute or chronic atrial stretch causes a reduction in blood volume and therefore a reduction in cardiac output and systemic blood pressure**.**

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:

Key ward :-

- Obesity
- Hypertension
- Leptin
- Soluble leprin receptors
- Atrid Natrivretic pepride

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Abbreviation	Full name
TNF- α	tumor necrosis factor-α
ACE	angiotensin converting enzyme (ACE).
ACTH	adrenocorticotrophic hormone (ACTH)
AMPK	5-AMP-activated protein kinase
ANP	ATRIAL NATRIURETIC PEPTIDE
B-AR	β- adrenoceptor
BAT	brown adipose tissue
BMI	body mass index
cAMP	cyclic adenosine monophosphate (cAMP)-
CART	cocaine-amphetamine-regulated transcript
CCK	colechistokinine
CNTF	ciliary neurotrophic factor
CRF	corticotropin-releasing factor
CT- 1	cardiotrophin-1
EDRF	endothelium derived relaxing factor
ET-1	endothelin-1
GH	growth hormone
h-ANP	human-ANP
IGF-1	insulin-like growth factor-1
IL-6	interleukin-6
IR	Immunoreactive
JAKs	Janus kinases
LIF	leukaemia inhibitory factor
LPL	lipoprotein lipase (LPL)
MAPK	mitogen-activated protein kinase
MCH	melanin-concentrating hormone
NEP	neutral endopeptidase
NO	nitric oxide
NPC-R	natriuretic peptide clearance receptors
NPY	neuropeptide Y
OSM	oncostatin-M
PAI-1	plasminogen activator inhibitor-1
PI3K	phosphoinositide 3-kinase
PI3K	phosphoinositide 3-kinase
PPAR- γ	peroxisome proliferator-activated receptor
r	pearson correlation
STATs	signal transducers and activators of transcription
VLDL	very low-density lipoproteins
WAT	adipose tissue
α -MSH	α-melanocyte-stimulating hormone

Introduction

Obesity is a condition in which abnormal or excessive fat has accumulated that presents a risk to health. It is commonly defined as a body mass index (BMI) of 30 kg/m^2 or higher. It should be distinguished from overweight which is defined by a BMI more than 25 and less than 30 kg /m^2 **(World Health Organization, 2000)**.

Obesity is considered a world health problem, where its incidence and prevalence are rising steadily, along with several conditions associated with it, such as hypertension, diabetes, dyslipidemia, atherosclerosis, and 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. Hence, hypertension in obesity has become a topic of extensive ongoing research **(Paco et al., 2006)**.

Obesity as a disease is a complex interplay of genetic, socioeconomic and psychological factors, the result of which prolonged positive energy balance instead of normal homeostasis. Energy balance in the body is a complex interaction of several systems. Food intake is regulated by several nuclei in the hypothalamus including the ventricular, ventromedial and external hypothalamus. White adipose tissue is the lipid storage organ, and brown adipose tissue functions in thermogenesis. The autonomic nervous system acts essentially as the connecting pathway between the CNS and periphery. Finally, signals from neuropeptides and neuromediators control food intake as do hormonal and metabolic signals **(Kokot and Ficek, 1999)**.

There has been a revolution in our understanding of neuro-endocrine mechanisms regulating appetite, metabolism, and adiposity since the discovery of leptin **(Rahmouni et al., 2005).** Leptin is an adipocyte-derived hormone that acts in the hypothalamus to regulate appetite and energy expenditure and sympathetic outflow. Leptin promotes weight loss by reducing appetite and by increasing energy expenditure through stimulation of sympathetic nerve activity **(Haynes et al., 1997).**

The excitement that followed leptin discovery was soon modulated by the realization that obesity is associated with hyperleptinerma, defining a state of "leptin resistance" **(Flier, 2004).**

The association between obesity and hypertension is well known but the pathophysiology of weight-related changes on blood pressure is still a matter of debate. Several mechanisms have been implicated in the association between obesity and hypertension, including activation of sympathetic nervous system, renin–angiotensin system, abnormal renal sodium and water handling, insulin resistance, and physical compression of the kidney **(Haynes et al., 1998)**.

It has been speculated that obese individuals have an impaired natriuretic peptide response **(Dessi-Fulgheri et al., 1997).** Atrial natriuretic peptide (ANP) is a circulating neurotransmitter with important regulatory action on salt and water homeostasis as well as blood pressure **(Hender et al., 1987).** It is cardiac in origin and is secreted mainly in response to increased intra-atrial pressure **(Larsen et al., 1994).**

Abdel Hafez et al. (l994) detected a rise in the plasma ANP in obesity, which became more elevated if the obesity was associated with hypertension.

Aim of the work

The aim of the present work is to study the possible relation between serum leptin, soluble leptin receptors (sLR) and the atrial natriuretic peptide (ANP) in obese hypertensive patients.

1-OBESITY

Definition:

It is a condition in which excess body fat has accumulated to such an extent that health may be negatively affected. It is commonly defined as a body mass index (BMI) of 30 kg/m^2 or higher. Obesity should be distinguished from overweight which is defined by a BMI more than 25 and less than 30 kg /m^2 **(World Health Organization, 2000)**.

Obesity is best viewed as a symptom or group of diseases rather than a single disease entity **(Lukaski, 1991)**.

With rates of adult and childhood obesity increasing, authorities view it as a serious public health problem. Between 1980 and 2000, obesity among adults has more than doubled; obesity among adolescents has tripled. In the US, obesity is the second-leading cause of preventable death after smoking **(Barness et al., 2007).**

Diagnosis of Obesity:

According to the **National Institutes of Health (NIH) in 1998**, measurement of the abdominal fat or total body fat is not only important for the initial assessment of the degree of overweight and obesity, but also as a guide to the efficacy of weight loss treatment. To simplify diagnostic tools, body mass index and waist/hip circumference ratios are advocated.

I) Body mass index (BMI):

Body mass index (BMI) is a simple and widely used method for estimating body fat mass **(Mei et al., 2002)**. BMI is an accurate reflection of body fat percentage in the majority of the adult population. It is less accurate in people such as body builders and pregnant women in whom body composition is affected **(Xavier et al., 1998)**.

BMI is calculated by dividing the subject's weight by the square of his or her height, typically expressed as:

$$BMI = \text{weight (kilograms)} / \text{height}^2 \text{ (meters}^2\text{)}$$

The most commonly used definitions, established by the World Health Organization (WHO) in 1997 and published in 2000; provide the values of BMI listed in the table (1)**.**

Table (1): Classification of overweight and obesity by BMI

BMI	**Classification**
Less than 18.5	underweight
18.5–24.9	normal weight
25.0–29.9	overweight
30.0–34.9	class I obesity
35.0–39.9	class II obesity
Over 40.0	class III obesity

(World Health Organization, 2000)

The literature by **Gabriel (2006)** subdivided "class III obesity" into further categories: BMI > 40 is severe obesity, BMI of 40.0–49.9 is morbid obesity and a BMI of >50 is super obesity.

II) <u>Waist circumference and waist/hip ratio:</u>

Intra-abdominal or visceral fat has a particularly strong correlation with cardiovascular disease **(Yusuf et al., 2004)**. Waist circumference is positively correlated with abdominal fat content. It provides a clinical acceptable measurement for assessing the patient's abdominal fat content before and during weight loss treatment **(Janssen et al., 2004)**.

In people with a BMI over 35, measurement of waist circumference however adds little to the predictive power of BMI as most individuals with this BMI have an abnormal waist circumferences **(Xavier et al., 1998).**

Waist circumference is the narrowest circumference below the rib cage and above the umbilicus. The hip circumference is taken as the largest circumference at posterior extension of the buttocks. Upper abdominal body obesity (apple-shaped obesity) is common in males and is called android. While lower abdominal body obesity (pear-shaped obesity) is the pattern present in most females and is termed gynecoid **(Gray, 1989).**

The absolute waist circumference (>102 cm in men and >88 cm in women) or waist–hip ratio (>0.9 for men and >0.85 for women) are both used as measures of central obesity **(Yusuf et al., 2004)**.

III) <u>Total body fat (body fat %):</u>

Body fat percentage is total body fat expressed as a percentage of total body weight. It is generally agreed that men with more than 25% body fat and women with more than 33% body fat are obese **(Schwartz,2001)**

Body fat percentage can be estimated from a person's BMI by the following formula:

$$\text{Body fat\%} = (1.2 \times \text{BMI}) + (0.23 \times \text{age}) - 5.4 - (10.8 \times \text{gender})$$

{Gender is 0 if female and 1 if male}

This formula takes into account the fact that body fat percentage is 10% greater in women than in men for a given BMI. It recognizes that a person's percentage body fat increases as they age even if their weight remains constant. The results have an accuracy of 4%**.**

Direct attempts to determine body fat percent are difficult and often expensive. One of the most accurate methods is to weigh a person underwater which is known as