J Endocrinol Invest (2016) 39:349–354
DOI 10.1007/s40618-015-0412-6

ORIGINAL ARTICLE

Mild primary hyperparathyroidism as defined in the Italian Society of Endocrinology's Consensus Statement: prevalence and clinical features

E. Castellano[1] · F. Tassone[1] · R. Attanasio[2] · L. Gianotti[1] · M. Pellegrino[1] · G. Borretta[1]

Received: 17 September 2015 / Accepted: 16 November 2015 / Published online: 30 November 2015

Abstract
Background Mild primary hyperparathyroidism (PHPT) was recently clearly defined for the first time. Our study was thus aimed to pinpoint proportion and clinical characteristics of this kind of patients.
Design and patients We retrospectively evaluated our series of 360 consecutive patients with PHPT, selecting those with all features allowing a correct classification (serum total and ionized calcium, phosphate, creatinine, PTH, 25OHD, urinary calcium, renal and neck ultrasound, MIBI scintiscan, and DEXA at lumbar spine, femoral neck, and distal third of radius). Patients were defined asymptomatic (aPHPT) when bone or kidney was not involved and no hypercalcemic symptom occurred; mild PHPT was defined as aPHPT not meeting updated surgical criteria.
Results Seventy-five patients among 172 classified as aPHPT had all available data required for surgical evaluation and could be evaluated. Sixty/75 met surgical criteria and the remaining 15 were classified as mild. Mild PHPT patients had lower total and ionized calcium, urinary calcium, and PTH levels than aPHPT meeting surgical criteria, while vitamin D levels and BMD were similar.
Conclusions Mild PHPT strictly defined according to the last consensus represents a small subgroup with a less active form of the disease.

✉ E. Castellano
castellano.elena@libero.it

[1] Division of Endocrinology, Diabetes and Metabolism, Santa Croce and Carle Hospital, Via Michele Coppino 26, 12100 Cuneo, Italy

[2] Endocrinology Service, Galeazzi Institute, IRCCS, Milan, Italy

Keywords Mild primary hyperparathyroidism · Definition · Prevalence · Clinical features

Abbreviations

25OHD	25OH-vitamin D
aPHPT	Asymptomatic PHPT
BMD	Bone mineral density
DEXA	Dual X-ray absorptiometry
IQR	Interquartile range
MEN	Multiple endocrine neoplasm
MIBI	Tc99m sesta-methoxyisobutylisonitrile scan
PHPT	Primary hyperparathyroidism
PTH	Parathyroid hormone
SD	Standard deviation
SIE	Italian Society of Endocrinology
US	Ultrasound

Introduction

Recently, the Italian Society of Endocrinology (SIE)'s consensus statement on clinical management of mild primary hyperparathyroidism (PHPT) has been published [1]. In that statement, mild PHPT was defined as a disease in asymptomatic patients who do not meet surgical criteria set out by the updated International guidelines [2].

Until release of SIE consensus, no strict definition of mild PHPT was available [3], with the terms mild and asymptomatic often used interchangeably thus causing confusion. As a consequence, since the clinical-epidemiological characterization is influenced by the different criteria used for the diagnosis, the prevalence of mild PHPT is poorly known. In 1996, Silvelberg et al. [4] reported the prevalence of 50 % for asymptomatic PHPT patients not meeting surgical criteria, according to current guidelines [5].

Thereafter, guidelines have been repeatedly updated, with more and more patients considered eligible for parathyroid surgery [6].

We thus evaluated, in our consecutive series of 360 patients with PHPT, the prevalence of mild PHPT, as defined in SIE consensus, and investigated the demographic and clinical profile of this subgroup of patients.

Materials and methods

Design

A retrospective survey was performed on medical records of all patients diagnosed with PHPT and attending our Division from January 1998 to December 2013.

Patients diagnosed with familial hypocalciuric hypercalcaemia, MEN, or parathyroid carcinoma were excluded.

Patients

Patients had been referred by general practitioners, primary care clinics, and subspecialty clinics.

Diagnosis of PHPT had been established by the presence of hypercalcemia and concomitant inappropriately raised serum PTH levels on at least two separate occasions (reference range for calcium and PTH levels, 8.4–10.2 mg/dL and 15–65 ng/L, respectively).

Symptomatic PHPT was defined as bone or kidney involvement. As for the former, patients had undergone a routine radiographic evaluation of skull and hands, looking for subtle signs of *Osteitis Fibrosa Cystica*, such as subperiosteal resorption in fingers, salt and pepper appearance at the skull or brown tumors. Also patients with vertebral fractures detected by morphometric DEXA or standard RX and TC were classified as symptomatic.

As for kidney involvement, patients were classified as symptomatic either if they complained symptoms of nephro-uro-lithiasis or if stones (or calcinosis) were disclosed by routinely performed abdominal ultrasound (US).

We thus considered as asymptomatic PHPT (aPHPT) all patients without any bone or kidney involvement, and without hypercalcemic symptoms. We considered as mild PHPT all asymptomatic patients not meeting surgical criteria proposed in the IV international workshop [2].

Among asymptomatic PHPT patients, we selected those with all the followings available: baseline assessment of serum creatinine, 25OH-vitamin D (25OHD), total and ionized calcium, phosphate, and PTH; 24-hurinary calcium; parathyroid and renal US, MIBI scintiscan, and DEXA performed at three sites (lumbar spine, femoral neck, and distal third of radius).

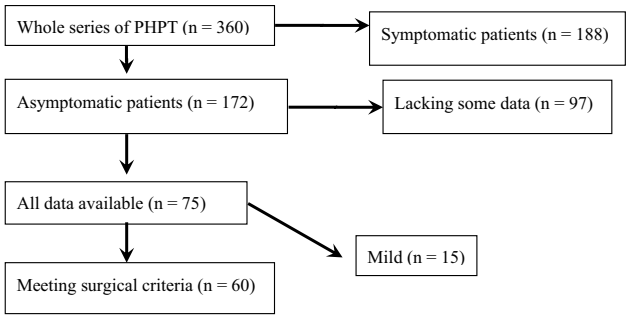

Fig. 1 Distribution of study patients

Figure 1 shows how study patients were distributed among different subgroups.

Methods

Serum total calcium, phosphate, and creatinine levels were assayed by automated analysis using colorimetric and enzymatic methods, while ionized serum calcium was analyzed by a specific probe after correction for pH.

Serum intact PTH concentrations were measured using a two-site immunochemiluminometric assay (Immulite 2000; DPC, Los Angeles, CA, USA) with an inter- and intra-assay coefficient of variation of 6.3–8.8 % and 4.2–5.7 %, respectively.

Serum 25OHD levels were measured by a radioimmunoassay (DIAsource 25OH-Vit.D3-Ria-CT Kit—DIAsource ImmunoAssays S.A., Nivelles, Belgium), with a detection limit of 0.6 ng/mL (1.5 nmol/L) and inter- and intra-assay coefficient of variation of 5.3 and 4.7 %, respectively. Our laboratory performed periodically a quality control of every kit used with the quality control material provided by the manufacturer. Our laboratory is a member of External Quality Assessment scheme for the estimation of 25OH vitamin D conducted by the QualiMedLab-CNR (Pisa, Italy), as a means of determining accuracy of results.

Bone mineral density (BMD) of the lumbar spine (L2–L4), femoral neck, and distal third of the non-dominant radius was measured by DEXA QDR-4500 (Hologic, Bedford, MA, USA). Data are reported as absolute measurements (in grams per square centimeter).

All patients underwent standard reno-vescical US performed by a 2- to 5-MHz-wide band convex transducer. For definitive diagnosis of stones, thus classifying any patient as positive or negative for nephrolithiasis, radiologists looked for hyperechogenic spots more than 2 mm in diameter with multiplanar evaluation of specific signs as echogenicity, posterior acoustic shadowing, or positive twinkle sign.

Table 1 Clinical and biochemical data of the whole series of PHPT patients ($n = 360$)

Age (years)	60.9 ± 13.6
Female	276 (76.7 %)
Symptomatic	188 (52.2 %)
Asymptomatic	172 (47.8 %)
PTH (ng/L)	132 [140]
Total serum calcium (mg/dL)	11.18 ± 1.18
Ionized calcium (mmol/L)	1.46 ± 0.18
Serum phosphate (mg/dL)	2.57 ± 0.65
25OH vitamin D (ng/mL)	24 [23]
Urinary calcium (mg/24 h)	240 ± 167
Creatinine (mg/dL)	0.87 ± 0.8
Distal third radius BMD (g/cm^2)	0.43 ± 0.12
Lumbar spine BMD (g/cm^2)	0.81 ± 0.18
Femoral neck BMD (g/cm^2)	0.71 ± 0.16
Nephrolithiasis	141 (39 %)
Positive pre-surgical localization	272 (75.5 %)

Normally distributed data are expressed as mean ± SD, not normally distributed ones as median and [IQR], categorical ones as absolute number and percentage

PHPT primary hyperparathyroidism, *PTH* parathyroid hormone, *BMD* bone mass density

Statistical analysis

Variables were preliminarily tested for normal distribution with the Shapiro–Wilks' *W* test, and according to results, data are expressed as mean ± SD, or median and interquartile range (IQR) as appropriate.

Mann–Whitney *U* test and *t* test for unpaired samples were used to compare continuous variables with non-normal and normal distribution, respectively.

Differences in categorical variables were sought by χ^2 or Fisher's test, as appropriate.

Level of statistical significance was set at $p < 0.05$.

Calculations were performed using Statistica for Windows, release 5.1 (Statsoft Inc., Tulsa, OK, USA).

Results

Three-hundred and sixty consecutive PHPT patients were evaluated (Fig. 1). Their demographic and clinical characteristics are detailed in Table 1.

Seventy-five of 172 patients classified as aPHPT fulfilled pre-specified inclusion and exclusion criteria and were submitted to analysis. The patients of this subgroup were not statistically different from the remaining 97 aPHPT patients as for age, sex, serum creatinine, PTH, total and ionized calcium, phosphate, 25OHD, and BMD levels at the three sites (Table 2).

Among these 75 patients, 15 were classified with mild disease and 60 met surgical criteria. Table 3 shows the comparison between these two subgroups. Proportion of females and mean age, as well as serum phosphate, creatinine, and 25OHD levels, were not statistically different. On the contrary, serum total and ionized calcium, PTH and 24-h urinary calcium levels were significantly lower in mild than in non-mild aPHPT. Lastly, neither BMD nor the percentage of patients with positive pre-surgical localization were significantly different between the two groups.

Table 2 Asymptomatic PHPT patients ($n = 172$) splited according to the availability of all parameters proposed by last workshop for surgical decision

	All parameters available ($n = 75$)	Others ($n = 97$)	Statistical significance p value
Age (years)	63.2 ± 11.3	64.4 ± 14.1	0.55
Female	60 (80 %)	84 (86.6 %)	0.245
PTH (ng/L)	118 [72]	124.5 [134.5]	0.75
Total serum calcium (mg/dL)	10.8 ± 0.7	11.02 ± 0.84	0.062
Ionized calcium (mmol/L)	1.39 ± 0.12	1.43 ± 0.11	0.37
Serum phosphate (mg/dL)	2.7 ± 0.78	2.55 ± 0.57	0.16
25OH vitamin D (ng/mL)	36 [21.7]	25 [23.5]	0.99
Urinary calcium (mg/24 h)	209 ± 152	260 ± 178	0.1
Creatinine (mg/dL)	0.84 ± 0.19	0.93 ± 0.4	0.076
Distal third radius BMD (g/cm^2)	0.43 ± 0.11	0.43 ± 0.13	1
Lumbar spine BMD (g/cm^2)	0.84 ± 0.15	0.81 ± 0.17	0.299
Femoral neck BMD (g/cm^2)	0.73 ± 0.12	0.70 ± 0.18	0.215
Positive pre-surgical localization	55 (73.3 %)	59 (60.8 %)	0.085

Normally distributed data are expressed as mean ± SD, not normally distributed ones as median and [IQR], categorical ones as absolute number and percentage. Data were analyzed by Student's *T* test for independent sample or χ^2, as appropriate

Table 3 Comparison between mild PHPT patients and the group of asymptomatic PHPT patients meeting surgical criteria

	Mild ($n = 15$)	Asymptomatic meeting surgical criteria ($n = 60$)	Symptomatic ($n = 188$)	Statistical significance p value	
				Mild vs. asymptomatic meeting surgical criteria	Mild vs. symptomatic patients
Age (years)	64.3 ± 9.1	63.1 ± 12.1	58.2 ± 13.7	0.67	0.09
Female	13 (86.7 %)	47 (78.3 %)	132 (70.2 %)	0.47	0.28
PTH (ng/L)	95 [40]	125.5 [99.2]	153 [164]	0.004	0.001
Total serum calcium (mg/dL)	10.48 ± 0.39	10.88 ± 0.73	11.4 ± 1.4	0.043	0.012
Ionized calcium (mmol/L)	1.32 ± 0.07	1.40 ± 0.12	1.48 ± 0.24	0.012	0.011
Serum phosphate (mg/dL)	2.82 ± 1.03	2.65 ± 0.66	2.53 ± 0.64	0.47	0.11
25OH vitamin D (ng/mL)	21 [21]	28 [23]	23 [22]	0.59	0.55
Urinary calcium (mg/24 h)	115 ± 89	232 ± 157	251 ± 169	0.006	0.002
Creatinine (mg/dL)	0.79 ± 0.13	0.84 ± 0.2	0.85 ± 0.3	0.336	0.443
Distal third radius BMD (g/cm^2)	0.45 ± 0.08	0.43 ± 0.12	0.42 ± 0.13	0.611	0.38
Lumbar spine BMD (g/cm^2)	0.82 ± 0.11	0.85 ± 0.16	0.81 ± 0.19	0.685	0.52
Femoral neck BMD (g/cm^2)	0.74 ± 0.12	0.72 ± 0.12	0.71 ± 0.18	0.577	0.84
Positive pre-surgical localization	11 (73.3 %)	44 (73.3 %)	158 (84 %)	1	0.28

Data are analyzed with Student's T test for independent sample or by χ^2, as appropriate

Discussion

In our series, mild PHPT, identified with the criteria recently advocated in SIE consensus [1], represents the less common clinical form of PHPT, namely only one fifth of asymptomatic patients. In addition, patients with mild disease had total and ionized calcium, PTH, and 24-h urinary calcium levels significantly lower than the asymptomatic patients meeting surgical criteria.

The prevalence of mild PHPT is poorly understood, primarily because its definition was never specified in a clear and unambiguous way [3, 7]. The term mild has been indeed variously used in the literature, sometimes to define less severe forms of the disease, exclusively on the basis of the serum calcium criterion [7, 8], other times as a synonym for asymptomatic disease [9, 10].

The term asymptomatic PHPT is used to describe PHPT without any involvement of the classic target organs or hypercalcemic symptoms [11]. These patients may not be truly asymptomatic as they may carry undiagnosed vertebral fractures [12, 13], renal stones [13, 14], and vague neuropsychiatric [15] or neuromuscular symptoms [16].

Actually, the latest international guidelines [2], recommending the routine use of renal imaging and suggesting to look for vertebral fractures by vertebral morphometry, lead to reclassify patients with silent target organs involvement. Consequently, the application of the latest guidelines may influence the clinical classification of PHPT, reducing the proportion of asymptomatic patients [13, 14].

In 2011, Bollerslev et al. [3], in the lack of specific definition, suggested that mild PHPT was a condition characterized by an excess of PTH producing stable hypercalcemia, without any hypercalcemic symptoms or clinical evidence of bone, renal, or stone disease. However, in the guidelines of the IV workshop of 2014 [2], the mild PHPT profile was not specifically defined.

In 2015, SIE released a precise definition of mild PHPT, which applies only to asymptomatic patients not meeting contemporary surgical criteria [1]. The proportion of aPHPT patients not meeting surgical criteria was estimated at 50 % from Silverberg and Bilezikian in 1996 [4], while up-to-date data are still lacking. In particular, no data are available about the prevalence of aPHPT not meeting surgical criteria, screened on the basis of the latest guidelines.

In our series, the rate of mild PHPT was indeed particularly restricted, amounting to 20 % of asymptomatic patients and thus to about 10 % of the whole PHPT group.

It is likely that surgical criteria used by Silverberg [4], less stringent than those retrospectively applied by us [2] in this study, affected the results by expanding the prevalence of asymptomatic patients not meeting surgical criteria [6].

The reduction of mild PHPT rate in our series may have been affected by other factors. First, we investigated routinely nephrolithiasis with renal US in all patients. Patients with silent renal stones were accordingly classified as symptomatic thus reducing below 50 % the proportion of asymptomatic patients, in contrast with data reported in other studies [17]. As reported in a previous paper of our group [14], also a little part of the patients reclassified on the basis of renal imaging would have been classified as mild without considering silent nephrolithiasis.

Moreover, BMD was routinely measured at three sites (lumbar spine, femoral neck, and distal third of radius) in our series, an additional factor likely contributing to reduce the proportion of mild among aPHPT patients. Since cortical bone DEXA data are more representative of the disease's impact on the skeleton [18], the lack of BMD evaluation at the distal third of radius may likely result in underestimation of osteoporosis and thus in overestimation of mild PHPT rate [19].

Finally, our data show, as expected, that mild PHPT is a less active form of the disease. In fact, not only calcium but also PTH levels, a sensitive index of disease activity [20], were significantly lower than in other asymptomatic patients. Furthermore, there was a non-significant trend to higher phosphate levels in mild patients. In this regard, interestingly, there were no differences in vitamin D levels between mild and asymptomatic patients meeting surgical criteria. This finding suggests that mild PHPT is a less severe disease in itself, regardless of vitamin D repletion [21].

Strengths and limits of our study need to be taken into account.

First, a large series of PHPT patients were thoroughly evaluated. Furthermore, this is a monocentric study, where all examinations and measurements were performed in the same laboratory, assuring a good quality of data. Finally, all patients underwent renal US, allowing to identify even silent kidney damage.

The greatest limit is the retrospective nature of the study. In addition, despite the large size of overall series, the sample examined in the study was reduced, according to the extension of criteria to assess the surgical indication recently proposed by guidelines.

Furthermore, morphometric fractures were in most cases looked for only by DEXA, thus leading to their underestimation and by consequence to overestimation of mild PHPT. Since the rate of morphometric fractures in aPHPT was reportedly higher in subjects meeting surgical criteria [12], the putative overestimation of mild PHPT might have been counterbalanced.

On the other hand, we have to take into account the possibility that some mild PHPT patients did not come to medical attention and, if diagnosed, escaped referral to a specialized center.

In conclusion, our data show that mild PHPT, as defined by SIE consensus, correctly identifies patients with a less active form of the disease, representing the less common one in the clinical spectrum of PHPT.

Compliance with ethical standards

Funding This research did not receive any specific Grant from any funding agency in the public, commercial, or not-for profit sector.

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent For this type of study formal consent is not required.

References

1. Marcocci C, Brandi ML, Scillitani A, Corbetta S, Faggiano A, Gianotti L, Migliaccio S, Minisola S (2015) Italian Society of Endocrinology Consensus Statement: definition, evaluation and management of patients with mild primary hyperparathyroidism. J Endocrinol Invest 38:577–593
2. Bilezikian JP, Brandi ML, Eastell R, Silverberg SJ, Udelsman R, Marcocci C, Potts JT Jr (2014) Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. J Clin Endocrinol Metab 99:3561–3569
3. Bollerslev J, Marcocci C, Sosa M, Nordenstrom J, Bouillon R, Mosekilde L (2011) Current evidence for recommendation of surgery, medical treatment and vitamin D repletion in mild primary hyperparathyroidism. Eur J Endocrinol 165:851–864
4. Silverberg SJ, Bilezikian JP (1996) Evaluation and management of primary hyperparathyroidism. J Clin Endocrinol Metab 8:2036–2040
5. (1990) Diagnosis and management of asymptomatic primary hyperparathyroidism. National Institutes of Health Consensus Development Conference. Consens Statement 8:1–18
6. Sklavenitis-Pistofidis R, Papaioannou O, Kotsa K (2015) Primary hyperparathyroidism and the road to surgery: appraisal of the proceedings of the four international workshops (1990, 2002, 2008, 2014) on primary hyperparathyroidism. Hormones (Athens) 14:201–210
7. Iwata S, Walker MD, Di Tullio MR, Hyodo E, Jin Z, Liu R, Sacco RL, Homma S, Silverberg SJ (2012) Aortic valve calcification in mild primary hyperparathyroidism. J Clin Endocrinol Metab 97:132–137

8. Wermers RA, Khosla S, Atkinson EJ, Achenbach SJ, Oberg AL, Grant CS, Melton LJ III (2006) Incidence of primary hyperparathyroidism in Rochester, Minnesota, 1993–2001: an update on the changing epidemiology of the disease. J Bone Min Res 21:171–177
9. Rao DS, Wilson RJ, Kleerekoper M, Parfitt AM (1988) Lack of biochemical progression or continuation of accelerated bone loss in mild asymptomatic primary hyperparathyroidism: evidence for biphasic disease course. J Clin Endocrinol Metab 67:1294–1298
10. Bollerslev J, Jansson S, Mollerup CL, Nordenström J, Lundgren E, Tørring O, Varhaug JE, Baranowski M, Aanderud S, Franco C, Freyschuss B, Isaksen GA, Ueland T, Rosen T (2007) Medical observation, compared with parathyroidectomy, for asymptomatic primary hyperparathyroidism: a prospective, randomized trial. J Clin Endocrinol Metab 92:1687–1692
11. Macfarlane DP, Yu N, Leese GP (2015) Asymptomatic and mild primary hyperparathyroidism. Ann Endocrinol (Paris) 76:120–127
12. Vignali E, Viccica G, Diacinti D, Cetani F, Cianferotti L, Ambrogini E, Banti C, Del Fiacco R, Bilezikian JP, Pinchera A, Marcocci C (2009) Morphometric vertebral fractures in postmenopausal women with primary hyperparathyroidism. J Clin Endocrinol Metab 94:2306–2312
13. Cipriani C, Biamonte F, Costa AG, Zhang C, Biondi P, Diacinti D, Pepe J, Piemonte S, Scillitani A, Minisola S, Bilezikian JP (2015) Prevalence of kidney stones and vertebral fractures in primary hyperparathyroidism using imaging technology. J Clin Endocrinol Metab 100:1309–1315
14. Cassibba S, Pellegrino M, Gianotti L, Baffoni C, Baralis E, Attanasio R, Guarnieri A, Borretta G, Tassone F (2014) Silent renal stones in primary hyperparathyroidism: prevalence and clinical features. Endocr Pract 20:1137–1142
15. Blanchard C, Mathonnet M, Sebag F, Caillard C, Hamy A, Volteau C, Heymann MF, Wyart V, Drui D, Roy M et al (2013) Surgery for 'asymptomatic' mild primary hyperparathyroidism improves some clinical symptoms postoperatively. Eur J Endocrinol 169:665–672
16. Silverberg SJ, Walker MD, Bilezikian JP (2013) Asymptomatic primary hyperparathyroidism. J Clin Densitom 16:14–21
17. Eufrazino C, Veras A, Bandeira F (2013) Epidemiology of primary hyperparathyroidism and its non-classical manifestations in the City of Recife, Brazil. Clin Med Insights Endocrinol Diabetes 6:69–74
18. Saleem TF, Horwith M, Stack BC Jr (2004) Significance of primary hyperparathyroidism in the management of osteoporosis. Otolaryngol Clin North Am 37:751–761
19. Wood K, Dhital S, Chen H, Sippel RS (2012) What is the utility of distal forearm DXA in primary hyperparathyroidism? Oncologist 17:322–325
20. Ziegler R (2001) Hypercalcemic crisis. J Am Soc Nephrol 12(Suppl 17):S3–S9
21. Rathi MS, Gonzalez S, Wright D, Ellis NR, Peacey SR (2014) Management of hypovitaminosis D in patients with primary hyperparathyroidism. J Endocrinol Invest 37:467–471