

Circulating leptin and adiponectin levels in patients with primary hyperparathyroidism

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Received 6 May 2006; accepted 3 August 2006

Abstract

Primary hyperparathyroidism (PHPT) has been associated with high cardiovascular morbidity and mortality; its pathogenesis is not fully understood. Moreover, many metabolic abnormalities are frequently present in patients with PHPT. Several substances (such as leptin and adiponectin) are secreted from adipocytes, which may contribute to regulate energy homeostasis and the development of cardiovascular diseases. We examined the relationship between leptin and adiponectin levels and metabolic disorders in 67 newly diagnosed never-treated patients with PHPT and in 46 healthy subjects (HS). Twenty (29.8%) patients with PHPT presented a metabolic syndrome (as defined by Adult Treatment Panel III criteria). Serum leptin and adiponectin levels in HS were 6.28 ± 3.3 ng/mL (range, 1.7–19.2 ng/mL) and 6.65 ± 1.7 μ g/mL (range, 3.72–10.86 μ g/mL), respectively. In all patients with PHPT, the mean leptin levels (34.28 ± 20.4 ng/mL) were significantly higher than those of HS ($P < .01$) and, in particular, in PHPT patients with metabolic syndrome (52.63 ± 31.2 ng/mL) and positively correlated with body mass index, waist circumference, and cholesterol. The mean adiponectin level was significantly lower (4.34 ± 3.5 μ g/mL) only in PHPT patients with metabolic syndrome ($P < .005$) and negatively correlated with waist circumference and fasting glucose. We concluded that increased serum level of leptin and decreased serum level of adiponectin coexist in patients with PHPT and may represent a pathogenetic factor for cardiovascular disease in this condition.

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1. Introduction

Adipose tissue has long been considered a passive, inactive tissue. However, research in the past decade has demonstrated that adipose tissue plays an important role in energy regulation via endocrine, paracrine, and autocrine signals [1–3]. These functions enable adipocytes to influence the metabolic activity of adipose tissue as well as other tissues, including the brain, liver, and muscle. Several hormones and other factors are secreted from adipocytes (namely, adipokines) and most of these factors, upon secretion into the bloodstream, act as endocrine signals at multiple distant sites to regulate energy homeostasis [2,4]. They belong to the group of adipose regulatory peptides that

include leptin, adiponectin, interleukin 6, and tumor necrosis factor α [2,4]. Most of these adipokines greatly contribute to the development of cardiovascular diseases associated with obesity [5].

In particular, leptin is a hormone produced by adipocytes with levels proportional to those of fat mass [6]. During periods of weight loss, plasma leptin levels decline [2,7]; in addition, leptin decreases the appetite and enhances thermogenesis [2,8]. Deficiency of leptin gene expression leads to hyperplasia and obesity [7]. Adiponectin expressed by adipocytes seems to increase tissue sensitivity to insulin [9], and plasma levels of adiponectin seem to decrease with obesity and are positively associated with whole-body insulin sensitivity [9]. Hypoadiponectinemia may contribute to atherogenesis associated with obesity [10,11].

Primary hyperparathyroidism (PHPT), caused by solitary parathyroid adenomas in 85% of cases and a diffuse hyperplasia in most of the remaining cases [12], results in

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overproduction of parathyroid hormone (PTH), which mobilizes calcium to the bloodstream.

This chronic disease, whose pathogenesis is not fully understood, is associated with high cardiovascular morbidity and mortality [13,14]. PHPT is reported to be associated with hypertension [15,16], arrhythmia [17], and structural and functional alterations in the heart and vascular wall [18,19]. An increased prevalence of cardiac structural abnormalities such as left ventricular hypertrophy and valvular and myocardial calcification has been observed [18,20,21].

Moreover, many metabolic abnormalities such as impairment of glucose tolerance or diabetes [22,23], altered lipid profile, in particular low levels of high-density lipoprotein cholesterol (HDL-C), high levels of small dense low-density lipoprotein cholesterol (LDL-C) [24], and high levels of serum uric acid [24,25] are frequently present in patients with PHPT.

The aim of the study was to evaluate serum leptin and adiponectin concentrations in patients with PHPT at diagnosis and to correlate these adipokines with hormonal, metabolic, and some cardiovascular parameters.

2. Materials and methods

2.1. Patients

From December 2002 to July 2005 at the Internal Medicine and Hypertension Day Hospital, Clinical Sciences Department, “La Sapienza” University of Rome, Italy, we enrolled 67 consecutive patients with PHPT (mean age, 57.9 ± 12.2 years; range, 29–85 years). Of these patients, 16.4% were men and 83.6% were women.

The diagnosis of PHPT was established according to laboratory data characterized by the persistence of high levels of total calcium, ionized calcium, and PTH. All patients underwent neck ultrasonography and technetium Tc 99m MIBI imaging. None of the patients had renal insufficiency (creatinine level <1.3 mg/dL). Forty-six healthy subjects (HS) (16 men and 30 women; age, 58.1 ± 12.9 years; range, 28–84 years) were included in this study as a control group. None of these subjects were receiving any medical treatment.

The exclusion criteria included pregnancy, steroid treatment, and comorbid conditions and criticality.

Informed consent was obtained from all the subjects and our institutional review board approved the protocol.

2.2. Study protocol

Anthropometric parameters (body mass index [BMI] and waist circumference [WC]) were measured in all subjects. Glucose metabolism (fasting blood glucose) lipid profile (by total cholesterol, HDL-C, LDL-C, and triglyceride concentrations) serum uric acid, mineral metabolism (total calcium, ionized calcium, phosphorus, magnesium, calciuria, phosphaturia, and PTH), blood pressure (by

systolic blood pressure [SBP] and diastolic blood pressure [DBP] values), and heart rate (HR) were measured in all patients.

2.3. Biochemistry

Biochemical variables were estimated after an overnight fast by anaerobic sampling. Routine clinical methods were used to estimate values in blood for total serum calcium (adjusted for albumin), serum creatinine, fasting blood glucose, total triglycerides, total cholesterol, HDL-C, LDL-C, and serum uric acid levels. Ionized calcium concentration, measured with a potentiometric analyzer at pH 7.4, ranged from 1.17 to 1.33 mmol/L. Intact PTH (PTH-i) was measured by using a radioimmunoassay method (RIA commercial kits, Diasorin PTH, Stillwater, MN).

2.4. Adipokine assays

Samples of venous blood obtained were immediately centrifuged and the serum was stored at -80°C until assayed. Leptin levels were measured by using the enzyme-linked immunosorbent assay (ELISA) kit from DRG Instruments GmbH, Marburg, Germany. With this method, the intra- and interassay coefficients of variation obtained for leptin were 7.4% and 9.6%, respectively.

Adiponectin levels were measured by using the Human Adiponectin ELISA Kit (BioVendor Laboratory Medicine, Candler, NC). With this method, the intra- and interassay coefficients of variation for adiponectin were 6.2% and 7.2%, respectively.

2.5. Statistical analysis

All data are expressed as mean \pm SD. Statistical analysis was performed by using Sigmapstat Software (Jandel Corporation), and all values were analyzed with analysis of variance (ANOVA) followed by Student *t* test whenever appropriate. Correlations between adipokine values and calcium-phosphorus parameters, glucose and lipid metabolism, and hemodynamic parameters were calculated by using the Pearson coefficient of linear correlation. A *P* value less than .05 was considered significant.

3. Results

The results of demographic, biochemical, and hemodynamic parameter calculations in all groups are reported in Table 1. As expected, in patients with PHPT, serum calcium and PTH levels were higher than in HS ($P < .001$). All patients with PHPT presented higher SBP and DBP values than did HS ($P < .05$). Our results demonstrate that in patients with PHPT, hypertensive status was present in 58.2% of patients. In Table 1, we report the metabolism (glucose, lipids, and uric acid) parameters shown in all patients with PHPT and HS. Patients with PHPT presented significantly higher fasting glucose, total cholesterol, LDL-C, triglycerides, and uric acid values ($P < .05$) and lower HDL-C levels ($P < .05$) than those of the HS.

Table 1

The demographic, biochemical, and hemodynamic parameters studied in all patients with PHPT and in HS

| | Sex (M/F) | Age (y) | SBP (mm Hg) | DBP (mm Hg) | HR (beats/min) | Ca ⁺ (mg/dL) | Ca ²⁺ (mmol/L) | P (mg/dL) | Mg ⁺ (mg/dL) |
|---------------|--------------|-------------|----------------|----------------|-------------------|----------------------------|------------------------------|--------------|----------------------------|
| PHPT (n = 67) | 11/56 | 57.9 ± 12.2 | 125 ± 15 | 76 ± 13 | 73 ± 7 | 11.1 ± 1.1 | 1.48 ± 0.15 | 2.7 ± 0.6 | 1.87 ± 0.23 |
| HS (n = 46) | 10/36 | 58.1 ± 12.9 | 115 ± 4 | 74 ± 5 | 75 ± 6 | 9.4 ± 0.34 | 1.21 ± 0.02 | 3.43 ± 0.3 | 1.89 ± 0.20 |
| P | – | – | .05 | .05 | NS | .001 | .001 | .001 | NS |

NS indicates nonsignificant.

Moreover, 20 (29.8%) patients with PHPT presented metabolic syndrome as defined by the National Cholesterol Education Program Adult Treatment Panel III criteria [26]; in particular, we included patients that presented abnormalities in 3 of 5 variables (abdominal obesity, with a WC >102 cm in men and >88 cm in women; hypertriglyceridemia, with triglycerides level ≥150 mg/dL; low levels of HDL-C, <40 mg/dL in men and <50 mg/dL in women; high blood pressure ≥130/85 mm Hg; impaired glucose regulation with fasting glucose ≥110 mg/dL) (Table 2). In particular, 85% of PHPT patients with the metabolic syndrome had greater WC. No statistical difference was found for mineral biochemical parameters between PHPT patients with or without the metabolic syndrome (Table 2).

Serum leptin and adiponectin levels in HS were 6.28 ± 3.3 ng/mL (range, 1.7–19.2 ng/mL) and 6.65 ± 1.7 μg/mL (range, 3.72–10.86 μg/mL), respectively. In all patients with PHPT, the mean serum leptin level (34.28 ± 20.4 ng/mL) was significantly higher than those of HS ($P < .01$) (Fig. 1). In particular, PHPT patients with the metabolic syndrome had elevated values of serum leptin (52.63 ± 31.2 ng/mL) as compared with PHPT patients without the metabolic syndrome (25.11 ± 24.1 ng/mL) ($P < .01$) (Fig. 1).

Serum adiponectin levels were 6.15 ± 4.5, 6.95 ± 4.7, and 4.34 ± 3.5 μg/mL in all PHPT patients, PHPT patients without metabolic syndrome, and PHPT patients with metabolic syndrome, respectively (Fig. 2). The mean serum adiponectin level in the PHPT patients with metabolic syndrome was significantly lower than those of other groups tested ($P < .005$) (Fig. 2).

For the whole PHPT group there was a positive correlation between serum leptin concentration and BMI ($r = 0.659$, $P < .001$), serum leptin and WC ($r = 0.584$, $P < .001$), serum leptin and serum alkaline phosphatase

($r = 0.389$, $P < .03$), and between serum adiponectin and total cholesterol ($r = 0.322$, $P < .05$) and serum adiponectin and LDL-C ($r = 0.370$, $P < .03$).

In PHPT patients with metabolic syndrome there was a negative correlation between serum adiponectin and WC ($r = -0.541$, $P < .001$) and between serum adiponectin and fasting glucose ($r = -0.326$, $P < .01$), and a positive correlation between serum adiponectin and serum ionized magnesium ($r = 0.653$, $P < .02$). In addition, in this group we found a positive correlation between serum leptin and BMI, WC, serum magnesium, and serum alkaline phosphatase ($r = 0.391$, $P < .03$; $r = 0.397$, $P < .03$; $r = 0.394$, $P < .05$; $r = 0.389$, $P < .03$ respectively). No correlations were found between serum adipokines and cardiovascular parameters (blood pressure, heart rate) in all tested groups.

4. Discussion

To our knowledge, this is the first study of adipocyte hormones, namely, leptin and adiponectin, in patients affected by PHPT. In fact, we found that circulating concentrations of leptin were significantly greater in PHPT patients compared with HS and correlated with BMI and WC. Moreover, serum adiponectin values in all PHPT patients in the study were similar to those of HS. However, in PHPT patients with metabolic syndrome the serum adiponectin concentrations were significantly lower than in HS and negatively correlated with WC.

The mechanism of the increase in circulating leptin in PHPT patients (with or without metabolic syndrome) and of the decrease in circulating adiponectin in PHPT patients with metabolic syndrome is not clear. It is probable that the alterations of these 2 circulating adipokines may be correlated with visceral fat.

Table 2

The demographic, biochemical, and hemodynamic parameters studied in all PHPT patients, PHPT patients with metabolic syndrome (PHPT + MS), and PHPT patients without metabolic syndrome (PHPT – MS)

| | Sex (M/F) | Age (y) | SBP (mm Hg) | DBP (mm Hg) | HR (beats/min) | BMI (kg/m ²) | WC (cm) | Ca ⁺ (mg/dL) | Ca ²⁺ (mmol/L) | P (mg/dL) | Mg ⁺ (mg/dL) |
|-----------------------|--------------|-------------|----------------|----------------|-------------------|-----------------------------|-------------|----------------------------|------------------------------|--------------|----------------------------|
| PHPT (n = 67) | 11/56 | 57.9 ± 12.2 | 125 ± 15 | 76 ± 13 | 73 ± 7 | 27.6 ± 5.1 | 89.1 ± 10.6 | 11.1 ± 1.1 | 1.48 ± 0.15 | 2.7 ± 0.6 | 1.87 ± 0.23 |
| PHPT + MS (n = 20) | 2/18 | 60.9 ± 12.7 | 128 ± 15 | 78 ± 10 | 75 ± 9 | 30 ± 4.3 | 98.6 ± 9.6 | 11.2 ± 1.1 | 1.49 ± 0.15 | 2.7 ± 0.5 | |
| PHPT – MS (n = 47) | 9/38 | 56.6 ± 11.8 | 124 ± 14 | 75 ± 14 | 72 ± 6 | 26.6 ± 5.1 | 85.1 ± 8.3 | 11.1 ± 1.1 | 1.48 ± 0.15 | 2.7 ± 0.6 | |
| P | – | NS | .05 | .05 | .05 | .001 | .005 | NS | NS | NS | |

| Mg ²⁺ (mmol/L) | PTH (pg/mL) | Creatinemia (mg/dL) | BMI (kg/m ²) | WC (cm) | Fasting glucose (mg/dL) | Cholesterol (mg/dL) | LDL-C (mg/dL) | HDL-C (mg/dL) | Triglycerides (mg/dL) | Uric acid (mg/dL) |
|------------------------------|----------------|------------------------|-----------------------------|-------------|----------------------------|------------------------|------------------|------------------|--------------------------|----------------------|
| 0.59 ± 0.09 | 109 ± 79.6 | 0.96 ± 0.41 | 27.6 ± 5.1 | 89.1 ± 10.6 | 92.9 ± 13.5 | 219.2 ± 44.1 | 138 ± 43.5 | 50.6 ± 11.6 | 126.9 ± 53 | 5.1 ± 1.4 |
| 0.6 ± 0.11 | 29 ± 2.3 | 0.94 ± 0.34 | 25.2 ± 1.2 | 80.1 ± 4.3 | 83.9 ± 8 | 192 ± 34.5 | 116.8 ± 35.3 | 57.3 ± 14.9 | 94.55 ± 32.1 | 3.6 ± 1.1 |
| .01 | .001 | NS | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 |

It has been shown that these adipokines contribute, with different actions, to the development of atherosclerosis and cardiovascular disease [5,27].

PHPT is a pathologic condition characterized by excessive secretion of PTH from one or more parathyroid glands not related to homeostatic requirements and associated with hypercalcemia [12]. Clinical presentation of PHPT has geographic differences [28], and this disease variant is accompanied by a lack of clinically apparent symptoms and mild or no signs of complications (nephrolithiasis, osteopenia or osteoporosis, gout, peptic ulcer disease, depression, and pancreatitis) in a substantial proportion of currently recognized individuals [29]. In Western Europe and North America, patients with PHPT nowadays are usually discovered during an early, asymptomatic phase of the disease [30].

Recent investigations suggest that individuals with PHPT are at increased risk for cardiovascular disease [31], and patients with PHPT have also been reported to have an increased risk of premature death from cardiovascular disease in some studies [13,14].

Leptin, a bioactive substance synthesized and secreted by adipocytes, which controls food intake and energy expenditure, may play—through both direct and indirect actions—an important role in cardiovascular functions [6]. There is equilibrium between fat mass and leptin, which by crossing the blood-brain barrier is able to act on hypothalamic nuclei and regulate food intake [32]. A number of studies have shown that the circulating level of leptin is increased in obese subjects and that this is more evident in women than in men [33].

Regulation of the serum leptin concentration is sex dependent because leptin levels are higher in women than in men [34], and this sex difference is also found for PHPT; in fact, PHPT is more prevalent in women older than 50 years [28].

Several mechanisms are hypothesized to explain how leptin increases the risk of cardiovascular events. That leptin and its receptor are expressed in atherosclerotic plaques [35] indicates that leptin may be involved in the development of cardiovascular disease. Leptin has many potentially atherogenic effects, such as stimulation of endothelial production of proatherosclerotic endothelin-1 [36], induction of migration and proliferation of vascular smooth muscle cells [37], stimulation of inflammatory cells [38], and induction of calcification of vascular cells [35].

The relationship between leptin and parathyroid gland activity (such as PTH and markers of bone turnover) has recently been reported by some studies that found that serum leptin levels were connected to bone resorption and bone formation (both inversely related to serum leptin level) in hemodialysis patients [39] and that serum leptin related inversely to serum PTH in male dialysis patients [40]. In our patients with PHPT, serum leptin levels did not correlate with serum calcium and PTH concentrations but positively correlated with alkaline phosphatase levels, and this supports the suggestion that this adipocyte hormone could, in part, participate in bone turnover in PHPT. This hypothesis is supported by the evidence that leptin possesses direct and indirect peripheral effects on bone cells [41].

Another important finding of our study was the decrease in serum adiponectin levels in PHPT patients with metabolic syndrome.

Adiponectin is a recently isolated protein that is produced by white adipose tissue having a 247-amino-acid base structure [10]. Previous studies have shown that adiponectin appears abundant in circulating plasma with levels in the range 5 to 10 µg/mL in humans [42]. Interestingly, plasma concentrations are negatively correlated with BMI [43], whereas leptin increases with BMI [32]. The negative correlation of adiponectin levels and visceral adiposity is

| Mg ²⁺ (mmol/L) | PTH (pg/mL) | Creatinemia (mg/dL) | BMI (kg/m ²) | WC (cm) | Fasting glucose (mg/dL) | Cholesterol (mg/dL) | LDL-C (mg/dL) | HDL-C (mg/dL) | Triglycerides (mg/dL) | Uric acid (mg/dL) |
|------------------------------|----------------|------------------------|-----------------------------|-------------|-------------------------------|------------------------|------------------|------------------|--------------------------|----------------------|
| 0.59 ± 0.09 | 109 ± 79.6 | 0.96 ± 0.41 | 27.6 ± 5.1 | 89.1 ± 10.6 | 92.9 ± 13.5 | 219.2 ± 44.1 | 138 ± 43.5 | 54.6 ± 11.6 | 126.9 ± 53 | 5.1 ± 1.4 |
| 0.57 ± 0.07 | 126 ± 98.23 | 0.96 ± 0.31 | 30 ± 4.3° | 98.6 ± 9.6° | 102.2 ± 14.7* | 219 ± 27.5 | 137.2 ± 38.9 | 44.3 ± 5.5* | 165.7 ± 52.9* | 5.8 ± 1.2* |
| 0.59 ± 0.1 | 103 ± 70.3 | 0.96 ± 0.45 | 26.6 ± 5.1 | 85.1 ± 8.3 | 88.6 ± 10.5 | 219 ± 50.4 | 138.4 ± 46.1 | 59.4 ± 10.3 | 107.9 ± 42 | 4.7 ± 1.4 |
| NS | NS | NS | .001 | .005 | .001 | NS | NS | .001 | .001 | .003 |

stronger than that between adiponectin levels and subcutaneous adiposity [44]. In fact, in humans, serum adiponectin levels seem to decrease with obesity and are inversely correlated with body weight and visceral area [45,46], suggesting that serum adiponectin levels are dependent on fat distribution. In our PHPT patients with metabolic syndrome, 85% have greater WC, and the mean serum adiponectin level was significantly lower and inversely correlated with WC. Our results extend these previous findings and indicate that visceral adiposity is a strong determinant of hypoadiponectinemia in PHPT patients with metabolic syndrome.

The mechanism by which serum adiponectin levels are reduced in patients with visceral fat accumulation has not yet been clarified.

It has been suggested that visceral fat may inhibit adiponectin secretion by some inhibiting factors for adiponectin synthesis or secretion [10]. This hypothesis is supported by the evidence that tumor necrosis factor α is an inhibitor of adiponectin promoter activity [47].

Moreover, in our PHPT patients with metabolic syndrome, we revealed a negative correlation between plasma adiponectin levels and fasting glucose.

The inverse association of serum adiponectin level with fasting glucose suggests that hyperglycemia is an adiponectin-deficient state.

Plasma adiponectin concentrations are lower in people who have type 2 diabetes mellitus [48], and the plasma concentrations have been shown to correlate strongly with insulin sensitivity [49].

Adiponectin levels are inversely related to insulin, and insulin has inhibitory effects on the levels of adiponectin [50].

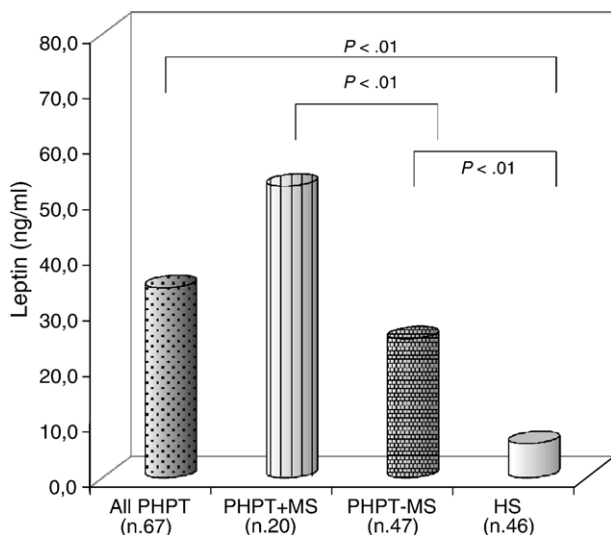


Fig. 1. Serum leptin levels (ng/mL) in studied groups. All PHPT indicates all patients with PHPT; PHPT + MS, patients affected by PHPT with metabolic syndrome; PHPT – MS, patients affected by PHPT without metabolic syndrome; HS, healthy subjects.

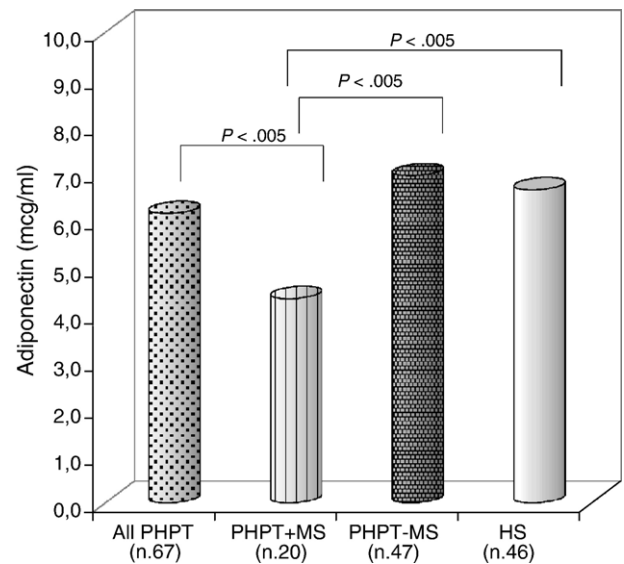


Fig. 2. Serum adiponectin levels ($\mu\text{g/mL}$) in studied groups. Abbreviations as in Fig. 1.

These data, together with recent evidence that adiponectin possesses anti-inflammatory properties and may modulate the process of atherogenesis [50], suggest that adiponectin deficiency associated with metabolic syndrome may contribute to accelerated atherosclerosis in PHPT. The link between plasma adiponectin and coronary artery disease is well established. It was shown that patients with coronary artery disease had lower plasma adiponectin than controls [51]. The levels of plasma adiponectin in subjects with more coronary artery disease risk factors tend to be lower [52]. The link between adiponectin and coronary artery disease is at least, in part, mediated by its relationship with the metabolic syndrome [53].

One of the limitations of this article is that we did not study insulin resistance (which occurs in obesity and in metabolic syndrome) in our PHPT patients. However, our purpose here was to focus on differences in adipokine levels in PHPT, but not to assess insulin resistance and its relationship to metabolic syndrome in PHPT.

5. Conclusions

Significant findings in our study are as follows: (1) about 30% of patients with PHPT presented a metabolic syndrome as defined by the Adult Treatment Panel III criteria; (2) serum leptin levels in PHPT patients were significantly higher than those of HS and, in particular, in PHPT patients with the metabolic syndrome; (3) serum adiponectin levels were significantly lower in the PHPT patients with metabolic syndrome compared with the controls; (4) positive correlations were found between leptin and BMI and between WC and alkaline phosphatase in PHPT patients with metabolic syndrome; and (5) negative correlations between adiponectin and BMI and WC and fasting glucose were found in PHPT patients with metabolic syndrome.

We conclude that increased serum levels of leptin and decreased serum levels of adiponectin coexist in patients with PHPT and may represent a pathogenetic factor for cardiovascular disease in this condition.

Acknowledgments

The study was supported in part by Banca Credito Cooperativo di Roma.

The authors thank Mr Giovanni Clemente for technical assistance.

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