Int J Clin Exp Med 2014;7(12):5445-5452
www.ijcem.com /ISSN:1940-5901/IJCEM0002741

Original Article

Clinical value of calcium load test in differential diagnosis of different types of hyperparathyroidism

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Received September 23, 2014; Accepted November 25, 2014; Epub December 15, 2014; Published December 30, 2014

Abstract: Objective: To investigate the clinical value of calcium load test in the differentiation of various types of hyperparathyroidism (HPT). Methods: A total of 56 healthy subjects (Control) and 68 patients with different types of HPT hyperparathyroidism were recruited into this study. Results: In primary HPT (PHPT) group, the inhibition rate of PTH (PTH-IR) was significantly smaller than those in Control, SHPT1 and CuHPT group (all $P = 0.000$). There was no significant difference in the PTH-IR among Control, mild secondary HPT (SHPT1) and cause-unknown HPT (CuHPT) group. In severe secondary HPT (SHPT2) group, the PTH-IR was significantly smaller than those in Control ($P = 0.005$), SHPT1 ($P = 0.001$) and CuHPT group ($P = 0.002$), but was similar to that in tertiary HPT (THPT) group ($P = 0.644$). ROC curve showed PTH-IR of < 71.26% could differentiate PHPT patients from controls; PTH-IR of < 82.26% could differentiate PHPT patients from SHPT1 patients; PTH-IR of < 82.60% could differentiate SHPT1 patients from SHPT2 patients. Conclusion: Calcium load test could effectively differentiate mild PHPT patients from mild SHPT patients and healthy subjects. In SHPT patients, the autonomous tendency of the parathyroid gland gradually increases with the deterioration of impaired renal function, resulting in similar parathyroid response to calcium between severe SHPT and THPT. The autonomous property of the parathyroid gland may become one of the indications for parathyroidectomy in SHPT patients.

Keywords: Hyperparathyroidism, calcium load test, differentiation

Introduction

Hyperparathyroidism can be classified as primary hyperparathyroidism (PHPT), secondary hyperparathyroidism (SHPT) and tertiary hyperparathyroidism (THPT) [1]. PHPT refers to a clinical syndrome caused by excessive secretion of parathyroid hormone (PTH) which results from intrinsic factors (such as genetic abnormalities [2]) induced adenoma, hyperplasia or adenocarcinoma, The parathyroid gland has functional autonomy, i.e. the secretion of PTH is not inhibited by the serum calcium in a negative feedback. SHPT is the compensatorily increased PTH secretion for the malabsorption of intestinal calcium mainly caused by chronic kidney diseases, chronic intestinal disease, and severe vitamin D deficiency or excessive excretion of calcium by the kidney, In these situations, the parathyroid function is stimulated by calcium deficiency (presenting with normocalcemia or hypocalcemia) and thus theoretically the parathyroid gland has no functional autonomy. THPT is a state that the parathyroid glands have been stimulated by the long-term calcium deficiency usually due to long-standing renal failure, and the stimulated parathyroid gland has been assumed to have quasi-autonomous function, presenting with elevated serum PTH and hypercalcemia [3].

Patients with typical PHPT usually manifest hypercalcemia and elevated serum PTH level, and thus the diagnosis of PHPT is easy in these cases. However, some patients can present with elevated PTH level with normal or intermittently elevated serum calcium level, even hypocalcemia [4], which makes the diagnosis of PHPT difficult. PHPT is now considered as a biphasic disease in which serum PTH level increases without hypercalcemia and clinical manifestations at the first phase, followed by con-

tinuous elevations of both serum calcium and PTH levels and the development of clinical manifestations at the second phase [5, 6]. Thus, the early diagnosis of PHPT is sometimes difficult, and one of the important diagnostic issues is to differentiate PHPT from mild SHPT. Because the PTH level in healthy subjects should be normal, therefore the differentiation between early PHPT patients and healthy subjects should be easy.

Another clinical challenge is to determine whether SHPT has transited into THPT. If so, parathyroidectomy (PTX) can be one of the therapeutic strategies [7].

Calcium load test is to apply certain amount of calcium in a limited time into blood to see the inhibitory effect of calcium to PTH secretion. The calcium load test was employed in the present study to determine the autonomous property of the parathyroid gland, aiming to differentiate mild PHPT from mild SHPT, and to differentiate severe SHPT from THPT. Our findings may provide evidence for the early diagnosis of PHPT and the therapeutic decision for severe SHPT.

Patients and methods

Study participants

A total of 56 healthy subjects and 68 patients with hyperparathyroidism (including PHPT, SHPT and THPT) were recruited consecutively from January 2008 to July 2014. For healthy controls, the inclusion criteria were as follows: 1) males aged 20-60 years old or females aged 20 years old to before menopause; 2) exclusion of following diseases after medical history review, physical examination and laboratory examinations: ① endocrine and metabolic diseases such as osteoporosis, osteomalacia/rickets, diabetes, hyperthyroidism/hypothyroidism, Cushing's syndrome/adrenocortical hypofunction and hypogonadism; ② chronic liver diseases and intestinal diseases; ③ chronic kidney diseases and urolithiasis; ④ autoimmune diseases; ⑤ hematological diseases; ⑥ chronic obstructive pulmonary disease; ⑦ taking any drugs which could influence bone metabolism.

For PHPT patients (n = 23), the inclusion criteria were as follows: 1) no heart diseases, and normal electrocardiogram; 2) serum total calcium was < 13 mg/dl (3.25 mM) and PHPT was suspected. In this group, serum PTH in all patients was consistently higher than the upper limit of normal, 20 patients had consistent or intermittent hypercalcemia and 3 had normocalcemia. The neck ultrasonography showed parathyroid mass in majority of patients while no suspected parathyroid mass in several patients. The parathyroid ECT scanning (MIBI as the tracer) showed one site of hyperparathyroid tissue in 20 patients, and no positive sign in 3 patients whose parathyroid masses were detected by ultrasonography. Pathological examination after parathyroidectomy showed 21 patients had single parathyroid adenoma, 2 patients had parathyroid hyperplasia in one gland (pre-operative serum calcium and PTH were higher than the upper limit of normal and ECT scanning showed one site of positive sign in these 2 patients). The final diagnosis for all the patients was PHPT after parathyroidectomy, among them 1 patient was also diagnosed as multiple endocrine neoplasia type 1 (MEN1) because this patient had a surgery for insulinoma 14 years ago. Calcium load test was done before parathyroidectomy.

All the SHPT patients had normocalcemia or hypocalcemia, elevated PTH level and chronic kidney diseases. According to the serum Cr level, SHPT patients were divided into 2 subgroups: ① SHPT1 group (n = 13): patients had mild increase in serum Cr (137~300 μmol/L); ② SHPT2 group (n = 14): patients had severe increase in serum Cr (> 300 μmol/L), 11 of the 14 patients received hemodialysis, calcium load test was done at the day before hemodialysis. All the SHPT patients were treated with oral calcium and active vitamin D3 in various dosages, but the mentioned therapy was discontinued in the morning on the day of calcium load test.

THPT patients (n = 5): All the patients had a long history of chronic renal failure, presently had hypercalcemia and elevated PTH in the absence of calcium supplement, pathological examination confirmed parathyroid adenoma or parathyroid hyperplasia after parathyroidectomy.

The CuHPT patients (n = 13): All the patients had normal serum Cr and calcium levels, elevated PTH levels. The cause of increase in serum PTH level was still unclear after medical history reviewing, physical examination, detection of liver and kidney functions, ultrasonogra-

Table 1. The clinical biochemical parameters at baseline and after calcium infusion

	Ctr	PHPT	SHPT1	SHPT2	THPT	CuHPT
Age	32.6 ± 9.4[#] (23.0~45.0)	60.3 ± 15.2[*] (29.0~85.0)	54.0 ± 12.7[*] (23.0~76.0)	43.2 ± 12.8[*] (27.0~67.0)	52.2 ± 12.0[*] (42.0~72.0)	50.2 ± 13.2[*] (31~74)
Ca (mM) (Ref: 2.15~2.65)	2.23 ± 0.13 (2.18~2.50)	2.74 ± 0.23[*,#] (2.28~3.25)	2.28 ± 0.12 (2.13~2.55)	2.30 ± 0.16 (2.07~2.60)	2.81 ± 0.17[*,#] (2.65~3.01)	2.18 ± 0.19 (2.16~2.60)
Pi (mM) (Ref: 0.81~1.45)	1.07 ± 0.30 (0.86~1.40)	0.91 ± 0.20[#] (0.63~1.41)	1.25 ± 0.20 (0.99~1.60)	2.11 ± 0.65[*,#] (0.88~3.11)	2.02 ± 0.79 (1.14~2.95)	1.13 ± 0.33 (0.82~1.74)
ALB (g/L) (Ref: 35~55)	42.24 ± 3.09 (36.60~47.80)	43.32 ± 3.88 (36.30~49.80)	40.56 ± 4.95 (35.30~49.70)	38.09 ± 5.72 (29.50~48.20)	33.64 ± 3.75[*,#] (28.90~39.40)	42.29 ± 3.06 (36.90~45.40)
sCr (uM) (Ref: 44~136)	54.47 ± 16.34[#] (37.8~71.14)	68.23 ± 21.13[#] (40.20~111.50)	202.38 ± 48.87[*] (143.40~268.90)	924.14 ± 360.96[*,#] (393.40~1374.60)	937.34 ± 155.23[*,#] (766.70~1165.10)	59.61 ± 17.72[#] (39.4~102.4)
ALP (U/L) (Ref: 30~120)	103.45± 17.43 (80.5~119.5)	178.47 ± 183.07 (58.20~689.00)	94.80 ± 21.11 (61.80~126.00)	346.90 ± 404.08 (60.90~1354.80)	817.08 ± 777.32 (172.60~2054.10)	156.49 ± 140.98 (49.1~441.0)
PTH (pg/ml) (Ref: 10~69)	34.43 ± 17.54[#] (6.22~68.90)	308.17 ± 516.90 (71.70~2500.00)	121.52 ± 42.39[*] (73.90~228.00)	1268.96 ± 1094.01[*,#] (135.00~3638.00)	1831.94 ± 455.98[*,#] (1188.90~2254.70)	147.11 ± 73.90[*] (76.80~319.00)
PTH-IR (%)	86.06 ± 8.11 (64.07~95.50)	50.21 ± 16.45[*,#] (18.08~80.09)	91.24 ± 4.69 (84.43~97.71)	61.29 ± 19.07[*,#] (28.13~90.24)	51.06 ± 4.93[*,#] (46.49~56.44)	88.18 ± 7.83 (68.62~98.11)
⊿Ca (mM)	0.42 ± 0.17 (0.07~0.96)	0.45 ± 0.18 (0.11~0.88)	0.48 ± 0.07 0.37~0.60)	0.49 ± 0.17 (0.25~0.86)	0.42 ± 0.03 (0.39~0.46)	0.52 ± 0.18 (0.18~0.85)
PTH-IR/⊿Ca	2.44 ± 1.37 (0.89~10.11)	1.36 ± 0.74[*] (0.26~2.83)	1.91 ± 0.25 (1.60~2.37)	1.34 ± 0.52[*] (0.44~2.26)	1.23 ± 0.03[*] (1.19~1.28)	1.95 ± 0.96 (1.12~4.84)

Note: Data were expressed as mean ± standard deviation (Min~Max). ALB: albumin; ALP: alkaline phosphatase; PTH: parathyroid hormone; ⊿Ca = maximal Ca level-Ca level at 0 min; PTH-IR: PTH inhibition rate. PTH-IR = (PTH level at 0 min-minimal PTH level)/PTH level at 0 min). [*]$P < 0.05$ vs. control group; [#]$P < 0.05$ vs. SHPT1 group.

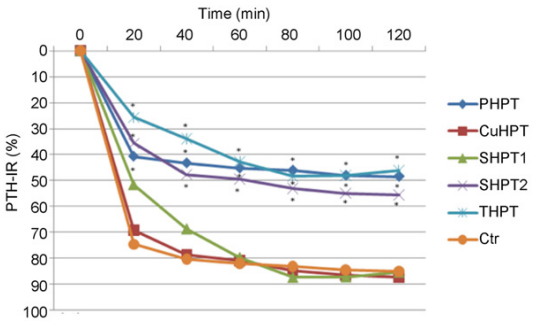

Figure 1. Mean PTH-IR at different time points of calcium infusion (*P < 0.05 vs. control group).

phy of the parathyroid gland, the CT and ECT scanning of the neck and chest.

All the subjects had informed consent for this study, and the study was approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University.

Calcium load test

In a fasting state, calcium (calcium gluconate in 5% glucose solution) was infused intravenously at 3 mg/kg.h within 2 h after 10 am. Blood was collected at 0, 20, 40, 60, 80, 100 and 120 min after the start of calcium infusion and processed for the measurement of serum calcium and PTH levels. The same patient's samples were measured in the same batch.

Biochemical analysis

Albumin (ALB), total Ca, Pi, alkaline phosphatase (ALP), in serum were measured with an automatic biochemical analyzer (Olympus, AU5400). Full length PTH was detected by electrochemiluminescence (ECL), the assay kit was from Roche. The serum total Ca concentration was recorded after it was normalized by the serum ALB level, the normalization formula was as the following: [40-ALB (g/L)] × 0.02 + actual total Ca (mmol/L).

Statistical analysis

All statistics were analyzed using SPSS version 19.0. Data were expressed as mean ± SD. Between-group differences were analyzed by ANOVA with LSD correction for continuous variables satisfying homogeneity of variance and Dunnett's T3 correction for continuous variables not satisfying homogeneity of variance. Bivariate correlations were estimated using Spearman's correlation test. $P < 0.05$ was considered statistically significant. The areas under the receiver operating characteristic (ROC) curves (AUC) were used to estimate the power of calcium load test in order to distinguish different types of hyperparathyroidism. The normal range of AUC was 0.5-1.0. AUC 0.5 means no diagnostic value, AUC 0.5-0.7 means low value, AUC 0.7-0.9 means moderate value and AUC above 0.9 means high value. The optimal cut-off point was calculated as the maximum value of (sensitivity + specificity-1) [8], i.e., it is at the crossing point of sensitivity curve and specificity curve.

Results

Baseline and biochemical characteristics

The biochemical parameters at baseline and after calcium infusion are shown in **Table 1**. The overall ⊿Ca (maximal Ca level-Ca level at 0 min) was similar among groups ($P = 0.303$). The age, serum calcium, serum phosphorus, ALB, sCr, ALP, PTH, PTH inhibition rate [PTH-IR = (PTH level at 0 min-minimal PTH level)/PTH level at 0 min]] and PTH-IR/⊿Ca were significantly different among groups ($P < 0.05$).

Calcium load test

As shown in **Table 1**, PTH-IR in PHPT was significantly smaller than those in control group, SHPT1 group and CuHPT group ($P = 0.000$); PTH-IR in SHPT1 was markedly larger than those in SHPT2 group ($P = 0.001$) and THPT group ($P = 0.000$). The PTH-IR at different time points after calcium infusion was shown in **Figure 1**. PTH level reached the minimal level at 80-120 min after the initiation of calcium infusion. There were no significant differences in PTH-IR among Control, CuHPT and SHPT1 group ($P > 0.05$, between groups) and among PHPT, SHPT2 and THPT group ($P > 0.05$, between groups).

PTH-IR/⊿Ca reflects the sensitivity of parathyroid cells to the change in serum calcium, suggesting the autonomous property of the parathyroid gland. Significant difference was observed in the PTH-IR/⊿Ca among these 6 groups ($P = 0.000$). In addition, PTH-IR/⊿Ca in control group was significantly higher than that in PHPT ($P = 0.000$), SHPT2 ($P = 0.001$) and THPT ($P = 0.015$), and was similar with those in SHPT1 and CuHPT group ($P > 0.05$).

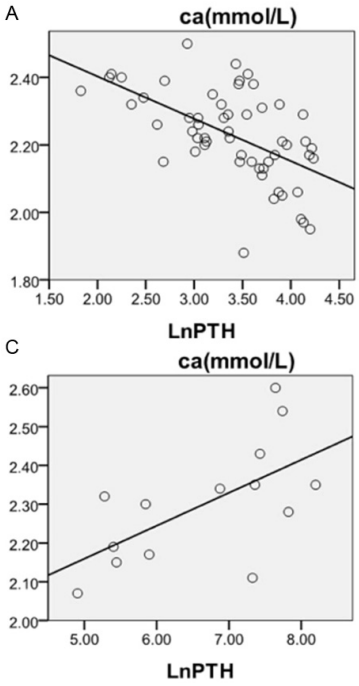

Figure 2. The correlation of serum Ca level and PTH level in Control group (A, r = -0.584, *P* = 0.000), in PHPT group (B, r = 0.531, *P* = 0.009) and in SHPT2 group (C, r = 0.634, *P* = 0.015) (Horizontal ordinate: Natural logarithm of PTH; longitudinal coordinate: serum calcium concentration).

Table 2. ROC curve analysis of PTH-IR

	Cut-off point	AUC	Sensitivity	Specificity	*P*
PHPT vs. Ctr	71.26%	0.974	89.3%	95.7%	0.000
PHPT vs. SHPT1	82.26%	1.000	100.0%	100.0%	0.000
SHPT1 vs. SHPT2	82.60%	0.973	100.0%	92.9%	0.000
SHPT1 vs. THPT	70.44%	1.000	100.0%	100.0%	0.001

Ca-PTH correlation analysis

As shown in **Figure 2**, baseline serum calcium and PTH concentration were in a negative linear relationship in control group (r = -0.584, *P* = 0.000). A positive correlation between the two parameters was noted in PHPT group (r = 0.531, *P* = 0.009) and SHPT2 group (r = 0.634, *P* = 0.015).

ROC curve analysis

According to ROC curve, PTH-IR of < 71.26% could effectively differentiate PHPT patients from controls; PTH-IR of < 82.26% could effectively differentiate PHPT patients from SHPT1 patients; PTH-IR of < 70.44% could effectively differentiate THPT patients from SHPT1 patients; PTH-IR of < 82.60% could effectively differentiate SHPT2 patients from SHPT1 patients. The sensitivity and specificity of the optimal cut-off value are shown in **Table 2**.

Discussion

Our results showed that calcium load test could differentiate hyperparathyroidism of different types, and thus could be used for the classification of hyperparathyroidism. Our findings revealed that the PTH-IR in PHPT group was significantly smaller than that in SHPT1 group (*P* = 0.000), and a reduction of 82.26% in serum PTH from baseline during calcium load test could differentiate mild PHPT from mild SHPT with the sensitivity and specificity of 100%. This high sensitivity and specificity suggested that calcium load test is a reliable tool for the early diagnosis of PHPT and could be used in clinical practice.

Figure 1 showed that the change in PTH-IR was similar among Control group, CuHPT group and SHPT1 group in the calcium load test. PTH was easy to be inhibited by calcium infusion in these groups which were then grouped as Panel 1. The change in PTH-IR was similar among PHPT group, SHPT2 group and THPT group, in these groups, PTH was not inhibited by calcium infusion and thus they were grouped as Panel 2. ROC curve analysis showed that PTH-IR of < 81.85% could effectively differentiate Panel 1 from Panel 2. Medical history reviewing and serum Cr measurement may assist the clinical application of calcium load test in the differentiation among different types of hyperparathyroidism.

Extracellular calcium concentration is a major determinant of PTH secretion. Calcium-sensing receptor (CaSR) is considered to play an important role in the maintenance of stable serum calcium by inhibiting PTH secretion, PTH gene expression and the proliferation of parathyroid cells and up-regulateing the expression of vitamin D receptor [9, 10]. Calcium mediated PTH secretion is normally regulated in healthy subjects, and thus the baseline calcium was negatively associated with PTH level in control group (r = -0.584, *P* = 0.000). However, this regulatory process is impaired in PHPT patients, in whom the parathyroid cells have reduced sensitivity to calcium and the calcium set-point is up-regu-

lated, and thus finally results in autonomous excessive secretion of PTH. It was demonstrated that the reduction in PTH levels after either oral (1000 mg/50 kg) or intravenous (4.4 mg/kg.h) load of calcium were significantly smaller in PHPT compared with healthy subjects and the baseline serum calcium is positively associated with PTH [11]. Similar findings were observed in our study: PTH-IR in PHPT group was 50.21 ± 16.45% and significantly smaller than that in control group (P = 0.000); PTH-IR/⊿Ca in PHPT group was markedly smaller than that in control group (P = 0.000); Baseline serum calcium level was positively associated with PTH level (r = 0.531, P = 0.009).

The PTH-IR in SHPT1 group was similar to that in control group, suggesting the regulatory function of the parathyroid gland is still normal in patients with mild renal dysfunction. However, in patients with moderate to severe renal dysfunction (sCr ≥ 300 μmol/L), the PTH-IR was only 61.29 ± 19.07%, which was similar to that in THPT group (51.06 ± 4.93%; P = 0.644), the baseline calcium was positively associated with PTH (r = 0.634, P = 0.015) and the PTH-IR/⊿Ca was significantly smaller than that in control group (P = 0.001). These findings suggested that although serum calcium was normal in moderate to severe SHPT, the parathyroid gland had already become autonomous. These results reminded us that the autonomous tendency of parathyroid gland increased with the deterioration of impaired renal function in SHPT patients, so as to reach to autonomous state as in PHPT even before THPT occurs.

The evidence for selecting the optimal time point of surgery is still deficient for SHPT patients, Serum PTH concentration is usually a major indication for PTX, Patients with severe SHPT combined with hypercalcemia and/or hyperphosphatemia, or severe drug resistant SHPT (blood iPTH > 800 pg/ml [12] or > 600 pg/ml [13]) are usually considered to receive PTX. Other investigators even proposed that PTX should be done for patients with iPTH > 500 pg/ml [14]. Our results showed that for patients with moderate to severe SHPT, although the serum calcium was normal, the parathyroid gland had already changed to autonomous state, suggesting that the Ca induced inhibition of PTH secretion is compromised. There is evidence showing that long-term excessive secretion of PTH may accompany the progression of diffuse hyperplasia into nodular hyperplasia in the parathyroid gland of patients with moderate to severe SHPT and the expression of CaSR and vitamin D receptor reduces significantly [15-17], leading to the parathyroid resistance to active vitamin D3 and calcium. In the present study, although oral calcium and active vitamin D3 were administered in SHPT2 patients, the serum PTH was still at a high level, suggesting the resistance of parathyroid cells to calcium and vitamin D. Thus, we recommend that besides PTH level, the autonomous state (as indicated by calcium load test) of the parathyroid gland could be an indication for PTX.

In CuHPT patients, the causes of PTH level increase were not identified although medical history reviewing, test of liver and kidney function, ultrasonography of the neck, CT and ECT scan (MIBI as the tracer) to the neck and chest had all been done. They could suffer from mild SHPT or mild PHPT, Because the PTH-IR in CuHPT group was very similar to that in SHPT1 group and control group (P > 0.9), and significantly larger than that in PHPT group and THPT group (P = 0.000), therefore, our estimation is that these CuHPT patients might be mainly ill with occult SHPT which requires to be confirmed by follow up. In addition, the PTH-IR in 3 PHPT patients with normocalcemia is respectively 80.09%, 71.10% and 66.20%, all of which were smaller than the cut-off point (82.26%) for differentiating PHPT from SHPT1. This evidence from the small samples might support our above estimation.

In previous studies, calcium load test was only used to differentiate PHPT patients from healthy subjects on the basis of PTH-IR [11, 18-21]. In our study, all types of hyperparathyroidism patients including PHPT, SHPT and THPT patients were recruited, and ROC curve was employed to determine the optimal cut-off value of PTH-IR for the differentiation of hyperparathyroidism of various types. The AUC was 0.973-1.000, suggesting that the calcium load test is effective for the differentiation. In addition, the calcium load test used in our study was superior to previously used method. Compared with the study of Lips et al [11] in which rapid intravenous infusion of calcium (30 seconds) and short observation time (20 minutes) was used, and the difference of PTH-IR in PHPT and healthy subjects was small (the PTH-IR was 49% in PHPT and 60% in the healthy), our study took slow intravenous calcium infusion, long-time observation (120 minutes) and frequent blood

sampling (every 20 minutes), such protocol is helpful to find the minimal PTH level (it was seen at 80-120 min after the initiation of calcium infusion in our study). Zhao et al [20] performed calcium load test by infusion of calcium at 4 mg/kg.h which was higher than that used in our study (3 mg/kg.h), however the PTH-IR in our healthy subjects was as high as 86.06 ± 8.11%, which was similar to 80 ± 1% in Zhao's report (P = 0.261). Thus, in the condition of keeping similar power, we speculate that low dose calcium is beneficial to reduce the extent of increase in serum calcium during the calcium infusion, which should improve the safety of calcium load test.

There were some limitations in our study: 1) the sample size was small in certain groups, which may bias our conclusion; 2) for patients with elevated PTH of unknown causes, physical examination and laboratory examination failed to diagnose them as PHPT or SHPT, and long-term follow up is required.

In conclusion, calcium load test is effective to differentiate mild PHPT from mild SHPT patients and healthy subjects. In SHPT patients, the autonomous tendency of the parathyroid gland increases with the deterioration of impaired renal function, resulting in similar parathyroid responses to calcium load in moderate-severe SHPT and THPT. The autonomous state of the parathyroid gland might be one of the indications for parathyroidectomy in SHPT patients.

Acknowledgements

This study was supported by the New Clinical Technique Research Fund of the First Affiliated Hosital of Nanjing Medical University and Key Discipline Fund of Affiliated Tongji Hospital of Tongji University.

Disclosure of conflict of interest

None.

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