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Normocalcemic Primary Hyperparathyroidism

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1. Introduction

Normocalcemic primary hyperparathyroidism is a new entity which possibly represents a fruste form of the classic clinically symptomatic disease and which has generated a considerable scientific interest in the last decade. Its official recognition is just as recent as in 2008, when an international conference took place for clarifying its nature and relevance (Bilezikian et al., 2009). Its true prevalence is mostly unknown although it is clear that it is recognized more and more in different clinical settings, from internal medicine outpatient clinics to endocrine or rheumatologists consultations. It is a challenging situation for either the clinician and the patient, as therapeutic recommendations are nowadays nor established and different patients may be advised to receive certain active treatment or just follow-up, or even no follow-up. In this chapter the current data in relation to this emergent condition are presented.

2. Definition and biochemical considerations

Normocalcemic primary hyperparathyroidism (NPHPT) is defined by a situation in which persistently normal serum calcium levels are observed in the presence of high levels of parathyroid hormone (PTH). The term normocalcemic primary hyperparathyroidism was first used in the decade of the 60's by Wills (Wills et al., 1967), who described a group of patients with characteristics different from those with classic primary hyperparathyroidism in which the patients presented a paucity of clinical symptoms and signs and hypercalcemia was absent. No other terms have been used, such as subclinical hyperparathyroidism or low grade primary hyperparathyroidism have been used in the definition of this condition, as it has been the case for similar endocrine disturbances like i.e. subclinical hypothyroidism. The definition of normocalcemic primary HPT' includes total albumin-corrected serum calcium within the normal range and serum parathyroid hormone (PTH) relatively elevated in comparison to the serum calcium level.

Under such a biological combination a search for causes that may reveal a secondary hyperparathyroidism syndrome is the first step that the clinician uses to face, and mostly all situations that could favor vitamin D deficiency, a condition very prevalent all over the world (Silverberg et al., 2009), need to be ruled out. In fact this is a major problem, as in

most cases it is not known if the reference range of a given PTH assay has been made with a population in which vitamin D deficiency exclusion criteria has been considered. PTH is a heterogeneous molecule, and in the last 25 years its measurement has been performed with different assays which have been experimented technological evolution. We have been using different generations of assays and currently we under in the third generation era; the sensitivity of second- and third generation PTH assays in detecting elevated PTH values seems to be similar (Eastell R et al., 2009). By using a second-generation PTH assay it has been recognized how important it is to exclude subjects with low serum 25OHD levels in establishing a reference range for PTH (Souberbielle JC et al., 2001). When this is taken into account, the upper limit of the PTH reference interval for second-generation assays decreased from 65 to 46 ng/liter, a 29% reduction. The same applies for establishing a reference interval for "whole PTH" assays the upper limit decreasing from 44 to 34 ng/L, a 27% reduction; finally, the upper limit of the reference interval remains also lower for third generation assays than for second-generation ones. It has to be mentioned that in parallel, vitamin D references values have been established in the last decades, and moreover, there is still a debate going on in relation to what are the lower normal values (Looker et al., 2008). In some studies, values below 20 ng/mL were taken as the lower limit of vitamin D sufficiency, whereas other studies have reported that PTH levels in normocalcemic individuals continue to decline until levels of 25OHD above 30 ng/ml have been achieved (Chapuy et al., 1992, 2002; Dawson-Hughes et al., 1997). This emphasizes the importance of establishing an international consensus on a reference range for 25OHD, if we are to improve the reference range of PTH by excluding subjects with vitamin D insufficiency. A very interesting approach has been recently proposed by Harvey et al (Harvey A et al., 2011), by using a nomogram in which vitamin D and age are included for refining the diagnosis of primary hyperparathyroidism.

3. Epidemiology

There is virtually no data in relation to the epidemiology of NPHPT. Lundgren and cols. (Lundgren E et al., 2002; Tordjman et al., 2004) studied more than 5,000 postmenopausal women between the ages of 55 and 75 in Swedish survey. They found that 16% of individuals had normal serum calcium levels (< 9.9 mg/dL) and elevated PTH. This group included both those with vitamin D deficiency which was not ruled out and non-deficient cases which could effectively considered as the true cases of normocalcemic PHPT. Taken together both situations, the prevalence seems really surprising and thus will imply that this disorder is the most prevalent endocrine disorder so far. More data are warranted in order to confirm such a potential high prevalence.

4. Clinical presentation

It is not known if NPHPT is an indolent disease or if it may have an impact similar, to certain extent, to the classic primary hyperparathyroidism bone metabolism dysfunction and renal damage as a consequence of sustained circulating increased PTH. It is also not known if increased PTH per se may have pathological consequences as the disorder goes on -if it would be true that progression is universal in all cases- and if therapeutic intervention aimed to normalize PTH may have any benefit at short and long term in these patients. Therefore it is very important to conduct studies in order to clarify all this lack of information.

Usually, NPHPT is discovered in the context of an evaluation of patients with low bone density in specialized metabolic bone units, in whom secondary causes for increased PTH concentration have been carefully ruled out. However, some patients can present with some clinical features of classical hyperparathyroidism, such as fragility fracture and kidney stones. Lowe et al. (Lowe et al., 2007) evaluated thirty-seven patients who met criteria of NPHPT. At the moment of presentation, 14% of the patients had a history of nephrolithiasis and 46 % had a history of fracture in adulthood. Bone mineral density assessment showed that 57% had osteoporosis in at least one site (lumbar-spine, hip or distal radius), 19% had osteoporosis at two of three sites and 8% were osteoporotic at all three sites. Osteoporosis was more common at the lumbar spine (34%) and hip (38%) than in the distal radius (28%), in contrast to the hypercalcemic form of hyperparathyroidism, where preponderance of bone density loss more at the cortical radius site is observed.

There are few studies that evaluated the evolution of this entity at long term. These patients are at some risk of disease progression, further developing features of classical hyperparathyroidism in certain cases. Also, some of these patients will become hypercalcemic over time, and it is observed that those with the higher serum calcium average concentrations and those who were somewhat older were more likely to develop hypercalcemia. On the other hand, some of these patients will suffer from kidney stones, decline in BMD, osteoporosis, and even fractures.

In the cohort of Lowe et al. (Lowe et al., 2007) 41% of the patients showed evidence for progressive hyperparathyroid disease at a median follow up of 3 years: 19% became hypercalcemic, 3% presented kidney stones, 29 % presented progressive cortical bone loss (occurring at all sites) and decline of BMD greater than 10% in 16%; 11% presented new osteoporotic lesions and 3% bone fracture. But on the other side, they also observed that some of the patients with the longest follow up (8 years) did not show evidence of disease progression and may never develop the more typical hypercalcemic phenotype of the disease. Therefore, in some patients there is a progression of the disease and in some other not, and until now there is no way to segregate both cohorts and prediction of progression is not currently feasible.

Overt primary hyperparathyroidism is associated with an increased frequency of dyslipidemia, hypertension, overweight and impaired glucose tolerance. It remains unclear whether NPHPT goes together with such cardiovascular risk factors seen in a much active hyperparathyroid situation when circulating calcium is high. There is very few information in NPHPT and in the only study performed so far (Hagström et al., 2006) some degree of relationship seems to exist although vitamin D deficiency was not assessed in this cohort and it is very well known how important vitamin D sufficiency for cardiovascular protection is (Adams & Hewison., 2010). The relevance of this latter study (Hagström et al., 2006) is that it was performed in general population, while most of the data of NPHPT have been obtained in subjects which have received medical attention mostly because of bone or kidney problems, implying a bias in the interpretation of the non symptomatic nature of this entity.

NPHPT has a pleiotropic phenotypic presentation and nowadays it remains unclear whether it could be the initial phase or and indolent form of classic hyperparathyroidism. Data suggest that it is not the early stage of mild asymptomatic hyperparathyroidism but it could be the earliest form of symptomatic hyperparathyroidism, where the patients have already developed some signs and symptoms of the disease but show normal serum calcium concentration, suggesting that this entity may not be as indolent as previously thought.

5. Treatment of asymptomatic HPT

Currently there are no guidelines for the management of NPHPT. Even asymptomatic HPT (defined as hyperparathyroidism that lacks specific symptoms or signs traditionally associated with hypercalcemia) treatment is a controversial subject. Third Workshop on the Management of Asymptomatic Primary Hyperparathyroidism in 2009 tried to clarify surgical/medical versus follow up management depending on severity of the manifestations of disease and age of the patient (Bilezikian et al, 2009).

From First Workshop on the Management of Asymptomatic Primary Hyperparathyroidism in 1990 to present time surgical indications have been changing to an earlier parathyroid surgery (Table 1).

	1990	2002	2008
Serum Calcium (>upper limit of normal)	1-1.6 mg/dl (0.25-0.4 mmol/l)	1.0 mg/dl (0.25 mmol/l)	1.0 mg/dl (0.25 mmol/l)
24 h urinary for calcium	>400 mg/d (>10 mmol/d)	>400 mg/d (>10 mmol/d)	Not recommended
Creatinine clearance (calculated)	Reduced 30%	Reduced 30%	Reduced to < 60 ml/min
BMD	Z-score < -2.0 in forearm	T score < -2.5 at any site	T score < -2.5 at any site and/or previous fracture fragility
Age (year)	<50	<50	<50

Table 1. Evolution of guidelines recommendations for parathyroid surgery in asymptomatic HPT (Bilezikian et al, 2009)

However, pharmacologic approach to management of asymptomatic HPT (selected estrogen receptor modulators, biphosphonates and calcimimetics) is limited to patients in whom surgical treatment is not possible mostly because of surgical risk but in whom serum calcium levels or BMD should be treated.

Anyway, Third Workshop concluded that although surgery is an attractive and definitive choice it is also recognized that medical management can be appropriate in those who do not meet surgical indications or are unable or unwilling to proceed with parathyroidectomy. For those cases, follow-up is advised by Third Workshop (table 2)

	1990	2002	2008
Serum Calcium	Biannually	Biannually	Annually
24 h urinary calcium	Annually	Not recommended	Not recommended
Creatinine clearance (24 h collections)	Annually	Not recommended	Not recommended
Serum creatinine	Annually	Annually	Annually
Bone density	Annually (forearm)	Annually (3 sites)	Every 1-2 years (3 sites)
Abdominal X ray (ultrasound)	Annually	Not recommended	Not recommended

Table 2. Evolution of management guidelines for patients with asymptomatic primary hyperparathyroidism who do not undergo parathyroidectomy. (Bilezikian et al, 2009)

5.1.1 Surgical treatment of asymptomatic HPT

Current guidelines to surgical management of Asymptomatic HPT include (Table 1) (Udelsman et al, 2009):

1. Serum calcium threshold 1 mg/dl (0.25 mM/liter) above the upper limits of normal range.
2. Peri - Postmenopausal men and women older than 50, with T score of 2.5 or less at the lumbar spine, femoral neck, total hip, or 33% (one third) radius. In premenopausal women and in men younger than 50, the Z-score of 2.5 or less is recommended as the cutpoint.
3. Age less than 50 years old
4. A GFR less than 60ml/min.1.73m² defined a stage 3 level of renal insufficiency according to the K/DOQI guidelines.

As main change with other consensus statement hypercalciuria in the absence of renal stones or nephrolithiasis, is no longer regarded as an indication for parathyroid surgery as its presence without any other factors has not been established as a kidney stone risk factor.

Asymptomatic HPT has been related to neurocognitive compromise, bone density and fracture risk, nephrolithiasis, even with cardiovascular risk and survival. Unfortunately, the scientific evidence in this area is low. Clinical trials are needed to demonstrate the improvements in these parameters after parathyroidectomy.

Surgical experience is the main variable to avoid surgery complications in parathyroidectomy, Therefore number of cases per year is the most important predictor of clinical outcomes. The type of operative procedure and the employment of operative adjuncts is highly institution specific and should be based on the expertise and resource availability of the surgeon and institution.

Localization techniques of enlarged parathyroid gland (sestamibi scan, CT scan, MRI, between others) have a secondary role on parathyroid surgery and it is confined to localization assistance, never for diagnosis purpose.

^{99m}Tc-Sestamibi is probably the most used and sensitive probe to parathyroid localization. Its main characteristic is the capacity of diagnosis of ectopic parathyroid glands and functional information. Neck ultrasound plays a principal role on thyroid nodule and parathyroid gland enlargement evaluation but it is highly dependent on experience and interest of the radiologist performing the study (Soto Gd et al, 2010). Combination of both non invasive techniques as complementary methods are highly recommended because of its safety and sensitive.

In special circumstances other imaging techniques could be of interest (CT scan, MRI, PET scan); even, invasive procedures as parathyroid fine needle aspiration and arteriography and selective venous sampling for PTH. However, all these procedures are expensive, time consuming, and with limited but not negligible risks. Actually, its used is limited to minimally invasive surgery where localization parathyroid gland is essential and in those cases without information in conventional techniques (Udelsman et al, 2009).

5.1.2 Medical treatment of asymptomatic HPT

To the date, pharmacologic approach to management of asymptomatic HPT is limited to patients in whom surgical treatment is not possible because of surgical risk but in whom serum calcium levels or BMD should be treated.

Selective estrogen receptor modulators and bisphosphonates could be of interest in Asymptomatic HPT treatment because of potential BMD increase and fracture risk reduction. Unfortunately, none of this treatment have been evaluated in clinical assays neither in hyperparathyroidism nor HPHPT (Khan et al, 2009). Only alendronate treatment was shown to improve BMD in lumbar spine of patients with primary hyperparathyroidism without changes in calcium levels to a degree comparable both to their effects in eucalcemic populations (Khan et al, 2004) What is more, fracture outcome data are not available until now with any of the treatments evaluated.

Calcimimetics is a new pharmacology class that acts as an allosteric modulator of the calcium sensing receptor (CASR) acting to sensitize this receptor to the extracellular calcium. Cinacalcet has been shown to be effective in reducing or normalizing serum calcium levels in several groups of patients with primary hyperparathyroidism with slightly reduces PTH levels and no effects on bone mineral density (Peacock et al, 2005 & Marcocci et al, 2011). Unfortunately, there are no data as to whether long term treatment with cinacalcet can prevent the complications of PHPT.

At present, medical treatment is limited for those individuals with Asymptomatic HPT who are unable to undergo corrective surgery for whom skeleton protection is the primary reason for intervention (biphosphonates) or control of serum calcium levels are required (cinacalcet). Further investigation is required in this field

6. Conclusion

Normocalcemic primary hyperparathyroidism is a new entity which possibly represents a fruste form of the classic clinically symptomatic disease and which has generated a considerable scientific interest in the last decade. It is a challenging situation for either the clinician and the patient, as therapeutic recommendations are nowadays nor established and different patients may be advised to receive certain active treatment or just follow-up, or even no follow-up. Further investigation is required to select the best treatment for each patient.

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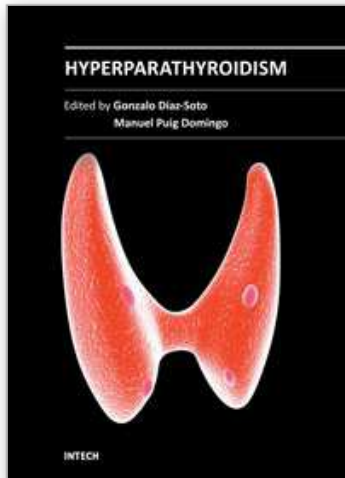
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This book is the result of the collaboration between worldwide authorities of different specialities in hyperparathyroidism. It aims to provide a general but deep view of primary/secondary and tertiary hyperparathyroidism, from a physiological basis to hyperparathyroidism in hemodialyzed patients, as well as new treatment approaches, techniques and surgical scenarios. We hope that the medical and paramedical researchers will find this book helpful and stimulating. We look forward to sharing knowledge of hyperparathyroidism with a wider audience.

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