Patients with normocalcemic primary hyperparathyroidism may have similar metabolic profile as hypercalcemic patients

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Abstract. Primary hyperparathyroidism is well known to be associated with cardiovascular morbidity and mortality. However, it is unclear whether normocalcemic primary hyperparathyroidism (NC-PHPT) and hypercalcemic primary hyperparathyroidism (HC-PHPT) share the same risk factors. We aimed to determine prevalence of metabolic syndrome in NC-PHPT and compare metabolic syndrome parameters and insulin resistance in NC-PHPT subjects with those in HC-PHPT and control subjects. After excluding patients with secondary hyperparathyroidism, the study enrolled 25 patients with NC-PHPT, 24 patients with HC-PHPT and 30 age-gender matched controls. All participants were evaluated using the International Diabetes Federation (IDF)-2006 metabolic syndrome criteria. Compared with HC-PHPT patients, NC-PHPT patients had similar prevalence of metabolic syndrome, glucose intolerance, and previous history of hypertension/antihypertensive medications, but compared with controls, NC-PHPT patients had significantly higher prevalence of glucose intolerance and previous history of hypertension/antihypertensive medications. Not serum calcium but PTH concentration was found to be significantly higher in those with glucose intolerance. Serum fasting triglyceride concentration and waist circumference were found to be positively correlated only with serum PTH concentration. In conclusion, patients with NC-PHPT may be prone to similar metabolic disturbances linked to higher cardiovascular risk like patients with HC-PHPT. Although NC-PHPT is thought to occur early in the development of the classical disease, it should be monitored regularly because of its metabolic consequences.

Key words: Normocalcemic primary hyperparathyroidism, Metabolic syndrome, Insulin sensitivity, Glucose intolerance

NORMOCALCEMIC PRIMARY HYPERPARATHYROIDISM (NC-PHPT) is a new clinical entity increasingly diagnosed with the widespread usage of parathyroid hormone (PTH) assays over the past decade. Normocalcemic PHPT is considered in patients with normal total and ionized serum calcium (Ca) concentrations and persistently elevated PTH levels. The diagnosis can only be made after exclusion of all secondary causes of hyperparathyroidism, such as chronic kidney disease, vitamin D insufficiency, hypercalciuria, malabsorption syndromes or use of medications altering Ca homeostasis (lithium, thiazides…) [1-3]. A biphasic course is proposed in the development of this new presentation. During the first subclinical phase, serum Ca is normal while PTH levels are elevated. The second phase is the clinical stage that is usually recognized with hypercalcemic period [4]. Its true prevalence, natural history and clinical significance are not well-defined.

Patients with primary hyperparathyroidism (PHPT) have an increased morbidity and mortality mainly due to metabolic abnormalities that leads to cardiovascular (CV) diseases [5-9]. Several aspects of metabolic syndrome (MS) such as obesity, hypertension (HT), insulin resistance, glucose intolerance, diabetes mellitus (DM) and hyperlipidemia are more prevalent in PHPT.
than controls [10]. It is unknown whether NC-PHPT is an indolent disease or has an impact similar to that of classical PHPT. As high serum Ca concentrations stimulate higher insulin levels by regulating intracellular free Ca concentrations [11], it is expected that CV risk factors would correlate with the severity of hypercalcemia in PHPT. However, the connection between the biochemical disturbances and the cardiovascular disorders in patients with PHPT is not necessarily a cause-and-effect relationship. An atherogenic metabolic profile has been reported in patients with NC-PHPT [12]. It is unclear whether NC-PHPT carries the same risk for increased CV morbidity as the hypercalcemic form [13]. There are few and contradictory data available regarding metabolic abnormalities of normocalcemic PHPT patients in the literature [12, 14-16].

The aim of this study was to determine whether patients with NC-PHPT differ from those with HC-PHPT and control subjects matched for age-gender for the indices of metabolic syndrome and insulin resistance.

Materials and Methods

Subjects

Twenty-five patients with NC-PHPT, 24 patients with HC-PHPT and 30 age, gender and body mass index (BMI) matched healthy controls, who were admitted to Endocrinology Outpatient Clinics in Sısi Hamidiye Etfal Training and Research Hospital within a six-month period, were enrolled into the study (Table 1). All of the patients were referred to our clinics for hypercalcemia found incidentally and/or normocalcemic hyperparathyroidism found during osteoporosis screening in other clinics. All patients with NC-PHPT had concomitantly elevated serum PTH concentrations (range: 70-128 pg/mL), repeatedly normal ionized Ca (range: 1.14-1.3 mmol/L) and total serum Ca concentrations (range: 9.1-10.14 mg/dL) when corrected for serum albumin using the formula: corrected calcium=(4-serum albumin) × 0.8 + serum Ca. Low 25-hydroxyvitamin D concentrations (25(OH)D3) in this group was corrected with vitamin D replacement to the physiologically normal range (≥30 ng/dL). Vitamin D level was replaced by cholecalciferol 50,000 U/week given orally for 8 weeks period. Patients whose serum PTH concentrations remained high after replacement of 25(OH)D3 to ≥30 ng/dL were included in the study. Serum Ca concentrations were also remained normal before and after the replacement therapy in all patient in NC-PHPT group. Patients with HC-PHPT had elevated serum total Ca concentrations (range: 10.4-12.8 mg/dL) with an inappropriately elevated serum PTH levels (range: 82-428 pg/mL). Control group was constituted from healthy subjects that admitted to our hospital for the evaluation of osteoporosis screening. In the control group, measured serum calcium and PTH concentrations were in the normal range value.

Following secondary causes of hyperparathyroidism were excluded in all patients: 1) Vitamin D3 deficiency (25(OH)D3 < 30 ng/mL) [3]. 2) Hypercalciuria (>400 mg per 24 hour) 3) Decreased creatinine clearance (<60 mL/minute) [3]. 4) Medications (lithium, phenytoin, thiazide and loop diuretics) 5) Gastrointestinal disorders (history of malabsorption syndromes like gluten enteropathy or gastrointestinal surgery, low urinary calcium (<50 mg/day)). Patients with familial

| Table 1 Demographic and biochemical features of the patients with NC-PHPT, HC-PHPT and controls |
| NC-PHPT | HC-PHPT | Control |
| --- | --- | --- |
| **Age (years)** | 52.88 ± 11.71 | 56.63 ± 12.70 | 53.63 ± 7.43 | 0.429 |
| **Cr (mg/dL)** | 0.75 ± 0.1 | 0.74 ± 0.13 | 0.80 ± 0.11 | 0.165 |
| **Cr Cl (mL/min)** | 107.47 ± 22.91 | 98.45 ± 26.43 | - | 0.249 |
| **Ca (mg/dL)** | 9.71 ± 0.34 | 11.52 ± 1.30 | 9.58 ± 0.32 | <0.001a |
| **PO4 (mg/dL)** | 3.26 ± 0.47 | 2.71 ± 0.54 | 3.66 ± 0.49 | <0.001b |
| **PTH (pg/mL)** | 91.61 ± 17.31 | 170.28 ± 111.26 | 47.84 ± 9.49 | <0.001b |
| **24hrUCa (mg/24h)** | 212.71 ± 22.91 | 281.70 ± 129.65 | - | 0.052 |
| **ALP (U/L)** | 78.64 ± 22.95 | 112.04 ± 67.68 | 69.23 ± 21.47 | <0.001a |
| **25OHD3 (ng/mL)** | 17.04 ± 11.32 | 13.51 ± 9.01 | - | 0.331 |

| Gender | Female | Male |
| --- | --- | --- |
| **n (%)** | 23 (92%) | 2 (8%) |
| **n (%)** | 20 (83.3%) | 4 (16.7%) |
| **n (%)** | 21 (70%) | 9 (30.9%) |

^a Significantly higher values in HC-PHPT than NC-PHPT and control groups. But NC-PHPT and controls didn’t show significant difference. ^b Significant difference between all groups. ANOVA(Tukey test)/ Kruskal-Wallis.
hypocalciuric hypercalcemia were also excluded by 24 hour urine calcium excretion (24hUCa) and calcium-creatinine clearance formula. Neither the subjects with PHPT nor controls were taking any medication that known to effect on serum calcium.

The study protocol was approved by the local ethical committee and was performed in accordance with the Declaration of Helsinki. All the subjects gave their oral and written informed consent to participate in the study.

Methods
This was a cross-sectional, case control study of consecutive patients seen for PHPT. All participants underwent a comprehensive medical evaluation including clinical history and physical examination. Metabolic syndrome parameters such as waist circumference, abnormal glucose intolerance/DM/antihyperglycemic therapy/insulin resistance, hyperlipidemia/antihyperlipidemic therapy, hypertension/antihypertensive therapy were evaluated. Blood samples were obtained early in the morning after an overnight fast for the measurement of serum Ca, phosphorus (PO₄), alkaline phosphatase (ALP), PTH, albumin, creatinine (Cr), glucose, insulin, HbA1c, triglyceride, total cholesterol (Total-C), low density lipoprotein cholesterol (LDL-C) and high density cholesterol (HDL-C). Insulin resistance was evaluated with homeostasis model assessment (HOMA-IR) using the formula: fasting glucose (mg/dL) × fasting insulin (μIU/mL)/405 [17]. Blood pressure was measured twice using a manual sphygomanometer after 5 minutes resting. Height (cm), weight (kg), waist circumference (cm) were recorded as weight (kg) divided by height squared (m²). Waist circumference is defined as the minimal abdominal circumference located midway between the lower rib margin and the iliac crest. The presence of MS was assessed according to the criteria of International Diabetes Federation (IDF) - 2006 [18]. Metabolic syndrome was diagnosed if 2 or more of the followings were present while the waist circumference was over 80 cm in females and 94 cm in males: blood pressure ≥130/85 mmHg, glucose ≥100 mg/dL or history of type 2 DM, triglyceride ≥150 mg/dL, HDL-C <40 mg/dL in males and <50 mg/dL in females.

Biochemical analysis
Serum total Ca concentration (normal range: 8.6-10.2 mg/dL) and 24 hour urine Ca excretion (normal range:100-321 mg/24 hr) were assessed by ortho-cresolphthalein dye-binding method in Cobas c 701/702 (Roche Diagnostics, Mannheim, Germany) with the intra- and interassay coefficient variant of 0.9-1.2% and 1.2-1.4% for serum Ca; 0.8-1.4% and 1.2-1.3%, for urine Ca, respectively. Intact serum PTH (normal range:15-65 pg/mL) was measured with a electrochemiluminescence immunoassay (ECLIA) in Cobas c 601 (Roche Diagnostics, Mannheim, Germany) with the interassay and intraassay coefficient variant of 1.1-2 and 2.8-3.4%, respectively. Plasma glucose (normal range:74-106 mg/dL) was analysed using hexokinase enzymatic method (Olympus AU 2700), HbA1c (normal range:4-6%) was determined by HPLC method in TOSOH G8 (Tosoh Bioscience, San Francisco, CA, USA). Serum fasting insulin concentrations (normal range:2.6-24.9 μIU/mL) were measured by ECLIA in Cobas 602 (Roche Diagnostics, Mannheim, Germany) with the interassay and intraassay coefficient variant of 0.9-1.5% and 2.4-4.9%. Fasting total serum cholesterol, triglyceride and lipoprotein fractions were determined by calorimetric method in Cobas c 701 (Roche Diagnostics, Mannheim, Germany). LDL-C was calculated with Friedewald’s Formula: (total cholesterol-(HDL-C)-(triglyceride × 0.45)) in mg/dL.

Statistical analysis
Analysis of absolute data and percentage distributions was done by means of descriptive statistics and presented as mean, standart deviations, percentage and frequency. Distribution of the variables was checked with Kolmogorov Simirnov test for normality. Quantitative values were analysed with ANOVA (Tukey test), Kruskal-Wallis and Mann-Whitney U test. Qualitative values were analysed with Chi-square and Fischer’s test. Correlation between parameters were sought by performing Pearson’s linear regression or Spearman’s statistics for nonparametric data. p-value <0.05 was considered as significant. SPSS 21.0 was used for the statistical analysis.

Results
Baseline characteristciscs
Baseline demographic and biochemical data are summarized in Table 1. The groups did not differ with respect to age, gender, and serum creatinine levels. Normocalcemic and hypercalcemic PHPT groups had similar creatinine clearance and urine Ca excretion. As expected, hypercalcemic PHPT patients have significantly high serum calcium, PTH and ALP con-
Yener Ozturk et al. concentrations and low serum phosphorous levels than the other groups. Serum calcium and ALP concentrations were not different in normocalcemic PHPT and control group. But normocalcemic PHPT group had significantly low serum phosphorous concentrations and high PTH levels than control group.

**Table 2: Antropometric and biochemical data of the HC-PHPT, NC-PHPT patients and controls evaluating the metabolic profile**

|                      | NC-PHPT (Mean ± S.D.) | HC-PHPT (Mean ± S.D.) | Control (Mean ± S.D.) | P      |
|----------------------|-----------------------|-----------------------|-----------------------|--------|
| Weight (kg)          | 79.52 ± 13.95         | 77.38 ± 15.74         | 77.23 ± 12.37         | 0.805  |
| BMI (kg/m²)          | 31.52 ± 5.63          | 31.00 ± 6.15          | 29.51 ± 5.35          | 0.394  |
| WC (cm)              | 103.88 ± 11.83        | 106.54 ± 12.05        | 97.00 ± 10.09         | 0.007a |
| SystolicBP (mmHg)    | 127.80 ± 17.92        | 128.33 ± 17.86        | 120.17 ± 23.87        | 0.253  |
| DiastolicBP (mmHg)   | 78.40 ± 11.43         | 79.79 ± 9.83          | 78.50 ± 12.05         | 0.888  |
| Glucose (mg/dL)      | 102.52 ± 17.29        | 96.13 ± 13.75         | 91.90 ± 7.42          | 0.015b |
| Insulin (IU/L)       | 3.01 ± 1.54           | 18.43 ± 18.44         | 11.25 ± 6.61          | 0.258  |
| HOMA-IR              | 3.01 ± 1.54           | 4.65 ± 5.18           | 7.60 ± 1.57           | 0.125  |
| HbA1c (%)            | 5.93 ± 0.66           | 6.20 ± 0.76           | 5.94 ± 0.26           | 0.170  |
| Total-C (mg/dL)      | 203.08 ± 35.35        | 210.29 ± 36.03        | 230.17 ± 38.17        | 0.021c |
| Triglyceride (mg/dL) | 137.04 ± 69.85        | 157.42 ± 75.58        | 136.63 ± 83.60        | 0.553  |
| HDL-C (mg/dL)        | 52.72 ± 10.46         | 51.79 ± 12.42         | 60.97 ± 19.35         | 0.051  |
| HDL-C (mg/dL)        | 121.28 ± 34.04        | 126.79 ± 32.54        | 140.30 ± 31.94        | 0.091  |

BMI, Body mass index; WC, Waist circumference; BP, Blood pressure. ANOVA (Tukey test)/ Kruskal-wallis.

**Table 3: Comparisons of the prevalence of metabolic diseases of HC-PHPT, NC-PHPT and controls**

|                      | NC-PHPT (n) (%) | HC-PHPT (n) (%) | Control (n) (%) | p      |
|----------------------|----------------|----------------|----------------|--------|
| DM/IGT               | 7/25 28%       | 3/24 12.5%     | 0/30 0%        | 0.008a |
| Anti-HG Tx           | 6/25 24%       | 3/24 12.5%     | 0/30 0%        | 0.020a |
| HT                   | 12/25 48%      | 15/24 62.5%    | 6/30 20%       | 0.005b |
| Anti-HT Tx           | 11/25 44%      | 14/24 58.3%    | 4/30 13.3%     | 0.002b |
| HL                   | 9/25 36%       | 8/24 33.3%     | 19/30 63.3%    | 0.045b |
| Anti-HL Tx           | 6/25 24%       | 3/24 12.5%     | 1/30 3.3%      | 0.072  |
| MS                   | 13/25 52%      | 16/24 66.7%    | 9/30 30%       | 0.025d |

DM/IGT, Diabetes mellitus/ Impaired glucose tolerance; Anti-HG Tx, Antihyperglycemic therapy; HT, hypertension; Anti-HT Tx, Antihypertensive therapy; HL, Hyperlipidemia; Anti-HL Tx, Antihyperlipidemic therapy; MS, Metabolic Syndrome. Chi-square test (Fischer test). a Significant difference between NC-PHPT and controls. b Significantly lower values in control group than the other groups. But no significant difference between NC and HC-PHPT groups. c Significantly high in control group than the other groups. d Significantly high in HC-PHPT than controls. No difference between NC-PHPT and the others.

**Table 4: Comparison of carbohydrate intolerance and hypertension in regards to serum Ca and PTH levels**

|                      | DM/IGT (-) (n) | DM/IGT (+) (n) | p      |
|----------------------|----------------|----------------|--------|
| Ca (mg/dL)           | 10.2 ± 1.2     | 10.3 ± 0.7     | 0.189  |
| PTH (pg/mL)          | 97.5 ± 84.5    | 108.3 ± 32.5   | 0.027  |
| HT (-)               | 10.0 ± 0.8     | 10.5 ± 1.5     | 0.188  |
| PTH (pg/mL)          | 78.6 ± 54.2    | 127.2 ± 99.8   | 0.011  |

Mann-Whitney U Test

**Metabolic profile**

Anthropometric and biochemical data of the groups and prevalence of the metabolic diseases are summarized in Table 2 and Table 3, respectively. The groups didn’t differ in regards to weight and BMI. But patients with HC-PHPT had higher waist circumference than controls. The waist circumference of NC-PHPT group was similar with HC-PHPT and higher than control group but didn’t reach to the significant level. Fasting glucose concentrations was significantly higher in NC-PHPT group than the controls but didn’t differ from HC-PHPT. No statistically significant difference was found between groups in regards to fasting serum insulin and HbA1c levels. Preexisting glucose intolerance (DM/IGT) was documented in a significantly greater proportion of NC-PHPT patients than the controls. But HC-PHPT and NC-PHPT group didn’t differ in regards to preexisting glucose intolerance. When subjects were reevaluated for the previous diagnosis of impaired glucose tolerance (IGT/DM), not serum Ca but serum PTH concentration was found to be significantly higher in IGT/DM-positive group (Table 4).
There was no significant difference for systolic and diastolic BP. The prevalence of preexisting diagnosis of HT or history of anti-HT medications were similar between NC-PHPT and HC-PHPT groups but they were both significantly higher than the control group (Table 3). The groups didn’t differ in regards to serum fasting lipid levels except for total cholesterol. Serum total cholesterol was significantly higher in control group. But when the groups were reevaluated for the previous diagnosis of hyperlipidemia and antihyperlipidemic therapy, we found that prevalence of antihyperlipidemic therapy was highest in NC-PHPT group. HC-PHPT group had a high prevalence also; however, these rates didn’t reach to significance level. When subjects were evaluated according to the previous diagnosis of hypertension, not serum Ca but only serum PTH concentration was found to be significantly high in hypertensive subjects (Table 3, Table 4).

When 25(OH)D$_3$ concentrations of patients with NC-PHPT and HC-PHPT were evaluated for the correlation with metabolic variables, no difference was recorded for glucose, fasting insulin, HOMA-IR, WC, BMI, HbA1c and lipid parameters.

The prevalence of metabolic syndrome according to the criteria of IDF-2006 in NC-PHPT, HC-PHPT and control groups were 13/25 (52%), 16/24 (66.7%) and 9/30 (30%), respectively. HC-PHPT group had significantly high frequency than the control group. But the prevalence of MS was not different in NC-PHPT group from HC-PHPT group. Control group had lower rates of MS but not significantly different (Table 3).

### Correlations

Serum Ca and PTH concentrations were positively correlated with serum fasting insulin ($r=0.345$; $p<0.001$, $r=0.463$; $p<0.001$) and HOMA-IR levels ($r=0.331$; $p=0.003$, $r=0.434$; $p<0.001$). Fasting serum glucose, HbA1c and lipid levels except for triglyceride didn’t show any correlations with serum Ca and PTH levels. Serum fasting triglyceride concentration was found to be positively correlated only with serum PTH concentration ($r=0.295$; $p=0.008$). Body mass index was correlated neither with serum Ca nor with PTH concentrations. However, WC was found to be positively correlated with serum PTH concentration ($r=0.338$; $p=0.002$) but not with serum Ca concentration (Table 5).

### Discussion

In this study, we investigated the components of metabolic syndrome and its prevalence in patients with NC-PHPT, HC-PHPT and control subjects. To the best of our knowledge, this is the first study evaluating MS in patients with NC-PHPT. One of the major findings is that the prevalence of metabolic syndrome in NC-PHPT was not different from HC-PHPT group while HC-PHPT group had significantly high rate of metabolic syndrome relative to the control group. We also found that waist circumference of the patients with HC-PHPT was significantly higher than the controls but patients with NC-PHPT had similar data with HC-PHPT group. The prevalence of metabolic abnormalities such as glucose intolerance, HT and hyperlipidemia of NC-PHPT patients were also similar with HC-PHPT group.

Glucose intolerance, as an important component of MS, may contribute to the CV abnormalities in PHPT. It is known that hypercalcemia stimulate higher insulin levels by high intracellular free Ca concentrations in PHPT [19]. Hypercalcemia can cause impairment in insulin stimulated glucose uptake and at the post-binding steps of insulin action [20]. If this alteration persists, it can lead to glucose intolerance. Hagström et al., when studied the association between serum calcium and insulin sensitivity, found that endogenous calcium may be involved early in the development of diabetes by the effects on insulin sensitivity rather than insulin secretion [21]. However, serum PTH concentration was also shown to be an independent determinant of insulin sensitivity in healthy subjects by hyperglycemic clamp test in study of Chiu, et al. [22].

### Table 5 Correlation of serum Ca and PTH levels with metabolic parameters

|            | Glucose | Insulin | HbA1c | HOMA-IR | HDL-C | Triglyceride | WC   | BMI   |
|------------|---------|---------|-------|---------|-------|--------------|------|-------|
| Ca $r$     | 0.014   | 0.341   | 0.173 | 0.327   | -0.152| 0.209        | 0.178| -0.052|
| $p$        | 0.902   | 0.002   | 0.127 | 0.003   | 0.182 | 0.065        | 0.116| 0.651 |
| PTH $r$    | 0.052   | 0.463   | 0.103 | 0.434   | -0.215| 0.295        | 0.338| 0.187 |
| $p$        | 0.652   | <0.001  | 0.567 | <0.001  | 0.057 | 0.008        | 0.002| 0.098 |

Pearson’s linear regression or Spearman’s statistics. WC, waist circumference; BMI, Body mass index.
ity was assessed by hyperglycemic clamp in 52 normotensive, healthy subjects with glucose tolerance. First phase of insulin response was found to be positively correlated with plasma PTH. The role of PTH in regulating insulin sensitivity is provided by other studies [23, 24] although the reports are inconsistent and performed in patients with relatively late-stage PHPT. In our study, fasting serum glucose and prevalence of preexisting diagnosis of glucose intolerance were similar in NC-PHPT and HC-PHPT groups. Normocalcemic group showed significantly higher values than controls. Serum PTH concentrations were significantly high in patients with known glucose intolerance than the ones that had normal glucose tolerance. But serum Ca concentrations were similar. According to these results, not only serum Ca but also serum PTH concentrations are thought to play an important role in developing glucose intolerance in PHPT.

The relationship between insulin sensitivity and hyperparathyroidism was investigated in several studies. Tassone et al., investigated the frequency of insulin resistance and glucose intolerance in 122 patients with PHPT. Oral glucose tolerance test (OGTT) -derived data were used for insulin sensitivity and compared with the results of 61 healthy subjects. The authors found reduced basal and stimulated indices of insulin sensitivity in patients with PHPT and showed for the first time that serum Ca significantly and independently contributed to impaired insulin sensitivity [25]. In the report by Kumar et al., decreased insulin sensitivity and glucose intolerance were found in 19 patients with PHPT compared to controls. No significant correlation was demonstrated between insulin sensitivity, PTH and ionized Ca [26]. In a different study, Rudman et al., reported that there was no significant change in insulin resistance after surgery in mild hypercalcaemic PHPT patients [27]. But limited data are available in NC-PHPT for insulin sensitivity. A case-control study reported by Cakir et al. investigated insulin resistance in NC-PHPT patients [16]. In this study, 18 patients with NC-PHPT and 18 matched controls had comparisons of glucose metabolism as assessed by OGTT. In both groups, the rate of impaired glucose tolerance was similar. The authors concluded as insulin resistance and glucose intolerance were not present in NC-PHPT. They mentioned that hypercalcemia rather than PTH levels was important on insulin resistance. Ayturk et al., investigated insulin sensitivity in asymptomatic PHPT patients, in whom 20 were normocalcemic. When compared with healthy controls, no differences were found in the prevalence of preexisting DM, undiagnosed IGT and newly diagnosed DM [14]. In our study, no significant difference was found between groups for insulin resistance in terms of fasting serum insulin and HOMA-IR index. However, both serum Ca and PTH levels were positively correlated with fasting serum insulin concentrations. Serum PTH was also positively correlated with serum fasting triglyceride and BMI which are important factors in developing metabolic syndrome. Also, when the similar prevalence of preexisting glucose intolerance found in HC and NC-PHPT was taken into consideration, serum PTH concentration was thought to play a critical role in developing metabolic disturbances in PHPT.

Normocalcemic PHPT patients were determined to have similar rates of traditional CV risk factors when compared with the control group in the study by Tordjman et al. The authors observed a lower rate of CV morbidity in patients with NC-PHPT when compared with hypercalcemic patients [15]. In our study, we found similar rates of preexisting diagnosis of HT in patients with HC-PHPT and NC-PHPT that was significantly higher than the control group. Interestingly, hyperlipidemia was higher in control group than the others. It can be attributable to the significantly higher usage of antihyperlipidemic therapy in NC and HC patients than the controls. Not excluding the patients taking antihyperlipidemic medications might lead to this complex result. Patients with metabolic abnormalities such as glucose intolerance and HT had significantly higher serum PTH but similar Ca concentrations in our study.

In the literature, there are conflicting data about metabolic abnormalities in NC-PHPT. One of the most important reason is inappropriate and dissimilar characterization of the normocalcemic cohort. Criteria in diagnosing NC-PHPT such as normal ionized Ca and exclusion of secondary causes of hyperparathyroidism like hypercalciuria and 25(OH)D3 were not evaluated exactly in some of these studies. Tordjman et al. reported abnormal glucose tolerance in NC-PHPT group but 25(OH)D3 levels were not available on all patients, ionized Ca was not reported and 20% of patients had hypercalciuria [15]. Another study found increased BMI, glucose levels and proatherogenic lipids, but had no data on vitamin D levels [12]. 25(OH)D3 may contribute to insulin sensitivity by stimulating the expression of insulin receptor and enhancing
insulin responsiveness for glucose transport [28]. In our study we found no difference in terms of 25(OH)D3 concentrations between patients with NC and HC-PHPT. Also, there was no defined association between 25(OH)D3 and metabolic parameters.

A potential limitation of this study is that it is not powered to confirm the similar rates of metabolic disturbances in NC and HC-PHPT due to the small sample size and its cross-sectional design. However, the elevated rates of hypertension, ongoing antihyperlipidemic therapy and impaired glucose metabolism found in all PHPT subjects were significantly high than the control subjects.

In conclusion, the results of this study indicate that individuals with NC-PHPT may also exhibit metabolic disturbances associated with CV risks as HC-PHPT patients. Normocalcemic and hypercalcemic patients were found to have similar metabolic syndrome prevalences. Also, metabolic components of MS were seen at similar rates and higher than controls. Not only Ca but also serum PTH levels was thought to play role in developing glucose intolerance. However, our study provides a preliminary data in a small number of NC-PHPT patients. It has been demonstrated that 22% of NC-PHPT patients became hypercalcemic during 4-year follow-up [3]. So with a progressive course in PHPT from normocalcemic to hypercalcemic stage, the patients may be prone to metabolic risks for CV diseases. Even though data are limited, increased awareness to the metabolic aspects in NC-PHPT patients is proposed and subjects should be followed up regularly for cardiometabolic course also. Large, multicenter trials of long duration are required to confirm the changes in the metabolic variables of patients with NC-PHPT.

Disclosures

None of the authors have any potential conflicts of interest associated with this research.

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