

# Treatment of primary hyperparathyroidism

## *Benefits beyond calcium homeostasis*

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### ABSTRACT

*With the advent of minimally invasive parathyroidectomy, there is renewed interest in selecting patients with primary hyperparathyroidism (PHPT) who would benefit from surgical treatment. Encouraged by recent guidelines, a significant number of physicians continue to recommend long-term follow-up for patients lacking the "classical" symptoms of PHPT. The supportive reasoning is that many such patients with only minimal increases in calcium levels (< 2.8 mmol/l, < 11.2 mg/dl) never progress to more severe biochemical or clinical disease. There are however arguments in favour of early surgical treatment of such patients.*

**Key words:** primary hyperparathyroidism, quality of life, cardiac function

**P**rogressive loss in bone mineral density and raised risk of bone fracture become increasingly significant in an ageing population.

Left ventricular hypertrophy or dysfunction, increased risk of arrhythmia and/or myocardial infarction in addition to changes in atherogenic lipid profile and impaired glucose tolerance translate into a raised risk of premature death. Subtle or profound changes in the quality of life identified using standardised questionnaires are sometimes recognised by patients only in retrospect (i.e. after resolution of symptoms following successful parathyroidectomy). In addition, many surgical series

fail to assess and record accurately the existence of such symptoms in PHPT patients.

Until a considerable breakthrough in the medical treatment of PHPT is made, parathyroid surgery should represent the first choice of treatment for all patients. When feasible, day-case minimally invasive parathyroidectomy provides additional advantages for frail patients unfit for more extensive neck surgery.

In an era dominated by a growing interest in quality of life following surgical interventions, minimally invasive parathyroidectomy for minimally symptomatic patients holds great potential for long-term benefits. □

### INTRODUCTION

**P**rimarily hyperparathyroidism (PHPT) is a condition diagnosed with increasing frequency in the western world. An elevation

of plasma calcium levels in the presence of inappropriate high PTH level is frequently encountered in routine blood tests performed

for unrelated conditions. However, based on the high incidence of PHPT in the general population, it is likely that only a minority of people suffering from this condition are seen in outpatient clinics. Of those diagnosed with PHPT, many are never referred for surgical intervention as they have a minimal increase in calcium levels and are often considered to be asymptomatic. An increasing body of evidence drives a change in this attitude towards early surgical treatment of all patients with PHPT. The benefits for patients would extend far beyond the correction of their biochemical abnormalities and could have a positive impact on a multitude of aspects insufficiently explored so far. □

### THE SCALE OF THE PROBLEM

Following introduction of automated serum calcium measurement in the early 1970s, determination of serum calcium became part of routine biochemical screening. This has led to an apparent incidence of up to 75 per 100,000 population due to identification of patients previously undiagnosed. In the United States the current annual incidence of PHPT is believed to be approximately 20 per 100,000. It is anticipated that these figures could rise again due to increasing screening for osteoporosis (which should include serum calcium determination) in women around the sixth decade of life, when the PHPT is more frequent.

If one extrapolates this estimated incidence of PHPT to the population of more than 20 million population of Romania, there could be some 4000 patients diagnosed every year. Such high figures seem disproportionate since over the last three years there were only 115 cases of PHPT managed in the CI Parhon National Institute of Endocrinology (average 40 cases/year). Nevertheless, there have been 340 patients treated over the last 5 years at the John Radcliffe Hospital, for a population of just over 500,000 (annual incidence increasing from 35 to 98/year during the study period).

Despite its high prevalence, PHPT represents a small part of the clinical workload and health care costs. Although it was estimated that in the United States PHPT is present in more than 1,5% of people age 65 years or older, representing several million people, surgery for PHPT is only performed on approximately 12,000 patients per year (1). It appears therefore that

the majority of patients remain undiagnosed or untreated.

A serious limitation of the efforts to establish the real incidence of PHPT is derived from the recent trend of diagnosing increasing number of patients lacking the classical symptoms of PHPT. In the western world the diagnosis of PHPT is rarely based on symptoms or signs of severe bone disease and/or renal lithiasis and the majority of patients will report only neuropsychic changes (tiredness, lethargy, somnolence, difficulties to concentrate).

Current guidelines from the NIH (National Institute of Health, USA) (2) recognise that most patients with PHPT have only a mild increase in calcium levels, have no symptoms and are unlikely to progress if merely observed. According to these guidelines (Table 1) only about 20% of patients with PHPT meet indications for surgical intervention. Despite these objective criteria for referral for surgical treatment, the management of asymptomatic mild PHPT varies widely. In a survey of endocrinologists in the United States, only 7% of all physicians referred more than 90% of their asymptomatic patients for surgical treatment, whereas 31% referred less than 10% of such patients (3). In contrast, a survey of the American Association of Endocrine Surgeons showed more than 72% of PHPT patients who underwent surgery were asymptomatic or minimally symptomatic and that high volume surgeons (>50 cases/year) had significantly lower thresholds for surgery with respect to preoperative biochemical abnormalities (4).

The debate whether patients with minimal symptoms of PHPT should undergo parathyroidectomy is in strong contrast with the reality in the developing world, where patients still present with severe symptoms and signs due to advanced disease (5). □

Criteria	2002 guidelines
Age	<50 yrs
Serum calcium (above upper limit of normal)	0,25 mmol/L (1 mg/dl)
24-h urinary calcium	> 100 mmol
creatinine clearance	reduced by 30%
bone mineral density	t-score < -2,5 SD (at any site)

TABLE 1. 2002 guidelines for parathyroid surgery in asymptomatic primary hyperparathyroidism (adapted from 2)

## LONG TERM COMPLICATIONS OF UNTREATED PRIMARY HYPERPARATHYROIDISM

### Osteoporosis

Bone densitometry using dual energy X-ray absorptiometry is an indispensable component in the monitoring of patients with PHPT. In modern practice skeletal X-rays are usually not done.

Bone mass is often reduced in patients with PHPT. Women with mild asymptomatic PHPT have bone loss from the appendicular and axial skeleton (radius  $-20\%$ , lumbar spine  $-17\%$  and femoral neck  $-11\%$ ) (6). Lower bone mineral density at the lumbar spine and femoral neck was confirmed in a case-control study including more than 27000 subjects recruited in an epidemiological survey in Tromsø, Norway (7). A prospective 2-year study also reported an increased rate of loss of total body bone mineral density in post-menopausal women with untreated mild asymptomatic PHPT (8).

After parathyroidectomy there is an increase in bone mineral density at the lumbar spine and femoral neck (8). Normalization of bone remodeling and a substantial increase in bone mineral density in regions rich in cancellous bone are apparent within 6 months after parathyroidectomy (9). At 12 months, there is a significant increase in lumbar spine, hip and whole body bone mineral content (10). Similar conclusion was drawn in a very recent study from Sweden involving 49 asymptomatic PHPT patients followed-up for 5 years after parathyroidectomy: surgery was expected to increase bone mass density in L2-L4 to the level of the controls, to increase femoral neck bone density in patients under 67 years of age and to preserve it in the elderly population (11).

In contrast with these data, other studies indicate that bone density is relatively well preserved (12). It was suggested that mild PHPT does not cause appreciable bone loss at clinically relevant fracture sites (spine and hip) and that the overall skeletal benefits of surgery are likely to be negligible (13). This view was supported by the results of a randomised, 17-year follow-up study of 48 women with asymptomatic PHPT, identified during a health screening survey in Sweden (14).

Despite conflicting data, the general consensus is that prolonged duration of untreated

PHPT is likely to be associated with an increasing risk of osteopenia. Long-term follow-up of patients who do not undergo surgical treatment therefore includes regular skeletal surveillance and interventions designed to reduce bone loss. The 1990 NIH guidelines for treatment of asymptomatic PHPT recommended surgical treatment when bone density is reduced more than 2SD below the bone density of age-gender- and race-matched control subject (z-score) (15). More recent guidelines recommend surgical intervention when bone density at the lumbar spine, hip or distal radius is  $-2.5$  SD below peak bone mass (t-score) (2).

### Risk of fracture

An increased risk of fractures in patients with PHPT was demonstrated by some studies (16) but was not confirmed by others (17). It is likely that the progressive increase in the age of the population will induce an increase in the number of old patients with PHPT, for whom the risk of fractures is even more significant. This could influence further the balance in favour of offering surgical treatment to this subgroup of patients.

### Cardiac morbidity

There is an acknowledged association between PHPT and an increased risk of hypertension and cardiac abnormalities such as left ventricular (LV) hypertrophy, valvular and myocardial calcifications, impaired vascular reactivity, alterations in cardiac conduction, reversible signs of myocardial ischemia and LV dysfunction and a possible increased risk of life-threatening arrhythmia (18).

The pathogenesis of hypertension in PHPT remains debatable because successful parathyroidectomy does not improve the blood pressure control. However, a mathematical model demonstrated that PHPT is a stronger predictor of increased arterial stiffness than age, gender, smoking, hypertension or diabetes mellitus (19).

LV hypertrophy was identified in 100% of hypertensive and 30% of normotensive patients with PHPT and serum PTH levels were associated with LV mass index values as the strongest predicting variable (20). Furthermore, LV hypertrophy decreased six months after parathyroidectomy, suggesting a direct action of PTH in the pathogenesis of LV hypertrophy (21). This possibility is reinforced by the findings of a study

in which patients with mild PHPT were randomized to parathyroidectomy either directly, or after 1 year of observation: at the beginning of the study LV mass index was increased in over half of the patients and after 2 years it remained significantly larger in patients with delayed treatment (21). It appears therefore that LV hypertrophy improves after parathyroidectomy and this positive effect might explain the decrease in the excess cardiovascular mortality after treatment for PHPT (22).

Significant data were derived from a study of 30 patients with PHPT who were re-examined 1 and 5 years after parathyroidectomy with echocardiography and a bicycle exercise test. The maximal blood pressure during the exercise was higher before but not 5 years after parathyroidectomy, the ST-segment depression diminished progressively after parathyroidectomy at 1 year (from -1,4 to -0,8 mm) and 5 years (further to -0.1 mm). In addition, the number of ventricular extrasystolic beats at exercise testing in the PHPT group before parathyroidectomy was higher than in the control group and the isovolemic relaxation time at rest was prolonged before parathyroidectomy (23). In addition to these observations, echocardiographic studies demonstrated a degree of LV dysfunction that could be partially reversed by parathyroidectomy (24).

Myocardial perfusion defects extending more than 15% (range 15-25%) were found in patients with PHPT and no history of myocardial infarction or angina pectoris (25). Such defects would explain the increased incidence of acute myocardial infarction up to 10 years prior to surgery and within the first year following parathyroidectomy identified in a study of 674 Danish patients (26).

### Glucose intolerance

In healthy, normotensive subjects, plasma PTH level is inversely correlated with insulin sensitivity index (27). Excessive secretion of PTH is thought to be involved in deteriorating insulin sensitivity and secretion. In PHPT, these abnormalities might translate into a high frequency of impaired glucose tolerance and type-2 diabetes mellitus, without differences between symptomatic and asymptomatic clinical presentation (28).

In a retrospective review of 87 patients with PHPT and diabetes, glucose control was stable in 40% of patients and improved in 37% of

patients after parathyroidectomy. This effect was independent of age, duration of diabetes and of PHPT, length of follow-up, or calcium levels (29). Since parathyroidectomy results in either stabilization or improved glucose control in three quarters of diabetic patients with PHPT, surgical treatment should be offered to all such patient irrespective of their symptoms.

This is an area poorly explored so far. In our series of 400 parathyroidectomies we found evidence that indeed some diabetic patients found easier to achieve glycemic control after parathyroidectomy but such improvements were not documented accurately. We are currently recruiting patients into a prospective trial investigating the ratio of insulin/glucose before and after parathyroidectomy.

### Lipid metabolism

Postmenopausal women with mild asymptomatic PHPT have decreased serum high-density lipoprotein (HDL)-cholesterol, increased total triglycerides, very-low-density lipoprotein (VLDL)-triglycerides and VLDL-cholesterol levels and an elevated atherogenic index. Parathyroidectomy normalised the dyslipidemia (30). In the same study, 5-year surveillance of PHPT without treatment was associated with a maintained increase in the atherogenic index and a decrease in HDL-cholesterol levels. As dyslipidaemia might contribute to the increased risk of cardiovascular diseases and death observed in PHPT, these findings also favour operative intervention in mild asymptomatic PHPT in postmenopausal females.

### Premature Death

Following screening of a large population of over 33,000 (followed for 10 years), men less than 50 years of age and with serum calcium greater than 2,60 mmol/L (10,4 mg/dl) had a doubled mortality rate (31). Similarly, mild hypercalcemia in 172 patients followed up for more than two decades was found to be accompanied by premature cardiovascular death in patients younger than 70 years; the hazard ratio for hypercalcemia as an independent cause of cardiovascular mortality was 1,72 (32).

Following parathyroidectomy, the postoperative mortality was found to remain increased in 896 consecutive patients followed-up for 12 years, with cardiovascular and malignant disease

representing the main cause of death (33,34). Similar findings have been reported in a cohort of 1578 Danish patients diagnosed with PHPT during 1977-1993 (35). An even larger Swedish study involving 10,995 patients (102,515 observed person-years) who had undergone parathyroidectomy during 1958-1997, confirmed an increased risk of dying after operation for PHPT (36). However, in patients operated on after 1985 the overall mortality did not differ from that of the normal population, suggesting that modern paradigms of surgical treatment normalize the risk of dying from PHPT when the disease is diagnosed and treated at an early stage.

The increased mortality found in studies that include European patients has not been identified in North American patients (37), possibly because of prompt diagnosis and definitive treatment.

### Neuropsychological abnormalities

Weakness and easy fatigability, lethargy, drowsiness, depression, intellectual weariness and increased sleep requirements are reported by some patients at the time of diagnosis or are recognised only in retrospect (i.e. after surgical treatment of patients initially considered to be asymptomatic). A wide variety of psychiatric symptoms ranging from mild personality changes to severe depression or psychosis have been described in patients with PHPT (reviewed in 38).

A spatial learning deficit and processing but normal verbal memory were identified in a prospective study of 55 patients with PHPT who were compared with patients with benign euthyroid thyroid disease (39). In a further study of 20 patients, the patients' concentration under stress, the total number of items processed, patients' ability to memorize numbers and their tendency to perform the tests carefully and accurately enhanced significantly postoperatively (40). These findings reflect the clinical observation of the patients' improved mental capacity after parathyroidectomy.

Prospective studies in which cognitive functioning was formally measured concluded there is an improvement in attention, memory and reasoning after parathyroidectomy (56). Although further longitudinal studies are warranted, data available suggest that evaluation of cognitive function and quality of life indices may

assist physicians in choosing whom to refer for parathyroidectomy.

### Are any patients truly asymptomatic?

There is abundant anecdotal evidence of patients who believed to be free of symptoms or signs of PHPT preoperatively but reported a change of complaints following parathyroidectomy.

In a prospective long-term follow-up study of 360 patients, only 6% were found to have asymptomatic PHPT and the true frequency could be confirmed only postoperatively because some of the patients were unaware of mild symptoms prior to surgery (41). Similar low incidence of purely asymptomatic PHPT was identified in an epidemiological cohort-study of 582 consecutive patients with PHPT who underwent parathyroidectomy. Although 116 patients were considered to be asymptomatic before operation (20,9%), only eight patients (<5% of the entire cohort) were definitely confirmed asymptomatic after the subtle abnormalities became evident in retrospect once calcium levels were corrected by parathyroidectomy. Postoperative improvement was reported in 81,4% of the "asymptomatic" patients (42).

Important insight is offered by analysis of patients with mild "asymptomatic" PHP who are unaware of their disorder. When 100 patients with PHPT (who lacked knowledge of their disease) were recruited from over 5000 women attending screening mammography, patients with PHPT had more psychic complaints of lassitude, fatigue, irritability, and lack of sexual and emotional interests, visited physicians more often and received more antihypertensive therapy (43).

Analysis of last 50 patients operated in our unit showed no correlation between number of symptoms identified by clinicians and the score of symptoms as self-assessed by patients using a standardised questionnaire. It appears that without a structured detailed history many patients would be labelled as "asymptomatic".

### Quality of life in PHPT

Asymptomatic mild PHPT in postmenopausal women is accompanied by a previously unrecognised morbidity, with potential impact on the health economy. For example, total duration of sickness benefits was

longer and there was an increased risk of sick leave (odds ratio 12) during the 5 years before being diagnosed with PHPT in a case-control cohort study of postmenopausal in a Swedish community (44).

The Medical Outcomes Study Short-Form Health Survey (SF-36) has been used by several investigators to assess the impact of parathyroidectomy on the quality of life of such patients. In a randomized trial of parathyroidectomy versus observation for asymptomatic PHPT with mild hypercalcaemia, the scores on two domains (i.e. emotional role functioning and social functioning) were significantly improved in the operative group (45). Using the SF-36 questionnaire it was shown that both high (>11 mg/dl) and low (<11 mg/dl) calcium groups have marked and virtually identical impairment of functional health status (46). Furthermore, both groups showed marked improvement in health status up to 6 months after operation, returning to normal or near normal in six of eight SF-36 domains. These data suggest that referral for surgical treatment of PHPT should not be delayed until serum calcium is severely elevated.

An interesting study was designed in order to determine whether preoperative and postoperative symptoms and outcome differ in patients who meet or fail to meet the 1990 NIH Consensus Conference for parathyroidectomy. Over a 3-year period, of the 178 consecutive patients undergoing parathyroidectomy for PHPT, 103 patients met the NIH criteria for parathyroidectomy whereas 75 patients did not. The preoperative incidence of nonspecific somatic and neuropsychiatric symptoms and the postoperative symptomatic improvement was equivalent in both groups (47). Very similar data derived from a large Canadian centre showed that preoperative symptoms score did not differ between in patients who met ( $n = 95$ ) or did not meet ( $n = 22$ ) NIH guidelines and both group of patients benefited equally from parathyroidectomy (48).

The subjective improvement in quality of life is also very obvious in the elderly patients, some of whom consider that some of the PHPT symptoms are "normal" during aging. Significant improvement of PHPT-associated symptoms of fatigue, weight loss, nocturia, bone pain, constipation and major depression was demonstrated in a retrospective study of patients with PHPT who were 80 years and older (49). □

## HEALTH ECONOMICS

### Cost of long term follow-up

According to current guidelines (2), patients with PHPT who do not undergo parathyroid surgery should be monitored on a regular basis. They should have serum calcium measurements repeated every 6 months and annual bone densitometry at three sites (lumbar spine, hip and forearm). Such patients should be reviewed in the clinic on an annual basis to assess any changes in their symptoms. In addition, many such patients would use regular medication.

Some examined the cost-effectiveness of surgical strategies and medical follow-up versus surgery (using a decision-analytic model for a hypothetical cohort of 55-year-old women to compare with a lifetime horizon costs). It was found that surgery is more effective than medical follow-up at a reasonable cost and can be preferred except in patients choosing medical follow-up (50).

Although it is difficult to make accurate financial comparison of therapeutic episodes within different health care systems, reasonable estimates suggest that the costs associated with 10 years follow-up are higher than the cost of surgical intervention.

### Minimally invasive parathyroidectomy (MIP) following localisation studies

Until recently, the surgical approach for PHPT was bilateral exploration of the neck. All four parathyroid glands were identified and the diseased gland or glands excised. With this approach some specialised surgeons reported cure rates of up to 95% with minimal morbidity. More recently, the introduction of technetium  $Tc^{99m}$  – sestamibi scanning has revolutionised parathyroid imaging, multiple studies reporting its ability to localise over 90% of parathyroid adenomas (51). Patients with concordant preoperative imaging (sestamibi scan and ultrasound) can safely be offered a MIP. This is achieved through a small skin incision ( $\approx 2$  cm) placed over the enlarged parathyroid gland (marked preoperatively) and can be performed under local or general anesthesia, with a shorter operating time and shorter hospital stay (52).

There are no randomized prospective trials comparing the results and costs associated with conventional surgery and MIP techniques.

However, a recent series of 656 consecutive parathyroid explorations compared the results obtained using conventional (n = 401) and MIP (n = 255) surgery. MIP was associated with a 50% reduction in operating time, a 7-fold reduction in length of hospital stay, and a mean cost savings of \$2693 per case (53).

Currently MIP is the procedure of choice for 92% of members of the *International Association of Endocrine Surgeons* favouring a minimal access approach (54). Several authors have already reported large series of focused MIP and the overall outcome appears to be not different from patients undergoing open parathyroidectomy in the same period. In a survey of the *American Association of Clinical Endocrinologists* in 2003, 80% of respondents indicated that MIP availability increases the number of patients who were referred for operation and lowers the endocrinologists' surgical referral threshold for PHPT (55). It seems likely that in the near future the majority of patients with PHPT will be treated as an outpatient basis with MIP. The main limitation to this procedure remains the availability of a surgeon highly experienced in this new technique. □

## SUMMARY

Surgery for symptomatic PHPT has remained unchallenged since it was introduced in the 1920s.

During the last decade, support has been gained for recommending parathyroid surgery to patients with asymptomatic PHPT. There is general agreement that if such patients have osteopenia or if they are in their perimenopausal years, they should undergo surgery. For patients who do not meet these criteria, some authors recommend long term monitoring to identify about a quarter of the patients who will show progression of disease over time. However, many of the long-term complications outlined in this review are unlikely to be monitored (e.g. left ventricular dysfunction, atherogenic index, glucose metabolism) and subtle nonspecific neuropsychiatric symptoms can easily be missed or ignored during many years of follow-up. Furthermore, changes in the quality of life are unlikely to be formally assessed and they have potential impact on the working patterns and lifestyle of patients in their 50s through 70s.

The data outlined in this paper reinforce the need for a very low threshold for initiating diagnostic tests in patients with possible PHPT and for recommending surgical intervention for all those with biochemically-confirmed PHPT.

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