

Effect of curative parathyroidectomy on insulin resistance

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ABSTRACT

Background: Primary hyperparathyroidism (PHPT) is characterized by inappropriately elevated serum parathyroid hormone (PTH) level despite elevated serum calcium. Insulin resistant is the basic pathophysiology, behind the higher prevalence of diabetes mellitus in patients with PHPT. However, the improvement in insulin resistance (IR) after curative parathyroidectomy (CPTX) has not been established yet, as the study results are conflicting. **Materials and Methods:** In this prospective interventional study, ten patients with mild PHPT (Group 1) and another ten patients with moderate to severe PHPT (Group 2) were undergone CPTX. The IR was assessed by homeostasis model assessment-IR (HOMA-IR), quantitative insulin sensitivity check index (QUICKI), fasting plasma glucose (FPG), and fasting serum insulin (FSI), before and 3 months after CPTX. **Results:** There was no significant change of FPG and FSI, before and after CPTX in Group 1 ($P = 0.179$ and $P = 0.104$) and Group 2 ($P = 0.376$ and $P = 0.488$). Before surgery, HOMA-IR was higher, and QUICKI was significantly lower, in both Group 1 ($P = 0.058$ and $P = 0.009$) and Group 2 ($P = 0.023$ and $P = 0.005$) as compared to published normal reference mean, with no significant difference between the groups. Three months after surgery HOMA-IR increased further and QUICKI remained unchanged as compared to baseline, in both Group 1 ($P = 0.072$ and 0.082) and Group 2 ($P = 0.54$ and 0.56), but statistically insignificant. **Conclusion:** IR remained unchanged after CPTX in mild as well as moderate to severe PHPT. Asymptomatic PHPT with abnormal IR should not be used as criteria for parathyroidectomy.

Key words: Homeostasis model assessment-insulin resistance, insulin resistance, parathyroidectomy, primary hyperparathyroidism, quantitative insulin sensitivity check index

INTRODUCTION

Primary hyperparathyroidism (PHPT) is characterized by inappropriately elevated serum parathyroid hormone (PTH) level despite elevated serum calcium.^[1] Classically, PHPT was described as disease of “bones, stones, abdominal groans, psychic moan, and fatigue overtones”.^[2] But nowadays with the use of routine biochemical testing, more and more

asymptomatic patients of PHPT are being diagnosed.^[2] Besides hypercalcemia-related complications, PHPT is also associated with increased risk of cardiovascular disease, hypercoagulable state, and metabolic syndrome.^[3-5] High prevalence of diabetes mellitus (DM) in patients with PHPT is well established^[6,7] and higher prevalence of PHPT in patients with DM has also been demonstrated.^[8] Insulin resistant is the basic pathophysiology behind the DM in PHPT. However, the improvement of insulin resistance (IR) after curative parathyroidectomy (CPTX) has not been established yet as the study results are

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conflicting. There are few studies, which demonstrated the improvement of IR after CPTX in patients with PHPT.^[9,10] But at the same time, few studies showed that there was no improvement in IR and metabolic risk factors after CPTX in patients with PHPT.^[11-13] The present study was designed to observe the effect of CPTX on peripheral IR in patients with PHPT of varying severity.

MATERIALS AND METHODS

Study design and study population

In this prospective interventional study, 20 patients with PHPT of varying severity were recruited consecutively, irrespective of their age and gender. Ten patients with mild PHPT (Group 1) were studied at Henry Ford Hospital, Detroit, Michigan, USA. Another ten patients with moderate to severe PHPT (Group 2) were studied at Post Graduate Institute of Medical Education and Research, Chandigarh, a tertiary care center in northern India. Patients with mild PHPT were asymptomatic, whereas the patients with moderate to severe PHPT were symptomatic, had higher PTH, calcium level and had evidence of bone disease on X-rays and/or nephrolithiasis.^[14] Patients with established diagnosis of DM, family history of DM in first-degree relatives and taking medications known to affect carbohydrate metabolism were excluded from the study. The study was conducted between February 2008 and October 2009. The respective institutional review and ethical committee approved the study and written informed consent was obtained from each patient.

Method

PHPT was diagnosed by the presence of serum albumin-adjusted hypercalcemia along with inappropriately raised or nonsuppressed serum PTH level, on at least two occasions. The reference range for calcium and intact PTH (iPTH) level was 8.4–10.2 mg/dl and 10–75 pg/ml, respectively. All patients underwent CPTX as per NIH guideline.^[14,15] The clinical and biochemical diagnosis of PHPT was confirmed by surgery, followed by histopathological examination of the parathyroid gland. All patients were re-evaluated 3 months after CPTX. Cure of PHPT was defined as normalization of serum calcium and >50% reduction.

The IR was assessed by two well-established methods of estimating IR by homeostasis model assessment of IR (HOMA-IR) and insulin sensitivity by quantitative insulin sensitivity check index (QUICKI). HOMA-IR and QUICKI were measured in all patients at baseline and 3 months after CPTX.

In all patients, fasting serum insulin (FSI) and plasma glucose were measured, 7 days prior and 3 months after surgery from the same sample. Fasting plasma glucose (FPG) was measured by glucose oxidase/glucose hexokinase by Dimension Vista System (Siemens, USA) and FSI (reference value <14 μ IU/ml) was measured by chemiluminescence assay (Centaur XP, Siemens, USA). HOMA-IR was calculated by using following formula, $HOMA-IR = (FSI [\mu IU/ml] \times FPG [mmol/L]) / 22.5$.^[16,17] QUICKI was calculated by using following formula, $QUICKI = 1 / (\log [I_0] + \log [G_0])$, where I_0 is the fasting insulin, and G_0 is the fasting glucose.^[18] The reference normal value for HOMA-IR and QUICKI were 2.06 ± 0.14 (0.7–6.5) and 0.382 ± 0.007 , respectively.^[17,18]

Serum iPTH, 25(OH) Vitamin D (Vitamin D) were measured by chemiluminescence assay and serum albumin, calcium; creatinine was measured in the institute laboratory by standard methods. Unfortunately, Vitamin D could not be measured after surgery in the Indian patients because of the financial constraints.

Statistical analysis

All continuous data were expressed as mean \pm standard deviation unless otherwise specified. Data analysis was performed using Statistical Package for the Social Sciences (SPSS) software, version 13 (IBM). Outcomes were analyzed by change of IR and insulin sensitivity before and after surgery. The data were checked for skewness. Paired *t*-test, ANOVA followed by *post hoc* multiple comparisons were used where applicable and a $P < 0.05$ was set as statistically significant.

RESULTS

Baseline data of study population

Relevant demographic, biochemical parameter of mild (Group 1) and moderate to severe (Group 2) PHPT groups are compared in Table 1. There were two men in the mild (1:4) and 4 men in the moderate to severe PHPT group (2:3). All patients had a single parathyroid adenoma, except one patient in Group 2 had a double adenoma. Indian patients with moderate to severe PHPT were younger ($P = 0.001$), had lower body mass index ($P = 0.107$) and higher iPTH level ($P = 0.001$) as compared to the American patients with mild PHPT [Table 1]. However, serum calcium ($P = 0.242$) and Vitamin D ($P = 0.049$) were lower in Indian patients as compared to American patients [Table 1]. Among the patients with moderate to severe PHPT, seven patients had nephrolithiasis and two had fracture bone as compared to none of the patients with mild PHPT.

Following surgery, serum Calcium (Ca^{2+}) was normalized in all patients. iPTH was normalized in patients with mild PHPT and reduced by >50% in Indian patients with moderate to severe PHPT ($P < 0.001$), but remained higher than normal after 3 months [Table 2]. Serum Vitamin D also improved significantly ($P = 0.012$), after CPTX in the US patients with mild PHPT (28.7 ± 10.3 vs. 37 ± 12.21 ng/ml).

Insulin resistance

FPG was similar before and after surgery in mild and moderate to severe PHPT [Table 2]. There was no significant difference in FPG between the groups before ($P = 0.59$) and after ($P = 0.085$) CPTX. There was no significant ($P = 0.683$) difference in FPG of the combined group before and 3 months after CPTX [Table 2]. FSI was also similar before and after CPTX in mild as well as in moderate to severe PHPT [Table 2]. FSI was higher preoperatively in moderate to severe PHPT as compared to mild PHPT ($P = 0.669$) and increased postoperatively in both the groups ($P = 0.27$), but could not reach to statistical significance [Table 2]. FSI did not differ significantly ($P = 0.977$) in the combined group before and after CPTX [Table 2].

Homeostasis model assessment of insulin resistance

Before surgery HOMA-IR was higher, both in patients with mild PHPT ($P = 0.058$) and with moderate to severe PHPT ($P = 0.023$) as compared to published normal reference mean (2.06 ± 0.14),^[17] with no significant difference ($P = 0.84$) between the groups [Table 2]. Three months after CPTX HOMA-IR increased further in all the groups, with no significant difference within and between the groups [Table 2]. Consequently, the

postoperative HOMA-IR was also significantly higher than normal reference mean for the mild ($P < 0.001$) and moderate to severe ($P = 0.004$), as well as in the combined PHPT group ($P < 0.01$) [Figure 1 and Table 2]. Although HOMA-IR was numerically higher in patients with moderate to severe PHPT as compared to mild PHPT, both before and after CPTX, the difference did not reach statistical significance [Table 2].

Quantitative insulin sensitivity check index

Before surgery QUICKI was significantly lower both in mild ($P = 0.009$) and moderate to severe ($P = 0.005$) PHPT groups, as compared to published normal reference mean (0.382 ± 0.007),^[18] with no significant difference ($P = 0.96$) between the groups [Table 2]. Three months after CPTX, QUICKI almost remained unchanged in the mild ($P = 0.082$), moderate to severe ($P = 0.56$), and combined PHPT groups ($P = 0.893$) [Table 2]. Postoperative QUICKI was significantly lower than normal reference mean in the mild ($P < 0.001$) and combined PHPT groups ($P < 0.001$) but not in the patients with moderate to severe PHPT ($P = 0.132$) [Figure 2]. There was no difference in QUICKI between the mild and moderate to severe PHPT group before and after CPTX ($P = 0.307$).

DISCUSSION

Exact pathophysiology of IR in PHPT has not well established yet. The proposed pathogenetic factors and mechanisms responsible for the IR in PHPT are hypercalcemia, high PTH, low phosphate, and body weight.^[19-23] Most likely the disturbance in carbohydrate metabolism is caused by interplay of all these three biochemical abnormalities.^[19-23] Hypercalcemia stimulates insulin secretion, impairs peripheral insulin sensitivity, and suppression of gluconeogenesis.^[24-26] In addition, there is also reduced binding of insulin to its peripheral receptors due to receptor downregulation.^[27] In animal models, PTH administration has been shown to cause a reduction in ATP content in pancreatic islets leading to impaired insulin

Table 1: Baseline data of the study population

Baseline parameter	Mild PHPT (n=10)	Moderate to severe PHPT (n=10)	P
Age (years)	60±15	32±12	0.001
BMI (kg/m ²)	29.1±7.6	23.7±5.2	0.107
iPTH (pg/ml)	136±47.5	1042±816	0.001
Calcium (mg/dl)	11.2±0.77	10.8±0.96	0.242
Vitamin D (ng/ml)	28.7±10.3	17.4±13.5	0.049

PHPT: Primary hyperparathyroidism, BMI: Body mass index, iPTH: Intact parathyroid hormone

Table 2: Parameters before and after parathyroidectomy

Parameter	Mild PHPT			Moderate to severe PHPT			Combined group (PHPT)		
	Baseline	3 months	P	Baseline	3 months	P	Baseline	3 months	P
Ca^{2+} (mg/dl)	11.2±0.77	9.8±0.25	<0.001	10.8±0.96	9.1±0.72	<0.001	11.0±0.87	9.4±0.62	<0.001
iPTH (pg/ml)	136±47.5	68±33.4	<0.001	1042±816	145±262	<0.001	589±730	106±186	<0.001
FPG (mg/dl)	94.9±8.16	101.0±17.0	0.179	93.0±7.59	89.2±10.4	0.376	94.0±7.73	95.5±15.2	0.683
FSI (μIU/ml)	12.0±6.34	14.7±8.34	0.104	13.6±9.01	22.1±33.2	0.488	12.8±7.69	18.2±23.2	0.977
HOMA-IR	2.88±1.73	3.81±2.58	0.072	3.06±2.06	5.21±8.23	0.54	2.98±1.86	4.47±5.82	0.292
QUICKI	0.341±0.045	0.323±0.026	0.082	0.340±0.042	0.355±0.067	0.56	0.340±0.042	0.338±0.051	0.893

Normal reference range/mean- Ca^{2+} : 8.4-10.2 (mg/dl), iPTH: 10-75 (pg/ml), FPG: <100 (mg/dl), FSI: <14 (μIU/ml), HOMA-IR: 2.06±0.14 and QUICKI: 0.382±0.007.

PHPT: Primary hyperparathyroidism, iPTH: Intact parathyroid hormone, FPG: Fasting plasma glucose, FSI: Fasting serum insulin, HOMA-IR: Homeostasis model assessment of insulin resistance, QUICKI: Quantitative insulin sensitivity check index

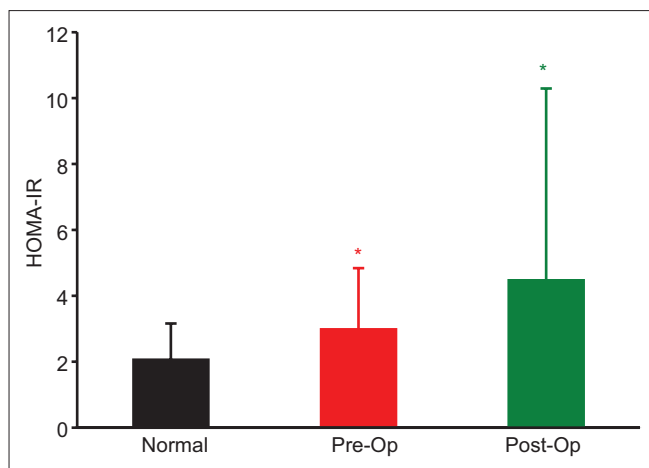


Figure 1: Comparison of homeostasis model assessment of insulin resistance of combined group (primary hyperparathyroidism) with the normal reference mean (2.06 ± 0.14), ($*P < 0.01$). There was no significant difference between the pre- and post-operative homeostasis model assessment of insulin resistance ($P = 0.292$)

release.^[28] Hypophosphatemia in PHPT is also known to cause impaired peripheral glucose utilization and decreased insulin responsiveness.^[21,22]

This study also showed hyperinsulinemia in the presence of hypercalcemia in both group of PHPT. Postoperatively, serum calcium normalized but serum insulin levels did not change significantly at 3 months. According to our study serum, calcium level did not correlate with HOMA-IR and QUICKI, before and after CPTX, as observed in previous studies.^[20,29] According to our study, PTH level reduced significantly after CPTX, but it did not correlate with serum insulin, HOMA-IR, and QUICKI, pre- or post-operatively in either group. The studies regarding the effect of PTH on hyperinsulinemia and IR are conflicting.^[30,31] In our study postoperatively, insulin level increased, and IR either increased numerically or remained unchanged. However, these did not achieve statistical significance, even though the PHT level decreased significantly after CPTX.

Like the previous study,^[32] our study also showed that HOMA-IR was significantly higher in patients with mild and moderate to severe PHPT, compared to normal reference mean ($P < 0.01$). But at the same time, few study showed that HOMA-IR remained unchange compared to baseline values even after 18 months without parathyroidectomy.^[33] Kautzky-Willer *et al.*^[34] assessed insulin sensitivity in PHPT, before and 3 months after CPTX by oral and intravenous glucose tolerance test. Even after 1 year of surgery, there was no improvement in insulin sensitivity. In contrast to our study, they showed decreased fasting blood glucose, serum insulin. These contrasting results may be due small

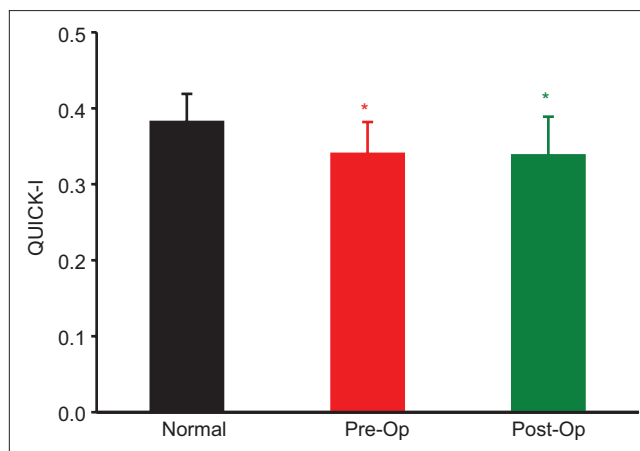


Figure 2: Comparison of quantitative insulin sensitivity check index of the combined group (primary hyperparathyroidism) with the normal reference mean (0.382 ± 0.007), ($*P < 0.01$). There was no significant difference between the pre- and post-operative quantitative insulin sensitivity check index ($P = 0.893$)

sample size, degree of hypercalcemia in patients (mean calcium 12 mg/dl) and use of intravenous and oral glucose tolerance test to assess insulin sensitivity.

However, the study results are conflicting regarding the improvement of IR after CPTX. Few studies revealed the improvement of IR after CPTX in patients with PHPT.^[9,10]

According to this study, there is IR in patients with mild as well as moderate to severe PHPT in the absence of DM, as reported previously.^[6,7,19,34] In addition, we also demonstrated that there is no significant improvement in HOMA-IR or QUICKI following CPTX, either in mild or in moderate to severe PHPT. According to our study, severity of IR also does not correlate with the severity of PHPT or PTH level. The therapeutic role of CPTX in symptomatic patients with moderate to severe PHPT is well established but at the same time, there is some doubt regarding role of CPTX in asymptomatic patients with mild PHPT.^[14] At presents, the patients with asymptomatic mild PHPT undergo CPTX as per NIH guideline.^[15,35] The significant clinical implication of this study is, asymptomatic mild PHPT with abnormal glucose metabolism should not be used as criteria for CPTX. Further study with larger sample size and longer duration of follow-up is needed, for better evaluation of the role of parathyroidectomy for improvement of IR in patients with PHPT.

Limitation

The major limitation was, small sample size and short period follow-up. A longer duration of follow-up may be needed for better evaluation of improvement in IR.

CONCLUSION

Peripheral IR (HOMA-IR) and insulin sensitivity (QUICKI) remained unchanged after CPTX in mild as well as moderate to severe PHPT. Both the HOMA-IR and QUICKI do not correlate with the severity of PHPT or PTH level. Asymptomatic mild PHPT with abnormal glucose metabolism should not be used as criteria for CPTX. However, further study is needed for the confirmation of our study result.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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