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ORIGINAL ARTICLE

Investigation of insulin resistance in patients with normocalcemic primary hyperparathyroidism

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Abstract While derangements in glucose metabolism in patients with primary hyperparathyroidism are well-defined, this issue is not investigated in patients with normocalcemic primary hyperparathyroidism (NPHPT). The aim of this study was to investigate the presence of insulin resistance in patients with NPHPT. Eighteen patients with NPHPT (two males and 16 females) and 18 healthy volunteers were enrolled into the study. Secondary causes of parathyroid hormone elevations were excluded in all patients. Blood samples were obtained for the measurement of serum calcium, phosphate, alkaline phosphatase (ALP), albumin, creatinine, glucose, and serum lipid levels. Glucose and insulin responses to oral glucose tolerance test (OGTT) were obtained. Homeostasis model assessment (HOMA-IR) was also used as an indice of insulin resistance. Patients and control subjects had similar age, body mass index, and sex distribution. Although within normal limits, serum calcium and ALP levels were higher in patients than in the control subjects. None of the patients and the control subjects had diabetes mellitus, while eight patients and six control subjects had impaired glucose tolerance. Insulin responses to OGTT and HOMA-IR were not significantly different among the patient and control subjects. In addition, both groups have similar serum lipid levels. Patients with NPHPT do not exhibit insulin resistance and glucose intolerance. Since so little is known about this form of disease, subjects should be monitored regularly for the metabolic aspects of the disease as well as the progression of their disease.

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Introduction

Primary hyperparathyroidism (PHPT) is the third most common endocrine disorder characterized by incompletely regulated, excessive secretion of parathyroid hormone (PTH) from parathyroid glands with a prevalence of 3 per 1,000 in the general population [1, 2]. Normocalcemic primary hyperparathyroidism (NPHPT) is a clinical phenomenon in which elevated serum PTH levels are observed with normal serum calcium concentrations in lack of secondary causes such as vitamin D deficiency, renal or liver disease or malabsorption. Available data do not suggest that NPHPT is a mild or asymptomatic form of classical PHPT [3].

While derangements in glucose and lipid metabolism in primary hyperparathyroid patients are well-defined [4–7], to the best of our knowledge only a few reports exist regarding metabolic abnormalities in patients with NPHPT [8, 9]. Moreover those studies fail to identify a truly normocalcemic primary hyperparathyroid state since the study population include vitamin D deficient individuals or the patients were limited to only postmenopausal women. In this study, we aimed to investigate insulin resistance in patients with NPHPT in whom secondary causes of PTH elevations rigorously excluded and make a comparison of the data obtained from healthy individuals.

Patients and methods

Eighteen patients with NPHPT (two males and 16 females) with a mean age of 49.9 ± 2.4 (range 35–65 years) years

and 18 age, gender and body mass index (BMI) matched healthy volunteers were enrolled into the study. The study was approved by the local Ethics Committee and all the patients and the control subjects gave informed consent. All patients had concomitantly elevated serum PTH concentration (reference range 10–65 pg/ml), and normal serum total calcium concentration associated with normal serum albumin levels. All patients had 25-hydroxy vitamin D (25 (OH)-D) concentrations higher than 20 ng/ml as described previously [1]. We have repeated serum calcium and PTH measurements at least three times with 2 week intervals before inclusion in order to exclude intermittent elevations of serum calcium levels. The individuals who participated in the study as controls were selected from hospital staff. None of the healthy controls and patients had hypertension, diabetes mellitus (DM), family history for DM or gestational DM, renal or liver diseases diagnosed previously, or receiving any prescriptions that known to effect on serum calcium level, glucose and lipid metabolism. All subjects were on free diet for at least 3 days before oral glucose tolerance test (OGTT).

At study entry all subjects underwent a physical examination; height and weight measurements were recorded for assessment of BMI. BMI was calculated as body weight divided by the square of the height (body weight (kg)/height $(m)^2$). Blood samples were obtained after an overnight fast for the measurement of serum calcium, phosphate, alkaline phosphatase (ALP), albumin, creatinine, glucose, triglycerides, total cholesterol (Total-C), low density lipoprotein cholesterol (LDL-C), and high density lipoprotein cholesterol (HDL-C) levels.

Standard OGTTs with 75 g glucose were performed between 0800 and 0900 h. Blood samples were taken just before (0 min) and 30, 60, 90, and 120 min after administration of glucose with 300 ml water orally for the measurement of serum glucose and insulin concentrations. Area under the curves (AUC) of glucose and insulin during OGTT were calculated according to trapezoid rule. Homeostasis model assessment (HOMA-IR) was also used as an indice of insulin resistance [10]. HOMA-IR was calculated as (fasting insulin (μu/ml) × fasting glucose (mmol/l)/22.5). Glucose tolerance was evaluated by using the criteria of the American Diabetes Association, and impaired glucose tolerance (IGT) was defined as a 2 h post load glucose of 140 mg/dl or greater and less than 200 mg/dl [11].

Serum's total calcium and phosphate levels were assayed by automated analysis using colorimetric and enzymatic methods. Serum intact PTH concentrations were measured by an electrochemiluminescence immunoassay (ECLIA) in Cobas e 601 (Roche Diagnostics, Mannheim, Germany) with the inter- and intra-assay coefficient of variation of 1.1–2.0 and 2.8–3.4%, respectively. Serum 25 (OH)-D was measured by HPLC method with Chromsystems in HPLC Agilent 1100 series (Germany). Lipid measurements were done by routine methods using commercial assays.

Statistical analysis was performed using the SPSS 13.0 program. All data were subjected to a Kolmogorov–Smirnov test for normality and data were presented as mean ± SEM. Because the groups were not normally distributed, Mann–Whitney *U* and Wilcoxon tests were used to compare the differences between groups and within groups, respectively. $p < 0.05$ was accepted as significancy.

Results

The demographic characteristics of the patient and control groups were similar as shown in Table 1. Patients and control subjects had similar age, BMI and sex distribution. Although within normal limits, serum calcium and ALP levels were higher in patients than in the control subjects. The patients with NPHPT had significantly ($p < 0.001$) higher serum PTH levels than controls (Table 1). Mean serum 25 (OH)-D level was 54.5 ± 12.4 ng/ml in the patient group.

Seventeen patients were evaluated by methoxy isobutyl isonitrile (MIBI) scintigraphy; three (17.6%) patients had positive MIBI scintigraphy, four (23.5%) patients had suspicious scintigraphy, and ten (58.5%) patients had negative scintigraphy. Two (11.1%) patients had history of nephrolithiasis, eight out of 17 patients (47%) had osteoporosis.

None of the patients and the control subjects had DM, while eight patients and six control subjects had IGT. Insulin responses to OGTT and HOMA-IR were not significantly different among the patient and control subjects (Table 2). In addition, both groups have similar serum lipid levels.

Table 1 Demographic and clinical features of patients and control subjects

	Patients with NPHPT $n = 18$	Control subjects $n = 18$	*p* value
Age (year)	49.9 ± 2.4	48.3 ± 1.8	NS
BMI (kg/m^2)	31.7 ± 1.2	32.1 ± 1.2	NS
Serum calcium (mg/dl)	9.7 ± 0.1	9.2 ± 0.1	<0.05
Serum phosphate (mg/dl)	3.1 ± 0.1	3.2 ± 0.1	NS
ALP (U/l)	79.6 ± 6.4	63.1 ± 4.2	<0.05
PTH (pg/ml)	148.6 ± 19.0	49.5 ± 2.2	<0.001

Data are presented as SEM

NS not significant, *NPHPT* normocalcemic primary hyperparathyroidism, *ALP* alkaline phosphatase, *PTH* parathyroid hormone

Table 2 Insulin resistance parameters and serum lipid profile of patients and control subjects

	Patients with NPHPT $n = 18$	Control subjects $n = 18$	p value
Fasting glucose (mg/dl)	84.6 ± 2.6	96.0 ± 2.6	NS
120 min glucose (mg/dl)	126.6 ± 8.2	113.0 ± 9.2	NS
HOMA-IR	4.0 ± 1.18	2.2 ± 0.3	NS
AUC glucose	17524.8 ± 1311.0	17340.8 ± 777.0	NS
AUC insulin	5430.8 ± 800.3	5837.9 ± 764.5	NS
Total cholesterol (mg/dl)	204.59 ± 8.66	216.72 ± 10.15	NS
HDL cholesterol (mg/dl)	49.54 ± 3.21	45.28 ± 2.05	NS
LDL cholesterol (mg/dl)	136.45 ± 8.36	144.44 ± 8.47	NS
Triglyceride (mg/dl)	130.24 ± 11.31	133.89 ± 12.50	NS

Data are presented as SEM

NS not significant, *HDL* high density lipoprotein, *LDL* low density lipoprotein

Discussion

Normocalcemic PHPT is being increasingly identified with the availability and widespread usage of PTH assays. It is questionable that NPHPT may be considered as an early, subclinical, asymptomatic phase of classical PHPT. Dimkovic et al. [12] investigated 414 patients who had renal stone disease and 40 of these patients (9.6%) were found to have elevated serum PTH level and normal serum calcium levels. Improvements in quality of life after parathyroidectomy in patients with NPHPT may indicate that this patient group is not truly asymptomatic and may share similar features with hypercalcemic population [13]. In our study population, overall 47% of the patients had osteoporosis. This is not surprising data since the findings leading to a diagnosis of NPHPT were first observed in patients who are referred for low bone mass. Eleven percent of our patients had nephrolithiasis and these data suggest that patients with NPHPT actually have involvement of different systems and are not truly asymptomatic.

The relationship between glucose and calcium metabolism was well-established with several previous studies. In a community-based cohort, Hagstrom et al. [14] investigated the association between serum calcium and insulin sensitivity and found that endogenous calcium may be involved early in the development of diabetes which is mediated by the effects on insulin sensitivity rather than insulin secretion. It has been shown that patients with PHPT have increased prevalence of type 2 diabetes mellitus and successful parathyroidectomy resulted in amelioration of glucose intolerance [15].

The picture consists of close relationship between PHPT and impaired glucose metabolism rises the question that do the patients with NPHPT also have alterations in glucose metabolism. To the best of our knowledge, there are limited data on this issue. In a study from Turkey, insulin sensitivity in 61 patients with asymptomatic PHPT was investigated. Twenty of them reported to be normocalcemic. No significant differences were found in the prevalence of preexisting DM, undiagnosed IGT and newly diagnosed DM, when compared with healthy controls. But inclusion criteria fail to determine a truly normocalcemic primary hyperparathyroid state since some patients have serum 25 (OH)-D levels lower than 20 ng/ml [8]. In a population based screening of postmenoposal women, 30 patients suffering from NPHPT were detected and reported to have higher blood glucose, BMI, very low density cholesterol, LDL-C/HDL-C ratio, triglycerides, and a lower HDL-C levels than the controls. Vitamin D deficiency could not be excluded because vitamin D measurements were not involved as an inclusion criterria [9].

Our aim was to investigate glucose and lipid metabolisms in patients with well-defined NPHPT. At least to our knowledge, there is no study investigating insulin resistance and glucose intolerance in patients with NPHPT. Indicators of insulin resistance, as determined by HOMA index and insulin responses to OGTT, were not different from the values of control group. None of the patients had DM during OGTT and similar (eight vs. six) number of cases showed IGT. It is interesting that while patients with NPHPT having negative effects on bone metabolism, effects on carbohydrate metabolism were not different from healthy subjects.

Several studies showed significant correlations between total calcium concentrations with fasting glucose and insulin resistance [16, 17]. Tassone et al. [18] investigated the frequency of insulin resistance and glucose intolerance in 122 patients with PHPT. They have used OGTT-derived estimates of insulin sensitivity and compared the data with 61 healthy subjects. The authors found reduced both basal and stimulated indices of insulin sensitivity markers in patients with PHPT and also showed for the first time that serum calcium level, significantly and independently, contributed to impaired insulin sensitivity. Recently, Yamaguchi et al. [17] examined patients with type 2 DM (271 men, 209 women) and analyzed the relationships between serum concentrations of calcium, intact PTH and diabetes related variables. They suggest that the serum

calcium not the PTH is potentially involved in the aggravation of hyperglycemia and insulin resistance in type 2 diabetic men. In the present study, data obtained from normocalcemic hyperparathyroid patients support the importance of hypercalcemia, rather than PTH levels, on insulin resistance from another point of view. However, we must note that the current study is cross-sectional and those patients may have altered glucose metabolism during follow-up, as it has been reported that with an average follow-up of 4 years, 22% of patients with NPHPT became hypercalcemic [19].

In conclusion, contrast to hypercalcemic PHPT, patients with NPHPT do not exhibit insulin resistance and glucose intolerance. Since so little is known about this form of disease, subjects should be monitored regularly for the metabolic aspects of the disease as well as the progression of their disease and larger studies with more patients would be helpful to make a deep understanding in the clinical features of patient population with NPHPT.

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