Relationship between adipocytokines (leptin, adiponectin) and arterial blood pressure

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ABSTRACT

Background: The relationship between adipose tissue hormones (adiponectin and leptin) and obese state is often reported; however their cardiovascular effects are not as well understood. We attempted to study the relation between circulating concentrations of the adipocytokines (leptin and adiponectin) and arterial blood pressure in order to determine whether the reported cardiovascular effects of the above-mentioned hormones are secondary to the obese state or not. Methods: The mean arterial blood pressure (MABP, as a measure of arterial blood pressure), body mass index (BMI, as a measure of obesity) and serum leptin and adiponectin concentrations were estimated in four groups of subjects: lean and obese normotensives and lean and obese hypertensives. *Results:* Serum leptin shows an increase in obese subjects compared to lean subjects; whether normo (22.0 ± 8.44 vs. 5.9 ± 2.9; P < 0.001) or hypertensives (26.4 ± 8.99 vs. 12.2 ± 5.43; P < 0.001). Lean hypertensive subject have higher values than lean normotensives. The same pattern was observed for leptin/ adiponectin ratio, with obese hypertensive subjects showing the highest concentration (3.0±1.41) and lean normotensives showing the lowest (0.5±0.29) An opposite pattern was observed for serum adiponectin, with obese hypertensive subjects showing the lowest concentration (9.36±1.71) and lean normotensives the highest (15.46±2.10). A positive and a negative correlation was observed between each of leptin and adiponectin respectively and mean arterial blood pressure (MABP). Serum adiponectin & serum leptin were inversely correlated in all groups (r = - 0.74; P < 0.01). *Conclusion:* The results suggest that obese subjects and subjects with essential hypertension (whether lean or obese) show higher serum leptin level and lower serum adiponectin than normotensives. Furthermore, the correlations between mean arterial blood pressure, and each of serum leptin and adiponectin could suggest that leptin and adiponectin play a contradictory role and/or could be involved in the pathophysiology or the regulation of essential hypertension regardless of the obese state. In addition, we suggest serum leptin to adiponectin ratio to be used as a potential index of hypertension and obesity.

INTRODUCTION

Recent advances in the biology of adipose tissue indicate that it is not simply an energy storage organ, but also a secretory organ, producing a variety of bioactive substances, called adipokines or adipocytokines. These consist of polypeptides but also non-protein factors, and are metabolically active molecules belonging to different functional categories like immunity, endocrine, metabolic, and cardiovascular functions. Recent advances using genomic and proteomic approaches have identified numerous new adipocyte secreted factors whose function remain to be established[1].

Obesity, the most common nutritional disorder in industrial countries, is associated with increased cardiovascular mortality and morbidity. Nevertheless, the molecular basis linking obesity with cardiovascular disturbances have not yet been fully clarified. There is considerable evidence linking altered production of some adipocyte hormones with the cardiovascular complications of obesity. Several of these factors, have now been shown to regulate, directly or indirectly, a number of the processes that contribute to the development of atherosclerosis, including hypertension, endothelial dysfunction, insulin resistance, and vascular remodeling. Therefore, the knowledge of alterations in the endocrine function of adipose tissue may help to further understand the high cardiovascular risk associated with obesity [2,3].

The pathogenesis of hypertension is not yet clearly defined. Increase in body weight is associated most of the time with hypertension, and it was reported that visceral obesity is strongly correlated with the development of diabetes, hypertension and cardio-vascular disease[4].

Leptin, secreted from adipocytes, is involved in the regulation of food intake, energy expenditure, and energy balance in humans. Beyond this function, it influences sexual and reproductive system development and actively participates not only in metabolic regulation but also in the control of blood pressure. It is also believed that this hormone takes part in the regulation of

hematopoietic, endocrine (other than reproductive) and sympathetic system functioning, and is involved in pathogenesis of arterial hypertension and diabetes [5,6,7].

Adiponectin (ADP), also called ACRP30, is a novel adipocyte-derived protein, consists of collagen-like fibrous and complement C1q-like globular domains, and circulates in human plasma in a multimeric form. The protein exhibits anti-diabetic and anti-atherogenic activities in probable relation to its ability to suppress the attachment of monocytes to endothelial cells, which is an early event in the atherosclerotic process. Plasma adiponectin concentrations are low in obese subjects, and hypoadiponectinemia is associated with numerous atherogenic diseases and syndromes (e.g. diabetes mellitus, dyslipidemia, endothelial dysfunction, hypertension, and obesity). Decreased ADP values in blood may be an independent risk factor of atherosclerotic complications[8,9,10].

The endocrine function of the adipose tissue could be an important determinant of metabolic alterations and cardiovascular risk in obesity. The aim of the present study is to analyze the relations between circulating concentrations of the adipocytokines (adiponectin and leptin) and each of mean arterial blood pressure (MABP) and body mass index (BMI) and to study the relationship between obesity and increased blood pressure.

SUBJECTS AND METHODS

We studied 60 male subjects and grouped them into four categories according to their BMI and MABP; the groups were matched for the subject age.

The subjects were classified as LN (lean normotensive), ON (obese normotensive), LH (lean hypertensive) and OH (obese hypertensive): Hypertension was defined as a supine value >140/90 mm Hg on at least three separate measurements. Mean arterial blood pressure (MABP) was calculated by the sum of diastolic blood pressure plus one-third of the pulse pressure[11].

- BMI was calculated as weight in kg divided by height in squared meters. These measurements were performed in the morning before breakfast with the subjects in the standing position, wearing light clothes and no shoes. Obesity was defined as a BMI > 30[12].
  Means and SD of the BMI and MAPB of the four groups are presented in Table 1 (first two columns).
- All subjects had a complete clinical examination including blood glucose, creatinine, uric acid measurements to exclude secondary causes of hypertension.
  Serum leptin and adiponectin were estimated by enzyme immunoassay (ELISA) technique [13,14].
- Leptin to adiponectin ratio is calculated.

Statistical analysis

Results are expressed as means ± standard deviations (SD). Comparison of means were performed by the Student`s t test. Pearson`s correlation coefficient (r) was determined to assess the degree of association between different variables15.

RESULTS

The results obtained in the enrolled subjects are presented in Table 1.

Serum leptin shows a significant increase in obese subjects compared to lean subjects whether normo (22.0 ± 8.44 vs. 5.9 ± 2.9; $P < 0.001$) or hypertensives (26.4 ± 8.99 vs. 12.2 ± 5.43; $P < 0.001$). Lean normotensive subjects show the lowest value, significant different ($P < 0.001$) from the other groups.

There was a significant decrease in serum adiponectin in ON compared to LN (10.59 ± 2.14 vs. 15.46 ± 2.10; $P < 0.001$); in OH compared to LH (9.36 ± 1.71 vs. 11.56 ± 2.52; $P < 0.05$); in LH compared to LN (11.56 ± 2.52 vs. 15.46 ± 2.10; $P < 0.001$); and in OH compared to ON (9.36 ± 1.71 vs. 10.59 ± 2.14; $P < 0.05$). (Table 1)

Concerning leptin / adiponectin ratio, a significant elevation was observed in all the studied groups (ON, LH, and OH) compared to the lean normotensives (LN). Highest ratio was found in obese hypertensive` group (OH). A significant elevation was observed in this group compared to LH and ON groups. Also ON group was significantly elevated compared to LN and LH group (Table 1)

A number of significant correlations was observed. Leptin and BMI ($r = 0.75$; $P < 0.01$ for all subjects; $r = 0.49$; $P < 0.01$ for obese subjects). Leptin and MABP ($r = 0.35$; $P < 0.05$ for all subjects; $r = 0.63$; $P < 0.01$ for hypertensive subjects; and $r = 0.49$; $P < 0.01$ for lean hypertensive subjects). Regarding Adiponectin, the negative correlations were: Adiponectin and BMI ($r = -0.60$; $P < 0.01$ for all subjects; $r = -0.39$; $P < 0.05$ for obese subjects). Adiponectin and MABP ($r = -0.51$; $P < 0.01$ for all subjects; $r = -0.67$; $P < 0.01$ for hypertensive subjects (Fig 1). $r = -0.58$; $P < 0.01$ for lean hypertensive subjects). Adiponectin and leptin showed a negative correlation ($r = -0.74$, $P < 0.01$ for all subjects; $r = -0.63$, $P < 0.01$ for hypertensive subjects; $r = -0.71$ $P < 0.01$ for obese subjects; $r = -0.67$; $P < 0.01$ for obese hypertensive subjects) (Fig 2).

DISCUSSION

The association between obesity and hypertension is well documented[16-18]; some of the mechanisms involved in this relationship are discussed here with a particular focus on the role of leptin and adiponectin. Obesity

Table 1
Serum levels of parameters measured in different groups studied; lean normotesives (LN), obese normotesives (ON), lean hypertensives (LH) and obese hypertensives (OH)

	BMI (kg/m^2)	MAP (mm Hg)	Leptin (ng/ml)	Adiponectin (ADP) (µg/ml)	Leptin / Adiponectin Ratio
LN	23.7 ± 1.18	88.6± 7.41	5.99 ± 2.93	15.46 ± 2.10	0.50± 0.29
ON	29.9 ± 1.49	91.7± 5.79	22.02± 8.44	10.59 ± 2.14	2.00 ± 0.94
LH	23.0 ± 1.56	119.8± 3.23	12.23± 5.43	11.56 ± 2.52	1.00 ± 0.56
OH	31.6 ± 1.48	126.2± 6.13	26.4 ± 8.99	9.36 ± 1.71	3.00 ± 1.41

Values are expressed as means ± SD *ADP: Adiponectin*

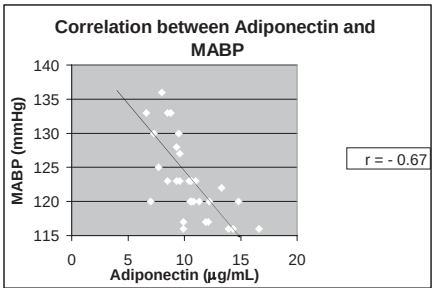

Figure 1
Correlation between serum Adiponectin (µg/ml) and MABP in hypertensives (n = 30)

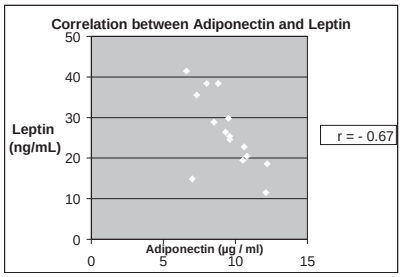

Figure 2
Correlation between serum Leptin (ng/ml) and serum Adiponectin (µg/ml) in obese hypertensive subjects (n = 15)

causes a constellation of maladaptive disorders that individually and synergistically contribute to hypertension, among other cardiovascular morbidities.

Leptin has multiple autonomic and cardiovascular actions, including sympathetic activation, increase in endothelium derived nitric oxide (NO), and angiogenesis. The predominant cardiovascular effect of chronic hyperleptinemia is a pressor effect mediated by increased sympathetic activity. This concept holds that in some obese states, there is preservation of the sympathoexcitatory actions of leptin despite resistance to the satiety and weight-reducing actions of the hormone. Selective leptin resistance might explain how hyperleptinemia could contribute to increase the sympathetic activity and arterial pressure in obese states where there is resistance to the metabolic (satiety and weight-reducing) actions of leptin. It is speculated here, that this concept may have potential implications for human obesity, which is often associated with elevated plasma leptin and partial resistance to the satiety effects of leptin. If selective leptin resistance occurs in obese humans, then leptin could contribute to the sympathetic over activity and hypertension despite resistance to its metabolic actions[19, 20].

In the present study the highest levels of leptin were observed in obese hypertensive subjects followed by obese normotensives and by lean hypertensives; the lowest value were observed in lean normotensive.

These results support the hypothesis that a possible link exists between leptin and hypertension and also suggest that other factors than obesity may lead to elevation of serum leptin in hypertensives.

These findings are in agreement with those of other Authors. Canatan et al.[4] reported plasma leptin and leptin/BMI levels in patients of both genders with hypertension were significantly higher than in normotensive subjects and that leptin and leptin/BMI levels in obese hypertensives were higher than obese normotensives.

Schorr et al. and Suter et al.[21,22] reported direct relationships between both plasma renin activity, aldosterone levels and leptin that support the potential importance of the relationship between leptin and blood pressure. Li et al.[23] reported that fasting leptin level showed good correlation with BMI, fasting true insulin, blood pressure and also triglycerides, and was significantly higher in hypertensive subjects than in normotensive subjects. Barba et al.[24] reported that elevated plasma leptin concentrations were associated with greater probability of hypertension, independently of potential confounders; logistic regression analysis showed that an increased prevalence of hypertension was associated with high plasma leptin levels when controlling for age and waist circumference or for age and BMI

Aneja et al.[25] suggested the putative role of leptin in the causation of hypertension could be the activation of

the sympathetic nervous system and a direct effect on the kidneys, resulting in increased sodium reabsorption. Obesity per se may have structural effects on the kidneys that may perpetuate hypertension, leading to an increased incidence of end-stage renal disease that results in further hypertension. Adipose tissue may elaborate angiotensin from its own local renin-angiotensin system.

Nishina et al.[26] indicated that systolic blood pressure was associated with hyperinsulinemia, hyperleptinemia and visceral fat accumulation regardless of a family history of hypertension in obese children, as well as later in adult obesity.

However, Wang et al.[27] reported that serum leptin concentrations are not directly related to blood pressure, but the levels are actually correlated with the degree of obesity and energy metabolism.

Increasing attention has also been paid to the direct vascular effects of plasma proteins that originate from adipose tissue, especially adiponectin, which exhibits potent anti-inflammatory and antiatherosclerotic effects. Adiponectin is now a recognized component of a novel signaling network among adipocytes, insulin-sensitive tissues, and vascular function that has important consequences for cardiovascular risk[28].

In our study, adiponectin concentrations show a pattern opposite to the one presented by leptin, with highest concentrations in lean normotensive subjects, lowest in obese hypertensives and similar intermediate levels in obese normotensive and lean hypertensive.

These results could possibly indicate a link between adiponectin, and each of obesity and hypertension whether essential or obesity-associated hypertension.

Our results confirm the reports from other Authors. Wolf[29] reported that in essential hypertensive patients, plasma adiponectin concentration was significantly lower than in normotensive healthy subjects. In all subjects a significant negative correlation was found between plasma adiponectin concentration and mean, systolic, and diastolic blood pressure, suggesting that adiponectin contributes to the clinical course of essential hypertension. He also found that plasma adiponectin concentration was decreased in obese and in type 2 diabetic humans. He concluded that adiponectin is likely to be involved in the regulation of energy homeostasis as it enhances insulin sensitivity and glucose tolerance, and appears to increase free fatty acid oxidation in muscle.

Stejskal et al.[30] reported that persons with hypertension and diabetes mellitus, individuals with atherogenic dyslipidemia or persons with inflammation signs had lower adiponectin values than individuals without these diseases and syndromes. Furuhashi et al.[31] also suggested that hypoadiponectinemia is related to insulin resistance in essential hypertension and that renin-angiotensin system blockade increases adiponectin concentrations with improvement in insulin sensitivity.

Dzielinska et al.[32] showed decreased plasma adiponectin concentration in hypertensive men with coronary artery disease as compared to normotensive healthy subjects. In another study, male patients with hypoadiponectinemia (<4.0 microg/mL) had a significant 2-fold increase in coronary artery disease prevalence, independent of well-known coronary artery disease risk factors. Multiple logistic regression analysis including plasma adiponectin level, diabetes mellitus, dyslipidemia, hypertension, smoking habits, and body mass index revealed that hypoadiponectinemia was significantly and independently correlated with coronary artery disease [33].

Other studies reported different results. Mallamaci et al.[34] reported that the difference in plasma adiponectin levels between hypertensive and normotensive subjects was not significant. The relationship between plasma adiponectin and renal function was confirmed in a multiple regression analysis, which showed that creatinine clearance was the only independent predictor of plasma adiponectin. Yang et al.[35] reported that in overweight/obese Asians, the plasma adiponectin levels significantly correlated with various indices of metabolic syndrome except hypertension. Skurk et al.[36] reported that in overweight hypertensive humans, leptin levels showed a positive association with BMI, whereas adiponectin was not correlated to BMI.

The pattern of the leptin/adiponectin ratio in the four groups indicates that this ratio could identify both obesity and hypertension (Table 1).

The negative correlations between serum adiponectin & serum leptin suggest that adiponectin and leptin have opposing roles regarding their metabolic and cardiovasular effects. While leptin is associated with increased BMI and increased blood pressure, adiponectin is associated with decreased BMI and decreased blood pressure. Thus, the two proteins could be used as markers of cardiovascular risk.

CONCLUSION

The previous results suggest that obese subjects and subjects with essential hypertension (whether lean or obese) show higher serum leptin level, lower serum adiponectin and higher leptin/adiponectin ratio compared to lean normotensives. Furthermore, a positive and negative correlation was found between mean blood pressure and serum leptin and adiponectin respectively, suggesting that both leptin and adiponectin may play a contradictory role or may be involved in the pathophysiology or the regulation of essential hypertension regardless of the obese state. In addition, we suggest leptin/adiponectin ratio to be used as a potential index of hypertension and obesity.

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