Is surgery necessary for ‘mild’ or ‘asymptomatic’ hyperparathyroidism?

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Abstract

A large majority of the currently diagnosed patients with hyperparathyroidism (PHPT) are mild or asymptomatic, mainly women after menopause. Following the debate held at the 16th European Congress of Endocrinology in Wrocław (Poland) from May 3–7, 2014, arguments are here presented by a surgeon and a medical practitioner considering these situations rather have to profit from surgery, or simply from survey. For the trained endocrine surgeon, it is evident that parathyroidectomy confirms the diagnosis and undoubtedly reduces the discomfort felt by certain patients, prevents all risks of complications, removes patients and medical teams from the monitoring and represents a real individual financial benefit. On the other hand, the medical practitioner considers that mild or asymptomatic PHPT is commonly stable, and very rare are the subjects at risk of complications, particularly of fractures; prevention of vascular and metabolic disorders, nephrolithiasis and bone rarefaction justify regular physical exercise, a safe alimentation, a sufficient calcium and high water intake, the correction of the frequent deficit in vitamin D; finally has also to be considered the impossibility to refer to specialized (endocrine) surgeons, the enormous cohort of subjects more than 50 years with ‘mild’ or ‘asymptomatic’ PHPT. The surgeon and the medical practitioner agree to consider that in patients with ‘mild’ or ‘asymptomatic’ disease, there is no place for medical treatments, in particular calcimimetics and bisphosphonates. Both agree that further studies are needed to clarify the long-term prognosis of operated and non-operated PHPT in term of fractures, cardiovascular risk and mortality. Individual and collective cost/benefit ratios of surgery or survey are also still imperfectly evaluated.

European Journal of Endocrinology
(2015) 173, D13–D20

Introduction

Hypercalcemia and subsequently primary hyperparathyroidism (PHPT) are found more frequently than expected (1). Therefore, PHPT has been added to the list of commonly diagnosed endocrine diseases. PHPT is a chronic disease displaying various clinical courses. By definition (2), only very few are ‘asymptomatic’ (i.e., free of symptoms, no organ manifestations even after careful screening) (3).

Many more patients are ‘classically symptomatic’ (bones, stones and abdominal groans, renal and/or bone manifestations, associated diseases, such as peptic ulcer, acute/chronic pancreatitis and hypercalcemic crisis) (1). As a consequence of routinely applying calcium analysis to document hypercalcemia, in our days the majority of

patients are ‘minimally (‘mild’) symptomatic,’ reporting complaints associated with the hypercalcemic syndrome – moans, depression, lethargy, apathy, changes in cognition, loss of memory, confusion, insomnia, headaches and myopathy with muscular weakness, polyuria and polydipsia, constipation, weight loss, vomiting, nausea, epigastric discomfort, overall decreased quality of life and/or hypertension and/or osteopenia (2).

The literature fails to yield a clear distinction between ‘mild’ and ‘asymptomatic’ PHPT (4). Therefore, many reports, even the recently published international consensus statements, have discussed ‘asymptomatic’ and ‘mildly’ symptomatic disease as one and the same phenomenon (5, 6, 7) (see section ‘Funding’).

'Mild' or 'asymptomatic' PHPT is defined as primary overactivity of one or more parathyroid glands, as supported by laboratory values, and in which there are no clear 'classical' symptoms related to excessive calcium or parathyroid hormone (PTH) and therefore no formal indications for surgery (5, 6, 7). Here, conditions of familial hypocalciuric hypercalcemia will be excluded.

The conventional criteria of 'mild' or 'asymptomatic' PHPT, used in the debate, are as follows (5, 6, 7):

- 1) Age >50 years, since progression appears to be lower at this age.
- 2) Level of blood calcium less than 1 mg/dl (0.25 mmol/l) above the upper limit of normal range. As a result, there are no clear signs as observed with more pronounced hypercalcemia (excessive weakness, constipation, polyuria–polydipsia syndrome, arterial hypertension).
- 3) Absence of nephrolithiasis.
- 4) No alteration in renal function (creatinine clearance >60 ml/min, as estimated by the Cockcroft-Gault or MDRD formulas).
- 5) No evidence of detrimental effect on bones (fragility fractures) or on bone mineral density parameters (*T*-score greater than −2.5 at the radius, lumbar spine or femoral neck).
- 6) Subject is potentially available for monitoring.

Is surgery necessary in principle? Or should it be forgone in favor of the survey or possible benefits of currently available medications?

This question was the subject of a debate at the European Congress of Endocrinology, held in Wrocław, Poland from May 3–7, 2014, with its content presented here.

Section 1: Discussion in favour of surgery for 'mild' or 'asymptomatic' primary PHPT

Bruno Niederle (Vienna – Austria) ► Observational studies of untreated 'mildly symptomatic' and 'asymptomatic' patients have documented a progression of disease in up to 37% of the cases. However, multivariate analysis has not identified a single or a set of biochemical parameters that would allow predicting the clinical course of these subjects (3). Careful analysis of patients has revealed that postoperative metabolic complications occur in those with a long history of PHPT. The death rate related directly or indirectly to PHPT ranges from 1% to 12%. Death in patients is mainly caused by cardiovascular disease (up to 68%) and acute or chronic renal failure (up to 8%) (4). The findings are consistent with the

hypothesis that untreated PHPT would bear an increased risk of death, particularly from cardiovascular diseases, but that this risk is gradually reduced after surgery (8). Acute complications with death are rare but may occur in the course of 'mild' PHPT (9). Altogether, the reports raise the question whether or not surgery had been too late in these patients.

For the first time, Yu *et al.* (10) demonstrated an increased risk of relative mortalities and morbidities among patients with untreated 'mild' PHPT, in a large unselected population.

In a prospective and randomized study evaluating the skeletal effects of early and delayed surgical treatment in patients with 'mild' PHPT comparing biochemical bone parameters and bone mineral density of hip and lumbar spine of both groups, the authors conclude indirectly that a prolonged exposure to 'mild' and seemingly stable PHPT may be a risk factor for hip fractures. The findings add to other reasons for surgical treatment of 'mild' PHPT without delay regardless of serum calcium levels (11). Benefits of surgery on bone mineral density, quality of life and psychological function have been demonstrated (12, 13).

In patients with mild asymptomatic PHPT, successful parathyroidectomy is followed by an improvement in bone mineral density and quality of life (13). In a prospective, randomized, controlled trial of parathyroidectomy vs observation in patients with asymptomatic PHPT, it has been suggested that decreased serum PTH levels may correlate with improved sleep and that parathyroidectomy may decrease sleepiness in patients with asymptomatic PHPT (14). In another randomized control trial, parathyroidectomy has been shown to improve functional capacity in asymptomatic older patients with PHPT (10).

Because of the unpredictable clinical and biochemical course of the disease, patients with PHPT initially diagnosed as 'mild' require close medical and biochemical observations in 6- to 12-month intervals (7, 15). The concept of 'watchful waiting' in 'mild' PHPT implies a high level of patient compliance, in addition to a high willingness to spend a large amount of money on a chronic disease that is curable by one surgical procedure in up to 98%, as regular biochemical and radiological follow-up examinations are mandatory not to oversee organ manifestations (7). Parathyroidectomy is more cost-effective than observation in managing asymptomatic 'mild' PHPT patients. Furthermore, in a cost-benefit calculation, pharmacologic therapies were not observed to be cost-effective (16).

The only curative treatment of PHPT is the surgical removal of the hyperfunctioning parathyroid tissue, applying a minimally invasive targeted approach in cases of single-gland disease whenever feasible (7).

A targeted approach is more cost-effective compared to traditional surgical bilateral exploration (17).

As summarized recently, all patients with PHPT who meet surgical criteria should be referred to an experienced endocrine surgeon to discuss the risks, benefits and potential complications of surgery (18). A randomized controlled clinical trial of surgery vs no surgery in patients with 'mild' asymptomatic PHPT demonstrated the benefit of surgery on bone mineral density, quality of life and psychological functions (12).

SF-36 Health Survey patients with 'classic' and 'mild' PHPT significantly improved in 9/10 and 10/10 scales, 1 year after surgery (19). Those with 'mild' disease had a statistically larger improvement than those with 'classic' disease in four scales. Therefore, the authors concluded that quality of life significantly improved in surgically treated patients with both 'mild' and 'classic' PHPT, supporting surgical treatment of 'mild' PHPT. Moreover, quality of life may improve more in patients with 'mild' rather than 'classic' disease (19).

Overall, patients benefit from surgery due to high single-procedure cure rates and overall low complication rates (20).

Section 2: Discussion against surgery for 'mild' or asymptomatic PHPT

Jean-Louis Wémeau (Lille – France) ► Seven reasons will be given to support our view for not considering the use of surgery for mild or asymptomatic PHPT.

1) It must now be accepted that the general description of primary PHPT has completely changed.

Historically, we owe a great debt of gratitude to Friedrich Daniel von Recklinghausen for the descriptions of pathological lesions of *osteitis fibrosa cystica* (1891), to Felix Mandl, already a famous surgeon from Vienna, who was the first in 1926 to surgically cure a patient of parathyroid adenoma.

However, the lessons of Fuller Albright (1948) need to be put on hold (21). He had been particularly impressed by the observation in the USA of Captain Charles Martell. At the end of WWI, the latter was of large build Master Mariner in the Merchant Marines. Over the years he complained of bone pain, recurrent renal lithiasis and had fractures and a very significant decrease in height.

After several failed cervicotomies, he was finally cured by the removal of a mediastinal adenoma. However, the surgical treatment of PHPT did not prevent progression of the disease, leading to his death from kidney failure in 1932. As a result, Albright taught generations of endocrinologists that PHPT is a rare disorder that should be considered in the event of bone involvement or recurrent renal lithiasis and requires early surgery in order to avoid the development of irreversible and fatal renal impairment.

2) PHPT is now a very frequently recognized disorder.

It is in fact the third most common endocrinopathy (following diabetes mellitus and thyroid diseases). Its prevalence is commonly estimated at 1 in 1000 (22). However, the most recent estimations in Europe, from Scandinavia (23, 24, 25) and Scotland (26), suggest that the prevalence is instead 1% in the general population, and 3–4% in post-menopausal women.

In Rochester, Minnesota (USA), the incidence of PHPT increased considerably between 1970 and 1975, along with the widespread use of blood calcium assays. The incidence of the disease seemed to decline thereafter (27). All the current prospective studies, however, clearly show that PHPT is increasingly frequent both in the USA and Europe. The prevalence after adjustment for age tripled in Los Angeles between 1995 and 2010 (28). In Denmark, amongst women over the age of 50 years, the incidence increased fivefold between 1977 and 2000 (25). In this respect, mild or asymptomatic PHPT must be considered an extremely common condition.

If it is accepted that the population of Europe has just over 500 million inhabitants, that the European population aged >50 years is nearly 25%, then the proportion of subjects with PHPT beyond their 50s would be close to 3%. As the overall proportion of mild or asymptomatic cases of PHPT is estimated at 80%, then Europe should have about three million subjects over the age of 50 with mild or asymptomatic PHPT.

That said, how many specialized surgeons in Europe are available for the surgical treatment of these three million subjects with mild or asymptomatic PHPT? Indeed, it is commonly agreed that, notwithstanding the progress made in imaging, only very specialized surgeons are capable of managing patients with PHPT.

3) Mild and asymptomatic primary PHPT is a disorder that is usually stable or sometimes very slightly progressive.

PHPT hardly seems progressive in subjects beyond the age of 50 years with regard to their clinical condition,

levels of blood and urine calcium and bone mineral density parameters.

This was shown in New York in a population of 121 non-operated patients who had been followed for 10 years (29). More recently, similar results were observed in populations with mild or asymptomatic PHPT, from the Prospective Colombia University Natural Study. In 49 non-operated subjects, the calcium concentrations remained stable for 13 years, with a secondary mild but significant increase in blood calcium (from 2.62 to 2.78 mmol/l) (30). In the Parathyroid Epidemiology and Audit Research Study (PEARS) in Tayside (Scotland, UK), 904 subjects with mild PHPT were followed for 10 years. The degree of hypercalcemia remained stable in 87 subjects, and an only temporary increase was seen in about 85% of the subjects. Ultimately, only 1% of the original cohort had a steady increase in the levels of blood calcium lasting over 6 months (31).

4) *The benefits of surgery on bone mineral density in subjects with mild or asymptomatic primary PHPT have been proven. However, there is much less evidence that surgery is beneficial to fracture risk.*

After parathyroidectomy, all surveys indeed show a rapid increase of close to 10% in the bone mineral density parameters at two sites (lumbar spine, femoral neck) after 6 months or 1 year, but not beyond that (32, 33). However, in observing changes in the bone mineral density parameters of patients who were not operated during these studies, it can be seen that they had no worsening of bone mineral density at any of the sites studied. The study of Rubin (30) has shown stability for up to 8–9 years but deterioration at the hip and distal 1/3 radius afterwards.

Additionally, in the PEARS Study there was not a significant reduction in the number of fractures in 200 patients with mild PHPT treated with parathyroidectomy (34).

In the Italian study of post-menopausal women, the fracture risk was increased in patients with PHPT, but there was no statistically significant difference between the symptomatic and asymptomatic patients who did not have the criteria required for surgery (35). Therefore, as emphasized by Macfarlane in the recent article in *The Lancet*, no prospective or randomized controlled trials have demonstrated benefits on the risk of fracture (36).

5) *It is unclear whether parathyroidectomy improves neuropsychological symptoms and cardiovascular outcomes and reduces mortality.*

With regard to quality of life, mental and physical wellbeing in one study did not differ between patients with mild or asymptomatic PHPT and the control subjects at baseline (12). After parathyroidectomy however, there was a subtle but significant increase in the SF-36 and SCL-90R scale parameters in two studies from USA and Italy (12, 13).

In contrast, in the large, controlled and randomized study of 191 patients in Scandinavia, there were differences at baseline in the SF-36 quality of life questionnaire, as well as in the symptoms assessing the psychological state (on the Comprehensive Psychopathological Rating Scale). In this survey however, the symptoms had not changed 2 years after the parathyroidectomy (37).

With regard to symptoms, it is possible that patients with PHPT report more fatigue, pain, polydipsia and digestive disorders (constipation, dyspepsia). In the study by Eigelberger (38), these symptoms were more frequent before the operation for mild PHPT than in subjects requiring thyroidectomy. The benefits of surgery in terms of these signs were greater after parathyroidectomy than in subjects who had thyroidectomy. It should be mentioned that there is no data on the long-term assessment of these symptoms on the quality of metabolic and hormonal control after surgery. The study of Bollerslev *et al.* (39) reports data on metabolic parameters up to 2 years.

In contrast, in the study by Kahal (40), before the intervention for mild PHPT or thyroid disease, there were differences in the assessment for depression but no difference for anxiety or on the Mood Rate Scale. These parameters remained unchanged afterwards in subjects with thyroid disease after hemithyroidectomy.

With regard to mortality, in a 20-year observational study in Denmark of over 3200 patients, survival was shown to be greater in the population of patients with PHPT treated surgically compared with the population that had only been monitored (41). In both groups, the observed survival was lower than that of the general population, especially as a result of excessive deaths from cardiovascular causes. It should be emphasized that the difference in survival of these operated and non-operated populations diminished over time. Moreover, the study was non-prospective and non-randomized, and the patients who had surgery were younger.

Increased mortality in patients with PHPT was also mentioned in Sweden, with a relative risk of 1.7 (42), and in Scotland with a relative risk of 1.6 (31, 36).

In contrast, the risk of death from cardiovascular causes was surprisingly lower in the survey conducted in Rochester (27), with a relative risk of 0.69.

A variety of factors contribute to the increase in cardiovascular risk: hypertension (41, 42, 43, 44, 45), dyslipidemia (46, 47), endothelial dysfunction (48), insulin resistance (31, 49, 50), left ventricular hypertrophy (51, 52), increased thickness of the carotid intima and increased arterial resistance (53). There is no evidence of a direct individual role in mortality in patients with PHPT. In various studies though not in all, observations have been made after surgery of decreases in arterial hypertension, in the non-dipping pattern of blood pressure, the metabolic syndrome, and cardiac and left ventricular hypertrophy (45, 51).

It should be noted that authors ordinarily correlate these factors with the PTH level but not with the blood calcium level. This is clearly obvious for systolic arterial pressure (45), left ventricular hypertrophy (51) and arterial resistance (53).

It must be pointed out, however, that in PHPT, there is an inverse correlation found in all the studies between the level of 25-hydroxycholecalciferol and PTH. Also in the general population, vitamin D deficiency contributes to increased plasma levels of PTH, but it is also correlated with insulin resistance, the metabolic syndrome, atherosclerosis, arterial hypertension and left ventricular hypertrophy (54). FGF 23, a phosphatonin that is increased with PHPT, could also contribute to increased cardiovascular risk (55).

As a result, the very common condition of vitamin D deficiency in patients with PHPT is a possible confounding factor, which contributes to the increased PTH and increased cardiovascular risk.

Similarly, it should be emphasized that replacement doses of vitamin D in non-operated patients with mild PHPT after 6 months also improved the bone mineral density parameters. In the study conducted in Lille (France), the effects of correcting a vitamin D deficiency after 6 months of treatment in subjects with deficient bone mineral density parameters appeared to be identical to that of parathyroidectomy in subjects without deficiencies (56). The safety and validity of correcting vitamin D deficiency in PHPT have been well established in various surveys, particularly in the meta-analysis by Shah (57).

6) We have also considered the cost of surgery for all the subjects with primary PHPT.

The cost-effectiveness ratio in euros compared to the quality-adjusted life years increased with the age of the subjects. In France, it was shown that the cost of surgery and of monitoring are nearly equal, but the cost-effectiveness ratio tends to favor surgery for patients

between the ages of 40 and 80 years (17). In the USA, the cost of surgery is also somewhat high, but the surgery was slightly more effective. Finally, the estimation seemed primarily dependent on the definition of the quality of life (16, 58, 59).

Clearly, in all the surveys, the most costly approach is the prescription of medication.

7) It needs to be emphasized that medical treatment has no role for patients with mild or asymptomatic PHPT.

Estrogen, which can only be used in certain post-menopausal women, increases the bone mineral density parameters at the femoral neck and lumbar spine but has no effect on blood calcium and PTH levels (60). Raloxifene, an oral selective estrogen receptor modulator (SERM), has not been well evaluated (61). Bisphosphonates, such as alendronate, temporarily increase the levels of PTH in the first month; they have no effect on the level of blood calcium, and they progressively reduce bone turnover markers. They also slightly increase the bone mineral density parameters at the lumbar spine and hip but not at the distal radius. Their possible long-term disadvantages must not be overlooked (62, 63, 64).

Finally, the calcimimetic cinacalcet, an allosteric stimulator of the calcium receptor, is capable of chronically and significantly reducing the blood calcium and PTH levels. But even in the long-term, it has no effect on bone mineralization (65).

Some anti-resorption agents and calcimimetics appear long-term expensive, are not necessarily well tolerated and also have some adverse effects.

For all of these reasons, if you think that the patient is symptomatic or requires treatment, please choose surgery.

Finally on my point of view: PHPT is a very common condition. Most cases involve women over the age of 60 years and are mild or asymptomatic, rarely appearing progressive. Surgery would seem expensive for the entire cohort of these countless subjects, without a clear demonstration of its value in the majority of people.

For this reason, in accordance with international consensus, the use of oral calcium, supplementation with sufficient doses of natural vitamin D, high water intake, regular physical exercise and minimal medical supervision seem to be adequate and effective for the majority of subjects with mild or asymptomatic PHPT.

Conclusion

Both authors think that 'mild' or 'asymptomatic' PHPT (used in the same context here and in the reviewed

literature) is a common situation, where the decision over treatment or monitoring does not constitute an emergency. It has to be considered in the context of the prevention of potential complications. It must take into account the local skills, and the general condition and wishes of the concerned patients. A multidisciplinary conference with the clinical endocrinologist, the endocrine surgeon and the affected patient may be of value to address all relevant issues of permanent follow-up and definitive (=surgical) treatment.

The surgeon and the medical practitioner agree that medical therapies, in particular calcimimetics and bisphosphonates, have no place in patients with mild or asymptomatic disease, with the exception of correction of vitamin D deficiency before surgery or for the simply surveyed subjects. Both authors agree that further studies are needed to clarify the long-term prognosis of operated and non-operated PHPT in term of fractures, cardiovascular risk and mortality. Individual and collective cost/benefit ratios of surgery or survey are also still imperfectly evaluated.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Acknowledgement

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

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Received 11 March 2015

Revised version received 15 June 2015

Accepted 22 June 2015