

# Changes in serum leptin and adiponectin concentrations and insulin resistance after curative parathyroidectomy in moderate to severe primary hyperparathyroidism

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## ABSTRACT

**Introduction:** Primary hyperparathyroidism (PHPT) is considered a state of insulin resistance. However, it is unclear whether the state of insulin resistance and adverse levels of adipocytokines are reversed in PHPT patients who have undergone curative parathyroidectomy.

**Methods:** Ten consecutive patients with PHPT were studied at baseline and three months after curative parathyroid surgery in this prospective interventional study. Fasting blood calcium, intact parathyroid hormone (PTH), glucose, insulin, adiponectin and leptin concentrations were measured. Insulin resistance was assessed using the homeostasis model assessment of insulin resistance (HOMA-IR) and insulin sensitivity, by the quantitative insulin sensitivity check index (QUICKI).

**Results:** Four out of the ten patients were male. The mean age of the patients was 32.40 +/- 11.42 years, and the mean body mass index was 23.70 +/- 5.19 kg/m<sup>2</sup>. The HOMA-IR value was found to be higher, while the QUICKI value was significantly lower before surgery in patients with PHPT compared to the published reference ranges. Serum leptin concentrations were higher in patients with PHPT than in normal healthy individuals; however, there was no difference in the adiponectin concentrations. There was no statistical difference in the mean values of fasting plasma glucose, plasma insulin, leptin, adiponectin, as well as the HOMA-IR and QUICKI estimates three months postoperatively, as compared to the preoperative measures.

**Conclusion:** Peripheral insulin resistance/sensitivity and the concentrations of leptin and adiponectin did not change three months after curative parathyroidectomy.

**Keywords:** adiponectin, hyperparathyroidism, insulin resistance, leptin, parathyroidectomy

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## INTRODUCTION

Since autoanalysers to measure plasma calcium became widely used, most of the currently identified cases of primary hyperparathyroidism (PHPT) have been diagnosed incidentally before any classical symptoms of PHPT develop.<sup>(1)</sup> Therefore, attention has now been directed toward non-classical manifestations of the disease, such as abnormalities in carbohydrate and lipid metabolism as well as cardiovascular manifestations.<sup>(2)</sup> PHPT has been reported to be associated with hypertension,<sup>(3)</sup> arrhythmia,<sup>(4)</sup> structural and functional alterations in the heart and vascular wall,<sup>(5)</sup> left ventricular hypertrophy<sup>(6)</sup> and valvular calcification.<sup>(7)</sup> Metabolic abnormalities such as impairment of glucose tolerance or diabetes mellitus and altered lipid profile also frequently occur in patients with PHPT.<sup>(8-10)</sup> Furthermore, studies have demonstrated that PHPT is associated with excess cardiovascular morbidity and mortality.<sup>(11,12)</sup> Leptin and adiponectin are well-characterised adipocytokines that play important roles in insulin resistance. Adiponectin, which is expressed by adipocytes, seems to increase tissue sensitivity to insulin, and plasma levels of adiponectin are positively correlated with whole-body insulin sensitivity.<sup>(13)</sup> In contrast, leptin is associated with insulin resistance. Hypoadiponectinaemia and hyperleptinaemia may contribute to atherogenesis and adverse cardiovascular outcomes.<sup>(14)</sup> Few studies have examined the issue of insulin resistance in PHPT.<sup>(15-17)</sup> To our knowledge, only two studies have addressed the level

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of adipocytokines in PHPT,<sup>(18,19)</sup> and only one study has measured changes in the level of adipocytokines before and after parathyroidectomy.<sup>(19)</sup>

It is not clear whether curative parathyroidectomy reverses the state of insulin resistance and adverse levels of adipocytokines in patients with symptomatic PHPT. In the current study, we analysed serum leptin and adiponectin concentrations, indirect measures of insulin resistance (using homeostasis model assessment of insulin resistance [HOMA-IR]) and sensitivity (using quantitative insulin sensitivity check index [QUICKI]) before curative parathyroidectomy and three months post procedure in patients with moderate to severe PHPT.

## METHODS

Ten consecutive patients with PHPT (four male and six female) were recruited from the Department of Endocrinology, Postgraduate Institute of Medical Education and Research, Chandigarh, India. The study was conducted from February 2008 to October 2009, and was approved by the institute's Ethics Committee. Moderate to severe PHPT was defined by the findings of elevated serum parathyroid hormone (PTH) levels ( $\geq 250$  pg/ml) and albumin-adjusted hypercalcaemia. All patients underwent preoperative localisation by ultrasonography and/or <sup>99m</sup>Tc-sestamibi scintigraphy before proceeding to parathyroid surgery. Histopathological reports confirmed single parathyroid adenoma in all the patients. Cure of PHPT was defined as normalisation of serum calcium and PTH, or  $> 50\%$  reduction in PTH compared to the pre-operative value.

Patients with diabetes mellitus or having a family history of diabetes mellitus in first-degree relatives and those taking medications known to alter carbohydrate metabolism were excluded from the study. Calcium profile, PTH, serum leptin and adiponectin levels were measured in all patients. Body mass index (BMI) was calculated as weight (kg) divided by height ( $m^2$ ). Blood samples were taken after an overnight fast from the antecubital vein between 0830 and 0900 hours in fasting states. The samples were centrifuged and plasma aliquots were kept at  $-20^\circ\text{C}$  until the analysis. All the patients were reassessed three months after curative surgery.

Fasting venous blood samples were taken at baseline and after three months of curative parathyroidectomy. Serum albumin-adjusted calcium (reference range (RR) 8.2–10.2 mg/dl) and serum creatinine (RR 0.4–1.2 mg/dl) levels were measured in our laboratory using a Roche modular P800 autoanalyzer (Roche Diagnostics, Mannheim, Germany). Fasting plasma glucose (RR 70–100 mg/dl) was estimated using the

glucose oxidase method (Autopak, Bayer Diagnostic Ltd, Baroda, India) and fasting insulin (RR 2.6–24.9  $\mu\text{U/ml}$ ), by chemiluminescence assay (Elecsys 2010, Roche Diagnostics, Mannheim, Germany). PTH (RR 15–65 pg/ml) was estimated by radioimmunoassay, and serum 25 hydroxyvitamin D (RR 11–43 ng/ml) by chemiluminescence assay (DiaSorin Inc, Stillwater, MN, USA). Intra- and inter-assay coefficient of variability (CV) were 10%–15%. Insulin resistance and sensitivity were calculated by HOMA-IR ( $2.06 \pm 0.14$  [0.7–6.5])<sup>(20)</sup> and QUICKI ( $0.382 \pm 0.007$ )<sup>(21)</sup>, respectively.

Adiponectin levels were measured by enzyme-linked immunosorbent assay (ELISA) using the human adiponectin kit (BioVendor Laboratory Medicine Inc, Candler, NC, USA). The intra- and inter-assay CV were 6.4% and 7.3%, respectively, and the upper detection limit was 100  $\mu\text{g/dl}$ . Leptin was measured by solid phase ELISA using DRG Leptin (Sandwich) EIA-2395 kits (DRG GmbH, Marburg, Germany). The minimum detectable concentration of leptin by this assay was 1.0 ng/ml. A total of 28 normal, healthy volunteers were studied in order to establish the normal levels of leptin and adiponectin. Serum leptin and adiponectin concentrations were  $4.1 \pm 3.4$  ng/mL and  $10.4 \pm 4.3$   $\mu\text{g/mL}$ , respectively.

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 10.0 (SPSS Inc, Chicago, IL, USA). Data was reported as mean  $\pm$  standard deviation (SD), unless otherwise specified. Comparisons between variables before and after parathyroidectomy were made using paired *t*-test. Correlations between variables were analysed by correlation coefficients (*r*). A *p*-value  $< 0.05$  was considered statistically significant in all comparisons.

## RESULTS

All ten patients were symptomatic. Three patients presented with renal symptoms and seven with skeletal symptoms. The mean age of the patients was  $32.4 \pm 11.4$  years. The mean duration of symptoms before diagnosis of hyperparathyroidism was 48 months. The mean BMI of the patients was  $23.7 \pm 5.2$   $\text{kg/m}^2$ . Three patients were hypertensive. Preoperative localisation suggested a single adenoma in all the cases, for which all the patients underwent surgery. The mean weight of the parathyroid adenomas was  $8.7 \pm 8.2$  g (range 0.85–26 g).

The pre- and postoperative biochemical parameters are shown in Table I. There was a significant reduction in calcium ( $p < 0.001$ ) and PTH ( $p = 0.01$ ) levels after curative parathyroid surgery, whereas the serum phosphorus ( $p < 0.44$ ) and alkaline phosphatase ( $p < 0.19$ )

**Table I. Changes in markers three months post curative parathyroidectomy (n = 10).**

Parameter	Mean $\pm$ SD		p-value
	Preoperative	Postoperative	
Serum calcium (mg/dL)	10.7 $\pm$ 0.9	9.1 $\pm$ 0.7	< 0.001
Serum phosphorus (mg/dL)	3.2 $\pm$ 0.2	3.4 $\pm$ 0.5	< 0.44
Serum alkaline phosphatase (KA)*	37.8 $\pm$ 27.9	23.0 $\pm$ 16.6	< 0.19
PTH (pg/mL)	1042.0 $\pm$ 816.3	231.0 $\pm$ 283.7	0.01
Serum leptin (ng/mL)	13.8 $\pm$ 15.3	16.2 $\pm$ 16.9	0.32
Serum adiponectin ( $\mu$ g/mL)	10.6 $\pm$ 5.5	13.1 $\pm$ 8.6	0.51
Serum insulin ( $\mu$ U/mL)	13.6 $\pm$ 9.0	22.1 $\pm$ 33.2	0.48
FPG (mg/dL)	93.0 $\pm$ 7.5	89.2 $\pm$ 10.4	0.42
HOMA-IR	3.1 $\pm$ 2.0	4.7 $\pm$ 7.9	0.49
QUICKI	0.3 $\pm$ 0.1	0.4 $\pm$ 0.1	0.31

\* 1 KA unit = 7.1 IU/L.

SD: standard deviation; PTH: parathyroid hormone; FPG: fasting plasma glucose; HOMA-IR: homeostasis model assessment of insulin resistance; QUICKI: quantitative insulin sensitivity check index

levels did not change significantly. Fasting plasma glucose, plasma insulin as well as HOMA-IR and QUICKI values are shown in Table I. The HOMA-IR values of our patients were higher before surgery compared to the published reference mean values ( $p = 0.02$ ). Similarly, the QUICKI values were significantly lower in PHPT patients before surgery compared to the published standard reference mean values ( $p = 0.05$ ). However, there was no statistically significant difference between pre- and postoperative (three months) fasting plasma glucose, plasma insulin, HOMA-IR and QUICKI values. No correlation was noted between serum calcium and HOMA-IR values preoperatively ( $r = 0.39$ ,  $p = 0.59$ ) and postoperatively ( $r = 0.09$ ,  $p = 0.12$ ). Similarly, no correlation was observed between the serum phosphorus/PTH levels and HOMA-IR and QUICKI values.

The levels of serum leptin and adiponectin before curative parathyroidectomy and three months post procedure are shown in Table I. Serum leptin levels were significantly higher in patients with PHPT (13.8  $\pm$  15.3 ng/ml) compared to healthy volunteers (4.1  $\pm$  3.4 ng/ml;  $p = 0.01$ ). However, no statistically significant ( $p = 0.63$ ) difference was observed in the adiponectin concentration between PHPT patients (10.6  $\pm$  5.5  $\mu$ g/ml) and the healthy controls (10.4  $\pm$  4.29  $\mu$ g/ml). There was also no statistical difference between the pre- and postoperative concentrations of these adipocytokines ( $p = 0.32$  and  $p = 0.51$  for leptin and adiponectin, respectively).

## DISCUSSION

The current study revealed that preoperative serum leptin levels were elevated in PHPT patients, while serum

adiponectin levels were comparable to those of the healthy controls. Three months after curative parathyroidectomy, the levels of adipocytokines as well as the HOMA-IR and QUICKI values did not change significantly. In developing countries, patients with PHPT were found to be more likely to be symptomatic than those in Western countries, and their mean age of presentation was younger than commonly observed in the West.<sup>(22,23)</sup> The patients in our study were young (mean age 32 years) and not obese (mean BMI 23.7 kg/m<sup>2</sup>), and they had the typical findings of patients in the developing world.

The prevalence of type 2 diabetes mellitus in patients with PHPT is significantly higher than that in the general population,<sup>(24)</sup> and a number of studies have shown that PHPT is associated with insulin resistance.<sup>(15-17)</sup> The proposed mechanisms include hypercalcaemia, high PTH and low phosphorus,<sup>(25,26)</sup> but the contribution of each is yet unknown. Studies have shown that hypercalcaemia results in hyperinsulinaemia,<sup>(25,27)</sup> however, we did not find any correlation between either calcium or phosphorus level and serum insulin, HOMA-IR and QUICKI values. Furthermore, hyperinsulinaemia was not corrected despite curative parathyroidectomy. Similar observations have been reported by other studies.<sup>(27,28)</sup>

Serum leptin levels were higher in PHPT patients compared to the normal healthy volunteers, and curative parathyroidectomy did not result in a reduction in leptin levels. There was no statistical difference in the adiponectin concentrations in PHPT and healthy volunteers. Likewise, a few studies have found elevated leptin and reduced adiponectin levels in PHPT patients,<sup>(18,19)</sup> and a recently published study has suggested that these abnormalities are not reversed by surgery.<sup>(18,19)</sup> These findings are similar to those in our study, which showed that there was

no difference in leptin and adiponectin concentrations after curative parathyroidectomy.

The major limitation of our study is the short follow-up period, small sample size and use of QUICKI for measurement of insulin sensitivity instead of oral glucose tolerance test (using Matsuda index) or Bergmann's sensitivity index. However, this study has an implication in clinical practice in that insulin resistance and adipocytokine concentrations, which are potential contributors to unfavourable cardiovascular outcomes in PHPT, are not corrected by curative parathyroid surgery in the short term. Therefore, abnormal glucose metabolism and altered adipocytokine levels should not be used as an indication for parathyroid surgery. Our study has found that peripheral insulin sensitivity and resistance as well as levels of leptin and adiponectin did not change three months after curative parathyroidectomy; however, these results should be confirmed by further studies involving a larger sample size and longer follow-up periods.

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