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# Primary Hyperparathyroidism of Postmenopausal Women

## Prospective population-based case-control analysis on prevalence, clinical findings and treatment

*Minireview based on a doctoral thesis*

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## INTRODUCTION

Primary hyperparathyroidism (HPT) today is a common endocrine disease, which has been diagnosed with an increasing incidence during the recent decades (Heath et al. 1980, Palmer et al. 1988A, Bilezikian et al. 1994). Over time the characteristic mode of clinical presentation of HPT has changed from that of pronounced hypercalcemia accompanied by threatening complications to a seemingly innocuous disorder with few or no apparent symptoms (Bilezikian et al. 1994). Moreover postmenopausal females have become the largest subgroup of patients subjected to treatment of the disorder (Åkerström et al. 1986A). The earliest patients with HPT came to medical attention because of a severe bone disease, and it was soon discovered that many patients with HPT also had recurrent nephrolithiasis (Albright & Reifenstein 1948). Since most stone forming patients seemed to lack marked skeletal symptoms and since they usually had less pronounced hypercalcemia and neurological complications, it was suggested that there were two distinct types of primary HPT. Type I was characterised by large parathyroid glands, bone disease and severe, symptomatic hypercalcemia, while HPT type II related to smaller glands and a propensity to the formation of renal stones (Lloyd 1968).

## ABBREVIATIONS

| | | | |
|---|---|---|---|
| ANOVA | analysis of variance; | LDL | low density lipoprotein |
| BMD | bone mineral density; | mo | month |
| BMI | body mass index; | OR | odds ratio |
| CPRS | comprehensive psychopathological rating scale; | P | plasma |
| | | PTH | parathyroid hormone |
| DEXA | dual-energy x-ray absorptiometry; | S | serum |
| ERT | oestrogen replacement therapy; | SEM | standard error of the mean |
| Fura 2 | fura-2-tetraacetoxymethyl ester; | SD | standard deviation |
| HDL | high density lipoprotein; | VDR | vitamin D receptor |
| HPT | primary hyperparathyroidism; | VLDL | very low density lipoprotein |
| HRT | hormone replacement therapy; | | |
| HSCL | Hopkin's symptom checklist; | yr | year |

As measurements of the serum calcium concentration have become widely used, it has been increasingly evident that many HPT patients cannot be classified into any of these types. A third form of primary HPT therefore has been proposed, which exhibits few clinical features in common with the other types of HPT (Kleerekoper 1994A). The risk of progression into HPT types I or II also seems to be very limited for the third variant of the disease.

The NIH Consensus Conference in 1991 on HPT suggested conservative surveillance in the elderly patients, who exhibited consistent serum calcium values below 3.0 mmol/L and no apparent symptoms or complications of HPT (NIH Consensus Development Conference Statement 1991). Besides the necessity to explore influences of parathyroidectomy on the morbidity and mortality of HPT, there is limited information on the risks and benefits from conservative surveillance (Silverberg & Bilezikian 1996). The problems with the recommendation on surveillance also include the difficulty to determine if the unspecific psychiatric symptoms in the elderly are related to HPT, and possible to improve by treatment, or if they represent an irreversible process of ageing (Joborn et al. 1989A). Another problem is that the morbidity of HPT exhibits no simple relationship to the extent of hypercalcemia, whereby serum calcium becomes an unreliable determinant on the utility of active versus conservative treatment (Ljunghall et al. 1989, Rastad et al. 1992). Furthermore it has become increasingly evident that many patients with HPT have several risk factors for cardiovascular diseases and some studies on HPT substantiate the occurrence of premature death from mainly cardiovascular diseases (Palmer et al. 1987A, Ronni-Sivula & Sivula 1985, Hedbäck et al. 1990, Ljunghall et al. 1991A, Hedbäck & Oden 1998B). The therapeutic guidelines of the NIH conference have not been fully complied with, and many patients supposedly eligible to surveillance still undergo parathyroidectomy (Sosa et al. 1998). The need of prospective studies on the prevalence, clinical features and treatment of asymptomatic mild HPT was emphasised at the consensus conference.

## PREVALENCE OF HPT

HPT was considered a rare disorder during almost a century after description of the parathyroid glands (Sandström 1880). Since the introduction of automated serum calcium determination on liberal indications in the early 1970s, HPT has become a commonly diagnosed disorder (Bilezikian et al. 1994). Available prevalence studies, however, mainly have been based on determination of the total serum calcium concentration and rarely have utilised intact serum parathyroid hormone (PTH) values for the diagnosis of HPT. Moreover, none of them has included patients with normocalcemic HPT or attempted systematic surgical verification of the disorder.

HPT has been suggested to affect about 1% of the adult population in Sweden, and the prevalence rises with age in both the sexes (Christensson et al. 1976A, Heath et al. 1980, Palmer et al. 1988A). Elderly females are particularly prone to develop the disease and up to

about 3% of them have displayed signs consistent with HPT (Christensson et al. 1976A, Heath et al. 1980, Alarcon & Franceschini 1984, Palmer et al. 1988A, Lindstedt et al. 1992, Sorva et al. 1992). The characteristic patient with HPT today consequently is an elderly female, who is apparently asymptomatic and exhibits mild hypercalcemia (Christensson et al. 1976B, Mundy et al. 1980, Palmer et al. 1988A, Harrison & Wheeler 1991, Heath 1991, Bilezikian et al. 1994, Kleerekoper 1994A).

In addition an autopsy examination of cases without substantial renal diseases revealed a 10% prevalence of parathyroid gland abnormalities in both the sexes (Åkerström et al. 1986B). Together with the rapidly increasing number of elderly in Western societies, these findings have inferred expectations on a continuing rise in the incidence of HPT. A study from the United States, however, suggested a recent decrease in the frequency of HPT (Wermers et al. 1997). Comparison of hospital statistics with prevalence and incidence data has supported that about 10% of patients with HPT undergo parathyroidectomy in Sweden (Palmer et al. 1987B, Ljunghall et al. 1991B). The frequency of HPT in hospitalbased materials naturally differs from that obtained by population-based screening for several reasons (Boonstra & Jackson 1970, Heath et al. 1980, Mundy et al. 1980, Dent et al. 1987). Malignancies account for a greater proportion of cases with hypercalcemia in hospitalised individuals (Dent et al. 1987, Frolich 1998), while HPT is the most common cause of an elevated serum calcium value in outpatients (Heath et al. 1980, Palmer et al. 1988A, Lindstedt et al. 1992, Sorva et al. 1992). Moreover any material on patients recruited in the clinical routine is hampered bythefact that the patient has come to medical attention for a reason. In contemporary patients, such reasons most commonly seem to differ from the symptoms and complications commonly denoted as 'characteristic' of HPT (Kleerekoper & Bilezikian 1994B). Recurrent kidney stones, impaired renal function and low energy fractures consequently are rare in HPT today.

## DIAGNOSIS OF HPT

The diagnosis of HPT is established by laboratory tests, since the history and physical examination rarely give any clear indications of the disease (Bilezikian et al. 1994). In clinical practice hypercalcemia is usually present and serum phosphate tends to be in the lower part of the reference range. The total serum calcium value has satisfactory precision between laboratories, and the accuracy is increased when adjustments are made for alterations in serum albumin (Ladenson 1991, Ljunghall et al. 1991B). Pitfalls when measuring serum calcium are mostly preanalytic, i.e. related to non-fasting, variations in posture, and venous stasis during the sampling (Ladenson 1991, Ljunghall et al. 1991B). The ionised calcium level may be more sensitive to alterations in the PTH secretion, and it could improve the diagnosis of mild HPT (Benson et al. 1987, Ladenson 1991, Glendenning et al. 1998).

Measurement of the circulating PTH concentration is the most definite way to make the diagnosis of primary HPT. The development of sensitive immunometric assays for intact PTH

has simplified and increased the accuracy of the diagnosis of HPT considerably (Nussbaum 1991). By the use of these assays HPT can be separated from other causes of hypercalcemia also when the serum PTH value is within the normal range (Nussbaum 1991, Ljunghall et al. 1991C, Nussbaum & Potts 1994). About 20% of HPT patients, who are diagnosed in the clinical routine usually have normal serum PTH levels (Nussbaum 1991, Ljunghall et al. 1991C, Glendenning et al. 1998). The basis for the discrimination of HPT from any other cause of hypercalcemia is that the abnormal parathyroid glands exhibit partial resistance to the inhibitory action of extracellular calcium on the PTH release (Wallfelt et al. 1988B). Hypercalcemia of non-parathyroid origin, however, effectively suppresses the release, whereby the serum PTH value reaches the level below or just above the lower normal range. There exist two limitations in this line of reasoning, which are both clinically rare. Patients may exhibit primary HPT together with another potential cause of hypercalcemia. Malignancies and thyrotoxicosis are classical examples in this respect (Benson et al. 1987). In addition a few cases of non-parathyroid secretion of intact PTH have been described (Yoshimoto et al. 1989, Nussbaum et al. 1990, Strewler et al. 1993, Rizzoli et al. 1994).

A particular diagnostic challenge is to discriminate the euparathyroid individuals from those with mild HPT. Autopsy and clinical findings indicate a gradual and mostly slow progression of HPT over time, whereby it could be assumed that many of the patients, if not all, exhibit at least some period of normocalcemia (Ljunghall et al. 1980, Åkerström et al. 1986A, Palmer 1988A, Parfitt et al. 1991, Parfitt 1994). It has been calculated mathematically that about 25% of cases with clinically detected HPT should have a normal serum calcium value (Groth et al. 1983). Also clinical materials support the existence of normocalcemic HPT (Ljunghall et al. 1980, Siperstein et al. 1992, Hellman et al. 1992), but relevant diagnostic criteria have not been systematically analysed. Moreover there are variably strong positive relationships between serum calcium, serum PTH, and weight of the abnormal parathyroid tissue in HPT (Zamboni & Folse 1986, Benson et al. 1987, Wallfelt et al. 1988A, Wallfelt et al. 1990A, Williams et al. 1992, Carnaille et al. 1998). This suggests that the patients with truly mild HPT might comprise an operative challenge due to an exceptionally mild extent of the parathyroid enlargement.

## PARATHYROID CELL FUNCTIONS

The extracellular calcium concentration is the most potent regulator and promptly influences the secretion of PTH (Brown et al. 1985, Wallfelt et al. 1988B). An increased external calcium level triggers biphasic elevation of the intracellular calcium concentration in the parathyroid due to rapid intracellular calcium mobilisation (Epstein et al. 1985, Brown et al. 1987, Shoback et al. 1988) and calcium influx through the plasma membranes (Nemeth & Scarpa 1987, Wallfelt 1988B). The sigmoidal calcium-dependence of the intracellular calcium concentration and the PTH release is disturbed in HPT, and an abnormally high elevation of the calcium

concentration is required to elevate the intracellular calcium level and to suppress the secretion (Larsson et al. 1984, Wallfelt et al. 1988A). The extent of this abnormality largely correlates to the serum calcium level of the patient (Wallfelt et al. 1988A).

Defective expression and action of calcium sensing proteins on the parathyroid cell surface have been suggested to cause much of the calcium insensitivity of the PTH release in HPT (Chattopadhyay et al. 1996). Monoclonal anti-parathyroid antibodies were found to recognise such a putative calcium sensor (Juhlin et al. 1988). Decreased expression of this protein is a characteristic finding in parathyroid adenomas and hyperplasias (Juhlin et al. 1988, 1989).

A variety of other factors besides calcium can influence the function of parathyroid cells. Calcitriol impairs PTH gene transcription and hampers parathyroid cell proliferation (Nygren et al. 1988, Demay et al. 1992, Macdonald et al. 1994). The serum PTH level seems to increase with age (Sherman et al. 1990), which might relate both to reduced renal production of calcitriol and an impaired sensitivity of the intestine to the steroid (Eastell et al. 1991, Prince et al. 1995 Gallagher et al. 1998). Most studies have failed to identify receptors for oestrogen in the human parathyroid tissue, and conflicting results also exist with regards to any direct actions of this steroid on the PTH release (Prince et al. 1990, Prince 1994). Hormone replacement therapy (HRT) in postmenopausal women may normalise the biochemical signs of HPT due possibly to interference mainly in the bone (Turner et al. 1994). It also has been suggested that direct or indirect actions of the oestrogen receptor may interact in the relationship between calcium and PTH in both the parathyroid and its classical target tissues (Carling et al. 1997).

## SYMPTOMS AND COMPLICATIONS OF HPT

A variety of confounding factors must be considered, when symptoms of HPT have been analysed in patients recruited in the clinical routine. These include attitudes of the treating physicians with regard to the measurement serum calcium and to act upon an increase in the level, and "placebo" effects on the outcome of treatment. Many studies on the influences of treatment of HPT also lack appropriately matched controls. Ideally, studies on the frequency and severity of HPT-related symptoms should utilise population-based recruitment of the cases and controls.

### Renal symptoms of HPT

Renal failure today is an exceptionally rare complication of HPT in Western countries, although persistence of a renal calcium leak, a decreased urinary concentration capacity, and a reduction of the creatinine clearance can occur (Falkheden et al. 1980, Lins 1979, Mitlak et al. 1991). Kidney stones have been reported to be the single most common presenting manifestation of symptomatic HPT (Klugman et al. 1994). The pathogenesis of such stones remains

unclear and several metabolic causes have been implicated, like hypercalciuria, reduced inhibitory activity in the urine, and hyperuricosuria (Klugman et al. 1994).

The frequency of a renal stone disorder varies considerably between clinical materials of HPT, and has apparently decreased during recent decades (Klugman et al. 1994). Nephrolithiasis seems to affect only a small proportion of contemporary patients with HPT, and they particularly occur in the younger individuals in whom HPT is less common (Wallfelt et al. 1990B, Delbridge et al. 1998). It has been suggested that this may depend on age-related decreases in the calcitriol production, which infers a lessened urine calcium excretion and perhaps an increased risk to develop HPT (Kleeman et al 1987, Åkerström et al.1986B). An elevated urine calcium excretion and recurrent renal stone formation have been used to identify patients with normocalcemic HPT (Johansson et al. 1975, Ljunghall et al. 1980). Although the propensity for stone formation mostly is reduced after successful parathyroid surgery (Klugman et al. 1994), a considerable number of patients can experience recurrence of the stone disease despite the presence of postoperative normocalcemia (Möllerup & Lindewald 1999).

**Bone turnover**

Bone is a living tissue that is continuously remodelled to meet the demands on integrity and mineral metabolism. The remodelling of bone is influenced by a variety of factors, which include several hormone systems (Marcus 1987). PTH activates bone resorption and stimulates bone formation (Reeve et al. 1980, MacDonald et al. 1986, Dempster et al. 1993). Differential and concentration-dependent effects of PTH have been described (Parfitt 1976). High concentrations of PTH are catabolic mainly on the cortical bone, while a slight PTH elevation may be anabolic mainly for the trabecular bone (Peacock 1991, Christiansen et al. 1992, Parisien et al. 1992, Vogel et al. 1995).

The concept that PTH has both anabolic and catabolic effects on the skeleton was proposed many years ago (Bauer et al. 1929, Selye 1932). The major mechanism for the catabolic action is a stimulation of osteoclastic bone resorption, while the anabolic effect of PTH depends on complex interaction between PTH and the growth factors for bone (Canalis et al. 1994). Animal experiments have demonstrated that continuous infusion of PTH leads to enhanced resorption and bone loss (Hock & Gera 1992, Uzawa et al. 1995). On the other hand intermittent injection of the hormone has the capacity to stimulate bone formation (Hock & Gera 1992, Uzawa et al. 1995). Three controlled studies have demonstrated increased bone mineral density at the spine and hip in response to treatment with PTH (1-34) during periods up to three years (Finkelstein et al. 1994, Hodsman et al. 1997, Lindsay et al. 1997).

*The menopause*

An increased loss of bone occurs in postmenopausal women (Parfitt 1988). The first 5-10 years after the menopause, this loss amounts to about 2-3% of the bone mass annually and it mainly

affects the trabecular bone (Heany et al. 1978, Riggs & Melton 1983, Gallagher et al. 1987). Thereafter both cortical and trabecular bone are lost at a rate of about 0.5-0.75% per year (Riggs & Melton 1983, Lindsay 1988, Davies et al. 1991, Nordin et al. 1993). The menopause also is associated with an enhanced skeletal sensitivity to PTH (Joborn et al. 1991A), and the oestrogenised postmenopausal skeleton is less sensitive to the bone resorbing effects of PTH (Cosman et al. 1993). A suppression of the increased bone turnover and an increased bone mineral density (BMD) have recently been demonstrated following oestrogen therapy in postmenopausal females with HPT, although little effect on the serum calcium concentration was identified (Grey et al. 1996A,B).

**Skeletal symptoms of HPT**

The term osteitis fibrosa cystica was coined already a century ago to describe a severe form of bone affection in HPT (von Recklinghausen 1891). Also other skeletal abnormalities of HPT were described early (Albright et al. 1934). Such changes in HPT, however, have been replaced by characteristic findings of an increased bone turnover, which mostly reduces the cortical bone and the appendicular skeleton (Christiansen et al. 1997, Parisien et al. 1990, Parfitt et al. 1991, Grey et al.1994). Both the endostal resorption and the periostal apposition seem to be increased, and the imbalance between them decreases the cortical thickness (Adami et al. 1998). Patients with HPT have demonstrated reduced BMD in the distal forearm (Silverberg et al. 1989, Larsson et al. 1989) and in the femoral neck (Silverberg et al. 1989), while the findings in the spine are divergent (Silverberg et al. 1989, Block et al. 1989, Grey et al. 1994). An increased risk of fractures of the forearm, but not the hip, has been suggested (Larsson et al. 1989, Mallmin et al. 1991, Larsson et al. 1993). Also the overall risk of fragility fractures are conflicting in HPT (Melton et al. 1992, Kenny et al. 1995). A recent longitudinal, six-year study of postmenopausal females with asymptomatic, mild HPT disclosed neither biochemical indices, nor bone density measurements indicating progression of the disease (Silverberg et al. 1995A). In another report, however, postmenopausal females with mild HPT had accelerated bone loss at the femoral neck, but not the lumbar spine compared to age-matched controls over a two-year period (Guo et al. 1996).

Parathyroidectomy has been reported to result in an increased bone density at both cortical and trabecular sites (Mautalen et al. 1986, Martin et al. 1986, Warner et al. 1991, Silverberg et al. 1995B), although the bone loss seems to be only partially reversible (Martin et al. 1990, Silverberg et al. 1995B). Reduction of the bone mass has been described also for asymptomatic patients with mild HPT (Silverberg et al. 1989, McDermott et al. 1994), and the beneficial effect of surgery has been questioned in these cases (Larsson et al. 1993, Rao et al. 1988, Elvius et al. 1995). HPT patients on oestrogen replacement therapy (ERT) had higher bone density than untreated patients (McDermott et al. 1994). ERT has been suggested as an

alternative to surgery for the prevention of bone loss at least in the elderly women with mild HPT (Diamond et al. 1996).

**Hypercalcemia and the nervous system**

Calcium interacts with the excitability, impulse propagation and transmitter turnover of the nervous tissue and influences the synthesis, transport and release of biogenic amines (Dubovsky & Franks 1983, Rastad et al. 1992). Low concentrations of monoamine metabolites have been found in the cerebrospinal fluid of patients with HPT (Joborn et al. 1988A, Joborn et al. 1991B), who consequently mimic patients with endogenous depression (Post et al. 1980, van Praag 1982, Åsberg et al. 1984). These patient groups also demonstrate increased calcium levels in the cerebrospinal fluid (Dubovsky & Franks 1983, Cogan et al. 1978, Jimerson et al. 1980, Joborn et al. 1991B). It has been hypothesised that PTH may mediate increased permeability of the blood-brain barrier and thereby can enhance calcium entry into the nervous tissue (Joborn et al. 1991B). Abnormal EEG with dramatic improvements after surgery have been described in mild HPT (Cogan et al. 1978).

**Psychic symptoms of HPT**

HPT was related to psychic symptoms already decades ago (Eitinger 1942). The recognised proportion of patients with such manifestations, however, has increased with time particularly when structured interviews and elaborate tests have been utilised prospectively (Uden et al. 1992, Joborn et al. 1986A,B, 1988A, 1989A, Rastad et al. 1992, Burney et al. 1996, 1998). The presence of psychic symptoms still is controversial, however, and these derangements sometimes are considered as 'untraditional' indications for active treatment of HPT (Kleerekoper & Bilezikian 1994B).

Affective symptoms and a neurasthenic personality most commonly are included into the psychic disturbances of HPT (Petersen 1968, Joborn et al. 1986A, Brown et al. 1987). In particular the patients have substantiated fatigue, weakness, anxiety, mood swings, irritability and apathy (Karpati & Frame 1964, Alarcon & Franceschini 1984, Joborn et al. 1986A, 1988A, 1989A, Harrison & Wheeler 1991, Uden et al. 1992, Solomon et al. 1994, Pasieka & Parson 1998). More recent studies also suggest significant decreases in patients' quality of life (Burney et al. 1996, 1998, Pasieka & Parson 1998). There seem to be no simple relationship between the severity of psychic symptoms and the serum calcium level (Karpati & Frame 1964, Alarcon & Franceschini 1984, Joborn et al 1986A, Harrison & Wheeler 1991, Clark et al. 1991, Solomon et al. 1994, Chan et al. 1995), although more pronounced symptoms characteristically occur in the elderly with the most extensive hypercalcemia (Joborn et al. 1986A, Wallfelt et al. 1990B). Psychic symptoms are identified also in biochemically mild HPT, but they rarely are volunteered and usually must be actively searched for (Joborn et al. 1989A, Siperstein et al. 1992).

No or limited improvement of psychic symptoms has been reported after parathyroidectomy (Brown et al. 1987, Heath 1989). Most investigators, however, have described a substantial symptom relief lasting even for long periods of time (Ronni-Sivula & Sivula 1985, Joborn et al. 1986B, 1988A, McAllion & Paterson 1989, Solomon et al. 1994). This improvement has included a majority of the cases (Uden et al. 1992, Chan et al. 1995), and symptoms ranging from the affective derangements to dominant hemispheric functions as memory, learning and cognition (Numann et al. 1984), as well as estimates on the general mental health and quality of life (Burney et al. 1996, 1998, Pasieka & Parson 1998). Signs of organic brain syndrome may be dramatically improved in the elderly patients (Joborn et al. 1986A). A liberal attitude to parathyroid surgery in the elderly patients with psychic symptoms has been advocated (Öhrvall et al. 1994, Chigot et al. 1995). Although the clinical results of treatment may seem impressive, it should be borne in mind that no strict, randomised study has been performed (Okamoto et al. 1997) and that the extent of non-specific ("placebo") effects of the increased attention remains to be evaluated.

**Muscular symptoms of primary HPT**

Muscular atrophy and feelings of extreme weakness were described already in the first cases of osteitis fibrosa cystica (von Recklinghausen 1891, Mandl 1925). Muscular weakness subsequently has been reported in up to 80% of the patients with HPT (Karpati & Frame 1964, Patten et al. 1974, Tibblin et al. 1983, Ronni-Sivula & Sivula 1985, Öhrvall et al. 1994, Chan et al. 1995). Such evaluations have included strength and endurance of the thigh (Hedman et al. 1984, Wersäll et al. 1986, Colliander et al. 1998), arm and hands (Kristoffersson et al. 1992, Chou et al. 1995), and respiratory muscles (Kristoffersson et al. 1988). Structured interviews (Delbridge et al. 1988, Turken et al. 1989, Chan et al. 1995, Pasieka & Parson 1998) and various neurophysiological tests have also been analysed (Ljunghall et al. 1984, Turken et al. 1989).

There are controversies if the tiredness of HPT is mental, neuromuscular, muscular, or a combination of these factors (Tibblin et al. 1983, Ronni-Sivula & Sivula 1985, Delbridge et al. 1988, Clark et al. 1991, Chan et al. 1995). Normal neuromuscular examinations consequently have been described despite a generalised feeling of fatigue (Turken et al. 1989). Severe weakness of proximal muscles, especially of the lower extremities, histological abnormalities in the muscle fibres and an abnormal electromyogram were primarily thought to be part of a neurogenic lesion (Patten et al. 1974). Further studies could not prove disturbances in the neuromuscular transmission (Ljunghall et al. 1984), and an impaired muscle contraction per se seems to be one possible explanation (Joborn et al. 1989B).

Improvement of the muscle function after parathyroidectomy has been noted in several studies, especially when the tiredness and weakness have been regarded to be muscular (Hedman et al. 1984, Patten et al. 1974, Tibblin et al. 1983, Ronni-Sivula & Sivula 1985,

Delbridge et al. 1988, Joborn et al. 1988B, Kristoffersson et al. 1988, Heath 1989, Kristoffersson et al. 1992, Clark et al. 1991, Uden et al. 1992, Chan et al. 1995, Chou et al. 1995, Pasieka & Parson 1998). Other studies, however, have found no objective signs of improvement (Joborn et al. 1989B, Colliander et al. 1998). Methodological difficulties in such observations entail large intra-individual variations (Joborn et al. 1988B), and the possibility of a "training" effect on the voluntary component of the muscle contraction at repeated evaluation postoperatively (Joborn et al. 1989B). More pronounced improvement can occur in symptomatic patients with high serum calcium levels (Joborn et al. 1988B), but mostly there has been no correlation between the outcome of treatment and the preoperative serum calcium level. The need of carefully matched controls has been stressed, since improvement also was noted at follow up in the controls (Jansson et al. 1991A).

**Metabolic disturbances in HPT**

This denomination refers to a variety of disturbances in patients with HPT, which have become increasingly evident during recent years. The causal coupling to HPT, however, is complex, and several of these symptoms and signs usually are unaltered by surgical correction of the hyperparathyroid state. This observation suggests the need to evaluate also other treatment regimens, perhaps in combination with parathyroidectomy, in order to optimise the chances of improved morbidity and mortality of patients with HPT.

*Diabetes mellitus and glucose intolerance*

HPT has been associated with an impaired glucose tolerance and diabetes mellitus due possibly to a peripheral insulin insensitivity (Ljunghall et al. 1983, Kumar et al. 1994, Taylor & Khaleeli 1997, Valdemarsson et al. 1998). This insensitivity and the glucose intolerance of the patients are independent of other risk factors for diabetes mellitus, such as hypertension and obesity (Kumar et al. 1994). Although the excess of PTH and calcium and the trend to hypophosphatemia of HPT could contribute in this respect, fasting glucose levels and hemoglobin A1c values should be expected to remain unchanged by parathyroid surgery (Ljunghall et al. 1983, Bannon et al. 1988). The mechanisms for the putative relationships of HPT to these metabolic derangements are unknown. Animal experiments have indicated a critical role for vitamin D in the insulin secretion (Norman et al. 1980, Kadowaki & Norman 1984, Nyomba et al. 1984), which provides an attractive link to the parathyroid gland hyperfunction. However, studies in elderly patients with vitamin D deficiency did not demonstrate any change in the insulin secretion or glucose tolerance after correction of the nutritional disturbance (Nyomba et al. 1986), and no effect of calcitriol has been noted on the insulin-mediated glucose uptake of healthy subjects (Fliser et al. 1997A).

*Lipid metabolic disturbances*

Decreased levels of serum cholesterol and triglycerides have been reported in HPT (Christensson & Einarsson 1977). Fractionation of the lipoproteins clarified that HD and LD lipoproteins were lowered and seemed to increase directly after parathyroidectomy, and that the increased VLD lipoproteins values normalised some months later (Ljunghall et al. 1978). Excess PTH levels are thought to be responsible of the abnormal lipid metabolism, at least in secondary HPT where this excess is substantially greater than in primary HPT (Akmal et al. 1990).

*Body weight and obesity*

It has been described that patients with HPT exhibit an increased body mass index (BMI) with abnormal distribution of the body fat (Haight et al. 1976, Gray et al. 1994). Markedly overweight subjects can display moderately elevated PTH levels together with slightly lowered serum calcium levels, which presumably relate to an increased complex binding of calcium to e.g. free fatty acids. These derangements have been shown to be normalised by successful weight reduction (Andersen et al. 1988).

*Hypertension and cardiovascular derangements*

PTH has a multitude of effects on the regulation of the vascular tone and can affect also other cardiovascular functions (Lind & Ljunghall 1993, Rodriguez-Portales & Fardella 1994, Lind & Ljunghall 1995A, Schluter & Piper 1998). Whereas acute administration of PTH causes vasodilatation in experimental animals (Pang et al. 1980), subacute (Fliser et al. 1997B) or continuous (Hulter et al. 1986) infusion of physiological doses of the hormone raise the blood pressure in man.

An increased prevalence of hypertension has been shown in HPT (Christensson et al. 1977, Rubinoff et al. 1983, Christensson 1986, Lafferty & Hubay 1989), but this relationship has not been consistent in studies including cases with mild HPT (Mitlak et al. 1991). Parathyroid surgery does not seem to affect the hypertension (Mitlak et al. 1991, Heath & Heath 1991, Davies 1992), and the derangements could be indirectly associated (Ljunghall et al. 1989, Lind et al 1991, Lind & Ljunghall 1995A). In a small, but controlled study it was found that alphacalcidol (active vitamin D) reduced the raised blood pressure in patients with mild HPT (Lind et al. 1992). Recent analyses have suggested that the hypertension of HPT may be partially caused by noradrenergic blood pressure dysregulation, which seems to be causally linked to the secretion of a parathyroid hypertensive factor. This putative factor may increase the cytoplasmic calcium concentration and alter the vascular tone and reactivity (Schiffl et al. 1997). Endothelium-independent vasodilatation has been found to be impaired in patients with HPT, which indicates that the altered arterial reactivity in the course of the disease may predominantly involve the arterial media (Neunteufl et al. 1998).

HPT also has been attributed to a variety of cardiac disturbances like left ventricle hypertrophy, myocardial and valvular calcifications, increased enddiastolic left ventricle volume, and electrocardiographic abnormalities, which may improve after parathyroid surgery (Symons et al. 1985, Niederle et al. 1990, Stefenelli et al. 1992, Lind & Ljunghall 1995B, Dalberg et al. 1996, Stefenelli et al. 1997A,B). In hemodialysis patients receiving intravenous calcitriol, which reduced the elevated serum PTH levels, a regression of the myocardial hypertrophy without hemodynamic changes has been reported (Park et al. 1999).

*Anemia and hyperuricemia*

HPT has been associated with normochromic and normocytic anemia with improvement after parathyroid surgery (Falco et al. 1976, Boxer et al. 1977). Increased serum PTH levels per se was not thought to be the cause of the anemia (Foulks et al. 1989), and an improved erythropoetin sensitivity has been suggested as a possible explanation (Urena et al. 1991). On the other hand, HPT has also been coupled to polycythemia vera (Boivin & Bernard 1992). It has been hypothesised that PTH may influence the erythropoesis by the induction of stem cell proliferation at low levels and with an opposite action at more substantially elevated levels (Boivin & Bernard 1992). An increased serum urate concentration has been found in HPT patients, but not in those with hypercalcemia of other causes (Malette et al. 1974, Christensson 1977, Lind & Ljunghall 1992). A reduced tubular clearance unrelated to kidney stone formation, and with prospects on postoperative normalisation has been suggested (Ljunghall & Åkerström, 1982).

**Mortality**

Premature death has been described in four Scandinavian series of HPT and mild hypercalcemia (Ronni-Sivula & Sivula 1985, Palmer et al. 1987A, Hedbäck et al. 1990, Hedbäck & Oden 1998A,B). This circumstance recently has been refuted in two studies from the United States (Söreide et al. 1997, Wermer et al. 1998). The recorded excess mortality has been suggested to depend on cardiovascular disorders and a variety of malignant neoplasms in the patients with HPT. Several findings support the existence of this relevant threat to these patients. Population-based analyses of men have indicated even a relationship within the normal range of serum calcium values and the risk of death from cardiovascular disorders (Leifsson & Ahren 1996, Lind et al. 1997). The coupling of HPT to several risk factors for cardiovascular diseases (see above) coincides with the notion on an increased risk of dying from such diseases. Moreover the risk of dying in HPT has been correlated to the extent of hypercalcemia (Hedbäck & Oden 1995), and the risk has been found to be reversed with time after parathyroidectomy (Hedbäck et al. 1991).

## TREATMENT OF HPT

It should be remembered that the tradition to treat HPT mainly is based on experiences gained from symptomatic cases with unequivocal hypercalcemia. Mild, asymptomatic HPT does not necessarily require the same handling (Clark 1994).

### Medical treatment

Adequate hydration, a moderate dietary calcium intake, cautious use of loop-diuretics, and avoidance of thiazides are recommended in all patients with primary HPT (Shane 1991, Stock & Marcus 1994). Calcitonin and oral phosphate may be used, but their long-term efficacy and risks are unclear (Broadus et al. 1983, Rude 1996). Biphosphonates inhibit bone resorption in HPT (Rodan 1998), but not the PTH secretion (Ridefelt et al. 1995). They have been used in more severe HPT (Jansson et al. 1991B, Tal & Graves 1996). An increased serum PTH level has been found concomitant with the decreased serum calcium (Adami et al. 1990, Schmidli et al. 1990, Grotz et al. 1998), as would be expected if HPT is related to a decreased calcium control of the secretion. Recently a few new approaches have been attempted. A pure competitive antagonist of PTH with a high affinity for the PTH receptor *in vitro* and the ability to block the actions of PTH in the rat failed to lower serum PTH or calcium values in three patients with HPT (Rosen et al. 1997). Octreotide, a somatostatin analogue, has shown no discernible effects on biochemical parameters of the calcium homeostasis in patients with primary and secondary HPT (Zielke et al. 1997). A calcimimetic drug (R-568) reduced serum PTH and ionised calcium concentrations in postmenopausal women with HPT (Silverberg et al 1997).

### NIH Consensus Conference

The statement from this conference held in 1990 provided guidelines for the management of asymptomatic HPT (NIH Concensus Conference Statement 1991). Patients were considered to have mild HPT, when the serum calcium value was below 3.0 mmol/L. Parathyroid surgery was recommended at a greater extent of the hypercalcemia or when any of the following criteria were fulfilled; a creatinine clearance reduced by at least 30%, a urine calcium excretion increased above 400 mg per 24 hours, a bone mass lower than two standard deviations (SD) of age- and gender-matched persons. In addition, surgery was considered to be suitable in cases in whom medical surveillance was neither desirable nor suitable, for patients below 50 years of age, and for those with a history of recent kidney stones, or apparent neuromuscular and psychic symptoms. The need of prospective studies on clinical features of HPT and its surgical and non-surgical treatment regimens were underlined. Adherence to these recommendations was analysed in 1998, and the criteria for parathyroidectomy were found to vary widely even among highly experienced surgeons (Sosa et al. 1998). The controversies in the management of mild primary HPT obviously still exist.

**Parathyroid surgery**

Parathyroidectomy comprises the only available treatment option in HPT patients, which has been investigated more extensively. Parathyroidectomy today almost invariably is performed with a conservative attitude to the extent of glandular resection (Clark 1995). This strategy involves mere excision of the enlarged parathyroid glands irrespective of the patient having one, two or three macroscopically enlarged glands. A four-gland enlargement is exceptionally rare in non-familial primary HPT (Wallfelt et al. 1990B, Bonjer et al. 1992). Most centres utilising bilateral neck explorations limit the use of biopsies of overtly normal-sized glands in order to decrease the risks of postoperative hypoparathyroidism (Lafferty & Hubay 1989). Unilateral neck explorations have been utilised to treat patients with single parathyroid adenoma (Tibblin et al. 1982, Welsh et al. 1990, Robertson et al.1996, Vogel et al. 1998), and local tumour removal has been introduced more recently (Miccoli et al. 1998A,B, Norman et al. 1998). Percutaneous injection of ethanol into parathyroid tumours by ultrasonic guidance might be utilised in selected cases unsuitable for surgery (Karstrup et al. 1993, Verges et al. 1993). The problems with this technique mainly relate to the need of repeated injections, and the risk of recurrent nerve palsy (Harman et al. 1998).

*Serum calcium and PTH*

Longer term follow-up of series containing different proportions of patients with mild HPT have demonstrated reversed hypercalcemia from in 90-95% of the cases (Bruining et al. 1981, Lundgren et al. 1992) up to virtually all of the examined individuals (Ronni-Sivula & Sivula 1985, van Heerden & Grant 1991, Uden et al. 1992, Delbridge et al. 1998). Analyses of materials of mild HPT (Attie et al. 1976, Russel & Edis 1982, Gaz & Wang 1984) and elderly cases (Brothers & Thompson 1987, Öhrvall et al. 1994, Ruijs et al. 1994, Chigot et al. 1995) infer similar expectations regarding the serum calcium level. Serum PTH, however, might be elevated postoperatively, and the relevance of this alteration has not been clarified (Duh et al. 1986, Lundgren et al. 1992, Tisell et al. 1996, Bergenfelz et al. 1996). A long-term analysis suggested that such a rise may be due to age-related risks of impaired renal function with biochemical signs of secondary HPT (Lundgren et al. 1992).

*Persistence and recurrence of HPT*

The success rate of primary parathyroid explorations at larger centres has indicated that persistent postoperative hypercalcemia is truly rare (van Heerden & Grant 1991, Lundgren et al. 1992, Weber et al. 1994, Rafferty et al. 1997, Ryan & Lee 1997, Delbridge et al. 1998). Recurrence rates in patients followed for longer periods of time after extirpation of a single parathyroid gland seem to be below 2-3% (Ronni-Sivula & Sivula 1985, Rudberg et al. 1986, Lundgren et al. 1992). A slightly increased risk for such failures has occurred in some studies

of multiglandular parathyroid diseases (Ronni-Sivula & Sivula 1985, Wallfelt et al. 1990B, Szabo et al. 1998, Weber et al. 1994).

*Complications*

Persistent vocal cord paralysis almost never occurs in primary parathyroid explorations (van Heerden & Grant 1991, Weber et al. 1994, Ryan & Lee 1997), although less encouraging results have been found at centres performing an insufficient annual number of procedures (Malmaeus et al. 1988, Ready et al. 1996). A low risk for other types of postoperative morbidity and a negligible perioperative mortality also seem to prevail even in the elderly cases (Brothers & Thompson 1987, Öhrvall et al. 1994, Chigot et al. 1995, Ruijs et al. 1994). Depending on the operative approach and the definition of hypocalcemia, the incidence of permanent hypocalcemia varies from a few percent (Gaz & Wang 1984, Ronni-Sivula & Sivula 1985, Russel & Edis 1982, Rudberg et al. 1986) to more than 10% (Lafferty & Hubay 1989). If all cases with a total serum calcium value below the normal range and those with any type of calcium substitution are considered together, hypocalcemia may be registered in 4% of the cases (Lundgren et al. 1992).

**Sex steroids**

Sex steroids can affect the secretion of PTH (see above) as well as modify peripheral effects of the hormone in its target tissues. Dynamic tests of parathyroid function have displayed that ERT decreases the set point of PTH stimulation by calcium (Boucher et al. 1989). Oestrogen supplementation in women in the early postmenopause has been found to increase serum PTH and to enhance the renal conservation of calcium (McKane et al. 1995), and oestradiol in rats can stimulate the expression of the PTH receptor gene in the kidney (Cros et al. 1998). Menopause and oestrogen deficiency is associated with apparent intestinal resistance to vitamin D, which can be reversed by oestrogen replacement. Modulation of intestinal vitamin D receptor (VDR) activity by oestrogen, and subsequent influences on the intestinal calcium absorption could be one of the major protective mechanisms of oestrogen against osteoporosis (Liel et al. 1999).

The ability of oestrogen and oestrogen analogues to reduce the blood and urine levels of calcium in patients with HPT has long been recognised (Gallagher & Nordin 1972, Herbai & Ljunghall 1983, Herbai & Ljunghall 1984). Withdrawal of such a chronic medication, however, has resulted in rebound increases in the calcium levels within days to weeks (Marcus et al. 1984, Haldimann et al. 1982). Moreover, increased levels of serum PTH have been reported occasionally (McKane et al. 1995). Responses of the alkaline phosphatase activity and the urinary hydroxyproline excretion indicate a beneficial effect on the bone turnover, but ERT should not be expected to induce a true remission of HPT (Marcus et al. 1984, Selby & Peacock 1986). Progestins may have similar effects on the mineral metabolism and have been

tried in the treatment of HPT (Gallagher & Nordin 1975, Selby & Peacock 1986, Horowitz et al. 1987). Progesterin also can reduce the bone turnover, but its improvement of the calcemia and calcuria seems less reliable or complete in comparison with the oestrogens (Marcus 1991). Studies also have demonstrated that ERT can revert the bone mineral density and bone mass towards normal in postmenopausal HPT (McDermott et al. 1994, Guo et al. 1996, Gray et al. 1996A, Diamond et al. 1996A).

**Conservative surveillance in HPT**

The natural history might reflect many of the expectations on the outcome of conservative surveillance in HPT. Lessons from the past suggest that a significant proportion of the patients under such circumstances would develop complications involving a marked hypercalcemia, recurrent renal stones, and severe skeletal deformities. However, the nature of the disease may have changed over time. A hypothetical explanation for such a shift may relate to an improved vitamin D and calcium balance in the population, since HPT of developing countries mimics the experiences from the past (Soin et al. 1994, Silverberg & Bilezikian 1997). Alternatively the currently improved standard of care or other factors prevent the patients from developing such a severe disorder.

Conservatively managed patients with HPT have been recruited from screening surveys (Christensson et al. 1986A, Palmer et al. 1988A) and as hospital referrals (Purnell et al. 1971, Scholz & Purnell 1981, Corlew et al. 1985, Heath 1991, Parfitt et al. 1991). Their generally mild hypercalcemia was found to remain stable over time without any apparent deterioration of the kidney function. Few cases experienced progressive hypercalcemia, underwent parathyroidectomy, or developed complications (Scholz & Purnell 1981, Heath & Heath 1991, Rubinoff et al. 1983, Åkerström et al. 1997). Neither of these alterations, however, can be predicted in the individual cases (Corlew et al. 1985), and they can occur unexpectedly also in those who are monitored carefully (Corsello et al. 1991). Another sign of progressive HPT has been the occurrence of an increased serum PTH level despite that serum calcium has remained stable (Rudnicki & Transböl 1992).

Patients with conservatively managed HPT have substantiated persistent elevation of the diastolic and systolic blood pressures (Christensson 1986), and an increase in the incidence of hypertension in comparison to controls (Rubinoff et al. 1983). A significantly reduced BMD of the forearm has been reported to be unaltered, whereby it has been hypothesised that the bone loss occurs early in HPT and that the disease progression may be biphasic (Rao et al. 1988, Parfitt et al. 1991). The patients substantiate psychic symptoms upon detailed examination, but little is known about the development of these symptoms over time (Joborn et al. 1989A). Increased mortality has been found in hypercalcemic cases less than 70 years of age, but the presence of HPT was not biochemically or operatively verified in the majority of the cases (Palmer et al. 1987A). Consistent with most findings in HPT, however, the mortality was

related to the degree of hypercalcemia and cardiovascular diseases dominated as the cause of death (Palmer et al. 1987A). It has been concluded that conservative surveillance of HPT often is expensive, time-consuming, and difficult to maintain for longer periods of time (Scholz & Purnell 1981). Simplified management plans have been suggested with annual documentation of the blood biochemistry and the subjects' general well being (Heath & Heath 1991).

Bilezikian et al. recently have summarised their extensive personal experience of HPT (Silverberg & Bilezikian 1996, Silverberg & Bilezikian 1997), including a long-term prospective follow-up of a considerable number of patients (Silverberg et al. 1989, 1995A,B, 1996, Bil ezikian et al. 1994, Parisien et al. 1992, 1995). They conclude that the vast majority of patients with HPT are asymptomatic and that parathyroidectomy, still the only curative approach, is no longer the treatment of choice in all cases. Instead it has become increasingly necessary to utilise guidelines for the appropriate management of this common disorder. While such guidelines have been proposed in the NIH Consensus Document (NIH Consensus Conference Statement 1991), the gradually evolving understanding and experience of the modern forms of primary HPT necessitate an open mind for modification of these approaches. Population-based studies with structured evaluation and systematic follow-up seem warranted to provide a solid background for the future development in these respects.

## MATERIAL AND METHODS

### Screening and diagnosis of HPT

During a period of 17 months in 1991–1992, altogether 5 771 women between 55 to 75 years of age were offered analysis of the total serum calcium value in conjunction with a population-based screening mammography. Totally 5 202 women (90.1%) accepted to participate, and the 188 women with serum calcium $^{3}$2.55 mmol/L were analysed further. At this analysis of the women with serum creatinine <160 μmol/L (normal range, 64-106 μmol/L), no family history of hypercalcemia and a normal or elevated urine calcium excretion were regarded as probable HPT if any of the following requisites were fulfilled (i-iii); i, hypercalcemia (>2.60 mmol/L) combined with serum PTH $^{3}$25 ng/L; ii, total serum calcium 2.50-2.60 mmol/L and serum PTH $^{3}$35 ng/L; iii, serum calcium <2.50 mmol/L together with serum PTH above the upper reference limit (55 ng/L). The females with equivocal signs of HPT (n = 89) underwent reevaluation after six months with use of the same criteria for the recognition of probable HPT.

For each case a female with total serum calcium below 2.55 mmol/L and serum creatinine levels below 160 μmol/L was selected as control from the screened cohort by individual matching for age and quarter of the year for the biochemical investigation. None of the subjects had a history of malabsorption, and a single individual with lithium treatment had serum PTH of 70 ng/L (S-calcium 2.82 mmol/L). Cases and controls underwent extended evaluation for inclusion into a five-year treatment protocol. All cases and controls gave

informed consent to participate in the study, which was approved by the local Ethical Committee.

Histological verification of HPT was attained in 60 of the 61 cases subjected to parathyroidectomy, while one woman possibly had pathological parathyroid tissue outside the neck. Bilateral neck exploration and a generally conservative operative strategy were applied (Wallfelt et al. 1990B). All parathyroid specimens were evaluated by routine histology. Parathyroid adenoma was identified in the cases with a singularly enlarged parathyroid gland (upper reference weight 60 mg) with signs of hypercellularity and an abnormal fat distribution (Grimelius et al. 1998). Parathyroid hyperplasia was recognised when at least two abnormal parathyroid glands were found.

**Parathyroid tissue of operated cases**

The pathological parathyroid tissue of 57 of the operated cases was analysed further. These females were 65.5 ± 5.5 years old. They had undergone at least three determinations of the total serum calcium concentration and two or three analyses of the ionised plasma calcium and intact serum PTH values. Normocalcemic and hypercalcemic cases invariably exhibited a normal and an elevated level of total serum calcium, respectively. The remaining patients were considered to represent intermittent hypercalcemia with one (n = 14) or two (n = 7) elevated values of total serum calcium. All individuals demonstrated postoperative normocalcemia during evaluation for up to 2.5 years (mean, 1.1 yr.).

Cryosections of the parathyroid glands were reacted with the monoclonal anti-parathyroid antibody E11 and a conventional peroxidase-antiperoxidase technique (Juhlin et al. 1989, Bjerneroth et al. 1992). Cell suspensions were prepared enzymatically from the pathological parathyroid glands (n = 33 patients), and 10 normal human glands as described (Ridefelt et al. 1992). Cell viability routinely exceeded 95% upon Trypan blue exclusion. Cells were plated onto circular cover glasses and loaded for 30 min at 37°C with 1.0 µmol/L fura-2/AM for analysis of the cytoplasmic calcium concentration. Conventional microfluorometry with dual-wavelength excitation or the Magiscan image analysis system were used (Ridefelt et al. 1992, 1996). The cells were superfused at 37°C with buffer containing 0.5-3.0 mmol/L calcium. Emitted fluorescence was measured at 510 nm after excitation at 340 and 380 nm. Digital images were collected with an intensified CCD camera. The filter changer provided a 340, 380 nm image pair every 3.5 sec. The emission ratio at 340/380 nm excitation and a $K_d$ of 224 nM for the calcium-fura-2 complex were used to calculate the cytoplasmic calcium concentration (Grynkiewicz et al. 1985).

PTH release was determined in duplicates by incubations for 30 min at 37°C of 0.5-1.0 x $10^6$ cells. PTH was assayed radioimmunologically using a sheep antiserum raised against human PTH with $^{125}$I-labelled 44-68(Tyr) human PTH as tracer and human PTH (1-84) as standard. The assay mainly detects the mid-C region of human PTH (Jüppner et al. 1983). In

individuals providing enough cells (n = 20), calcium regulated set-points were calculated as the concentration of external calcium between 0.5-3.0 mmol/L, which provided half maximal effects on the steady-state cytoplasmic calcium concentration (3-5 analyses per specimen) and PTH release.

**Extended evaluation of cases and controls**

Altogether 102 cases and 95 controls underwent the extended evaluation, which included a medical history, physical examination, extensive biochemical investigation, and determination of BMD. Information was gathered by questionnaires on smoking habits, medications, and illnesses including fractures after the age of forty in the individuals and their parents. Seven cases (nine controls, not significant) had oral oestrogen supplementation, and 26 patients (five controls, $p = 0.0001$) received thiazides. Inquires were made on childbirth, oral anticontraceptives, and perimenopausal symptoms. The interval between the menopause and diagnosis of HPT differed by $5.1 \pm 3.9$ (SD) years in the case-control pairs. The daily physical activity and physical demands in current and previous occupations were scored arbitrarily from one to three. The clinical examination included measurement of the blood pressure, and hypertension was defined as systolic and diastolic pressures exceeding 160 and 95 mm Hg, respectively.

Inquires were made in the cases and controls to determine the presence or absence of symptoms commonly related to HPT. This included a history of kidney stones, muscular weakness, pain from muscles, bones or joints, increased fatigue, loss of energy, mental depression and failing memory during the last year. The Hopkin's Symptom Checklist (HSCL, Derogatis et al. 1974) and a modified version of the Comprehensive Psychopathological Rating Scale (CPRS, Åsberg et al. 1978) were utilised to detail mental symptoms during the last week. Bone mass was determined by dual energy X-ray absorptiometry (DEXA) with estimates for total body, lumbar spine (L2-4) and separately for the cervical neck, Ward's triangle, and the trochanter region of the hip. Regional body composition was expressed as percent fat, and the BMI was calculated.

**Prediagnostic sick leave in HPT**

Five years before the HPT screening neither the case nor the control had retired in 48 (44%) of the case-control pairs. The duration, cause, and type of sick leave were investigated in these pairs during the five-year period preceding the screening. The information on sick leave was provided by the Regional Social Insurance Office, which handled all sick leave information in the investigated population. The probable presence of HPT during this time period was unknown to all the cases. Three of the cases and the same number of controls were housewives at the time of the screening. The case or control of altogether 27 pairs retired because of diseases (9 cases, 5 controls) or age (3 cases, 10 controls) during the five-year period. Both the

case and control were excluded from analysis from the date of any full-time retirement in the pair to ensure equal years at risk for sick leave. Partial retirement (6 cases, 2 controls) was disregarded. Cases retiring during the study had similar serum calcium and PTH values as those completing the five-year analysis. The total duration of follow-up encompassed 348 person years with an individual mean of 3.6 ± 1.6 (SD) years.

The total duration of sick leave for each woman was divided by the length of follow-up within the study to standardise for variability between the case-control pairs. Benefits on full- or half-time, and short- or long-time (>1 week) were partially exclusive, and the recorded days for a particular sickness benefit were divided by the number of days at risk for this particular benefit type (sickday proportion). Physician's certificate on the cause of sick leave was required only for periods longer than one week. The diagnoses were grouped according to ICD9 and could be retrieved for 93% of the periods of long-time sickness benefit.

**Treatment of HPT**

Altogether 92 case-control pairs entered into the treatment study. Cases with serum calcium below 3.0 mmol/L and no marked symptoms of HPT underwent parathyroidectomy, HRT (oral oestradiol, 2 mg; noretisterone, 1 mg), HRT combined with parathyroidectomy, and surveillance. Randomisation between the regimens failed mainly because cases refused surgery or were considered an unacceptable operative risk (n = 30), and because of contraindications to HRT (n = 34). Thus cases without contraindications to HRT received this treatment with the intent to parathyroidectomise every second of those eligible to surgery after 3-9 months of HRT. All eligible cases were recommended parathyroid surgery at the one-year recall examination. Five cases were referred for immediate parathyroid surgery due to overtly symptomatic HPT and more extensive hypercalcemia. Examination of the other case-control pairs was performed one year (11.6 ± 1.11 (SD) mo), two years (29.3 ± 4.7 mo), and five years (67.9 ± 4.7 mo) after diagnosis. The control female was excluded from the study when the corresponding case was unable to attend the recall examination.

The one-year recall examination involved 84 case-control pairs. Twenty cases had utilised HRT for 10.8 ± 1.2 months, twelve had undergone parathyroidectomy 3.2 ± 2.0 months before the follow up and nine of them also had received HRT for 10.4 ± 0.9 months. Totally 52 cases had received no active treatment. The two-year examination included 82 cases and 81 controls. Parathyroid surgery had been performed in 43 cases (12.4 ± 7.6 mo before the examination), and 7 of them had maintained HRT during 21.0 ± 9.8 months. Four cases had been treated with HRT only (26.8 ± 4.79 mo), and 35 cases had undergone no active therapy. The five-year examination involved 69 cases and 62 controls. Altogether 49 cases had been surgically treated 46.0 ± 12.2 months before the investigation, and eleven of them also had received HRT during 31.4 ± 20.3 months. Three cases were on HRT alone and another 17 had undergone no active treatment.

Cases excluded during the study were older than those eligible to the five-year investigation (69.8 vs. 66.1 yr, $p = 0.03$), while there was no such difference among the controls (68.4 vs. 66.3 yr). Twenty controls had received HRT for variable periods of time during the study. Thiazides were utilised at the last encounter by twenty-two cases and four controls ($p = 0.0004$), and one case (two controls) had vitamin D or oral calcium supplementation. A single control fulfilled the biochemical criteria of HPT at the five-year examination.

**Protocol violations and drop outs**

The offer of calcium screening was accepted by 5 202 females (90.1%), who represented 71% of those invited to the mammographic screening. Among the 188 females with serum calcium $^{3}$2.55 mmol/L, 12 potential cases violated the study protocol. Seven of these women fulfilled the criteria of probable HPT, while the others were inconclusive in this respect. Seven controls were matched to two cases each due to late failure of the primarily selected ones to comply with the study. Out of 102 cases eligible for the extended examination, exclusion from the treatment study was performed for seven cases due to many years of HRT, recurrent HPT after previous parathyroidectomy ($n = 2$), and because of recently diagnosed malignancy ($n = 1$). The mean serum calcium concentration at diagnosis (2.58 vs. 2.58 mmol/L) did not differ between the excluded cases ($n = 17$) and those entering ($n = 92$) into the treatment study.

During the first year of treatment, one case chose to leave the study and two died. During the second year, a case and control left the study and another case died. The five-year examination involved 69 cases and 62 controls, since eight additional cases (four controls) had migrated or refused participation, and five cases (three controls) had died.

**Blood and urine analyses**

Blood and urine were collected after an overnight fast, with the exception of the screening occasion where non-fasting serum calcium was sampled. Total serum calcium (normal range, 2.20-2.60 mmol/L), and urine calcium (normal range, 0.6-5.0 mmol/24 hours) were measured by ortocrescolophthalein dye binding. Serum calcium values invariably were corrected for deviation of the serum albumin level from the normal mean of females above 50 years of age (Benson et al. 1987). Ionised plasma calcium (normal range, 1.10-1.30 mmol/L) was measured with an ion sensitive electrode (Kone Instruments, Espoo, Finland) and intact serum PTH (normal range, 12-55 ng/L) with the Allegro immunoradiometric sandwich assay (Nichols Institute, San Juan, CA). A 24-hour urine sample or the second morning urine collection was used to determine the urine calcium - creatinine excretion ratio. Serum creatinine (normal range, 64-106 µmol/L) and the urine creatinine levels were analysed by a Jaffe´s method.

Triglyceride and cholesterol concentrations of whole serum and the lipoprotein classes were determined in a Technicon Auto Analyser II (normal range, cholesterol 2.6-7.1 mmol/L,

triglycerides 0.23-1.70 mmol/L). Clinical routine methods were used to estimate blood urate (normal range, 120-340 mmol/L), glucose (normal range, 3.3-5.7 mmol/L), hemoglobin A1c (normal range, 3.8-5.2%), total alkaline phosphatases (normal range, 0.8-4.8 μkat/L), hemoglobin (normal range, 113-139 g/L), erythrocyte number (normal range, 3.7-5.0 x $10^{12}$/L), volume fraction (normal range 35-44%), mean corpuscular volume (normal range, 80-102 fL), leukocyte (normal range, 4.0-9.0 x 109/L) and platelet counts (normal range, 150-400 x $10^{9}$/L).

**Bone density**

Bone mass was determined by dual energy X-ray absorptiometry (DPX-L, Lunar Radiation Corp., Madison, WI, USA) with estimates for total body, lumbar spine (L2-4) and separately for the cervical neck, Ward's triangle and the trochanter region of the hip. Regional body composition was expressed as percent fat, and body mass index was calculated by dividing the body weight (in kg) by the square of the body height (in m).

**Statistics**

Student's unpaired and paired two-tailed t-tests, $\chi^2$-test, ANOVA, and Wilcoxon nonparametric tests were utilised for statistical evaluation. The relationship between sick leave and case/control status was also analysed with logistic regression, whereby the variable sickday proportion was considered both in continuous and categorised forms. Correlations utilised Pearson's coefficients and $p<0.05$ was considered as significant. Values were presented as means and standard deviations or as standard error of the mean, and they were logarithmically transformed prior to tests of group means.

## RESULTS AND COMMENTS

**Prevalence of HPT**

Altogether 109 women or 2.1% of the screened population fulfilled the predetermined biochemical criteria of HPT. This proportion largely complied with previous health examinations of Nordic female populations aged ³60 years and ³75 years (Palmer et al. 1988A, Lindstedt et al. 1992, Sorva et al. 1992). A major discrepancy towards these studies, however, involved the currently combined use of intact serum PTH and calcium values as primary means of diagnosis, which enabled recognition of HPT accompanied by normocalcemia. Elevation of fasting serum calcium alone would have contributed to the recognition of HPT in only 0.71% of the screened population. This finding supported a previous notion a decreased prevalence of HPT during recent decades (Wermer et al. 1997). Another alternative is that normocalcemic HPT has become substantially more common, and there exist no previous studies on the prevalence of this variant of HPT.

The analysis of serum calcium was accepted by 90.1% of the women attending the population-based screening. These women represented 45% of the underlying population, since 71% of the invited women attended the screening mammography and since this examination is offered every second year. Similar rates of mammographic attendance have been found in other urban areas in Sweden (Nyström et al. 1993, Lidbrink et al. 1995). HPT has been associated with a moderately increased risk of breast cancer (Palmer et al. 1988B), and a lowered proportion of females with breast problems in the screened cohort hypothetically could lead to an underestimation of the prevalence of HPT. By use of the Swedish Cancer Registry, it was demonstrated that altogether 189 (4%) of the females in the screening cohort had received the diagnosis of breast cancer before the current examination.

Another possible problem with the recruitment relates to the fact that HPT had been detected and successfully treated in many females already prior to the current examination. Again the Swedish Cancer Registry substantiated that 26 (0.5%) of the examined women had undergone operation for parathyroid adenoma prior to the screening. Mean age of those who underwent the calcium screening (65.8 yr) was similar to that of all females (65.4 yr) scheduled for the screening mammography during the investigated time period. This finding is important, since the prevalence of HPT rises with age particularly in women (Christensson et al. 1976A, Palmer et al. 1988A).

**Normocalcemic HPT**

At diagnosis the cases were 66.6 ± 5.8 years old and had fasting serum calcium and PTH values of 2.32-3.19 mmol/L and 34-300 ng/L, respectively (Table 1). Altogether 66% of the cases exhibited a normal total serum calcium concentration. Thirty of them substantiated normocalcemia, i.e. serum calcium concentration within the reference range of the laboratory (2.20-2.60 mmol/L) upon repeated testing ($^3$3 occasions). The mean value (SD) for the entire cohort (n = 5 202) was 2.37 ± 0.09 mmol/L, and for the matched controls at follow up 2.37 ± 0.09, 2.39 ± 0.75, and 2.36 ± 0.09 mmol/L. These findings support that normocalcemic HPT, based on repeated testing, should be expected to be diagnosed in 0.58% of postmenopausal Swedish females, and that they comprise 27.5% of the postmenopausal women with HPT. It should be emphasised that the findings naturally could be altered substantially by the use of other criteria for the recognition of HPT.

**Table 1.** Number of females with HPT and their mean (±SD) blood calcium (mmol/L) and PTH values (ng/L) according to the three criteria for biochemical diagnosis of HPT

| Biochemical criteria of HPT | N | Calcium | | PTH |
|---|---|---|---|---|
| | | Total | Ionised | |
| Total calcium >2.60, PTH ³25 | 37 | 2.72 ± 0.15 | 1.33 ± 0.08 | 86.1 ± 54.4 |
| Total calcium 2.50-2.60, PTH ³35 | 55 | 2.54 ± 0.03 | 1.26 ± 0.04 | 52.3 ± 15.0 |
| Total calcium <2.50, PTH >55 | 17 | 2.42 ± 0.05 | 1.23 ± 0.04 | 69.5 ± 10.4 |
| | 109 | 2.59 ± 0.14 | 1.28 ± 0.07 | 66.5 ± 36.3 |

**Diagnosis of HPT**

Diagnostic levels of intact serum PTH empirically were related to the serum calcium concentration to disclose HPT with minimal interference from other causes of hypercalcemia. In this context it is important to emphasise the strategy of repeated analyses during up to 11 months, the measurement of urinary calcium excretions, and the search for a family history (Nussbaum 1991, Lafferty 1991, Mallmin et al. 1991, Gunn & Wallace 1992). The cases revealed higher levels ($p = 0.0001$) of total and ionised calcium and intact PTH in blood, as well as urinary calcium excretions in comparison with the controls. The utilised criteria for the recognition of HPT included a higher serum PTH level when the total serum calcium concentration was lowered further into the normal range. Such an inverse relationship between serum calcium and PTH is uncharacteristic of HPT (Wallfelt et al. 1990A, Ljunghall et al. 1991C). Nevertheless the PTH level was positively correlated ($p = 0.0001$) to the total and ionised calcium values of the examined cases. It consequently could be assumed that the criteria of HPT diagnosis involved underestimation of the proportion of women with mild HPT, and that those with more substantial rise in serum PTH were over-represented among the recruited cases.

Altogether 61 of the cases were subjected to parathyroidectomy and the presence of pathological parathyroid tissue was verified in all but one of them. This operative failure exhibited biochemical signs of unequivocal HPT (S-calcium 2.62 mmol/L, S-PTH 80 ng/L) and supposedly had abnormal parathyroid tissue outside the field of exploration. Disregarding the five patients undergoing immediate parathyroid operation due to more extensive hypercalcemia and overt symptoms, the average calcium values were similar in the operated (2.59 mmol/L) and unoperated cases (2.54 mmol/L). Moreover these subgroups of women exhibited a similar mean age (65.9 vs. 67.7 yr) at diagnosis. These circumstances favour the presence of HPT also in the unoperated cases. They also suggested underestimation of the true prevalence of HPT, since negative operative findings should be expected to become gradually more common as the diagnostic criteria approaches the characteristics of euparathyroid individuals.

**Parathyroid tissue analysis**

Sixteen cases (28%) were normocalcemic among those providing parathyroid tissue for the experimental analysis, and another 20 (35%) and 21 (37%) of them exhibited persistent and intermittent hypercalcemia, respectively (Table 2). The total serum calcium value was 2.32-3.16 mmol/L (mean, 2.63 ± 0.02 (SEM) mmol/L) and intact serum PTH was 29-300 ng/L (mean, 71 ± 5.9 ng/L) in the cases. Mean weight of the abnormal parathyroid tissue was 584 ± 120 mg (84-4700 mg). It was numerically the smallest in the normocalcemic patients and correlated ($p = 0.001$) with the total serum calcium and serum PTH values (Wallfelt et al. 1990A, Ljunghall et al. 1991C).

Altogether 46 (81%) of the cases displayed parathyroid adenoma (mean weight, 604 ± 143 mg). The normocalcemic ones had the numerically highest proportion of chief cell adenoma, while hyperplasia was the least common in the persistently hypercalcemic cases (Table 2). This is consistent with previous examinations of normocalcemic HPT, although the relatively increased incidence of multiple gland involvement has varied (Johansson et al. 1975, Kristoffersson et al. 1987, Siperstein et al. 1992). Total weight of the hyperplastic parathyroid tissue was 504 ± 168 mg. It consisted of two (n = 9) or three (n = 2) abnormal glands in each patient, and the individual glands weighed 50-1 100 mg (mean, 231 mg). The commonly modest gland enlargement combined with the frequency of hyperplasia contributed to intraoperative difficulties in localisation of the glands and in the determining of the extent of their resection.

**Table 2.** Proportions of parathyroid adenoma and hyperplasia, and parenchymal characteristics in the cases with normocalcemia, and intermittent and persistent hypercalcemia

| Variable | Normocalcemia | Hypercalcemia | |
|---|---|---|---|
| | | Intermittent | Persistent |
| | n = 16 | n = 21 | n = 20 |
| Adenoma, % | 75 | 76 | 90 |
| chief cell, % | 92 | 87 | 79 |
| oxyphil cell, % | 8 | 13 | 21 |
| Chief cell hyperplasia, % | 25 | 24 | 10 |
| nodular, % | 75 | 43 | - |
| enlarged glands per patient | 2.0 | 2.2 | 2.5 |
| Total weight, mg | 270 ± 31 | 448 ± 199 | 981 ± 249 |

Examination with the E11 antibody displayed the characteristically abnormal immunoreactivity of the pathological parathyroid tissue (Juhlin et al. 1988, 1989, Bjerneroth et al. 1992). Consistent differences could not be seen between the specimens from the cases with normal or elevated serum calcium levels. The set-point for the cytoplasmic calcium

concentration was the least elevated in the normocalcemic cases. This finding was expected considering the correlation ($p<0.01$, 0.001) between this set-point and the total and ionised calcium levels in blood of the patients (Wallfelt et al. 1988B). Set-point for the PTH release was also numerically the least increased in the normocalcemic cases. Taken together this characterisation substantiated the same type of derangement in the parathyroid tissue from cases with normocalcemic and hypercalcemic HPT. The variation in extent of the functional abnormality between the patient groups suggested that hypercalcemic HPT might be preceded by a period of an elevated serum calcium concentration in the normal range.

**Symptoms and signs of "asymptomatic" HPT**

Fewer cases (24%) than controls (43%, $p = 0.01$) had any of the predefined symptoms of HPT. This result supported that the evaluated cases represented asymptomatic HPT in the sense that they essentially lacked "traditional" symptoms of the disorder (Kleerekoper & Bilezikian 1994B, Rastad et al. 1995). Moreover it emphasised the difficulty to appreciate symptomatic HPT in the elderly and to determine the indication for surgery on the basis of routine clinical information. The registered symptoms and signs of HPT in this study might accurately reflect the disease in the target population, since the female cases were recruited without subjective causes for seeking the medical advice. The present coupling of mild HPT to the existence of mental symptoms, risk factors for cardiovascular diseases, and bone loss suggest reappraisal of the treatment strategy in postmenopausal females with mildly hypercalcemic, "asymptomatic" HPT.

*Medical history*

Despite that the presence of HPT was unknown to all the cases, they visited physicians more often ($p = 0.008$) than the controls. Systolic and diastolic blood pressures were similar in the cases and controls, and nine versus eight individuals in these groups met the criteria of hypertension. The cases had therapy for hypertension more often than the controls (33 vs. 19, $p = 0.02$), and altogether 41 cases (20 controls) had therapy that could lower the blood pressure ($p = 0.001$). The prevalent use of antihypertensive therapy possibly contributed to the similarity in blood pressures between the cases and controls. The cases and controls were similarly old at menarche (13.7 vs. 13.6 yr) and menopause (49.3 vs. 50.3 yr), but the cases had given birth to more children (2.5 vs. 2.0, $p = 0.02$). Fewer patients than controls had experienced menopausal complaints (53 vs. 69%, $p = 0.02$) and had used HRT (27 vs. 42%, $p = 0.03$). These findings contradict previous notions on a premature menopause in HPT (Christensson 1976), and implicate childbirth as a potential risk factor for postmenopausal HPT.

*Psychic symptoms*

Analysis with CPRS and HSCL displayed that the cases had more complaints of lassitude and lack of initiative ($p = 0.007$-$0.029$), fatiguability, sleepiness during daytime and feeling of weakness ($p = 0.032$-$0.013$), irritability ($p = 0.009$), and lack of sexual and emotional interests ($p = 0.009$-$0.022$). As in most other analyses, there was no simple relationship between the extent of these symptoms and the degree of hypercalcemia (Rastad et al. 1992). Sums of CPRS and HSCL scores, however, did not differ between the cases and controls. This part of the study suggested that also "asymptomatic" HPT is characterised by psychic disturbances, which might be appreciable upon specific questioning. It should be emphasised, however, that any alleviation of these symptoms by treatment needs to be demonstrated before any conclusions are drawn on the clinical significance of these findings.

*Bone density and body composition*

BMD was lower ($p = 0.0004$-$0.008$) in total body, hip and spine, and the alkaline phosphatases were higher ($p = 0.02$) in the cases than the controls. These findings support the presence of an increased bone turnover in menopausal females with "asymptomatic" HPT. Discrepant time intervals after the menopause might be a confounder in this respect, since no matching of the controls was performed according to the menopausal age of the cases. Although HPT in this study was coupled to no reduction in this age, the difference in BMD seemed to decrease with time after the menopause. Consistent with previous notions (Rao et al. 1988), it could be hypothesised that the loss of bone might be premature, nonprogressive, and occur rather early in the course of mild HPT, while BMD is slowly reduced over time in the controls. Furthermore the cases gave a history of less menopausal complaints. Their lower use of HRT might have contributed to the recorded discrepancies in BMD. Unlike others (Grey et al. 1994), we found no differences in body weight or the variables of body composition between the cases and controls.

*Blood lipids, glucose, and other laboratory data*

Triglycerides (total, VLDL), and VLDL cholesterol were higher ($p = 0.0001$-$0.008$) in the cases, while HDL cholesterol was lower ($p = 0.014$) than in the controls. Six cases and controls had diabetes mellitus. Serum glucose was higher ($p = 0.02$), while the hemoglobin A1c values were similar as in the controls. Cases had a higher blood hemoglobin value, erythrocyte number and volume fraction, leukocyte count, glucose, and urate levels ($p = 0.0001$-$0.02$) than the controls. The raised red and white blood cell variables coincide with notions on PTH as a stimulator of the bone marrow (Boivin & Bernard 1992).

**Prediagnostic sick leave in "asymptomatic" HPT**

The duration of sick leave differed significantly between the cases and controls, and it was longer ($p = 0.005$-$0.03$) in the cases for all benefit types, except for short-time. Long-term sick leave in the cases was the greatest for musculoskeletal and cardiovascular diseases, and differed significantly from the controls only for the cardiovascular diseases (Table 3). Diagnoses on physician's certificates of long-term sick leave have been considered reliable when gathered into major disease groups (Ljungdahl & Bjurulf 1991). Cardiovascular risk factors such as hypertension, hyperlipidemia, and glucose intolerance are recognised phenomena in HPT (Ljunghall et al. 1978, Lind & Ljunghall 1993, 1995A, Kumar et al. 1994, Taylor & Khaleeli 1997, Rodriguez-Portales & Fardella 1994, Schluter & Piper 1998, Valdemarsson et al. 1998), and cardiovascular disorders have been suggested to cause premature death of these patients (Ronni-Sivula & Sivula 1985, Palmer et al. 1987A, Hedbäck et al. 1990, Hedbäck & Oden 1998A,B).

**Table 3.** Duration (mean±SD, days) of long-term sick leave according to diagnosis in the 48 female cases and controls

| Disease group (ICD9)* | Cases | Controls | P** |
|---|---|---|---|
| Infectious | 3.2 ± 6.8 | 4.4 ± 10 | 0.931 |
| Mental | 14 ± 86 | 31 ± 122 | 0.441 |
| Circulatory | 111 ± 345 | 1.0 ± 5.4 | 0.017 |
| Respiratory | 1.2 ± 4.3 | 13 ± 54 | 0.136 |
| Gastrointestinal | 3.4 ± 11 | 2.1 ± 6.1 | 0.398 |
| Musculoskeletal | 169 ± 387 | 51 ± 148 | 0.162 |

*Sick leave was rare or absent for tumour, endocrine, neurological and urogenital diseases
**Wilcoxon signed rank test

The periods of sick leave on full-time (164 ± 348 vs. 26 ± 66 days) and long-time (220 ± 387 vs. 71 ± 112 days) were longer in the cases compared with the controls ($p = 0.010$, 0.046), while no difference in the frequency of sick leave periods was found. Cases were on sick leave for 17% of the investigated time, while the corresponding 7% in the controls approached the value of all postmenopausal Swedish women (Swedish Insurance Board 1996). Short-term sick leave has been found to relate mainly to intercurrent infections (Hörnquist et al. 1990). Sickness benefit during half or more of the available days was substantially more common among the cases (27% vs. 2%). The odds ratio for having a sickday proportion of at least 0.50 (i.e. sick leave for at least half of the available days) was 11.9 (95% confidence interval 1.4-105) for cases compared to the controls. The total duration of cases' sickness benefit was not correlated to age, or the serum calcium and PTH values.

HPT characteristically is a slowly progressing disease (Palmer et al. 1988A, Ljunghall et al. 1991A, Parfitt et al. 1991, Wang et al. 1997), whereby a generally mild disorder probably existed in the cases during the entire observation period. The cases included into this analysis were representative of all the cases recruited by the screening with respect to the serum calcium and PTH values. However, they were younger than the other cases, who had retired from work more than five years before the screening occasion. Recall bias was unlikely, since insurance data was utilised, and the cases were ignorant of the diagnosis of HPT during the investigated period of time. The recorded type and duration of sick leave and the differences in these respects between the cases and controls consequently could reflect true and previously unrecognised effects of HPT. These findings expand the current knowledge on a common disorder, and further investigations will have to reveal any impact on the strategy of treatment of HPT.

**Influences of treatment on calcium and PTH in "asymptomatic" HPT**

At inclusion into the study, the subgroups of cases allocated to the different treatment regimens differed with respect to some of the investigated parameters. In particular the cases subjected to conservative follow up tended to be older and to exhibit lower blood calcium values compared to those receiving the active therapies. However, there were no significant discrepancies between the cases receiving HRT and the other two active treatments during the first year, and a discrepancy only in the serum creatinine value between those subjected to parathyroidectomy with and without HRT at the two-year investigation. The number of cases undergoing parathyroid surgery during the first study year (n = 3) and those subjected to HRT at the two- and five-year investigations (n = 3, 4) were too small to allow any conclusions.

*Parathyroidectomy with and without HRT*

The cases subjected to mere parathyroidectomy (n = 36, 38) before the last two follow-up examinations demonstrated significant reductions in total and ionised calcium, and PTH values in blood. These reductions normalised the difference between the cases and controls at entry into the study. Four normocalcemic cases had elevated serum PTH (62-89 ng/L) and three additional cases fulfilled the biochemical criteria of HPT postoperatively. The cases allocated to HRT and parathyroidectomy (n = 7-11) demonstrated significant reductions in the blood and urine calcium levels, and serum PTH on all the follow up examinations. The treatment normalised the difference towards the controls at the beginning of the study. One normocalcemic case had elevated serum PTH at the two-year follow up, and subsequently fulfilled the diagnostic criteria of HPT. No significant differences were recorded at the two- and five-year examinations between the cases subjected to parathyroidectomy with and without the addition of HRT.

*HRT and conservative follow up*

There were significant reductions (p = 0.0001-0.002) in the total and ionised calcium values in blood in the HRT subgroup, although the differences toward the controls (p = 0.0001-0.001) persisted at the one-year examination. Moreover there was a significant reduction (p = 0.02) in the urine calcium excretion and a trend to an increased serum PTH level. These actions were consistent with previous notions on HRT (Diamond et al. 1996, McDermott et al. 1994, McKane et al. 1995). Surgery in combination with HRT lowered the blood calcium and PTH levels to a significantly greater degree than HRT alone during the first year. The significant differences between the conservatively followed cases and their controls persisted throughout the study as could be expected from previous studies (Palmer et al. 1988A, Scholz & Purnell 1981, Parfitt et al. 1991, Rao et al. 1988, Corlew et al. 1985). A similar stability over time was noticed in the controls. When all controls were considered together, a decline in the ionised plasma calcium level and a rise in serum PTH were found at the five-year examination. One of the controls developed biochemical signs of HPT.

Cases who left the study for any reason were older than those carrying it through (69.8 vs. 66.1 yr), but there was no significant difference in their serum calcium concentration at the study entry. Medications influencing the calcium homeostasis were utilised, especially by the cases. The most common of these were thiazides, which can lower the urine calcium excretion (Klimiuk et al. 1981, Lafferty 1991). Exclusion of the case-control pairs in which the case (n = 22) or control (n = 4) utilised this medication did not alter the pattern of significant differences between the treatment subgroups. The same held true when only cases with serum calcium lower than 2.70 mmol/L at study inclusion (n = 74) were analysed.

This prospective case-control study underlines that parathyroid surgery is the only available mode of treatment for primary HPT, which can be expected to render basic variables of the calcium homeostasis indistinguishable to those of matched controls. Further analysis on symptoms of HPT, bone mass, cardiovascular risk factors, and ultimately survival will display any clinically relevant benefits from this normalisation in postmenopausal females with mild HPT.

## GENERAL SUMMARY

* Primary hyperparathyroidism (HPT) is a common endocrine disorder and postmenopausal females comprise a risk group. A cohort of women, 55-75 years old, was analysed for the prevalence, clinical characteristics and treatment of HPT. The female cases and their matched controls were recruited in association with population-based screening mammography.

* The prevalence of HPT was 2.1% in the postmenopausal women. The disease was diagnosed biochemically by repeated analysis of serum calcium values and intact serum parathyroid hormone (PTH) concentrations. Moreover absence of a substantially elevated serum creatinine value, a low urine calcium excretion, and a family history of hypercalcemia were required. The presence of pathological parathyroid tissue was verified in 60 out of 61 cases subjected to parathyroid surgery. The findings indicate that the presently utilised biochemical criteria are associated with underestimation of the prevalence of HPT, despite the fact that they extended into the normocalcemic range.

* Normocalcemia was present in 66% of the cases at diagnosis and almost one third of them substantiated persistent normocalcemia on repeated biochemical testing. Normocalcemic HPT consequently could be expected to occur in about 0.5% of postmenopausal Swedish females. The virtually consistent demonstration of abnormal parathyroid tissue in the surgically explored cases underlines that only a fraction of the cases with normocalcemic HPT were recognised.

* Examination of the pathological parathyroid tissue from normocalcemic cases, and patients with intermittent and persistent hypercalcemia demonstrated the characteristic functional and morphological abnormalities of HPT. These findings support that hypercalcemic HPT may be preceded by a period of PTH hypersecretion with elevation of the serum calcium concentration within the normal reference range.

* All the recruited cases were unaware of the existence of their biochemically mild HPT and simple questioning revealed no characteristic symptoms of the disorder in the majority of them. More detailed case-control examination nevertheless coupled HPT to significant psychic symptoms, bone loss, and risk factors of cardiovascular disease. These findings suggest reappraisal of the conservative treatment strategy in the overtly asymptomatic women with mild HPT.

* The requirement of sick leave has not been investigated in HPT, and it could be regarded as a coarse estimate of the morbidity of the characteristically slowly progressing disease. Case-control evaluation revealed an enhanced requirement of sick leave mainly due to cardiovascular diseases during five years before the diagnosis of HPT. In fact the odds ratio of being on sick leave for at least half the investigated period was almost 12 times higher in the cases than the controls. This influence of mild HPT provided new insights of the morbidity and economical impact of the disorder.

* Parathyroidectomy was the only treatment option that normalised the investigated indices of the calcium homeostasis in the postmenopausal females with mild HPT. Hormone replacement therapy reduced blood calcium levels moderately, tended to elevate the serum PTH level, and added no significant changes to the biochemical outcome of subsequent parathyroidectomy. Conservatively treated cases had essentially stable parameters over time. Further analysis on symptoms of HPT, bone mass, cardiovascular risk factors, and ultimately survival will display any clinical relevant benefits from this normalisation.

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