Parathyroidectomy Decreases Insulin Resistance Index in Patients with Primary Hyperparathyroidism

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Abstract Primary hyperparathyroidism (PHPT) has been considered a cause of insulin resistance (IR) and impaired glucose metabolism. However, there are conflicting results related with the recovery of insulin resistance in patients with PHPT following curative parathyroidectomy. Our aim is to evaluate the effects of curative parathyroidectomy on IR in patients with PHPT. This is a prospective interventional study. Twenty-one consecutive patients with symptomatic PHPT were included into the study. All patients underwent parathyroidectomy. Fasting serum glucose, calcium, phosphorous, parathormone, plasma insulin, and vitamin D levels were measured both at baseline and 2 months after parathyroidectomy. Insulin resistance was calculated by homeostasis of model assessment-insulin resistance (HOMA-IR). Two months after curative parathyroidectomy, serum levels of calcium ($p=0.001$), PTH ($p<0.001$), insulin ($p=0.003$), and HOMA-IR ($p=0.003$) decreased, while phosphorous levels increased ($p=0.001$). During this period, no changes were observed at vitamin D and glucose levels. We concluded that curative parathyroidectomy decreases HOMA-IR index in patients with PHPT. Studies with larger population and longer follow-up period are required to confirm our results.

Keywords Primary hyperparathyroidism · Parathyroidectomy · Insulin resistance · Homeostasis of model assessment-insulin resistance

Introduction

It is reported that primary hyperparathyroidism (PHPT) is associated with excess cardiovascular mortality and morbidity [1–3], and parathyroidectomy may restore these risks [4]. In patients with PHPT, impaired glucose tolerance (IGT) and diabetes mellitus (DM) are more frequently seen disorders [5–12] and may contribute to cardiovascular mortality and morbidity. Impaired glucose tolerance and DM prevalence are threefold higher in patients with PHPT, compared to general population [11, 12]. Hypophosphatemia, hypercalcemia, and increased PTH levels are thought to be the cause of altered glucose metabolism and insulin resistance (IR) [13–16]. Although there are numerous reports that PHPT increases IGT and DM prevalences, most of these reports are retrospective, give conflicting results, and show that curative parathyroidectomy has minimal or no effect on IR [17–23]. In literature, a few number of studies with small sample size show that curative parathyroidectomy improves both IR and glucose metabolism [16, 24].

In this prospective study, we aimed at evaluating IR before and 2 months after curative parathyroidectomy in PHPT.

Materials and Methods

This prospective study was conducted in The Departments of Endocrinology, Internal Medicine, and General Surgery of Konya Training and Research Hospital between September 2011 and February 2013.

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Twenty-one patients with symptomatic or asymptomatic PHPT were included. All patients were exposed to parathyroidectomy. All patients were selected for parathyroidectomy under the criteria of Third International Workshop guidelines in 2009 [25], including serum calcium concentration with 1 mg/dL or above the upper limit of normal, creatinine clearance lower than 60 mL/min, bone mineral density at the hip, lumbar spine, or distal radius, T score < -2.5 and/or previous fragility to fracture, and age level less than 50 years. Patients with DM using antihyperglycemic medication, those taking medications known to alter carbohydrate metabolism such as β -blockers, thiazide diuretics, and steroids, and with diseases affecting carbohydrate metabolism such as acromegaly and Cushing's syndrome and the conditions with pregnancy and history of known cancer were excluded. In preoperative period, age, gender, weight, and height data were recorded. Body mass index (BMI) was calculated as weight (in kilogram) divided by height square (in square meter). Preoperative fasting venous blood samples were drawn from the antecubital vein for the measurements of glucose, insulin, calcium, phosphorous, albumin, parathormone, and 25-hydroxyvitamin D levels. All laboratory analyses were repeated at postoperative second month. Standard oral glucose tolerance testing (OGTT) of 75 gr glucose was preoperatively performed in all participants with fasting blood glucose level between 100 and 125 mg/dL. Standard OGTT of 75 gr glucose was repeated both for patients exposed to OGTT at baseline and for those with fasting blood glucose level between 100 and 125 mg/dL at postoperative second month. Albumin-adjusted calcium levels [normal range (NR) 8.5–10.4 mg/dL] and phosphorous levels (NR 2.5–4.5) were measured via spectrophotometric method using the Abbott C-16000 autoanalyzer (Abbott Laboratories, Abbott Park, IL, USA). Parathormone levels (NR 11–67 pg/mL) were measured by Immulite 2000 using chemiluminescence method (Siemens Healthcare Diagnostics). Vitamin D levels (NR 25–80 μ g/dL) were measured by liquid chromatography tandem mass spectrometry (LC-MS/MS) (Applied Biosystems, USA). Fasting glucose levels (NR 70–105 mg/dL) were measured by glucose oxidase method using Abbott C-16000 autoanalyzer (Abbott Laboratories, Abbott Park, IL, USA). Fasting insulin levels (NR 6–27 μ IU/mL) were measured by chemiluminescence method using Immulite 2000 (Siemens Healthcare Diagnostics). Insulin resistance was calculated by homeostasis of model assessment-insulin resistance (HOMA-IR).

Data were reported as mean $\pm$ standard deviation (SD). Normality of the data was checked with the Shapiro-Wilks and the Kolmogorov-Smirnov tests. In the comparison of variables before and after parathyroidectomy, the paired t test was used. The Pearson's correlation analysis was performed by correlation coefficients (r). A p value < 0.05 was accepted as statistically significant. Statistical Package for the Social Sciences (SPSS) version 18.0 was used for statistical analysis.

Results

A total of 21 patients, four males (19 %), were included into the study. Minimal invasive parathyroidectomy was performed in 19 patients, and the others underwent open surgery under general anesthesia. All patients had single adenoma, and cure was achieved in all patients after operation. Mean age and BMI scores were 56.5 ± 12.5 years and 28.2 ± 5.6 kg/m², respectively. Parathyroid adenomas were located in the right-upper quadrant in one patient, right-lower quadrant in nine patients, left-upper quadrant in one patient, and left-lower quadrant in 10 patients. Serum and plasma measurements before and 2 months after the surgery are presented in Table 1. As anticipated, serum calcium and PTH levels were observed to decrease at postoperative second month ($p = 0.001$ and $p < 0.001$, respectively), while phosphorous levels were increased ($p = 0.001$). No change was seen in vitamin D levels during the study period. Although there was no change in serum glucose levels after the surgery, serum insulin and HOMA-IR levels were found to decrease ($p = 0.626$, $p = 0.003$, and $p = 0.003$, respectively) (Table 1, Fig. 1).

In the correlation analysis, a positive correlation was found between preoperative calcium levels and both preoperative serum insulin levels ($p = 0.028$, $r = 0.480$) and HOMA-IR levels ($p = 0.028$, $r = 0.478$). No correlation was found between other parameters.

A total of eight patients evaluated preoperatively had blood glucose levels higher than 100 mg/dL. Standard OGTT was performed in all the eight patients, and of these patients, impaired fasting glucose (IFG) was seen in five, IFG + IGT in two, and DM in one patient. Having repeated standard OGTT, IFG was found in two patients, DM in one with preoperative DM, and IFG + IGT in one at postoperative second month. Three patients with IFG and one with IFG + IGT in the preoperative period became normalized after OGTT was performed at postoperative second month. On the other hand, IFG was found in one patient with preoperative fasting blood glucose level lower than 100 mg/dL after OGTT at postoperative second month.

Discussion

In this study, we found a positive correlation between preoperative calcium and both insulin and HOMA-IR levels and also showed that curative parathyroidectomy decreases HOMA-IR levels.

Although it was reported that PHPT contributes to impaired glucose metabolism, conflicting reports, most of which were retrospective and with small sample size, are present about the effects of curative parathyroidectomy on glucose metabolism and IR. Early reports showed that curative parathyroidectomy decreased the need of insulin in two patients with type 2 DM

Table 1 Baseline and postoperative laboratory measurements and HOMA-IR levels of cases

	Preoperative	Postoperative second month	<i>p</i> values
Calcium (mg/dL)	10.9±0.7	9±0.6	0.001
Phosphorous (mg/dL)	2.8±0.7	3.3±0.6	0.001
Vitamin D (ng/mL)	19.4±18.7	19.9±13.5	0.795
Parathormone (pg/mL)	212.9±122.6	62.7±39.3	<0.001
Glucose (mg/dL)	95.8±12.5	96.1±11.4	0.626
Insulin (μIU/mL)	9.6±5.3	7.9±16.2	0.003
HOMA-IR	2.28±1.4	2.1±4.9	0.003

Results are given as mean±standard deviation, $p<0.05$ was accepted as significant. *HOMA-IR* homeostasis model assessment-insulin resistance

[26]. In a study performed by Almqvist et al., 1 year after parathyroidectomy in patients with mild PHPT, serum lipid profile and insulin sensitivity index were reported to remain unchanged, while serum adiponectin levels were increased [19]. Similar results were reported by Rudman et al., and no significant change was found in IR at 5 to 6 weeks after parathyroidectomy in 12 patients with PHPT [21]. In a subgroup analysis, despite its small sample size, it was reported that patients with higher preoperative HOMA-IR values, defined as >1.2 , showed an improvement in HOMA-IR index, compared to $\text{HOMA-IR}<1$. In the same study, it was concluded that parathyroidectomy improves IR only in patients with higher IR in the preoperative period [21]. In a retrospective study, Bannon et al. reviewed 36 insulin-requiring patients with DM undergoing curative parathyroidectomy and found that pre- and postoperative insulin requirements were similar and then claimed that co-existent DM should not be considered as a surgical indication in patients with PHPT [23]. In another study conducted with 10 patients with PHPT,

Fig. 1 Homeostasis of model assessment-insulin resistance levels before and after parathyroidectomy. *HOMA-IR* homeostasis of model assessment-insulin resistance

preoperative serum leptin levels were found to be higher than controls, and at the third month following parathyroidectomy, mean values of serum insulin, glucose, leptin, adiponectin, HOMA-IR, and QUICKI levels remained the same, compared to preoperative levels [17].

Limited number of reports asserts that parathyroidectomy has beneficial effects on glucose metabolism. In a study performed in patients with severe PHPT, parathyroidectomy was seen to improve IR significantly, evaluated by minimal model [16]. Khaleli et al. reported that compared to baseline, parathyroidectomy reduced fasting (5.6 ± 1 to 5.4 ± 0.8 mmol/L) and 2-h postprandial glucose levels (7.2 ± 3 to 6.3 ± 3.1 mmol/L), and also that 50 % of reduction in DM frequency, 33 % of reduction in IGT/IFG frequency, and 35 % of increase in normal glucose tolerance frequency were found [24]. In another report, although a reduction was found in insulin and glucose concentration levels during arginine infusion, no change was found in insulin sensitivity as measured by oral and intravenous glucose tolerance or tolbutamide tests after parathyroidectomy [27]. Although most of the abovementioned studies were performed in symptomatic PHPT, in the study performed by Ayturk et al., no changes were reported in glucose metabolism in patients with asymptomatic PHPT during 18-month follow-up [28].

In our study, HOMA-IR values were found to be within normal limits. On the other hand, the prevalence of IGT and DM was threefold higher than the general population as to PHPT. Taylor et al. reported that the prevalence of DM and IGT were 8 and 40 % in patients with PHPT, respectively [11]. Procopio et al. reported similar results that the prevalence of DM was 15.3 % in patients with PHPT and 5 % in controls, while the prevalence of IGT was 40.7 % in patients with PHPT and 25 % in controls [12]. In the present study, no patients with DM were treated with antihyperglycemic medications; therefore, it may be speculated that normal HOMA-IR values result from our inclusion criteria. At the baseline, only one of our patients suffered from DM and two from IGT. Also, this

speculation may be attributed to the reply to the question of why we found normal HOMA-IR levels though most of our patients were overweight.

How parathyroidectomy affects glucose metabolism still remains unknown. In patients with PHPT, altered serum calcium, phosphorous, and PTH levels could be the cause of IR. Increased intracellular calcium may reduce insulin-induced glucose uptake resulting in IR and β -cell dysfunction [11]. In subjects without DM, it was shown that serum phosphate levels were negatively correlated with postprandial 2-h blood glucose levels and positively with insulin sensitivity [13]. Serum phosphorus plays a role for ATP generation, and low level of serum phosphorous could lead to the disturbance of energy metabolism resulting in IR and IGT. Chiu et al. reported that intact PTH levels were independent determinants of insulin sensitivity and inversely correlated with insulin sensitivity assessed by using hyperglycemic clamp technique in 52 normotensive healthy subjects [15]. In another study, PTH infusion in mice was shown to decrease the effect of glucose utilization by 14 % [29].

In our study, a total of eight patients had blood glucose levels higher than 100 mg/dL preoperatively. Standard OGTT was performed in all these patients, and test results showed that five patients had IFG, two with IFG + IGT, and one with DM. At postoperative second month, IFG was detected in two patients, DM in one patient with preoperative DM, and IFG + IGT in one patient. In terms of OGTT results in four patients, three with IFG and one with IFG + IGT were found to be normal at postoperative second month. In addition, one patient with preoperative fasting blood glucose lower than 100 mg/dL was found to have IFG at postoperative second month. Therefore, it can be speculated that parathyroidectomy has positive effects on glucose metabolism in patients with IFG and IGT.

As a limitation of our study, the follow-up period was short. In order to evaluate the effect of surgical treatment of PHPT on IR, we designed our study in a way to be completed in 2 months.

In conclusion, in our study, the treatment of PHPT through surgery showed positive effects on IR in a short time although we have no information about long-term consequences, and we consider that surgical correction of hyperparathyroidism decreases HOMA-IR index and will lead to beneficial effects on glucose metabolism in patients with PHPT. The results of further studies with larger populations and longer follow-ups might be a breakthrough in considering surgical criteria in PHPT patients with DM.

Compliance with Ethical Standards Informed consents were taken from all participants, and the study protocol was approved by the Ethics Committee for Human Studies of Meram Medical School, Selçuk University.

Conflict of Interest Authors have no relevant conflict of interest to declare.

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