FONDAZIONE
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MENARINI

FLORENCE

September 19th - 21st, 2013

Palazzo Ximènes Panciatichi
Borgo Pinti, 68 - Florence (Italy)

4th International Workshop on:

THE MANAGEMENT OF ASYMPTOMATIC PRIMARY HYPERPARATHYROIDISM

Organized by

Università degli Studi di Firenze, Florence, Italy

Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

College of Physicians and Surgeons, Columbia University, New York, NY, USA

Fondazione Internazionale Menarini

ABSTRACT BOOK

Under the Auspices of:

REGIONE TOSCANA

COMUNE DI FIRENZE

UNIVERSITÀ DEGLI STUDI FIRENZE

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Historical overview

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Our meeting is focused on optimal management of hyperparathyroidism in 2013. Major advances have come through our ability to make reliable diagnosis by laboratory criteria alone; with this advance has come recognition that the disease is often much milder than the classic form of the disease with severe bone and renal involvement, raising new questions about optimal management.

Understanding this evolution in manifestations of hyperparathyroidism is best appreciated by reviewing historical perspective on the work, primarily of the last century, leading to the discovery of the parathyroid glands and eventual appreciation of their biological role, as well as subsequent work on the chemical properties of parathyroid hormone. In turn these advances led to understanding of the pathophysiologic consequences of excess or deficient parathyroid hormone and even the surprising finding in this century that parathyroid hormone can have unexpected therapeutic application in osteoporosis if administered in an appropriate dosing regimen.

There are fascinating aspects of the early work on the parathyroids and their biological role. There were intense controversies and debates and moving personal stories involving some of the pioneers. Much of the drama has been captured eloquently by Jorgen Nordenstrom in his recently published monograph, cited in the reference list below.

Although the parathyroids were first identified in a rhinoceros, credit for their identification in humans belongs to Ivar Sandstrom. Sadly, his discovery attracted very little attention, his hoped-for academic career did

not develop, and he ultimately committed suicide after wrestling with multiple personal problems.

It took another 40 years until the physiological role of the parathyroids and the pathophysiology of hormone excess and deficiency were finally clarified. In Europe, enlargement of the parathyroid glands was seen in bone disease but it was unclear whether it was the cause or effect of the bone disease. It was well established that removal of the parathyroid glands in animals led to tetany. Surprisingly, the view that the tetany was due to hypocalcemia was not accepted by many, in part because extracts of the gland failed to reverse the tetany. The problem was finally resolved by Collip when he deduced that the reason extracts of the parathyroids were inactive when injected was that the water-based extraction methods were too weak to release the active principle (which we know as parathyroid hormone). When he turned to hot acid extraction, he was able to reliably produce active extracts that would reverse tetany in parathyroidectomized animals. There was controversy here, also however, because Hansen claimed priority for the acid extraction technique. Collip received the bulk of the credit because of his academic status and, in fairness, because he was able to definitively demonstrate reversal of hypocalcemia with his PTH extracts, which Hansen without real resources struggled to show.

Now, over 80 years later, hyperparathyroidism is now readily recognized and definitively diagnosable prior to surgery. It presents a new set of management problems (is surgery always indicated?) because of the mildness of the disease in many patients. As will be discussed, although symptomatic bone and renal disease is rare, other issues about the potential deleterious consequences of untreated hyperparathyroidism even in the absence of symptoms arise and will be the subject of discussions by the assembled experts.

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Epidemiology of Primary Hyperparathyroidism

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Primary hyperparathyroidism (PHPT) is the third most common endocrine disorder. The epidemiology of this disorder is increasingly well understood, but significant limitations still exist in our understanding of the mortality, hospitalizations, incidence, prevalence, and costs associated with this condition. These limitations are due to the small number of population-based epidemiologic studies that have evaluated this condition. Further studies will be required to fully characterize the epidemiology of PHPT.

Mortality

In the U.S. population, PHPT appears to cause mortality much less often than morbidity. In 2005, only 83 deaths were reported in the U.S. due to hyperparathyroidism and other disorders of the parathyroid gland identified using the ICD-10 code E21.3, with most of these attributed to unspecified hyperparathyroidism (1). The total number of deaths from all causes in the U.S. in 2005 was around 2.4 million, for an estimated crude death rate for hyperparathyroidism of 0.35 per million per year. More accurate estimates of mortality due to PHPT based on death certificates are impossible to obtain because death certificates are typically incomplete for endocrine disorders.

Whether survival is decreased following diagnosis of PHPT is less clear. In 435 Rochester, Minnesota, residents operated on for PHPT from 1965 to 1992, survival was not decreased, with 58% still alive at 20 years, compared to 58% expected (2). Patients were followed for a mean of 12 years with mean serum calcium of 11.2 mg/dL, but did not have decreased survival compared to age- and sex-matched controls. Similar findings were reported in another Rochester study between 1965 and 1992, in which subjects diagnosed with PHPT with mean serum calcium of 10.9 mg/dL (3). This study showed that relative risk of cardiovascular death was reduced by 40% compared to controls, but that higher maximum serum calcium levels independently predicted mortality, with survival decreased in older subjects or those with serum calcium greater than 11.2 mg/dL. A total of 113 subjects died at a median of 24 years after initial diagnosis, but only one of the deaths was attributed to PHPT, and the distribution of underlying causes of death in this cohort was similar to that expected based on causes of death in the general U.S. population. In another study from Finland, few deaths were directly related to complications of PHPT or parathyroidectomy (4). Even with a case-fatality rate as high as 0.4%, as reported in another study (5), less than 100 deaths in the U.S. each year are thought to be related to parathyroidectomy, with about 12,000 parathyroidectomies done each year.

Several studies from Scandinavia have shown that cardiovascular mortality is increased in patients with PHPT who have severe or moderately severe hypercalcemia. Another study showed that increased mortality appeared to decrease with time after parathyroidectomy, but persisted long after surgical cure, implying that PHPT caused long-lasting damage to the cardiovascular system.

A recent prospective, record-linkage, population-based, matched cohort study of subjects with untreated mostly mild asymptomatic PHPT was performed from 1997 to 2006 to assess mortality and morbidities in Tayside, Scotland (6). Subjects were matched to five general population-based controls for age, sex, and calendar year of PHPT diagnosis. Compared to controls, risks of all-cause mortality, fatal cardiovascular disease, and non-fatal cardiovascular disease were increased in patients. Risk was also increased for all secondary outcomes, with the risk of renal failure and renal stones being the highest. Another study of the Tayside, Scotland, population, showed that patients with PHPT had increased risk of all-cause and cardiovascular mortality (7). This study identified 1,683 (69.1% female) patients with mild PHPT. Patients had a significantly increased risk of developing cardiovascular and cerebrovascular disease,

renal dysfunction, and fractures compared to the age- and sex-adjusted general population.

Hospitalizations

Many more patients are hospitalized for PHPT than die of the disorder each year. In 1999, about 22,000 patients were diagnosed with PHPT (ICD-9 code, 252.0) at hospital discharge. In about 5,000 of these cases, PHPT was the first diagnosis listed. The incidence of hospitalization for PHPT was 8.0 per 100,000 per year, counting all-listed diagnoses, and 1.8 per 100,000 per year for only the first-listed diagnoses. The latter figure was 60 times the reported death rate of 0.3 per million that year for PHPT. The hospitalization rate for first-listed diagnosis of PHPT was 4.7 per 100,000 per year in 1977, 2.9 per 100,000 per year in 1986, and 1.8 per 100,000 per year in 1999.

Surgery

Parathyroidectomies (ICD-9 code, 06.8) were performed on about 12,000 hospitalized patients in the U.S. in 1999 (8). Although indications for surgery were not specified, the fact that there were many more parathyroidectomies than first-listed discharge diagnoses of PHPT indicates that PHPT accounted for a substantial proportion of "all-listed" hospitalizations. Most surgeries performed were recorded as partial parathyroidectomies, or the records did not specify the degree of completeness of parathyroidectomy. The crude parathyroidectomy rate was estimated to be about 4.4 per 100,000 per year. A study from Sweden reported an estimated parathyroidectomy rate of 5 to 10 per 100,000 per year between 1965 and 1979 (9). More recent data regarding time trends in surgery are not available.

Incidence

Studies evaluating the incidence of PHPT in various regions of the world have shown that the ascertainment rate is strongly dependent on the frequency of biochemical screening for serum calcium. The incidence of PHPT in Rochester, Minnesota, from 1966-2001 has varied over time (10). From 1966 until June 1974, the age- and sex-adjusted incidence of PHPT was relatively low at 15.8 per 100,000 person-years, with rates in men lower than those in women. In the second half of 1974, with the introduction of multiple channel biochemical analyzers, the incidence increased to an age- and sex-adjusted peak of 129 per 100,000 person-years. The peak was 175 per 100,000 in women, and 80 per 100,000 in men during July 1974-June 1975. From 1975 to 1982, the rate decreased to 82.5 per 100,000. From 1983 to 1992 it decreased to 29.1 per 100,000, and from 1993 to 2001 it decreased to 21.6 per 100,000. Despite the decline in incidence after 1974, the rate in 2001 remained greater than during the pre-biochemical screening era before 1974, and higher in women than men.

Adami et al. reported similar patterns of change in the number of patients diagnosed with PHPT after introduction of serum calcium measurement with routine biochemical screening in 1971 in Verona, Italy (11). The peak incidence was estimated at 78 per 100,000 person-years in 1973-1976, with a decreasing rate after 1976. A similar effect was seen in several other centers where this was evaluated.

In the pre-screening era from 1965-June 1974 in Rochester, Minnesota, 20% of patients presented with symptoms at the time of diagnosis, whereas from 1993-2001, 95% were asymptomatic with mild hypercalcemia. Patients diagnosed in 1965-1982 had mean serum calcium of 10.9 mg/dL, whereas patients diagnosed after 1983 had mean serum calcium of 10.7 mg/dL. In 1965-June 1974, 29% of patients had surgery, whereas in 1993-2001, 80% of patients were observed without surgery.

The mean age at diagnosis of PHPT in Rochester, Minnesota, remained between 52 and 56 years from 1965 until 2001. The female to male ratio of the incidence of PHPT in women to men from 1993-2001 was 2:1, with age-adjusted rates of 28.4 versus 13.8 per 100,000 person-years, respectively. The highest incidence rate of 99 per 100,000 during this interval was seen in women aged 65-74 years old. However, the increased incidence of PHPT in women did not occur until after age 45 years. Prior to age 45 years, the incidence in men was 7.7 per 100,000, and 6.0 per 100,000 in women. PHPT is rare in children and adolescents, but serum calcium may be quite high in adolescents and young adults. Despite the annual fluctuations in the incidence in PHPT seen in Rochester, a seasonal effect on the diagnosis of PHPT was not detected.

The incidence of the less common normocalcemic PHPT, and incidence of PHPT due to rare multiple endocrine neoplasia (MEN) types 1 or 2A and other rare genetic forms are yet to be described.

Prevalence

No population-based North American studies on the prevalence of PHPT have been published to date. In a large clinical series composed mostly of outpatients, the estimated prevalence of PHPT was 1 per 1,000 (12). This estimate was less than the prevalence of 4.3 per 1,000 measured on screening examinations in Sweden (13), 3.0 per 1,000 for Norwegians 75 years or older (14), and 21 per 1,000 in Finns 75 years or older (15). The prevalence estimates of PHPT in these three Scandinavian studies depended on the screening threshold for hypercalcemia. When the serum calcium threshold was lowered from 2.77 to 2.55 mM, with normal serum calcium defined as less than 2.5 mM, the prevalence of hypercalcemia increased in women in the 6th decade from 4.3 per 1,000 to 21 per 1,000 (13,16).

Results of prevalence studies are influenced by the age and sex of the population studied. In women aged 55-75 years, the prevalence of PHPT in one study was estimated to be 21 per 1,000, seven times greater than the prevalence in the general population of 3.0 per 1,000 (16).

The prevalence of MEN1 is estimated to be 2-3 per 100,000, but prevalence estimates have not been established for MEN2A or other rare genetic forms of PHPT.

Conclusion

It is clear that data describing the impact of PHPT on the U.S. and other countries are limited. Several estimates of the incidence of PHPT have been published over the past several decades, but no population-based estimates of prevalence. It therefore remains unclear whether there are secular or geographic variations in the occurrence of PHPT. Better longer-term studies are needed to fully describe the epidemiology of PHPT, particularly in regard to recent incidence rates, prevalence, and cost.

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Pathophysiology

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The parathyroid glands and the kidney are key sites for calcium sensing for the maintenance of normal blood cation concentrations in mammals. The physiological control of calcium homeostasis by parathyroid tissue encompasses: 1) the regulation of secretion by calcium in normal and abnormal parathyroid tissue; 2) the relevance of other secretagogues for parathyroid hormone (PTH); 3) the intracellular mediators regulating PTH release; 4) the recognized secretory products of the parathyroid glands; and 5) the genetic and epigenetic bases of parathyroid function and proliferation.

The extracellular calcium-sensing receptor (CaR) enables the parathyroid glands to sense changes in the circulating calcium levels and to respond with changes in function directed at normalizing the blood calcium concentrations. Several disorders of calcium-sensing arise from inherited or acquired abnormalities in the reset the serum calcium concentrations. Inactivating mutations produce inherited forms of hypercalcemia, while activating mutations cause hypocalcemic syndromes. Similarly, inactivating or activating antibodies directed at the CaR produce respectively hyper- or hypocalcemic syndromes. Finally, calcylitics induce PTH secretion, while calcimimetics were developed to inhibit PTH secretion in conditions of hyperparathyroidism.

In addition to PTH the parathyroid cell is able to secrete several proteins and peptides, whose physiological function remains unknown.

The two recognized intracellular messengers that have received the greatest attention in the parathyroids are cAMP and cytosolic calcium.

While calcium is of major importance in the regulation of PTH release, a host of other factors were demonstrated able to modify the hormone secretion. The majority of these factors were originally defined *in vitro*, but for several of these an *in vivo* physiological relevance is not yet recognized.

Finally, recent findings defined the role of epigenetic regulation of parathyroid secretion and proliferaion through RNA interference.

A detailed consideration of all these factors will be presented and discussed.

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Genetic syndromes associated with primary hyperparathyroidism (PHPT)

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Primary hyperparathyroidism (PHPT) may occur as part of a complex syndrome, e.g. as part of a multiple endocrine neoplasia (MEN) syndrome, or as an isolated endocrinopathy, which is referred to as familial isolated hyperparathyroidism (FIHP) (Table 1)[1,2]. PHPT associated with complex syndromes, which may be inherited as autosomal dominant traits, comprise: MEN1, a disorder characterised by the combined occurrence of tumours of the parathyroids, pancreatic islets and anterior pituitary[1,3]; MEN2 (also referred to as MEN2a) a disorder characterised by the combined occurrence of medullary thyroid carcinoma (MTC), phaeochromocytoma and parathyroid tumours[4]; MEN3 (also referred to as MEN2b), a disorder characterised by the combined occurrence of MTC and phaeochromocytoma with rare occurrence of parathyroid tumours, but instead an association with a Marfanoid habitus, mucosal neuromas, medullated corneal fibres, and intestinal autonomic ganglion dysfunction leading to multiple diverticula and megacolon[1,4]; MEN4, a disorder characterised by the combined occurrence of parathyroid and anterior pituitary tumours in association with tumours of the gonads, adrenals and kidneys[1]; and the hyperparathyroidism-jaw-tumour (HPT-JT) syndrome, a disorder characterised by the combined occurrence of parathyroid tumours, which are often carcinomas, and ossifying jaw-fibromas in association with uterine tumours, renal tumours and rarely pancreatic adenocarcinomas, testicular mixed germ cell tumours and Hurthle cell thyroid adenomas[5] (Table 1). These syndromic forms of PHPT are due to mutations (Table 1) as follows: MEN1 is caused by abnormalities of a tumour suppressor, menin, located on chromosome 11q13, which is involved in transcriptional regulation, genome stability, cell division and

proliferation; MEN2 and MEN3 are due to mutations of RET, which encodes a tyrosine kinase receptor (TKR); MEN4 is due to mutations of CDNK1B which encodes the cyclin-dependent kinase inhibitor (CKI) p27kip1; and HPT-JT is due to mutations of parafibromin, also known as cell division cycle 73 (CDC73), which has a role in a key transcriptional regulatory complex that interacts with RNA polymerase II[1-5]. PHPT as an isolated endocrinopathy may occur as FIHP, which may be due to heterozygous mutations of menin, parafibromin or the calcium-sensing receptor (CaSR) or as neonatal severe primary hyperparathyroidism, which may be due to homozygous or compound heterozygous mutations of the CaSR, which is a G-protein coupled receptor (GPCR) [1,6-8]. Moreover, it is important to note that ~10% of patients presenting, below the age of 45 years, with non-familial (sporadic) PHPT may also have a de novo germline mutation of menin, parafibromin or CaSR[9], and this has implications for their future management, in requiring screening for the occurrence of tumours associated with the specific syndrome (Table 1), as well as for screening their children who may inherit the germline mutation. In summary, PHPT may occur as part of the hereditary syndromes of MEN1, MEN2, MEN3, MEN4 and HPT-JT, or as an isolated endocrinopathy due to mutations of menin, parafibromin or CaSR.

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Table 1

Genetic Disorders Associated with Primary Hyperparathyroidism (PHPT)

Disorder *	Gene/Protein	Chromosomal Location
MEN1	Menin	11q13
MEN2&3	RET	10q11.2
MEN4	CDKN1B(p27,KIP1)	12p13
HPT-JT	Parafibromin	1q31.2
FIHP	Menin, Parafibromin, CaSR	11q13, 1q31.2 3q21.1
NSHPT	CaSR	3q21.1

Multiple Endocrine Neoplasia (MEN), Hyperparathyroidism-Jaw Tumour (HPT-JT), Familial Isolated Hyperparathyroidism (FIHP), and Neonatal Severe Primary Hyperparathyroidism (NSHPT).

* Inheritance of all disorders is Autosomal Dominant , but NSHPT can be recessive.

Diagnosis: utility of the PHT assay

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Circulating PTH molecular forms have been progressively identified by 3 generations of PTH assays (1, 2, 3). The 1st generation of PTH assays was responsible for the description of circulating PTH immunoheterogeneity (4). These assays used various tracers, various standards and varied in their capacity to separate primary hyperparathyroidism from malignancy associated hypercalcemia (5). A study in veals performed with a N-and a C-assay, demonstrated that PTH(1-84) was the main form of PTH in hypocalcemiaand in large amount. In normocalcemia, there was a decreased in the amount of circulating PTH(1-84) and C-fragments became more evident. Finally, in hypercalcemia, circulating PTH was decreased and limited to C-PTH fragments (6). Small C-PTH fragments started their structure at amino-acids 34, 37, 41 and 43 of the bovine PTH structure (7), but at amino-acids 34, 37, 38 and 45 of the human PTH(1-84) structure (8). These fragments did not react with the type 1 PTH/PTHrP receptor (9). PTH(1-84) became the only molecular form to interact with the type 1 PTH/PTHrP receptor (10).

Second generation PTH IRMA caused a revolution. They used C-terminal antibodies linked to a solid phase and N-terminal revealing antibodies (2). They were easy to use, reliable and commercialized by Nichol's Institute. They were readily adapted by a majority of people. It is with this assay that we described that non-(1-84) fragments interfere significantly with intact PTH assays in uremic samples (11-13). The structure of these fragments started at positions 4, 7, 10 and 15 (14). They represented 45% of circulating PTH molecular forms in advance renal failure, but only 5% of circulating PTH in a normocalcemic individual measured with a first generation PTH assay (15). With this as well as with a carboxyl and a

mid-carboxylterminal assay, we demonstrated that a dynamic range of PTH values better discriminate patients with normocalcemic primary hyperparathyroidism than static PTH values (16).

Dogs given 1,25(OH)dihydroxyvitamin D_3 increased their C-PTH/I-PTH ratio while half-parathyroidectomy in dogs decreased the same ratio (17).Second and 3rd generation PTH assays were demonstrated to have a similar performance in detecting patients with primaryhyperparathyroidism (18).

In conclusion, we can state that PTH composition in a normocalcemic individual is made of 18% PTH(1-84), 2% N-PTH, 5% non-(1-84) PTH fragments, and of 75% small C-fragments missing a N-structure (15).

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Distinguishing Primary Hyperparathyroidism from Familial Hypocalciuric Hypercalcemia

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Primary hyperparathyroidism (PHPT) is a neoplastic disorder of the parathyroid gland(s) due to adenoma (85% of cases) or multigland disease (hyperplasia or multiple adenomas in ~14% of cases) with the remainder due to cancer (~1% of cases) (1,2). Familial hypocalciuric hypercalcemia (FHH) has 3 molecular etiologies. The pathogenesis of the parathyroid hormone (PTH) hypersecretion in FHH is defective extracellular calcium (Ca) sensing. Pathologically, all 4 glands show hyperplasia. FHH1, the commonest form of the disorder, is due to inactivating mutations in the coding sequence of the extracellular calcium-sensing receptor (CaSR) (~70% of cases) or in regulatory sequences in that gene in the remainder (3). FHH2 and FHH3 are due to loss of function mutations in the G protein alpha subunit 11 (GNA11) (4) and in adaptor protein 2 sigma 1 (5), respectively. All forms of FHH are rare (~1/100,000), while PHPT is relatively common disorder with prevalence as high as 1 to 3 per 1000 postmenopausal women.

The clinical presentation of both disorders is dominated by asymptomatic non-progressive hypercalcemia. This makes differentiating between mild PHPT and FHH in the individual patient quite challenging. One must carefully check the family history for the presence of hypercalcemia and the history of a prior parathyroidectomy that failed to resolve the hypercalcemia in the patient or a family member. One looks for autosomal dominant inheritance of hypercalcemia in families with FHH, recognizing that many affected individuals in families with the disorder will not have been detected and that sporadic mutations occur. Often in the initial evaluation of a patient who has failed for parathyroid surgery to resolve his hypercalcemia, one must initiate the screening of the available first-degree relatives.

Family screening and genetic testing for mutations in the CaSR, now widely available, can be both time-consuming and expensive (6,7). Therefore, the clinician must use the clinical features of PHPT and FHH to modulate the level of suspicion for the latter vs the much more common PHPT. FHH may become evident, like other forms of familial PHPT such as multiple endocrine neoplasia type 1 (MEN1), MEN2A, and the hyperparathyroidism-jaw tumor (HPT-JT) syndrome, at a much younger age than is the standard for PHPT. Average age of presentation for PHPT is in the sixth decade of life. The penetrance for hypercalcemia in FHH is high. Thus, screening a family of reasonable size should disclose other affected members with similar degrees of hypercalcemia who are also asymptomatic. The presence of the other classic tumors or conditions associated with MEN1 (pancreatic or pituitary), MEN2A (medullary carcinoma of the thyroid, pheochromocytoma, Hirschsprung's disease) or HPT-JT (various jaw tumor lesions) in the patient or other family members turns attention away from FHH as a cause for the hypercalcemia and points to one of these other much more concerning disorders.

Without a definitive family history of autosomal dominant hypercalcemia, the clinician must turn to a careful review of the available laboratory tests in the individual patient. Serum total or ionized Ca levels are usually mildly elevated or at the upper limit of normal for FHH. This is not a distinguishing feature from PHPT, although the higher the serum Ca level, the less likely the disorder is FHH. Intact PTH levels are often inappropriate for the elevated serum Ca but not frankly high in patients with FHH. Infrequently (~20% of patients), PTH levels are mildly elevated above the upper limit of normal. Serum phosphate may be slightly reduced in patients with FHH as it is in PHPT; this parameter is not helpful in differentiating the disorders. Serum magnesium may also be mildly elevated in patients with FHH but generally not in PHPT,

although this variable is not present consistently enough to be a reliable way to distinguish between the two disorders. All patients should have an assessment of vitamin D status with a 25-hydroxyvitamin D measurement. Should that level be low (e.g., less than 20 ng/ml or 50 nM) or frankly deficient (e.g., less than 10 ng/ml or 25 nM), levels of urinary Ca excretion, PTH, and phosphate can be affected and confuse the diagnosis.

The hallmark of FHH in its classic presentations is hypocalciuria. Earliest studies recommended the use of the renal calcium:creatinine clearance ratio (CCCR) to distinguish FHH and PHPT (7-9). This ratio is calculated from the simultaneous determination of serum Ca and creatinine and urinary Ca and creatinine from the appropriate samples by the following formula: urinary Ca X serum creatinine/serum Ca X urinary creatinineusing samples from a 24-hour urine collection (8). It was initially proposed that the majority of patients with PHPT manifest CCCR's of 0.01 or greater, while patients with FHH have CCCR's of 0.01 or less. It was recognized early on that there was overlap in this parameter between FHH and PHPT. Patients segregating at either ends of the spectrum could be more reliably diagnosed. Certainly the CCRR in non-parathyroid dependent hypercalcemia remained much higher than the contested range for FHH or PHPT.

As the spectrum of FHH has clarified itself in the present era with genetic identification of CaSR mutations as the benchmark for definitive diagnosis, it is increasingly clear that these CCCR cutoffs are not appropriate. It is also clear that a variety of clinical circumstances can affect urinary Ca excretion including dietary Ca intake, use of thiazide diuretics and lithium, and concurrent vitamin D deficiency. A sole biochemically-based diagnostic algorithm may simply not be feasible.Genetically proven FHH has been described in families with hypercalciuria and even with nephrolithiasis (10). Thus, a variety of measures of renal Ca handling have been proposed to differentiate PHPT from FHH. They include 24 hour urinary Ca excretion, Ca:creatinine excretion ratio, and theoretical tubular maximum Ca excretion as well as the CCCR. There is no evidence that these parameters outperform the CCCR in distinguishing FHH from PHPT. This issue was examined by Christensen et al (9). Based on their experience, up to 35% of genetically verified FHH patients have CCCR's of $\geq$ 0.01 and up to 24% of such patients have elevated PTH levels. Both parameters together would potentially persuade the evaluating clinician to make the diagnosis of PHPT. They analyzed the 3 indices of renal Ca excretion (CCCR, 24 hour urinary Ca, 24 hour Ca/creatinine excretion ratio) in 54 patients with genetically proven FHH and 97 patients with surgically proven/cured PHPT across a wide age range (19-86 years) (9). Their data indicate that the CCCR outperforms the other 2 renal indices in separating FHH from PHPT if the CCCR is less than 0.02. It is that group of patients whom these investigators recommended considering testing for CaSR mutations.

In summary, distinguishing between PHPT and FHH in an individual patient solely based on biochemical parameters is challenging. There are too many points of biochemical overlap. The clinician must consider the epidemiology of the two disorders, family history, and laboratory tests and at this point exercise clinical judgment as to when and in whom genetic testing should be done. The advent of cheaper and more widely available genetic testing may greatly simplify efforts to accurately make this diagnostic distinction in the future.

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Normocalcemic Primary Hyperparathyroidism

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Primary hyperparathyroidism (PHPT) is traditionally defined by hypercalcemia and elevated or inappropriately normal levels of PTH.[1,2] Over the past decade, a variant of this presentation has become widely recognized in which the serum calcium is consistently normal but the PTH is consistently elevated.[3-6] In the absence of any secondary causes for an elevated level of PTH, a likely diagnosis of normocalcemic PHPT (NPHPT) has been proposed. The existence of NPHPT supports a biphasic chronology of the clinical development of PHPT first put forward by Raoet al.[3] During the first phase, PTH levels are elevated but serum calcium is normal. The second phase has traditionally been recognized clinically because hypercalcemia surfaces. Although NPHPT was first formally recognized at the time of the Third International Workshop on the Management of Asymptomatic PHPT in 2008,[7] the entity remains incompletely described, particularly regarding its epidemiology, natural history, and management.

Most reports of NPHPT have come from referral centers in which patients have been already identified with, or suspected of, a metabolic bone disease.[8-12] These individuals, therefore, may not be completely representative of this disorder as originally proposed by Rao et al. They tend to have more skeletal involvement and, in general, be more symptomatic than patients with the most common asymptomatic hypercalcemic variant of PHPT. Unselected population-based studies are necessary for the identification of another proposed cohort of incidentally discovered patients with NPHPT. This presentation would be more akin to the manner in which most patients with hypercalcemic PHPT are discovered, namely incidentally.

The epidemiology of NPHPT has been investigated in a number of populations,[13-17] but interpretation of the data is confounded by differing methods used to exclude secondary hyperparathyroidism among the various studies. In general, the prevalence appears to be similar to the prevalence of hypercalcemic PHPT.

The diagnostic criteria for NPHPT should include consistently normal albumin-adjusted total as well as ionized calcium concentration.[5,6] Conditions resulting in secondary hyperparathyroidism must be excluded: 1) Vitamin D deficiency: The exact threshold value of 25-hydroxyvitamin that leads to an increase in PTH is controversial. The Institute of Medicine report[18] states that there is no conclusive evidence that 25-hydroxyvitamin D levels of ≤20 ng/mL are regularly associated with increases in PTH levels in population sampling. However, these studies are confounded by the lack of any prospective data that would track an individual's PTH level as the 25-hydroxyvitamin D level is increased from 20 to 30 ng/mL. To be confident that the elevated PTH level is not due to vitamin D insufficiency, it would seem advisable to ensure that the 25-hydroxyvitamin D level is consistently ≥30 ng/mL.Some individuals with PHPT and a normal serum calcium level will become hypercalcemic when 25-hydroxyvitamin D levels are normalized to levels ≥30 ng/mL. 2) Reduced creatinine clearance: Martinez etv al.[19-21] demonstrated that PTH begins to rise with a glomerular filtration rate (GFR) lower than 60 mL/min. It is also noteworthy that Walker et al.[22] have recently shown that in hypercalcemicPHPT, GFR<60 mL/min is associated with abnormal bone resorption and bone formation indices as determined by dynamic histomorphometric analysis of bone biopsies. Thus, it seems reasonable to require that GFR be higher than 60 mL/min if the diagnosis of NPHPT is to be substantiated. 3) Medications: Thiazide diuretics[23] and lithium[24] have both been associated with increased PTH levels and thus should be considered as a potential etiology for increased PTH levels in subjects on these medications. If it is safe to withdraw these drugs and the increased PTH level persists after several months, the diagnosis of NPHPT becomes more secure. 4) Hypercalciuria: Hypercalciuria as a primary renal abnormality can be associated with a secondary rise in PTH levels.[25] 5) Gastrointestinal disorders associated with calcium malabsorption: Usually, but not always, a malabsorption syndrome is clinically obvious.[26,27] A low normal serum calcium concentration, along with vitamin D deficiency and low urinary calcium excretion, can be clues to agastroenterological diagnosis.

Does NPHPT exist? Some patients with NPHPT have undergone parathyroid surgery. The demonstration that these subjects have clear parathyroid gland pathology substantiates the existence of NPHPT.[8,9]

There are no evidence-based guidelines for the management of NPHPT. One approach is to use current guidelines that are used for the management of the hypercalcemic form of PHPT.[7] This would lead to the recommendation of parathyroid surgery in some of these individuals. Monitoring guidelines in those who do not meet surgical guidelines would also follow the guidelines for the hypercalcemic variant of PHPT. At this workshop, it is anticipated that recommendations will be made either as pertaining only to NPHPT or to all forms of PHPT.

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Clinical Presentation of Primary Hyperparathyroidism in the United States

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Prior to the advent of the multichannel autoanalyzer in the early 1970's, Primary Hyperparathyroidism (PHPT) was characterized as a hypercalcemic disorder with classical, overt target organ involvement (1). Skeletal involvement was typified by radiological features such as the "salt and pepper" skull, an eroded distal 1/3 clavicle, subperiosteal bone resorption of the phalanges, brown tumors, and cysts. The serum calcium was often well over 11 mg/dL and the parathyroid hormone level (PTH) was concomitantly high. Kidney involvement was typified by nephrolithiasis and nephrocalcinosis. While this form of PHPT is still seen in the United States, it is most uncommon (2). Much more common is the form that is seen in connection with screening tests, in which the patient is not symptomatic nor is suspected of PHPT (3). The disease is discovered by accident. Asymptomatic PHPT has been the dominant clinical phenotype of PHPT in the United States for the past 40 years. Patients with PHPT still have target organ involvement but it is much less common as for example nephrolithiasis which has diminished in incidence to 17-20%. While skeletal involvement is not detected by X-rays anymore, it can be readily noted by dual energy X-ray absorptiometry (DXA). Classically, by DXA, lumbar spine bone mineral density (BMD) is relatively well preserved while the distal 1/3 radius is preferentially reduced. The proclivity of PTH to be more catabolic at the 1/3 radius, a cortical site, while much less so at the lumbar spine, a trabecular site, has given rise to the notion the trabecular skeleton is spared in this disease when it presents in its common asymptomatic form (4). Recent data obtained by high resolution imaging and other imaging modalities have raised questions about the selectivity of PTH to erode bone in PHPT (5-8). Non-specific symptomatology, which is frequently present but not easily attributable to PHPT, has led some investigators to search for ways in which new metrics can address this point (9-12). Asymptomatic PHPT has a natural history that includes long term, but not indefinite stability (13-14) and increases in BMD, after successful parathyroidectomy, at all three skeletal sites by DXA (15). In the United States over the past decade, yet another phenotype of PHPT has emerged due to an increasingly proactive approach to the evaluation of subjects with low bone density. In these subjects, the PTH level is typically measured as part of an extensive evaluation for low bone mass. Subjects are being discovered with elevated PTH levels despite consistently normal serum total and ionized calcium concentrations (16-18). These individuals do not have any known secondary cause for an elevated PTH level. This clinical phenotype is called normocalcemic PHPT. Over the past 10 years, the most noteworthy change in the presentation of PHPT in the United Sates is emergence of normocalcemic PHPT (19).

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Clinical presentation around the world: Europe

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Primary hyperparathyroidism (PHPT) is a frequent endocrine disorder around the world. There are no formal studies exploring the modalities used to characterize clinical presentation of PHPT in Europe even though there is no a priori reason to believe that the presentation differs within and between a defined area the world. However, PHPT in Europe may have different mode of presentation depending on the prevailing practice patterns (routine serum calcium determination for instance) and socio-economic conditions of the region. Another plausible reason is underlying variation in the degree of awareness of the condition among physicians and their ability to detect the disease.

In addition, many patients are now frequently diagnosed with PHPT during the routine evaluation of patients referred to tertiary care centers for the screening or investigation of the most common metabolic bone disease, osteoporosis. Our experience suggests that when these "asymptomatic" patients are thoroughly investigated further they frequently manifest both typical (i.e reduced bone mineral density, kidney stones) and atypical (cardiovascular, gastrointestinal) complications of the disease. The foregoing factors have important clinical implications for both identification of truly asymptomatic patients and development of "uniform" guidelines for management.

In this context we recently performed a comparative study of the biochemical and skeletal manifestations of PHPT in two Caucasian populations (US and Italian) of men and woman, matched for age and BMI in a retrospective cross-sectional observational study. Although the mean serum calcium levels were significantly higher in Italian men compared to women and Italians as a group compared to US patients, the

mean serum ionized calcium was similar. However, mean serum PTH levels did not differ either between the genders or between the countries. After adjusting for BMI, the mean BMD at the proximal hip in female US patients was significantly higher than in the Italian women. Thus it appears that despite similar levels of circulating PTH, Italian patients have more pronounced effects of the disease as assessed by serum total calcium, and more significant reductions in cortical bone in women as assessed by BMD (1).

In another recent study trying to address how PHPT impacts the Italian Hospital healthcare system, we found a decreased tendency in hospitalization from 2006-2011, most likely because of economic issues, but a concomitant increased in age of the patients, and most notably a progressive increase in the frequency of parathyroidectomy among patients admitted for PHPT (2).

Because of these regional differences in clinical presentation, detection rate, and prevailing practices, we believe that regions specific guidelines management of PHPT should be considered.

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Primary Hyperparathyroidism in Latin America

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In most Latin American countries available data on primary hyperparathyroidism are from case reports or small case series with the majority of patients being presented in the symptomatic form. During the last decade large series along with epidemiological studies have been reported especially from Brazil. In our institution, routine serum calcium measurements have now been used as part of medical examination for 30 years. In our first large report of 124 patients, 47% presented with no symptoms related to the disease, while 25% presented with severe skeletal involvement and osteitis fibrosa cystica, 25% with renal stone disease without overt bone involvement, and 2% with the typical neuropsychiatric syndrome. This same pattern was also seen in the city of Sao Paulo. Bone mineral density was extremely low in severely affected patients but showed remarkable recovery following surgical cure. Serum PTH and bone markers were considerably higher in these patients, who also had a high rate of vitamin D deficiency, and the parathyroid lesion was easier localized compared with asymptomatic patients. Regarding etiology, 87% had histological confirmation of a single adenoma, 6.4% multiple gland hyperplasia and 3.8% carcinoma. Data from Argentina in a series of 87 patients (78 females) of whom 44% had kidney stones, 83% of those sent to surgery had a single adenoma. Bone mineral density increased by 6.9% in lumbar spine and 3% in femoral neck 2 years after parathyroidectomy. We conducted an epidemiological study to determine the prevalence of PHPT in individuals attending public and private endocrine centers from the age of 18 years. The diagnostic criteria for PHPT were as follows: elevated serum calcium in two occasions plus serum PTH above 75o centile for the reference population (57pg/ml). From 4.207 patients we found a prevalence of 0,78% (95% CI 0,52-1,04) of which 81.8% were asymptomatic. The female/male ratio was 7.2:1,

and 89.7% of these women were postmenopausal. Mean age was 61.12 ± 15.73 years, serum calcium 10.63 ± 1.33mg/dl and serum PTH 182.48 ± 326.51 pg/ml. Osteitis fibrosa cystica was present in 6.1%; nephrolithiasis in 18.2% and acute neuropsychiatric syndrome in 3%; 51.5% had fatigue and 39.3% muscle weakness; 63.6% hypertension; 33% type 2 diabetes mellitus; 18.2% depression; 6.1% peptic ulcer and MEN-1. Normocalcemic primary hyperparathyroidism (NPHPT) is considered a variant of the more frequent form of the disease characterized by normal serum calcium levels associated with high serum PTH concentrations. From 70 patients with PHPT seen at our institution (33 normocalcemic and 37 with mild hypercalcemia),the frequency of nephrolithiasis was 18.2% in normocalcemic and 18.9% in the hypercalcemic patients (P = 0.937). Fifteen percent of normocalcemic patients had a previous history of fractures compared to 10.8% of hypercalcemic patients, although there was no statistically significant difference (P = 0.726). Conclusion: the presentation of PHPT is changing in Latin America particularly in Brazil where most epidemiological data are available, from a high rate of symptomatic disease towards a large number of asymptomatic patients as well as the normocalcemic variant.

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Primary Hyperparathyroidism in Asia

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Primary hyperparathyroidism (PHPT) has evolved from a traditional symptomatic disease into an asymptomatic disorder in United States and Europe since the 1970s. However, in Asian countries, like China and India, PHPT still presents in the classical way, namely with target organs, such as the kidneys and the skeleton affected and with more evident biochemical abnormalities. But a clear trend for PHPT to present more commonly as an asymptomatic disorder in China has been emerging over the past 5-10 years.

In Beijing, China, over a long period, 1958-1993, patients with PHPT demonstrated a much higher serum calcium level (12.4 ± 1.1 vs 10.7±10.7 mg/dl), and a remarkably higher elevated PTH concentration (21.4 vs 1.86 fold the upper limit of normal) than their American counterparts. Strikingly, 97% of the Beijing PHPT patients suffered from skeleton lesions (osteitisfibrosacystica, osteoporosis, and pathological fractures), kidney stones and other features of PHPT.

Recently, the changing clinical patterns of PHPT in Chinese patients from 2000 to 2010 have been reported. A total of 249 consecutive PHPT patients coming from 17 out of 31 provinces in China were diagnosed and treated from 2000 to 2010 in a single clinical center in Shanghai. As compared to patients from Western countries, Chinese patients were younger and less likely to be women (F:M, 2.07:1 vs approximately 3;1 in Western countries). Their serum levels of calcium (11.7±1.4 mmol/l), PTH [402 (103-2700) pg/ml, normal range 15-65pg/ml], and creatinine were all significantly higher, while serum albumin, 25(OH)D concentration [13(5.2-29.9)ng/ml] were much lower. Among all the PHPT patients, 60% of them manifested classical symptoms related with PHPT, such as polydipsia, polyuria, urolithiasis, bone pain, fatigue etc. Nearly 6% of PHPT cases in Chinese patients were malignant. Normocalcemic primary hyperparathyroidism was not identified.

Despite symptomatic PHPT still being common, there was a dramatic increase of asymptomatic PHPT cases in Shanghai cohort from less than 20% before 2006 to approximately 50% in 2007-2010. Such a change was mainly driven by more routine serum calcium testing and incidental discovery of a parathyroid nodule by neck ultrasonography.

Similarly, a survey in Hong Kong, China also demonstrated a steady increase in asympomatic PHPT cases from 5% (1973-1982) to 39% (1983-1992) to 59% (1993-2002).

In contrast to the evolving experience in China, other Asian countries, like India, Iran, Saudi Arabia and Thailand still report a predominance of symptomatic disease with skeletal and renal manifestations. Asymptomatic PHPT in these other Asian countries is still rarely seen (0-2.2%).

In summary, PHPT in China is rapidly evolving into a contemporary asymptomatic disease. If the current trend continues in China, the asymptomatic form of PHPT may well become the predominant one in the next 10-15 years. One might expect that other Asian countries where PHPT is a symptomatic disease, it too will begin to evolve with asymptomatic disease becoming evident over the next decade.

Bone Mineral Density in Asymptomatic Primary Hyperparathyroidism

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Primary hyperparathyroidism (PHPT) is associated with a high rate of bone remodeling that can result in bone loss and increased skeletal fragility. Bone mineral density (BMD) measured by dual-energy X-ray absorptiometry (DXA) is used to assess the skeletal health of clinical practice patients with PHPT and is included in guidelines for surgical intervention. BMD is also measured to monitor the skeletal effects of PHPT is patents who do not have surgery. DXA uses a 2-dimensional projection of the skeleton to measure areal BMD in g/cm^2. With PHPT, there is typically, but not always, a pattern of bone loss that is greatest at the forearm (33% radius), a skeletal site that is almost totally composed of cortical bone, and least at the lumbar spine, a skeletal site with a large component of trabecular bone; changes in BMD at the hip, where the mix of cortical and trabecular bone falls between the forearm and the lumbar spine, are usually intermediate (1). This is different than the BMD pattern usually seen in women with postmenopausal osteoporosis (PMO), where bone loss is often greatest at the lumbar spine, intermediate at the hip, and least at the forearm. Since PHPT commonly occurs in postmenopausal women, some may have both PMO and PHPT, with a pattern of bone loss reflecting the relative contribution of each disorder. Taken as a whole, the BMD data derived from DXA measurements suggest that longstanding elevation of serum parathyroid hormone (PTH) has catabolic effects on cortical bone and anabolic or at least neutral effects on trabecular bone. Despite the recommendation that patients with PHPT have BMD measured at 3 skeletal sites (lumbar spine, hip, and forearm) (2), a recent study suggests that the forearm is commonly not included in pre-operative DXAs (3).

Quantitative computed tomography (QCT) and peripheral QCT (pQCT) have been used to measure volumetric BMD (vBMD) in mg/cm^3 in patients with PHPT. QCT technology provides a measurement of cortical, trabecular, and integral (both cortical and trabecular) vBMD. Several studies (4;5) with pQCT have shown a decrease in trabecular as well as cortical bone in patients with PHPT, with thinning of the cortex due to apparent trabecularization of cortical bone. These findings raise the possibility of a catabolic effect on trabecular bone with sustained PTH elevation, which might explain the observation that PHPT appears to increase the risk of vertebral as well as nonvertebral fractures (6). There is evidence of cortical expansion with PHPT, probably due to an increase in periosteal bone formation (7).

Surgical treatment of PHPT is followed by BMD increases that are greatest and most rapid at the lumbar spine and hip, and least and slowest at the radius (8;9). Antiresorptive therapy with agents that include bisphosphonates and estrogen have been shown to increase BMD in patients with PHPT who do not have surgery (10). A meta-analysis of randomized controlled trials and observational studies concluded that increases in BMD are similar with surgery and antiresorptive therapy (11). Cinacalcet has been reported to decrease PTH and serum calcium levels in patients with PHPT, without a reduction in bone turnover markers or increase in BMD (10).

In summary, asymptomatic PHPT is associated with and elevated rate of bone remodeling and a modest reduction in BMD. Areal BMD by DXA shows a pattern of bone loss that predominately affects cortical skeletal sites, with apparent preservation of trabecular bone. vBMD measured by pQCT suggests a loss of trabecular as well as cortical bone. Changes in bone geometry (e.g., an increase in cross-sectional area) may partially offset loss of bone strength due to cortical thinning. Advanced imaging technologies may be better suited than DXA for defining changes in bone geometry and microarchitecture with PHPT. Parathyroid surgery and antiresorptive therapy with bisphosphonates and estrogen are associated with increases in BMD at the lumbar spine and hip.

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The Bone Biopsy in Primary Hyperparathyroidism

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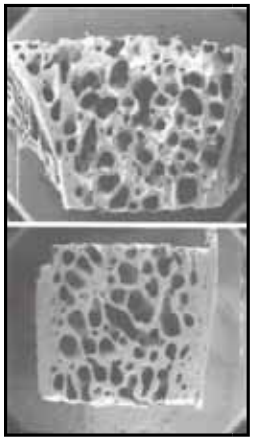
Nowadays the bone biopsy does not play a significant role in the diagnosis and management of patients with mild primary hyperparathyroidism (PHPT) but it remains an extremely useful research tool. Over the past four decades, histomorphometric analysis of iliac crest bone biopsies has been invaluable in elucidating the effects of PHPT on bone structure, turnover and, more recently, its material properties. The hallmark of skeletal involvement in PHPT is an increase in bone turnover, which is manifested in the biopsy by higher values for both static and dynamic indices of bone turnover (1-9). Parameters such as eroded surface, osteoid surface, mineralizing surface and activation frequency are all higher than age- and gender-matched controls. Osteoid perimeter, osteoid area, mineralizing perimeter, and tissue-based bone formation rate correlates well with serum concentrations of PTH. Eroded perimeter and mineralizing perimeter also correlate well with serum calcium and urinary cyclic adenosine monophosphate values, respectively (5). These correlations are highly reflective of the response of the skeleton to PTH, in spite of only minimal clinical manifestations and the complete absence of radiologic signs of bone disease. While high turnover states are generally associated with loss of bone mass and structure (e.g., estrogen deficiency), this is not the case in primary hyperparathyroidism, at least not in cancellous bone. Several studies, using both 2-dimensional histomorphometry and 3-dimensional microcomputed tomography, have shown that cancellous bone volume and trabecular connectivity are preserved and may even be increased in PHPT (1-9). Based on reconstruction of the remodeling sequence in PHPT it is thought that the activation frequency of remodeling cycles is increased, while the final erosion depth and wall width of completed structural units are decreased (2). This protective mechanism against bone loss results in normal or slightly increased bone balance.



Scanning electron micro- graphs of iliac crest bone biopsies from a patient with PHPT (Top) and an age and sex matched control (Bottom).
From Ref #3. .Note preservation of the inner cancellous bone and thinning of the outer cortices in PHPT.

In sharp contrast to the conservative effects of the PTH-induced increase in turnover on cancellous bone, cortical bone is dramatically affected (Figure). Cortical width is reduced and cortical porosity is increased and is correlated with circulating PTH levels (3,10). The cortical thinning has been attributed to increased osteoclastic erosion depth on the endocortical surface (11).

Many of the effects of PHPT on iliac bone structure and remodeling activity have been shown to be reversible upon parathyroidectomy, with a reduction in bone turnover and an increase in cancellous bone volume and a decrease in cortical porosity attributable to closure of the remodeling space (10,12).

With continued interest in bone quality, investigators have begun to use the bone biopsy to study the material properties of bone matrix. Using quantitative backscattered electron imaging, it has been demonstrated that mineralization density is reduced in PHPT and the heterogeneity of mineralization is increased, consistent with an increase in the proportion of newly formed bone undergoing primary mineralization. Similarly, the collagen is less mature with a reduced collagen cross-link ratio. These effects on mineralization density and collagen cross-links are reversed by parathyroidectomy (13,14).

Thus, PHPT exerts profound effects on both the structural and material properties of bone. Observations on the iliac crest bone biopsy, together with those from non-invasive imaging techniques, such as high resolution peripheral quantitative computed tomography, will continue to lead to a greater understanding of the differential effects of PHPT on

cortical and cancellous bone and, ultimately, on bone strength and fracture risk.

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High Resolution Imaging

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Technical advances have markedly improved the spatial resolution of in vivo imaging technique. High Resolution peripheral Quantitative Computed Tomography (HR-pQCT) permits non invasive assessment of trabecular and cortical microarchitecture and volumetric BMD at the distal radius and tibia with a nominal isotropic voxel size of 82 μm.
Bone microarchitecture parameters measured by HR-pQCT have been found to be associated with prevalent fracture in postmenopausal women and older men independently of areal bone mineral density measured by DXA [1-3]. HR-pQCT has also been used to assess age-related bone loss [4] and monitor variations in microarchitecture parameters following osteoporosis treatments [5,6]. In addition, HR-pQCT images coupled with microfinite element analysis (μFEA) can be used to estimate bone strength that was shown to be associated with prevalent fracture [7,8].

This technique has recently been applied to assess bone quality in patients with primary hyperparathyroidism (PHPT) [9-12]. Whereas most histomorphometric studies on iliac crest bone biopsies have found preservation of cancellous bone and impairment of cortical bone, structural deterioration of both cortical and trabecular compartments was observed with HR-pQCT.
In a case-control study, Hansen et al. reported an alteration of the cortical (decreased cortical area, thickness and volumetric BMD) and trabecular compartments (decreased trabecular volumetric BMD and trabecular number along with increased trabecular separation) at the radius but not the tibia in 27 women with PHPT compared to age-matched controls [9]. Cortical and trabecular impairments were also reported at both the radius and tibia in a study on 43 PHPT patients [11], as well as in a study on 51 postmenopausal women with PHPT [12]. In the latter study, women with PHPT showed decreased volumetric BMD, thinner cortices, and more widely spaced and heterogeneously distributed trabeculae, at both sites, compared to controls. The radius was affected to a greater extent in the trabecular compartment than the tibia, with fewer and thinner trabeculae in PHPT. These abnormalities resulted in decreased whole-bone stiffness [12].
Two studies have investigated the effect of parathyroidectomy in PHPT patients, showing that bone deficits were attenuated by successful surgery [10,11].

In conclusion, a deleterious effect of endogenous PTH excess was observed on both trabecular and cortical bone measured *in vivo* by HR-pQCT. This finding reconciles the increased vertebral fracture risk observed in PHPT patients [13]. Moreover, bone deficits may partly be reversible after successful parathyroidectomy.

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Trabecular Bone Score – TBS – a novel method to evaluate bone micro-architectural texture in patients with Primary Hyperparathyroidism

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Primary hyperparathyroidism (PHPT), a common endocrine disorder, is seen in most countries now as an asymptomatic disease (1-3). While overt skeletal disease, formerly a common finding (4), is rarely appreciated now, dual-energy X-ray absorptiometry (DXA) routinely detects evidence of skeletal involvement. The distal 1/3 radius, a dominant site of cortical bone, is typically more involved than the lumbar spine, a site of predominantly trabecular bone (5). Similarly, detailed analyses of iliac crest bone biopsies by histomorphometry and microCT show detrimental effects in cortical bone, whereas the trabecular compartment appears to be relatively well preserved. These findings, however, are not consistent with recent observations utilizing technologies that have greater resolving power than DXA, such as High Resolution peripheral Quantitative Computed Tomography (HRpQCT), in which both trabecular and cortical compartments are abnormal at the radius and tibia in postmenopausal women with PHPT (6, 7). These deficits are associated with reduced whole bone and trabecular stiffness by finite element analysis (FEA) (7). These more recent HRpQCT and FEA results are consistent with epidemiological evidence of increased fracture risk at both vertebral and non-vertebral sites in PHPT (8-11). While HRpQCT has added a dimension of insight not previously appreciated with regard to trabecular bone in PHPT, HRpQCT is not widely available and remains so far a research tool.

Trabecular bone score (TBS) is a novel gray-level textural analysis that can be applied to DXA images to estimate trabecular microarchitecture and has been shown to be associated to direct measures of bone microarchitecture and fracture risk(12-15). Using experimental variograms of 2D projection images, TBS differentiates between 3D bone structures that exhibit the same areal bone mineral density (aBMD), but different trabecular microarchitecture (13). A high TBS value decodes a dense trabecular network associated with greater bone strength, whereas a low TBS value translates a worse bone structure. TBS analysis is readily available from the lumbar spine DXA image without the need for further imaging or expensive instrumentation. In clinical studies, TBS enhanced DXA's ability to predict fracture risk (15-18) and, in a recent study involving over 29,000 postmenopausal women, TBS predicted osteoporotic fractures, independent of aBMD (14).

The ability of TBS to estimate trabecular micro-architectural texture and predict fracture risk, along with its direct measurement from DXA images, led us to investigate its potential utility in evaluating the trabecular skeleton in PHPT. To this end, we assessed TBS from spine DXA images in 22 postmenopausal women with PHPT, and correlated it with HRpQCT measurements of volumetric bone density, skeletal microarchitecture, and bone stiffness. The majorityof PHPT patients (77%) were asymptomatic. Only 1 subject had a history of nephrolithiasis, while 4 had a history of fragility fracture.TBS in PHPT was low at 1.24, representing abnormal trabecular microstructure (normal ≥1.35). Lumbar spine aBMD T-score by DXA was well above the WHO osteoporosis threshold (T-score ≤2.5) in the vast majority of subjects. Only 3 (14%) patients were classified as osteoporotic, 7 (32%) as osteopenic, whereas the remaining 12 (54%) subjects presented with normal L1-L4 T-scores by DXA. In marked contrast, TBS at the lumbar spine showed degraded microarchitecture (TBS≤1.20) in 8 (36%) patients, partially degraded (TBS>1.20 and <1.35) in an additional 8 (36%), and normal values (TBS≥1.35) in only 6 (27%) subjects.

TBS was significantly correlated with all radius HRpQCT and biomechanical measurements (r= 0.44 - 0.51; p<0.05) except total area, trabecular thickness, and trabecular stiffness. Significant correlations remained after adjusting for body weight.TBS was significantly correlated with tibia HRpQCT with regard to volumetric densities (r= 0.47 - 0.62), cortical thickness (r=0.52), trabecular bone volume (r=0.53), and whole bone stiffness (r=0.52) (p<0.05 for all). All indices of trabecular microarchitecture, except trabecular thickness, became significant after adjusting for body weight (r= 0.48 - 0.57).

We reported, for the first time, significant correlations between TBS and direct measurements of trabecular microstructure by HRpQCT. The positive relationship between TBS and whole bone stiffness assessed by FEA of HRpQCT images suggest that, in PHPT, low TBS may also indicate increased fracture risk. Moreover, our results demonstrate that TBS has the potential to identify PHPT subjects with abnormalities in trabecular bone not captured by lumbar spine aBMD. TBS, an indirect measurement of trabecular microarchitecture, has the major clinical advantage of being readily available from images of DXA, a test routinely performed in PHPT. With significant correlations between TBS and volumetric and microstructural indices, as well as biomechanical measurements by HRpQCT, a method that has greater resolving power but is not widely accessible, TBS could become a helpful clinical tool in the assessment of skeletal involvement in PHPT.

Supported in part by the following NIH grants: R01 DK32333, R01 AR051376, and the Brazilian National Council of Technological and Scientific Development – CNPq (BC Silva).

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Fracture Risk in Primary Hyperparathyroidism

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In overt PHPT, a decreased BMD and increased fracture risk is well known. However, only few data are available on patients with milder forms of the disease. In most published analyses, severity of disease on risk of fracture has not been accounted for. Most published fracture data, therefore, represent a mixture of patients with mild or asymptomatic disease and the more severe form. In cohort studies, an increased risk of any fracture has been reported by several investigators (1-4) and risk of fracture seems to be reduced following parathyroidectomy (PTx)(3;4).

Data on fractures at specific skeletal sites are less uniform. The risk of forearm fractures has been reported to be increased in several studies (3;4), whereas risk of hip fracture does not seem to be increased to any major degree. Only one study has reported a borderline significantly increased risk (3), whereas no increased risk has been found by other investigators (4;5). In a Danish cohort study, patients managed by surgery were showed to have a significantly lower hip fracture risk compared with those managed by medical observations(6). This may suggest a protective effect of PTx on hip fracture risk. However, as the study was non-randomized, selection bias may have influenced findings according to whether patients were referred to surgery or not. The fact that hip fracture risk does not seem to be increased in PHPT is in accordance with the finding that PHPT does not seem to be dominant feature in hip fracture patients (7).

Variable results have been reported on risk of vertebral fractures (VFx). In a study including 174 patients with mostly mild PHPT, risk of VFx was not increased compared with data from a historic control group (8). Neither was the prevalence of VFx increased in a group of 116 Japanese women with PHPT compared with 716 matched controls in terms of women referred to an outpatient clinic for evaluation of osteoporosis(9). However, in most studies, an increased risk of VFx has been reported (3;4;10;11). In two studies from Italy, an increased prevalence of VFx was found in patients with mild as well as with more severe forms of the disease. In a study from 2006, 98 women with mild (N=25) or “non-mild” disease were compared with 89 matched healthy controls. In this study, the prevalence of VFx was increased in both groups of patients compared with their matched controls, but prevalence did not differ according to severity of disease within the group of women with PHPT (10). In a more recent study, Vignali et al (11) assessed the prevalence of VFx using vertebral fracture assessment (VFA) by dual-energy x-ray absorptiometry (DXA). 150 women were compared with 300 matched healthy controls. VFx were significantly more prevalent in patients (24.6%) than in controls (4.0%). VFx were non-significantly more prevalent in symptomatic (34.1%) compared with asymptomatic (21.1%) patients. Within the group of asymptomatic patients, VFx were significantly more prevalent in those who met the criteria for PTx (28.1%) compared with those who did not (11.1%). However, compared with controls, the prevalence ofVFxwas only significantly higher in patients with symptomatic and asymptomaticPHPT who met the criteria for surgery, whereas VFx was only borderline more prevalent in asymptomatic subjects who did not meet criteria for surgery compared with controls (p=0.06).

The findings from densitometric and histomorphometric studies are somehow conflicting with the findings from epidemiological studies on distribution of fractures at different skeletal sites. In general, a low BMD has been found at cortical sites, whereas bone mass seems to be relatively well preserved in trabecular bone. Similarly, analyses of bone biopsies have shown cortical thinning, but maintenance of cancellous bone volume and connectivity in patients with PHPT.Based upon this, one would expect that the cortical skeleton would be at greater risk of fracture than the cancellous skeleton, i.e. a marked increased risk of VFx would not be expected. This may question, whether lumbar spine BMD measures bone strength as good in PHPT as in postmenopausal women without PHPT.In one study, lumbar spine BMD was, however, found to be significantly

associated withthe prevalence of VFx(11). Changes in bone composition and geometry probably weaken bone strength differently in PHPT and postmenopausal osteoporosis. Moreover, low vitamin D levels, as often encountered in PHPT may influence effects of high PTH levels on bone. In two studies on women with secondary hyperparathyroidism, an interaction was found(12;13). Compared with women with low PTH levels, high PTH levels were associated with a lower BMD and an increased fracture risk if 25OHD levels were below 80 nmol/l, whereas high PTH levels were not associated with adverse outcomes on bone in women with a replete vitamin D status. Moreover, in a histomorphometric study on 30 patients with mild PHPT, low 25OHD levels were associated with higher PTH levels, greater catabolic effects in the cortical bone, and greater anabolic effects in the trabecular bone.

Finally, it has to be recognized that available studies on fracture risk suffers from a number of limitations, including the retrospective nature of studies, different definitions of vertebral fractures, small study populations, and selection of patients and controls. Moreover, data on effect of PTx on fracture risk are limited by the non-randomized design of these studies. Although, placebo-controlled trials have shown increased BMD in response to antiresorptive drugs, no data are available on fracture risk.

In conclusion, data from mixed case populations suggest an increased risk of fractures in PHPT, although discrepant findings at different skeletal sites have been reported. Only few data are available on patients with mild PHPT, but recent data do suggest that risk of VFx is increased also in those with mild disease. Well-designed prospective clinical trials are needed to improve our knowledge on risk of fracture in asymptomatic PHPT and the correlation between BMD at different skeletal sites and risk of fracture.

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Bone turnover markers in Primary Hyperparathyroidism

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Bone turnover markers reflect the activity of bone cells. The bone formation markers reflect the work of the osteoblast (osteocalcin, procollagen I N-propeptide PINP, bone isoform of alkaline phosphatase) and the bone resorption markers the work of the osteoclast (C- and N-telopeptide of type I collagen CTX and NTX, deoxypyridinoline, tartrate-resistant acid phosphatase). The bone turnover makers can be measured precisely and reliably using automated immunoassay analysers. Care needs to be taken over the well-known sources of variability – the resorption markers have a striking circadian rhythm and it is important to measure them at a fixed time of day. A recent review stressed the importance of measuring bone turnover markers under carefully controlled conditions and for all research studies, measuring at least one marker of bone formation (PINP) and one of resorption (CTX)[1].

In a state of increased bone turnover, such as primary hyperparathyroidism, there may be an increase in the mean level of bone turnover markers, with up to half of patients with levels above the reference interval[2]. The markers remain increased in a stable fashion over several years in the absence of any treatment[3]. Surgery for primary hyperparathyroidism results in a normalisation of bone turnover markers; the greater the initial bone turnover markers, the greater the increase in bone mineral density after surgery[4]. Also, the greater the decrease in bone turnover markers the greater the increase in bone mineral density[5]. The changes in bone resorption occur within hours of surgery[6] and the changes in bone formation take several months to evolve, due to coupling.

Regulators of bone turnover have also been measured after surgery. Osteoprotegerin mediates the regulation of osteoclasts by osteoblasts. It might be expected to be low in primary hyperparathyroidism, but it is normal and doesn't change after surgery[7]. Sclerostin mediates the

regulation of osteoblast precursors by osteocytes; a low level results in increased bone formation. The levels are low in primary hyperparathyroidism and increase shortly after surgery[8].
Medical treatments for primary hyperparathyroidism also result in changes in bone turnover markers. Thus, menopausal hormone therapy results in a decrease in bone turnover markers [9]. Raloxifene has also been shown to decrease bone turnover markers in postmenopausal women with primary hyperparathyroidism[10]. Surprisingly, cinecalcet therapy does not lower bone turnover markers, even though it lowers parathyroid hormone levels. It may even increase bone turnover markers. In one trial, it was compared to alendronate which did decrease bone turnover markers in patients with primary hyperparathyroidism [11].
Thus, bone turnover markers allow the study of the effects of primary hyperparathyroidism on the skeleton. The level before treatment can predict the treatment response and allow the response to be monitored, whether the treatment is surgery or medical treatment[12].

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Sclerostin and Other Cytokines in Primary Hyperparathyroidism

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Primary hyperparathyroidism (PHPT) is characterized, biochemically, by hypercalcemia and an elevated level of PTH. In this setting, PTH is associated with a high turnover state, as determined by circulating biochemical markers of bone turnover and by dynamic histomorphometry of iliac crest bone biopsies [1, 2]. Furthermore,PTH is thought to influence sclerostin and other bone-active cytokines.

Sclerostin, a secretory product of the SOST gene, is produced mainly by osteocytes. It is an endogenous inhibitor of the Wntanabolic signaling pathway. Different from other markers that influence bone formation, which are products of osteoblast activity, sclerostin influences differentiation and survival of osteoblasts through actions to regulate the Wnt pathway [3]. Sclerostin levels are generallycorrelated with bone formation. In PHPT, sclerostin levels are lower than euparathyroid and hypoparathyroid controls [4, 5]. In a small series of patients followed for up to a year after parathyroidectomy (PTX), circulating sclerostin was shown to increase shortly after PTX but return to the age-referenced normal range within 10 days and to remain stable thereafter [6].

IL-6 is another cytokine that has a role in mediating the actions of PTH [7]. Circulating IL-6 levels have been shown to be elevated in PHPT [8-10]. Prospective studies of limited size have shown that IL-6 correlates with the degree of bone loss in PHPT, and that after PTX IL-6 levels fall [11].

The RANKL/OPG cytokine system is also perturbed in PHPT. RANKL levels are elevated in PHPT, and correlate with markers of bone resorption[12]. The rate of bone loss in women with PHPT and RANKL

levels combined with high IL-6/IL-6 soluble receptor levels tend to be enhanced. OPG levels remain in the normal range [12], but those with the highest OPG levels trend towards smaller postoperative changes in BMD [13].

Measurements of these cytokines in PHPT are helpful to elucidatethe mechanisms of bone loss and recovery of bone loss in PHPT.

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The Kidney in Primary Hyperparathyroidism

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The kidney occupies a unique position in primary hyperparathyroidism, setting both the concentration of calcium and phosphate in serum and determining the amount of calcium and phosphate in the total body (1). It does so by virtue of the action of parathyroid hormone on the renal tubule to regulate the reabsorption of the filtered calcium and phosphate and to stimulate secretion of 1, 25 dihydroxy vitamin D, the hormone regulating active gut absorption of calcium and phosphate. In addition, the kidney is one of the few organs that manifest clinical primary hyperparathyroid disease. Recurrent urinary calcium stone disease is common: more rarely, nephrocalcinosis may develop. Lastly, chronic reduction in glomerular filtration rate, either from complications of primary hyperparathyroidism itself or from comorbid diseases, induces abnormal mineral homeostasis that alters both the biochemical and the clinical manifestations of the disease.

Renal tubular reabsorption of calcium is regulated by parathyroid hormone acting in concert with a range of factors including calcium sensing receptor, filtered sodium load, and integrity of tubular calcium transporters including TRVP5/6(2). Calcium reabsorption does not have a classical tubular maximum: urine is never totally free of calcium and the slope of reabsorption on increased filtered load is always less than unity. In primary hyperparathyroidism the pathological increased parathyroid secretion induces a ‘right shift’ in the relationship between excreted and filtered calcium (3).
Renal tubular reabsorption of phosphate on the other hand, does have a classical tubular maximum capacity above which the relationship between filtered and excreted phosphate is unity (4). Parathyroid hormone decreases tubular reabsorption of phosphate largely by decreasing tubular Na/Pi-cotransporter activity (5).

Renal tubular 1 alpha hydroxylase activity is regulated by parathyroid hormone and in primary hyperparathyroidism serum 1, 25dihydroxy vitamin D is increased (6,7) resulting in increased active absorption of dietary calcium (7).
Thus the classical biochemical signature of primary hyperparathyroidism is increased serum parathyroid hormone accompanied by increased serum calcium, decreased serum phosphate, increased serum1, 25 dihydroxyvitamin D and absorptive hypercalciuria.

An early clinical manifestation of primary hyperparathyroidism is the development of recurrent urinary calcium stone disease (8). The stones are small, cause colic and are passed spontaneously in the urine. They are composed of calcium oxalate along with some calcium phosphate, and are readily seen on radiographic or ultrasound imaging of the urinary tract. About 3% of patients with urinary stone disease are due to primary hyperparathyroidism (9), and about 10% of patients with primary hyperparathyroidism may present with recurrent calcium stone disease (10). The cause of stone formation is multifactorial, but hyperabsorption of calcium and phosphate, high absorption of oxalate from increased bioavailability and increased urinary pH are important urinary factors that lead to oversaturation of urine with calcium oxalate and phosphate (1). In more severe forms of primary hyperparathyroidism, particularly when accompanied by decreased glomerular filtration rate, mineralization in the kidney tissue itself occurs (8). The mechanisms relate in part to the disturbed extracellular fluid levels of calcium and phosphate which promote ectopic calcification. Nephrocalcinosis needs to be distinguished from Randall plaques which are small deposits of calcium phosphate in the renal papillae (11) that are considered to be important in the pathogenesis in urinary calcium stone formation. Chronic renal failure not uncommonly develops in primary hyperparathyroidism either from recurrent urinary stone disease and its sequelae, or severe hypercalcemia. It ultimately results in secondary hyperparathyroidism complicating the primary disease. The result is an increase in parathyroid hormone with an inappropriate decrease in serum calcium, increase in serum phosphate,

and decrease in serum 1, 25 dihydroxy vitamin D, and decrease in calcium and phosphate absorption. These effects reduce the recurrence rate of urinary stones but increase the incidence of nephrocalcinosis and the severity of hyperparathyroid bone disease.

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Cardiovascular Consequences of Primary Hyperparathyroidism

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There has been considerable controversy concerning the presence, nature and reversibility of cardiovascular (CV) manifestations of PHPT. Both biochemical hallmarks of the disease, hypercalcemia and hyperparathyroidism, could have deleterious consequences in this regard. Yet while cardiovascular outcomes and mortality were clearly increased in classical disease, the effect of mild or asymptomatic disease on the cardiovascular system is less clear. Additions to the literature since the last international conference on PHPT will be reviewed.

Mortality: Data reviewed at the last international meeting suggested that CV mortality is no longer increased, except in those with the highest serum calcium levels. Newer data is available from the PEARS study of Tayside, Scotland (1, 2), which reported increased CV mortality in PHPT and reported further that PTH levels predicted risk. However, there are some limitations to these data. The diagnosis of PHPT was made in the absence of PTH levels in some cases, and vitamin D levels were not available, raising the possibility that PTH levels could have been a proxy for vitamin D deficiency, also a risk for CV mortality. Finally, it is unclear whether these data can be generalized to most patients with PHPT, given the extremely high overall mortality rate of this cohort (30%).

Heart: There are no data on cardiac outcomes. With regard to cardiac structure and function, limited randomized trial data are available. A single center subgroup of the Scandinavian RCT of surgery vs observation (n=49; mean serum calcium 10.6 mg/dl) found that baseline left ventricular dimension correlated with PTH levels, but there was no echocardiographic difference in cardiac structure or function (ejection fraction or diastolic function) between groups after 2 years (3). A case control study of 51 patients with mild PHPT (calcium 10.5 mg/dl) reported increased aortic valve calcification area that was associated with PTH levels, but found no other abnormality in cardiac structure or function, and no improvement in any cardiac index 2 years after parathyroidectomy (PTX) (4-6). Another case control study of mild PHPT (calcium 10.5 mg/dl) limited itself to the 12% of 410 consecutive patients undergoing PTX who had no CV risks (no history of CV disease, no HTN, no CV medication, no diabetes, BMI < 28, age: 18-70). They found no difference between PHPT and controls in any cardiac structural finding or in any measure of systolic or diastolic function; and no change after PTX (7). Thus in those with no CV risks, cardiac morphology and function were normal and unchanged after PTX. Several small studies assessed coronary calcifications. Streeten found no increase in coronary artery calcification score, although the pre-test likelihood of such a finding was very low, since the cohort was largely female and young (8). Other studies in this area included patients with normal serum calcium levels, raising the possibility of secondary rather than primary HPT (9,10). A study of coronary microvascular function in 100 PHPT patients with more severe hypercalcemia than we usually see (mean calcium 11.8 [2.95 mmol/L] PTH 188 pg/ml) found no differences in cardiac structure or diastolic function, but did find that coronary flow reserve (CFR) was lower than controls (3.0 ± 0.8 vs 3.8 ± 0.7; $p<0.0001$) (11). CFR was inversely associated with PTH ($r=-0.3$; $p<0.0004$) but not calcium levels. Further testing revealed normal coronary arteries in 26 of 27 patients with low CFR, raising interesting questions about this functional precursor of coronary disease. CFR improved 6 months after PTX, although these data were uncontrolled and could represent regression to the mean.

Large Vessel Disease: Studies prior to the last consensus conference (12,13) demonstrated increased aortic stiffness that was associated with PTH levels (13). These studies used an indirect measurement technique, augmentation index which is influenced by a BMI, blood pressure etc. Tordjman et al reported no difference in arterial stiffness (augmentation

index and large (C1) and small (C2) vessel compliance indices) between normocalcemic and hypercalcemic PHPT (14). These data are intriguing, because there are no data on CV effects of the normocalcemic variant, but are limited by the retrospective study design and likely selection bias (studies of vascular compliance were only performed on a subset of patients). Carotid structure and stiffness was assessed in 52 patients with mild PHPT (Calcium 10.5 mg/dl) (15). Intimal medial thickenss (IMT) was elevated, and those with carotid plaque had increase in plaque thickness, suggesting that PHPT may not initiate but could propogate abnormalities (similar to aortic valve calcification). This study, the first to directly measure large vessel compliance in PHPT, also found abnormal stiffness and distensibility, and that PTH levels, but not calcium concentration, predicted carotid stiffness (p=0.04), strain (p=0.06), and distensibility (p=0.07). It is unknown whether the clinical implications of these carotid abnormalities are the same in PHPT as in atherosclerosis in terms of predicting CV outcomes. This group did not find any improvement in IMT or carotid stiffness 1 or 2 years after PTX (6).

Cardiovascular Risk Factors: Important data emerged from those in the ongoing randomized controlled trial of surgery (n=54) vs observation (n=62) in mild PHPT (mean calcium 2.69+.11 mmol/L) in whom baseline and 2 yr data were available (16). After surgery and cure, total and HDL Cholesterol and ApoA increased, while blood pressure declined. However, the same salutary effects were seen in the non-operated cohort. No change was seen in BMI, glucose, insulin or insulin derivatives HOMA-B or HOMA-IR. Adiponectin increased in both groups by about 15%. Markers of endothelial function von Willebrands factor and VCAM did not change, nor did CRP or OPG. Case control data from the cohort above with no CV risk factors (7) found no difference at baseline in: Cholesterol, Apo-A1, Apo-B, Apo-B/Apo-A1 ratio/Von Willebrand Factor, CRP, homocysteine, IGF-1, PAI-1 (17). Systolic blood pressure and triglycerides were higher within the normal range in cases than controls. After PTX, BMI, Apo-B (but not Apo-B1/Apo-A1 ratio, the more important risk predictor for CV disease), and CRP all increased, but interpretation is limited by the fact that there was no longitudinal data in control subjects.

Summary and Conclusions: There are no prospective data available on CV outcomes in mild PHPT. Studies published since the last consensus conference have assessed varying CV risks, as well as structural and functional abnormalities in different vascular beds. The carotid bed seems to be more affected than the heart, with elevated carotid IMT and increased plaque thickness, while cardiac structure was mostly normal. When present, carotid plaque was thicker and aortic valve calcification area greater, suggesting that the hyperarathyroid state may be associated with propogation of vascular calcification once established. Available data highlights a closer association of some CV indices (left ventricular mass, coronary flow reserve, carotid stiffness and aortic plaque area) with PTH as opposed to calcium concentration in PHPT. Randomized controlled trial data found no benefit of surgery with regard to markers of the metabolic syndrome including hypertension, cholesterol, inflammatory markers, adipokines and other CV risk markers. They also found no benefit of surgery on cardiac structure or function. Observational studies in patients with and without CV risk factors also found no improvement in cardiac, carotid or other surrogate markers of cardiovascular risk. Thus, at this time, there are no data that suggest that surgery should be undertaken for the purpose of improving CV markers or anatomical abnormalities.

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Neurocognitive function in PHPT

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Classical primary hyperparathyroidism (PHPT) had obvious neuropsychological sequelae. Whether reversible psychiatric symptoms and cognitive deficits are present in asymptomatic PHPT has been an area of active research and debate. Many patients with asymptomatic PHPT report non-specific complaints including weakness, fatigue, depression and anxiety, decreased memory and concentration, loss of initiative, irritability, and sleep disturbance. Most, but not all, studies (1-14) have suggested that there are psychological and cognitive features of PHPT that improve after parathyroidectomy (PTX). Because of the difficulties inherent in performing studies of this nature, historically most investigations have been beleaguered by their observational design, small sample sizes, inclusion of subjects with symptomatic PHPT, or lack of control groups. Others have failed to use objective tests or performed testing at short intervals after surgery. These designs have limited conclusions regarding the causal association of such symptoms with PHPT and the benefit of PTX. Since post-PTX improvements in observational studies could be due to baseline differences between groups, or to biases introduced by their nonrandomized designs, more rigorously designed trials have been a priority.

At the time of the last International Workshop on Asymptomatic PHPT in 2008, 3 randomized clinical trials (RCTs) of PTX vs. observation upon quality of life (QOL) and psychological functioning in asymptomatic PHPT patients with mild hypercalcemia (calcium 10.2-10.8 mg/dl) had been published. Despite using the same tool [the Short Form-36 general health survey (SF-36), which measures functional health and well-being], findings varied between studies (15-17). While the balance of data in

these 3 RCTs does support a marginally beneficial effect of PTX on QOL and psychological functioning, the findings across studies were inconsistent. Thus, the 2008 Workshop on Asymptomatic PHPT did not add psychiatric and cognitive symptoms to the list of criteria for PTX (18). While the expert panel felt there was an association between such symptoms and PHPT, they noted that data regarding their exact nature and reversibility were still insufficient to warrant a separate indication for PTX. The last International Workshop identified the need for more data in these areas.

Since the last workshop, a small number of studies have investigated the psychiatric and cognitive features of PHPT. This summary will focus primarily on controlled studies in the areas of depression/psychiatric disease, quality of life and cognitive function. A recent relatively large prospective case-control study assessed the prevalence of depression in PHPT and the benefit of PTX for ameliorating symptoms (19). In 169 (symptomatic and asymptomatic) PHPT patients (mean calcium 10.6mg/dl), depression was twice as common compared to non-PHPT controls and depression scores weakly correlated with serum calcium. PTX resulted in greater improvement in depressive symptoms compared to those who were observed and compared to thyroid surgery controls. The authors concluded that depression was present in PHPT, related to calcium and that symptomatic improvement was not merely related to a surgical placebo effect. It is important to note, however, that PHPT patients self-selecting for surgery had higher calcium, PTH, lower vitamin D levels, were more likely to have symptomatic disease and had more depressive symptoms at baseline vs. those who were observed. Although the authors controlled for baseline depressive symptoms, selection bias and the lack of randomization, leaves uncertainty about whether treatment differences are due to surgery or other factors. Yu et al. conducted an epidemiologic cohort study in Scotland that included 1,424 patients with asymptomatic PHPT (serum calcium <12 mg/dl; mean 10.5mg/dl). The study utilized electronic medical records and ICD-9 codes to diagnose PHPT and various outcome measures. Compared to controls, those with PHPT (who had more co-morbidities at baseline) had a 4.25-fold (95%CI 2.33-7.77) increased risk of psychiatric disease (20). While the analysis controlled for baseline differences, it is difficult to attribute the increased risk of psychiatric illness to PHPT alone and the nature of the psychiatric disease is unclear. Another study from the United Kingdom evaluated symptoms of depression and anxiety using the Hospital Anxiety and Depression (HAD) scale and the Mood Rating Scale (MRS) in 24 patients with asymptomatic PHPT (mean calcium 10.8mg/dl). PHPT patients were compared pre- and post-PTX to 23 controls undergoing hemi-thyroidectomy (21). Patients with PHPT were older and more likely to be female. Pre-op PHPT had more depression but no increase in anxiety. After adjustment for age and gender, PHPT had improvement in depression but not anxiety, while there were no changes in the hemithyroidectomy group. All 3 studies suggest the presence of depression or psychiatric disease in PHPT and in the 2 studies that assessed patients post-PTX, there was improvement in depressive symptoms.

In addition to psychiatric disease, quality of life (QOL) has been further evaluated with a focus on long-term benefits of PTX. Pasieka et al. reported 10-year data on QOL after PTX (22). QOL was assessed using the Parathyroid Assessment of Symptoms Scores (PAS), which has been shown to correlate with SF-36 scores (23). Data were available on 78 of the original 122 symptomatic and asymptomatic PHPT patients (mean calcium 11mg/dl) and 39 of 58 thyroidectomy study participants who were followed for a mean of 10 and 11 years respectively. At baseline PHPT had worse QOL compared to controls. PTX resulted in a reduction in PAS that was sustained for 10-years versus controls who had no improvement. Amstrup et al. (24) also reported on QOL using the SF-36 after PTX in a cross-sectional study of 51 PHPT patients (symptoms and calcium not reported) who had been successfully treated with PTX at least 5 years earlier versus 51 population-based age matched controls. Their results indicated that reduced QOL persisted in former PHPT patients. The authors concluded that a change in surgical guidelines was not warranted though they acknowledged that the reduced QOL in their participants was difficult to attribute solely to the history of PHPT. In

contrast, Leong et al. studied QOL using the SF-36 in 24 PHPT patients (median calcium 11.2mg/dl) pre- and 6-months postoperatively. Pre-operatively median scores were lower compared to national averages in all 8 domains. Post-PTX, there were improvements in 6 of 8 domains: physical and social functioning, physical and emotional role limitations, energy and mental health. Median physical component summary score and the mental component summary scores were improved such that the MCS was comparable to the national average. Results from an uncontrolled study in Japan are difficult to interpret given the lack of a validated questionnaire, but post-PTX there were no changes in asymptomatic PHPT (mean calcium 11.0mg/dl) patient's subjective assessment of neuropsychological symptoms including tiring easily, forgetfulness, decreased concentration, depression, irritability, uneasiness or sleeplessness (25). These data suggest impaired QOL, but improvement was inconsistent across studies.

More emphasis has been placed on assessing cognitive function since 2008. In 2009, Walker et al. (26) found that those with mild (symptomatic and asymptomatic) PHPT (n=39; mean calcium 10.6) performed worse on validated tests of verbal memory and non-verbal abstraction/pattern recognition compared with 89 non-PHPT controls (26). Non-verbal abstraction and some aspects of verbal memory improved after PTX such that scores were no longer different than controls. Both baseline differences and postoperative improvement were independent of anxiety and depressive symptoms, which were more common in PHPT. The magnitude of change in cognitive function was small (within 1 SD) and the lack of a surgical control group, however, raises the possibility of a placebo-effect of surgery. Babinska et al. (27) conducted a similar prospective case-control study of 35 PHPT patients (mean calcium 11.1mg/dl) undergoing PTX compared to 35 non-PHPT surgical controls. PHPT had more depression as well as impaired concentration, nonverbal learning, direct memory, verbal fluency, and visual constructive abilities. Depressive symptoms were associated with worse cognitive performance. Controlling for depression, PTX was associated with an improvement in visual memory and visual-constructive abilities. Since 2008 only one randomized controlled study of PTX vs. observation has been performed. This small study (n=18) by Perrier et al. focused on cognition in asymptomatic PHPT (mean calcium 10.5 mg/dl) (28) and also assessed sleep and brain function using functional magnetic resonance imaging (fMRI). Though there were no differences in change in sleep time (which correlated with change in PTH) between treatment groups, daytime sleepiness decreased temporarily in those who underwent PTX vs. observation (at 6 weeks post-operatively), but differences were no longer significant at 6 months. Additionally, there were no between-group differences in changes in cognition. There were no changes in fMRI voxel counts, though the change in PTH level was associated with change in voxel activity in the left pre-central gyrus at 6 months. In an uncontrolled study, Benge et al. (29) assessed the presence of cognitive dysfunction in 111 PHPT patients (mean calcium 10.7) at baseline compared to normative data. Changes in cognition among 67 patients who returned for repeat testing 1 month post-PTX were also evaluated. Though mean Z-scores on all tests of cognitive function were not impaired (as defined by a Z-score $\leq$ -1.5), the percentage of participants whose performance was considered impaired ranged from 3.6% on the tests of attention and visual processing to 29% on tests of eye-hand coordination and motor speed. 35% of participants met criteria for clinically significant impairment (defined as $\geq$ 3 Z-scores $\leq$ -1.5). Using practice effect corrected reliable change indices $\geq$ 10% of participants had improvements in the areas of fine motor speed and information processing. In another uncontrolled study, Roman et al. (30) studied 212 (symptomatic and asymptomatic) PHPT patients (mean calcium 10.8 mg/dl) undergoing PTX. The authors noted post-PTX improvement in depression, anxiety, verbal memory and spatial working memory. Change in PTH was associated with reduced post-operative anxiety and improved performance was associated with decreases in depression and anxiety. While, there was significant attrition in this study and no control group, there were no differences in baseline neurocognitive performance between those who did and did not return for follow-up. In aggregate these studies suggest that various aspects of cognition, including verbal and visual memory, hand/eye coordination

and information processing, as well as pattern recognition may be affected by PHPT. However, the specific components of cognition affected by PHPT varied across studies, making definitive conclusions difficult. Further, the improvements post-PTX noted in observational studies were not confirmed by the only RCT of cognition, though the study was underpowered.

Progress toward improved understanding of the psychological and cognitive effects of PHPT has been made over the last 5 years. Depressive symptoms, present in PHPT, affect performance on cognitive testing. The presence of PHPT is associated with worse cognitive function but the specific aspects of cognition that are affected vary across studies. The improvement in depression observed in these case-control studies contrasts with the lack of benefit in larger RCTs. Improvements in cognitive function post-PTX observed in small case-control studies, need to be confirmed by large randomized studies of PTX vs. observation.

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Preoperative Imaging

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The skilled surgeon is able to localize the pathologic parathyroid gland(s) in more than 90% of cases.
The intraoperative assay of parathyroid hormone (PTH) is crucial for the evaluation of the effect of pathologic parathyroid gland(s) removal.
Therefore, there is a role of preoperative localization techniques in hyperparathyroidism?
In our opinion the accurate use of US, MRI, CT and nuclear medicine (NM) diagnostic techniques can still represent a useful tool in surgery planning even for the experienced surgeon. The identification of a single parathyroid gland with increased volume suggests the possibility of a parathyroid adenoma. On the contrary, the finding of an increased volume of more than one gland suggests the hypothesis of parathyroid hyperplasia or multiple adenomas. The failure to detect pathologic parathyroid gland(s) could also suggest the presence of parathyroid hyperplasia, with smaller glandular increase.
Mini-invasive parathyroid surgery associated to intra-operative PTH assay is a suitable technique in the first case (leaving the neck exploration to the rare cases in which PTH levels fail to fall below 50% of the initial value after the removal of the gland), whilst in the second case the exploration of all the glands with open neck surgery represents the approach of choice. The presence of a intrathoracic pathologic parathyroid gland requires of course a different surgical approach, and an unnecessary neck exploration can be avoided.

The pre-operative localization of pathologic parathyroid glands relies on the following features:

- the anatomic site of normal parathyroid location in the neck is scarcely subjected to variations.

- the diagnosis of a parathyroid adenoma is usually simple (bigger dimensions, high metabolic activity): on the contrary hyperplastic parathyroids are often not easily identified (lower sizes, often low metabolic activity).
- the spatial resolution needed is sub-millimetric.
- the contrastographic resolution must allow the distinction between parathyroid glands and the surrounding structures (thyroid nodules, lymph nodes, muscles, mesenchyma).
- the technique used must rely on different parameters: site, morphology, structure or functional characteristics.
- the technique or combination of techniques must cover the entire anatomic area of parathyroid gland possible localization.
- the technique(s) must show precise anatomical landmarks, useful during the surgical intervention.

With CT scan and MR imaging it is possible to identify nodules with a diameter slightly lower than 1 cm. However often CT (1) cannot differentiate the nature of a nodule (lymph node, thyroid nodule, neurinoma, parathyroid nodule).
MR imaging (2), with T1 and T2 signals analysis, gives a bit more accurate information on the parathyroid nature of a nodule.
Both CT and MR give good spatial localization of the nodules detected in the neck region.

US technique performed by skilled radiologist allows the detection and diagnosis of the parathyroid nature of a nodule (minimum 3-4 mm in diameter) based on site, morphology, echoic pattern and vascular characteristics, with accurate spatial localization. No information can be obtained in the rare occurrence of nodules in the mediastinal region caudally to the innominate vein.

Nuclear medicine techniques for parathyroid imaging use single or double tracer methods: 99m-2-methoxyisobutyl-isonitrile (MIBI) or MIBI plus 123 Iodine. The single tracer exam can be performed with planar analysis in 'double phase' or with SPECT analysis with double or single detection. The double phase planar technique shows a high accuracy (3-4), particularly with the use of pinhole collimation instead than parallel-hole (5). The SPECT technique is actually considered more accurate (6,7,8,9,10).
NM planar techniques are suitable for differential diagnosis but have low sensibility for nodules lower that 1 cm in size. Improvement in sensibility can be obtained with SPECT, useful also for a better spatial resolution (6,7,8,9,10).

The combination of two different methods can lead to an improvement in the localization of the suspected parathyroid pathologic gland. In particular, combination of US/NM (1) techniques can detect almost all the hyperfunctioning glands also with slightly increased size (1). The possibility of US evaluation directly on surgery room may represent a further useful guide for the surgeon.

The following diagnostic pathway is suggested:

1°: MIBI scintigraphy possibly with dual phase SPECT imaging.
2°: positivity in neck, or absence of positivity: high resolution US
3°: mediastinal positivity: CT.

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Extensive Personal Surgical Experience

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Optimal treatment of Primary Hyperparathyroidism (1^0HPTH) requires a procedure designed to correct the underlying causative lesions(s), avoids morbidity or mortality, and is both cost-effective and durable. Although perfection is unattainable, modern parathyroid surgery approaches these goals.

The etiology causing 1^0HPTH for the majority (85%) of patients is a single adenoma which, when removed, results in a durable cure. Approximately 15% of patients have multi-gland disease that can also be effectively treated during an initial exploration, although the long-term results are not as favorable as those seen in patients with a single adenoma.

Minimally Invasive Parathyroidectomy (MIP) has emerged as a nearly ideal procedure for the majority of patients with 1^0HPTH. It relies upon preoperative imaging (ultrasound, sestamibi or CT scans) to localize enlarged parathyroid gland(s) and thereby guide surgical exploration. The operation is readily performed under local or regional anesthesia and a rapid intraoperative parathyroid hormone (PTH) assay is employed to confirm the adequacy of resection and obviate unnecessary exploration. MIP can accommodate patients with multi-gland disease as well as patients who require remedial cervical explorations following previous parathyroid or thyroid procedures. Due to limited exploration and avoidance of general anesthesia, MIP patients can be treated on an outpatient bases with appropriate backup.

We have demonstrated the superiority of MIP compared to conventional parathyroid surgery in a series of 1,650 consecutive patients. MIP is associated with improvements in the cure rate (99.4%) and complication rate (1.4%) compared to conventional exploration with a cure rate of 97.1% and a complication rate of 3.1%. In addition, the hospital length of stay and total hospital charges are also improved compared to conventional surgery. We have recently demonstrated in a prospective trial that MIP results in minimal changes to vocal cord function. In addition, we have now developed computer software based on our extensive data that accurately predicts operative cure rates in real-time based on analysis of PTH values during parathyroidectomy. This information assists intraoperative decision making by allowing the surgeon to conclude a case with a high degree of curative confidence; alternatively, it prompts additional exploration to treat residual disease.

In summary, the vast majority of patients with asymptomatic1^0HPTH are candidates for MIP. Patients who are not appropriate for MIP can also be treated with surgical procedures resulting in highly favorable outcomes.

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Extensive Personal Experience - Europe

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Bilateral neck exploration without need of localization studies has for decades been the standard surgical procedure for treatment of sporadic primary hyperparathyroidism (HPT). The procedure has been associated with excellent long-term outcome, with cure rates at experienced centers of 95-98% or more, and with exceedingly low complication rate. Despite this, there has during the last decade been a marked paradigm change concerning the strategy of parathyroid surgery [1]. With the background that 75 -90% of HPT patients, have single adenoma disease, the conventional bilateral procedure has for many been considered to represent unnecessary extended surgery[1,2]. More limited unilateral or focused exploration for HPT has become the currently frequently recommended standard. Routine bilateral exploration has become more and more uncommon, and even been suggested to be relegated to the past, by bearing higher risk for complications. This has been questionable for surgeons, with long experience from doing the conventional bilateral exploration with the best outcome. New methods of unilateral or focused parathyroidectomy, have been claimed to have the benefit of being more rapid, possible to undertake in local anaesthesia as outpatient procedures, and with improved patient comfort and cosmetic results. The less invasive procedures would also have the advantage to be possible to undertake by surgeons without vast experience, and without profoundly disturbing the anatomy, with the implication that a needed reoperation could be easy to perform in un-dissected areas of the neck.

The general interest of focused minimally invasive parathyroid surgery has had the important outcome to lead to improved accuracy of localization techniques, mainly ^{99}mTc-sestamibi (MIBI) scintigraphy with 3D single photon emission computed tomography (SPECT), and parathyroid ultrasonography, increasingly performed by surgeons with new and efficient equipment. Ultrasound-guided fine-needle aspiration

for PTH determination has been commonly used to efficiently verify that a MIBI visualized lesion represents a parathyroid adenoma, and made it possible to distinguish mainly thyroid lesions, .e.g. Hurthle cell adenoma, with similar MIBI entrapment. Concordant MIBI and ultrasound localization has been noted in two third of patients and have been suggested to imply secure adenoma localization. A 4D-CT has been demonstrated to provide even more efficient localization than both MIBI scintigraphy and ultrasound, but higher radiation exposure has often limited the use of this method to re-operative patients. Normal parathyroid glands have been rarely imaged with any technique. A rapid method for intraoperative PTH (IOPTH) determination have been developed, routinely using the "Miami criteria", implying a PTH drop > 50%, which has been calculated to verify adequate resection of parathyroid adenomas [2]. However, MIBI localization has appeared inefficient with multiglandular parathyroid disease (MGD), and 80% drop in IOPTH, or drop to (low) normal values of the assay at 20 min, have been suggested to be needed to exclude abnormality in associated glands [2-8]. This has appeared especially important in MEN-1 cases with commonly recognized size discrepancy between individual glands. When IOPTH monitoring has tended to prolong operations, some groups have used a value 4 hours after operation to decide if immediate reoperation should be considered, and IOPTH measurements have then sometimes been mainly used to prove parathyroid origin of an excised tumor.

The reported rates of MGD have with the Miami criteria been considerably lower than previously reported rates of enlarged glands detected by bilateral open surgery (3-9% vs 15-30%), which has led to suggestions that all lesions may not be functional [2]. However, Siperstein et al. could show by bilateral exploration in patients subjected to adenoma removal, that IOPTH would correctly predict presence of MGD in only 22% [2]. Using both preoperative imaging with ultrasound and MIBI scintigraphy, together with IOPTH, left as many as 16% of patients with a missed adenoma, which in 20% was larger than the preoperatively identified lesion. The experience from bilateral open surgery have generally indicated that enlarged and abnormal parathyroid glands contribute to the disease process, as even small lesions have to be removed to provide cure.

The issue has been substantiated in reports from J Norman et al. [9], who since 1994 strongly advocated a unilateral approach, but after 15 000 operations abandoned the procedure. Routine IOPTH had not been performed, and failed operations had occurred mainly due to inability to recognize the presence of MGD. The authors claimed that IOPTH monitoring in reoperative patients (before a first operation at another institution), had been unable to predict presence of additional adenomas, as even patients with 90% decrease in IOPTH levels had been found with a missed second adenoma. It was only when adopting routine bilateral exploration as an equally rapid method, that the failures became rare.

In sporadic HPT, MGD occurs in 10 – 25 %, is more frequent in patients with mild hypercalcemia, as young renal stone patients, and in postmenopausal females, possibly related to slight vitamin D deficiency and/or slight renal impairment. Two-gland hyperplasia (or double adenomas) may occur in two thirds of patients, whereas three or four gland involvement have been more rare, 10-15% [8,10]. Since recurrence rate has generally been low, it has been considered sufficient to excise only enlarged glands. Familial HPT has become increasingly important to recognize among patients with MGD, since especially these cases risk poor long-term results of limited surgery. MEN1 is the most common, and most important syndrome to diagnose, since lesions tend to develop asynchronously, and have high recurrence rate. Bilateral exploration at the first operation should visualize all parathyroid glands, to allow removal of the largest, diseased glands, and leave the least involved gland as remnant. MEN1 is detected by genetic testing and biochemical screening, which is recommended for HPT patients <40 years of age, even in absence of family history, and all patients with MGD [8,10] . The rare HPT-Jaw tumor syndrome may be diagnosed by a somewhat more complicated genetic testing, and should be suspected in patients with severe hypercalcemia, presence of typical ossifying jaw fibromas, occasional cystic or unusually large parathyroid tumors, and all cases of parathyroid carcinoma. Familial hypocalciuric hypercalcemia (FHH) may

be recognized in children (<10 years), but elderly HPT patients with vitamin D deficiency may have similar low urinary calcium excretion [8,10,11]. A two-stage test is recommended with determination of calcium/creatinine clearance ratio with cut off values <0.02, followed by CASR gene analysis [8,10-12]. FHH patients should generally not be subjected to surgery except in rare cases, who have developed more marked hypercalcemia and distinct tumors detected by ultrasound. MEN2A cases with HPT most often harbor the codon 634 mutation, generally have diagnosed medullary thyroid carcinoma, mild parathyroid disease, and need to be treated with excision of enlarged glands only.

It is crucially important that patients where an adenoma has not been localized by preoperative imaging may still be offered needed surgery, and not have to wait until scanning becomes positive. The goal should not be to necessarily undertake a focused operation. The knowledge obtained with new imaging techniques should be used to speed up and help focus surgery even if bilateral exploration is done. The training how to perform an adequate bilateral exploration must be the important focus for younger surgeons. The knowledge how to open up fascial layers and explore the appropriate areas without much dissection, recognize the typical fat lobulations and the colours and texture of normal and pathological parathyroid glands is an art that needs to be taught by surgeons with experience [9,12]. The outcome of surgery, patient comfort and risk for complications, are probably still mostly dependent on the skill and experience of the surgeon than the procedure per se. For a majority of patients a slightly larger incision needed for excellent bilateral exploration is of no importance. Evolvement of new methods for localization or robotic surgery may change this, but at present it should still be most important to remember important pearls concerning parathyroid surgery that have been learned during several decades.

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Intraoperative monitoring with PTH

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In the last years, the indications to parathyroidectomy for sporadic primary hyperparathyroidism (HPT) has making clear that surgery for patients with any bone fragility is more efficacious than medical therapy and can be conducted with a minimal invasive procedure (MIP).
During the last two decades MIP has largely replaced the traditional bilateral neck exploration. The last procedure consists in exposing all the parathyroid glands and removing those judged as pathological mostly on the basis of macroscopic criteria. Differently, MIP is conducted with a little cervical incision and a monolateral exploration focused only on the parathyroid gland selected on the basis of preoperative imaging. Videoassisted technology and local anesthesia can be utilized for this procedure. However, MIP caused many questions: the preoperative localization examines commonly employed are sestamibi scans and cervical ultrasound, but often one of the two examines is not informative and can also happen that none of the two is accurate. Particularly, in the contest of asymptomatic HPT, MIBI or sonography can miss the small adenoma eventually responsible of the HPT. Furthermore, current localization studies cannot distinguish between single or multiple gland disease. The removal of one pathological parathyroid gland does not guarantee the cure since in only 80-85% of cases a single parathyroid gland adenoma is responsible of HPT. In the other 15-20% of primary HPT more than one parathyroid gland is pathological in the subset of a multiglandular disease (MGD). Therefore, it seem rationale to confirm intraoperatively that all the hypersecreting parathyroid tissue has been removed. The best method to achieve this goal is the rapid PTH assay (i.o.PTH). The chemioluminescent assay is well standardized employing about 10 minutes for the result with an optimal correlation with the standard PTH assay. Knowing the value of PTH during surgery allows to guide surgery indicating if the resection that has been performed is

adequate or if it is necessary to continue the exploration for other pathological parathyroid glands. The method is based on the decay of the circulating PTH once the hypersecreting gland is removed, but requires some assumptions: a short half-life of PTH, the same clearance of PTH among different patients, a stable secretory activity of the pathological gland, a similar secretion of PTH by all the pathological glands, and an inhibition of secretion of the normal glands in presence of a parathyroid adenoma. Nevertheless, the experience with i.o.PTH has been positive with a very low percentage of false positives or false negatives and an optimal accuracy of the method. Controversies exist about the criteria that can be adopted for i.o.PTH monitoring, such as which value is considered the basal, which number of samples is necessary, which timing of the samples and which percentage of decrease must be considered for a positive test. Many criteria have been described and adopted during the last decades. The most followed is the Miami criterion (>50% drop from the highest preincision or preexcision value 10 minutes after excision) that was shown to be more accurate than other criteria (Vienna or Halle criteria). An accuracy between 97% AND 100% has been achieved in several large series of single parathyroid adenoma with a very low percent of false positive or false negative tests. However, if i.o.PTH is able to distinguish between single or MGD is matter of debate, as a great percentage of false positives in the evenience of MGD is observed after removal of the first pathological parathyroid gland if the Miami criterion is adopted. However, if a clear slope of the curve of decreasing PTH is observed utilizing several samples false positives become rare up to absent in some case series. Also in MEN1 HPT setting i.o.PTH can be useful. In these patients a progressive decrease of PTH levels has been observed reaching a PTH value close to the dosable levels. The method makes possible to sure that all the hypersecreting tissue is removed, but not that all the potential pathological tissue is taken out. However, the i.o.PTH assay cannot substitute other pre or intra-operative examines (sestaMIBI, sonography, TC, radioguided surgery, pathology in frozen sections) useful for localizing the parathyroid gland especially if ectopic. Finally the cost of the test should not discourage to add i.o.PTH assay to the surgical procedure. Firstly, the costs can be reduced by performing the assay in the central laboratory verifying a rapid turnaround time. Secondly the i.o.PTH assay could be advantageous in term of cost/effectiveness avoiding or reducing either failed operation or need of re-operation or post-operative medical cures. Furthermore, i.o.PTH allows to made a tailored surgery excising parathyroid glands on the basis of their hypersecretory state, but not on their increased volume. During the neck exploration the surgeon can judge the parathyroid glands as pathological according to the size, color and consistency of a discovered cervical nodule, but this can be misleading because sometimes a thyroid nodule can accurately be interpreted as parathyroid adenoma. Furthermore, frozen sections can distinguish between parathyroid and nonparathyroid tissue, but do not have the same accuracy in distinguish between normal and pathological parathyroid gland and in discriminating between adenoma and hyperplasia. It is well known that either the size or the histopathology of the parathyroid gland does not correlate with its secretory activity.

In conclusion, i.o.PTH must be considered useful, as other preoperative exams including genetic tests, sonography or sestaMIBI, to finally specify the type of primary HPT that the surgeon is going to treat.

Unusual Locations of Parathyroid Adenomas

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Surgical management of parathyroid gland disease may sometimes be difficult, mainly due to the surgeon's failure to successfully detect enlarged parathyroids in “unusual” locations. By definition, these “unusually located” glands are called “ectopic parathyroids” and may occur when parathyroid tissue co-localizes with tissues that share the same embryologic origin.

The diagnosis and treatment of hyperfunctioning “ectopic” parathyroid glands (hyperplastic or adenomatous) may result in persisting disease after initial parathyroid surgery when not preoperatively suspected. It may be a major surgical challenge, even when localised, in planning and performing re-operations.

Analysing literature approximately 6–16% of parathyroid glands are found in an ectopic position. The ectopic gland(s) could be one (or more) of the four glands or may be supernumerary and can be found in various locations in the neck or in the mediastinum.

A careful dissection based on a detailed knowledge of the wide anatomic and embryologic variations of parathyroid gland location is necessary to find one or more enlarged glands. The majority of these ectopic glands is located along the esophagus (superior gland) or is hidden in the thyreo-thymic ligament (inferior gland). It is found rarely in the carotic sheet or in the deep anterior, middle or posterior mediastinum.

In 98% the ectopic gland localised in the thoracic outlet can be removed by a cervical approach, in 2% a more extended procedure is necessary. These enlarged parathyroid glands are mainly located deep in the anterior, middle or posterior mediastinum. Partial or total sternotomy is effective, but should be limited because of invasiveness and increased morbidity. Thoracoscopic surgery is feasible for resection of deep mediastinal parathyroid lesions. This approach represents a less invasive, effective, and safe alternative and seems the current technique of choice.

Surgery of Hereditary Forms of Primary Hyperparathyroidism

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Parathyroidectomy for patients with hereditary forms of primary hyperparathyroidism is more challenging than for those with sporadic primary hyperparathyroidism. Patients with hereditary hyperparathyroidism have higher risks of persistent or recurrent hyperparathyroidism after parathyroidectomy. The extent of parathyroid resection affects whether normocalcemia is achieved and for how long, the risk for hypoparathyroidism, the risk of surgical complications such as recurrent laryngeal nerve (RLN) injury, and the risks and ease of anticipated future parathyroid reoperations.

Hereditary forms of primary hyperparathyroidism or familial primary hyperparathyroidism (FHPT) accounts for about 5% of primary hyperparathyroidism. [Sharma 2009] It is associated with multiple endocrine neoplasia type 1 (MEN1, *MEN1*) and type 2 (MEN2, *RET*), hyperparathyroidism-jaw tumor syndrome (HPT-JT, *CDC73*/*HRPT2*), and familial hypocalciuric hypercalcemia (FHH, *CASR*). [Hendy 2013] Familial isolated hyperparathyroidism (FIHPT) appears to be a heterogeneous group; some are associated with *CASR* mutations, some with *CDC73*/*HRPT2* mutations and other with *MEN1* mutations. [Marx 2002, Simonds 2004, Cetani 2006, Masi 2008]

Genetically all parathyroid cells in a patient with hereditary primary hyperparathyroidism have the mutation. Depending on the disease, some may inappropriately secrete PTH and cause hypercalcemia from birth (*CASR*), others may require additional genetic changes to produce clones of cells that eventually secrete enough PTH to cause hypercalcemia. The ease of these additional genetic changes likely influences the risk of developing primary hyperparathyroidism. Such genetic predisposition increases the risks of both persistent disease and recurrent disease.

Changing Paradigm

The traditional simplistic paradigm of adenoma versus hyperplasia dictates to the surgeons to either resect the adenoma/s or to subtotally resect enough hyperplasia tissue to achieve normocalcemia. This paradigm works well for sporadic primary hyperparathyroidism. Surgical failures in sporadic primary hyperparathyroidism are usually persistent disease caused by not finding and resecting ectopic tumors or supernumerary glands. Recurrent disease, defined as re-development of hypercalcemia more than 6 months post parathyroidectomy after initially achieving normocalcemia, is uncommon for sporadic primary hyperparathyroidism.

In contrast, for hereditary primary hyperparathyroidism this simple paradigm does not work as well. Conceptually, a surgical "cure" for a genetic predisposition for primary hyperparathyroidism is only attainable after a total, complete, removal of all parathyroid tissue, with expected permanent hypoparathyroidism. Any operation less than a total parathyroidectomy leaves abnormal parathyroid tissue at risk for causing recurrent disease. Therefore the surgical strategy for familial HPT needs to be more practical; the extent of resection is dictated by a compromise to achieve long term eucalcemia without causing permanent hypoparathyroidism (a "Goldilocks operation", not too much-and-not too little).

Instead of a simple surgical "cure" the goals of surgery for patients with hereditary forms of primary hyperparathyroidism are to achieve normocalcemia for as long as possible, to avoid permanent hypoparathyroidism, to minimize surgical complications, and to facilitate possible future reoperations. [Carling 2005] These goals sometimes are in conflict, so parathyroid operation in these patients is always a compromise to optimize the overall wellbeing of the patients. Thus an individualized approach is necessary. In addition, because these genetic conditions are rare, there are few high level evidence-based recommendations to guide their surgical treatment. [Stålberg 2009] What is routinely recommended should always be modified by the surgeons' and patients' concerns and preferences.

MEN1

The most common recommended initial operations for MEN1 patients with primary hyperparathyroidism is subtotal parathyroidectomy, removing usually 3 ½ glands, leaving a viable 50 mg remnant from the most normal appearing gland that is biopsy confirmed and well-marked with a suture or a clip. [Carling 2005, Stålberg 2009, Schreinemakers 2011, Twigt 2013] Concurrent bilateral cervical thymectomy is also recommended because of a 15% chance of finding parathyroid tissue in the cervical thymus. [VanderWalde 2006] The multi-institutional French and Belgian GENEM study of 256 patients with MEN1 showed that since 1990, majority (51%) of patients underwent subtotal parathyroidectomy. After operation 19% had persistent disease and 15% had postoperative hypocalcemia. [Goudet 2001] The DUTCHMEN1 study of 73 MEN 1patients with long term postoperative followup showed the rate of persistent or recurrent hyperparathyroidism to be 53% after less than subtotal parathyroidectomy, 17% after subtotal parathyroidectomy and 19% after total parathyroidectomy with autotransplantation. Postoperative hypoparathyroidism of ≥6 months occurred in 24% after less than subtotal parathyroidectomy, 39% after subtotal parathyroidectomy, and 66% after total parathyroidectomy with autotransplantation. [Pieterman 2012]

Total parathyroidectomy with autotransplantation is, therefore, a more aggressive surgical option with a higher risk of permanent hypoparathyroidism and a potential, but not proven, lower risk of recurrent hyperparathyroidism. The potentially easier subsequent operations in finding and resecting regrown autografts from the forearm, versus finding and resection remnant parathyroid in the neck, may not offset the known higher risk of permanent hypoparathyroidism.

The least aggressive surgical option is a simple adenomaectomy with minimal neck exploration (minimally invasive parathyroidectomy, MIP, or focused-targeted-limited parathyroidectomy) guided by preoperative localization studies such as sestamibi scan and ultrasound and intraoperative monitoring of serum PTH levels. A significant proportion of patients with MEN1 may not have recurrence after resection of only one adenoma, and such recurrence may only occur after many years of followup. [Kraimp 1992] Simple focused adenomaectomy could be an option in some patients with clear preoperative localization studies showing only one enlarged hyper-functioning parathyroid gland. One should expect the risk for persistent or recurrent disease to be higher and the recurrences are likely to occur sooner than patient after a subtotal parathyroidectomy.

Another surgical option that is intermediately aggressive between subtotal parathyroidectomy and adenomaectomy is a “unilateral neck clearance”. Both glands from the same side of the neck are resected including an ipsilateral cervical thymectomy, with the expectation that any future reoperation will only be needed in the contralateral not-yet-explored side. Again, these less aggressive options incur lower risk for permanent hypoparathyroidism but with a higher risk of persistent and recurrent hyperparathyroidism.

To maximize the benefits of these less-than subtotal parathyroidectomy, the contralateral neck should not be explored, so as to minimize the risk of RLN injury in future operations. If both sides of the neck need to be explored then a subtotal parathyroidectomy is probably a better option. In general, initial parathyroid exploration is associated with a 1% risk of permanent injury to RLN, re-exploration in a scared-in neck is associated with a 5% risk.

Recent preliminary findings from the DUTCHMEN1 study found possible genotype-phenotype correlation for manifestation of primary hyperparathyroidism in MEN1 patients. After less than a subtotal parathyroidectomy, patients with nonsense or frameshift mutations in exons 2, 9, and 10 had a significantly lower risk of persistent or recurrent hyperparathyroidism than patients with other mutations. [Pieterman 2012] Perhaps in the future, genotyping may guide the surgeons to individualize the aggressiveness of initial parathyroidectomy for patients with MEN1 associated primary hyperparathyroidism.

Reoperations for recurrent hyperparathyroidism in MEN1 usually involved limited exploration to avoid the higher risk of RLN injury in a scar-in neck. Reoperations are usually guided by prior operative findings, results of preoperative localization studies (usually concordance of two of

the following localization studies: SPECT-sestamibi scan, ultrasound, FNA for cytology and PTH measurement of the aspirate, 4D-CT, Gd-enhanced MRI, and selective venous sampling for PTH). Preoperative laryngoscopy is recommended to assess for potential asymptomatic unilateral RLN injury from prior operations. Cryopreservation of resected parathyroid tissue is also recommended for all reoperations and for initial operations when more than an adenomaectomy is done. [VanderWalde 2006]

MEN 2A

In contrast to patients with MEN1, those with MEN2 are less likely to develop primary hyperparathyroidism and even less likely to develop recurrent disease after parathyroidectomy. MEN2B is not associated with primary hyperparathyroidism. The recommended initial parathyroid operation for MEN2A patients is adenomaectomy only. [Carling 2005, Stålberg 2009, Scholten 2011, Twigt 2013] MEN2A patients have an almost certain risk of developing C-cell hyperplasia and medullary thyroid cancer (MTC); the timing and aggressiveness of MTC depend on the specific mutation (a genotype-phenotype correlation). Thus, all MEN2A patients almost certainly will require a total thyroidectomy during their life time, either to treat clinical disease or for prophylaxis after genetic screening. Many parathyroidectomies in MEN2A patients are performed at the same time of a total thyroidectomy. Bilateral exploration of all the parathyroid glands is part of total thyroidectomy. During this exploration, the usual strategy used in sporadic primary hyperparathyroidism will suffice, i.e., resecting only the abnormal appearing gland/s, and avoid injuring the normal appearing glands.

Recurrent primary hyperparathyroidism in MEN 2A is very rare. Some patients, however, may require a parathyroidectomy in a reoperative neck because MEN2A was not recognized at the initial thyroid operation. Such reoperations should be treated like all reoperative parathyroidectomy in patients with sporadic primary hyperparathyroidism. Reoperative parathyroidectomy requires preoperative laryngoscopy and localization studies guided focused parathyroidectomy with cryopreservation. Before operating on patients with MEN2A, the presence of pheochromocytoma should be ruled out by normal levels of plasma free metanephrines or 24-hour urinary fractionated metanephrines. Alpha-adrenergic blockage and adrenalectomy for pheochromocytoma should take precedence over parathyroidectomy and thyroidectomy.

HPT-JT

Patients with HPT-JT mutation are at risk for developing both parathyroid cancer and parathyroid adenomas. Because this syndrome is rare it is usually suspected only after the patient has already undergone a parathyroidectomy, usually for cancer. Parathyroid cancer is suspected clinically when a hyperparathyroid patient has a large, especially palpable, tumor and has severe hypercalcemia. Intraoperatively parathyroid cancer can be recognized by apparent scaring with fibrous bands and local adhesions especially to the thyroid, despite not having had a prior neck operation. When suspected, the cancer should be resected with a concurrent thyroid lobectomy including any invaded muscles. [Harari 2011]

Recurrences are common. The differential diagnoses in recurrent disease include systemic metastasis (treated with cinacalcet and perhaps chemotherapy), local cancer recurrence, or development of a new adenoma or cancer (both treated with repeat resection if possible). Some surgeons recommend subtotal parathyroidectomy in patients with known HPT-JP syndrome, but high level evidence is lacking. [Stålberg 2009] The French national study suggests that HPT-JT/HRPT2 deletion mutations may be underdiagnosed. [Bricaire 2013]

Localization studies and ioPTH for familial HPT

Preoperative localization studies (SPECT-sestamibi scan, ultrasound, FNA for cytology and PTH measurement of the aspirate, 4D-CT, Gd-enhanced MRI, and selective venous sampling for PTH) and intraoperative monitoring of PTH level (ioPTH) have been used to help focus the area of dissection and to guide the extent of resection in patients with familial HPT [Carling 2005, Stålberg 2009]. These are mandatory for reoperations and are helpful during initial operations if the surgeons

and the patients opt for a less than bilateral exploration (i.e. adenomaectomy or unilateral clearance).

Similar to sporadic primary hyperparathyroidism, both localization studies and ioPTH monitoring are more accurate for patients with a solitary adenoma, and much less accurate for patients with multigland disease. Thus they need to be used and interpreted cautiously in patients with familial HPT. For example, in one series of 28 patients with FIHPT, 68% had multiple gland disease, but sestamibi scans failed to identify multigland disease in 52%. [Sharma 2009] Another study from Tasmania showed that although sestamibi scan is not useful for the first time reoperation when the location of remnant is already known, it is very accurate for the subsequent reoperations for supernumerary glands [Shepherd 2000] Other have found that less than subtotal parathyroidectomy may be considered in patients with familial HPT using preoperative localization studies and intraoperative PTH monitoring. [Kandil 2010] In one study of 15 patients with familial isolated HPT, who underwent limited operation guided by ioPTH, 14/15 had a single gland excision with a surgical success rate of 93%. [Carneiro 2002]

Clinical suspicion for hereditary primary hyperparathyroidism

Not all patients with hereditary primary hyperparathyroidism are recognized before their initial operation, especially if there is no family history of the disease. Clinically, patients with higher risk of having multigland disease and possible hereditary primary hyperparathyroidism include young patients, those with negative preoperative localization studies, and those who had a prior failed parathyroidectomy.

In some studies, young patients (≤45 years of age) have been found to be more likely to have clinically occult hereditary forms of HPT. In one study, where 136/1161 patients were 45 or younger, the prevalence of familial HPT in young patients was 24% (24/102). [Starker 2012] Two-third (16/24) were clinically diagnosed and one-third (8/24) were occult and only diagnosed after genetic testing. Of these 24 patients with familial HPT, 15 had *MEN1*, 4 had *RET*, 3 had *CASR* and 2 had *HRPT2*/*CDC73* mutations. Of the 8 patients with occult familial HPT, 4 had *MEN1*, 3 had *CASR*, and 1 had *HRPT2*/*CDC73* mutations. [Starker 2012]

On the other hand, other studies found that occult familial HPT is not common even in young patients and that young patients can be managed with the same preoperative and intraoperative approach as those presenting with sporadic primary HPT of any age. [Skandarajah 2010] In this study of 1253 patients, 87 (6.2%) were younger than 40; the prevalence of MEN1 was 13% in these younger patients. Of the 33 patients consented to genetic study, 12 (10 MEN1, 2 MEN2A) were clinically diagnosed (by syndromic findings or family history) before surgery. Of the other 21 patients without known familial HPT, 12 underwent conventional bilateral exploration and 9 had focused endoscopic parathyroidectomy. Nineteen patients (91%) had uniglandular disease and all 19 were cured. Only one of the 21 patients (4.7%) was found to have occult MEN1 by genetic testing and had double adenomas excised. [Skandarajah 2010]

Conclusion

The surgical aggressiveness of parathyroidectomy ranges from minimally invasive parathyroidectomy, unilateral neck clearance, subtotal parathyroidectomy, to total parathyroidectomy and parathyroid autotransplantation (the latter three combined with ipsilateral or bilateral cervical thymectomy). The risk of multiple gland disease and recurrent disease varies with different forms of hereditary primary hyperparathyroidism; they are highest in MEN1patients and lowest in MEN2A. Therefore the default surgical recommendation for the former is a subtotal parathyroidectomy and for the latter is a simple adenomaectomy. HPT-JT needs special consideration because of risk of local recurrence from cancer. Because of the lack of high level evidence, surgeons should not be dogmatic regarding a particular surgical strategy in the management of patients with hereditary forms of primary hyperparathyroidism. Instead of a simple surgical “cure” the goals of surgery are to achieve normocalcemia for as long as possible, to avoid permanent hypoparathyroidism, to minimize surgical complications, and to facilitate possible future reoperations. What the patient needs is a

"Goldilocks operation" that is individualized balancing various competing goals.

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Vitamin D

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Section of Specialized Endocrinology, Oslo University Hospital and University of Oslo Circulating levels of 25-OH Vitamin D (Vit D) are typically low in patients with Primary Hyperparathyroidism (PHPT), however with a huge geographical variation (1), which might be ascribed to access to medical service, differences in sun exposure and nutritional status. Most patients in Western societies have only moderately decreased levels of Vit D, in contrasts to developing countries where severe cases of PHPT with marked Vit D insufficiency are accompanied by very high levels of PTH, and massive symptoms (2;3).

The low levels of Vit D in asymptomatic PHPT can only for a minor part be explained by increased conversion (activation) of 25-OH Vit D to 1,25-(OH)2 Vit D by the PTH regulated 1α-hydrocylase. The reason for this is that the concentration of 25-OH D is more than thousand times higher than the active hormone. The primary explanation for the low Vit D levels seems to be an increased inactivation and degradation in Vit D sensitive tissue (4) and the increased body mass seen in PHPT (5). In alignment, a spontaneous increase of Vit D levels has been observed after successful surgery of patients with asymptomatic PHPT(6).

Treatment with Vit D in asymptomatic patients with PHPT has the purpose to unmask the calcium level in order to stratify treatment in relation to international guidelines (7). Several studies have investigated the effect of Vit D on PTH levels, bone turnover markers and bone mineral density in asymptomatic PHPT, and Vit D supplementation has been recommended to prevent postoperative hypocalcemia (7-13). So far, no large scale, prospective, randomized and placebo controlled studies have investigated the effect of primary treatment with Vit D on PTH levels or morbidity in asymptomatic PHPT. The studies performed so far indicate a modest decrease in PTH concentrations with ambiguous effects on biochemical markers of bone turnover and bone mineral density (8-10;13). A few patients may develop a significant increase in calcium levels and also in the urinary excretion of calcium. No studies have been performed in a time aspect long enough to delineate potential risks for urinary concrements.

While awaiting prospective and randomized studies on the effects of Vit D treatment in patients with asymptomatic PHPT, it is recommended to replete Vit D deficiency in order to optimize diagnostic strategies for stratification to overall treatment of the disease. Calcium levels and urinary excretion of calcium should be monitored during repletion.

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Medical Management of Asymptomatic Primary Hyperparathyroidism: Bisphosphonates and HRT

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The key questions to be addressed by the working group pertaining to the medical management of PHPT with bisphosphonates and HRT were addressed. An electronic literature search was completed in MEDLINE and EMBASE using OVID on all published literature between 2000 and 2013. The key words were combined to find the relevant articles which were subsequently reviewed and critically appraised and graded based on the quality of evidence. The questions addressed and the results of the literature search are presented below.

1) Are there novel data on the efficacy and safety of long-term bisphosphonate therapy in patients with PHPT?

Amino-bisphosphonates are effective in lowering serum calcium in hypercalcemia of malignancy.(1) They have also been evaluated in primary hyperparathyroidism and their impact on bone density, biomarkers, serum calcium, and PTH have been evaluated.(2) The first amino-bisphosphonate to be evaluated in primary hyperparathyroidism was pamidronate.(3) In doses of 30mg intravenously in 10 patients transient decreases in serum calcium from 10.88 +/- 0.24mg/dL to 996 +/- 0.16mg/dL were observed after 1 week of administration.(3) Serum PTH was observed to rise transiently and this was in association with a decrease in serum calcium.(3) Risedronate has also been evaluated in PHPT and was given in doses of 20 and 40mg/day for 7 days.(4) Decreases in serum calcium were seen after 1 week of administration (4) Alendronate is the amino-bisphosphonate which has been most extensively investigated and has been observed to decrease bone remodelling and increase bone density in individuals with hyperparathyroidism.(5,6,7,8) Alendronate given open label to 32 patients in doses of 10mg/day over 24 months resulted in increases in bone mineral density at the lumbar spine by 7.3% +/- 1.7% (P <0.001). Small gains were seen at the femoral neck and there were non-significant transient changes in serum calcium and PTH which returned to baseline by 3 months.(7)

In 40 postmenopausal women, Alendronate was given in 10mg daily doses in comparison to placebo over a 48 week period. This was then followed by a no treatment phase of 24 weeks. This randomized controlled trial evaluated bone density at the femoral neck , lumbar spine and the distal forearm. Increases were seen at the femoral neck site by 4.17% +/- 6.01% versus a fall in the placebo group by 0.25 +/- 3.3% (P=0.011). The lumbar spine bone density increased by 3.79% +/- 4.04% in comparison to the placebo group which had an increase in the lumbar spine bone density of 0.192 +/- 2.8% (P=0.016)(6). A significant decrease in serum calcium was observed in this study from a mean of 2.82mmols/L to 2.74mmols/L at 48 weeks (P=0.018). There were no significant changes in PTH. Urine calcium did not change. Bone turnover markers decreased with Alendronate and decreases were seen in bone specific alkaline phosphatase, osteocalcin, and urinary NTX at 48 weeks. The bone turnover markers rose in the group following cessation of Alendronate therapy.(6)

In an international multicenter randomized controlled trial, 44 patients were treated with Alendronate 10mg daily in comparison to placebo for the first year. In the second year, the placebo group was crossed over to Alendronate.(8) BMD was monitored by DXA every 6 months at the femoral neck, total hip and distal one third radial sites. There were significant increases in bone density observed at the lumbar spine in comparison to baseline by 6.8%+/-0.94% p<0.001 (8) in this study. Urinary NTX decreased by 66% (P<0.001) at 3 months. Bone specific alkaline phosphatase decreased by 49% (P<0.001) at 6 months. There were no significant changes seen in serum calcium. Both total and ionized

calcium levels were stable. PTH and urine calcium also did not show any significant change in this randomized controlled trial.

The randomized controlled trial data which has been published to date consistently demonstrates decreases in bone remodelling and increases at the lumbar spine and the proximal femoral BMD. These suggest improvements in strength; however, there are no data available to confirm the effect of bisphosphonate therapy on fracture risk. The effect on serum calcium has been inconsistent and may be affected by baseline vitamin D levels.(2)

Recently a study of cinacalcet in combination with alendronate has evaluated 23 patients with PHPT retrospectively. Cinacalcet was given with alendronate in 10 of the 23 patients and as a single agent in the remaining 13 patients. There were no differences on the impact of combination therapy or monotherapy with cinacalcet alone on serum calcium or PTH. Both groups were effective in lowering serum calcium and PTH. Improvements in BMD however were noted only in the combination group with the aminobisphosphonate present in comparison to cincalcet alone.(9) This study confirmsthe results of previous investigators evaluating bisphosphonates and their efficacy in improving bone mineral density in PHPT.

2) Is bisphosphonate therapy effective in the male with PHPT?

Currently there is very limited data evaluating antiresorptivetherapy in men with PHPT .
In the international study evaluating alendronate in PHPT over 2 years (8) the male patients were separately evaluated.(10)
Patients were randomly assigned to receive either alendronate or placebo during the first year, and all patients received alendronate in the second year. In the first year 3 men received alendronate and 6 received placebo.In the second year the men receiving placebo were switched to alendronate .The skeletal effects of alendronate therapy in the 9 men during their first year of treatment were compared to the 6 men receiving placebo for a year as well as the 24 postmenopausal women during their first year of alendronate therapy.(10)
A 4.8% increase in BMD at the lumbar spine (P = .1) was noted in the men on alendronate therapy for 1 year (n = 9) in comparison to the men who received 1 year of placebo (n = 6). Relative to baseline, men receiving alendronate showed a significant 4.4% gain in BMD at the lumbar spine (P = .009) and a 2.95% gain in total hip BMD (P =.027). Decreases in biomarkers were also observed with bisphosphonate therapy with a 47% decline in serum levels of bone-specific alkaline phosphatase activity with alendronate therapy (P = .003). Changes in BMD in the male population were similar to previously reported effects of alendronate therapy in postmenopausal women with PHPT.
In conclusion the limited published data suggests similar improvements in BMD and reductions in bone remodeling with alendronate therapy as seen in women. Further study is needed to confirm the effects of bisphosphonates on skeletal protection and fracture efficacy in men with PHPT.

3) Is there still a role for estrogen therapy in postmenopausal women with PHPT (i.e.: early postmenopausal period)?

Hormone replacement therapy has been evaluated in preventing the skeletal complications of primary hyperparathyroidism and also in its effectiveness in lowering serum calcium and PTH. Early uncontrolled studies did suggest a lowering of serum calcium; however, randomized controlled trial data published by Grey and colleagues did not confirm this effect.(11) Hormone replacement therapy given in the form of conjugated equine estrogen 0.625mg/day and medroxyprogesterone acetate 5mg/day was compared to placebo in this randomized controlled trial over 24 months. Bone density at the total body site increased by 1.3% +/- 0.4% (P=0.004). The lumbar spine bone density rose by 5.2% +/- 1.4% (P=0.002). The femoral neck bone density increased by 3.4% +/-

1.5% (P=0.05). In the hormone replacement therapy group alkaline phosphatase levels decreased by 22% (P=0.0004) in comparison to placebo. There were no changes in serum ionized calcium or PTH.(11)

Hormone replacement therapy has been shown to decrease bone remodelling. It is effective in reducing urinary calcium excretion and increases bone density throughout the skeleton in postmenopausal women with mild primary hyperparathyroidism. No effects have been observed on ionized calcium or PTH. HRT may be a useful option for those unable or unwilling to proceed with parathyroidectomy especially in the presence of menopausal symptoms. There are no fracture data evaluating the affects of hormone replacement therapy in primary hyperparathyroidism.(11)

Raloxifene has been evaluated in primary hyperparathyroidism. Eighteen postmenopausal women with asymptomatic primary hyperparathyroidism were randomized to 8 weeks of Raloxifene 60mg/day or placebo followed by a 4 week washout phase. During this time, total calcium decreased by 8 weeks of Raloxifene therapy from 10.8 +/- 0.2 to 10.4 +/- 0.2mg/dL (P<0.05)(12) Rubin et al, JCEM, 2003). Osteocalcin also was found to decrease by 17% after Raloxifene was implemented and serum NTX decreased by 18% in postmenopausal women with primary hyperparathyroidism. There were no effects on PTH 1,25 hydroxyvitamin D, alkaline phosphatase, or urine calcium.(12) In another study evaluating 3 patients with PHPT bone loss was prevented at the spine and hip.(13)

Bisphosphonates and hormone replacement therapy are effective in maintaining bone density and lowering bone remodelling. Currently there are no fracture data available with the medical options which have been evaluated. In individuals for whom medical monitoring is suitable targeted medical intervention appears to be of benefit.(14,15)

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Non-surgical approaches. Pharmacological 2: Cinacalcet

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Cinacalcet hydrochloride is an allosteric modulator of the calcium-sensing receptor (CASR), acting to sensitize this receptor to the extracellular calcium (1). Cinacalcet increases the affinity of the receptor for extracellular calcium, leading to an inhibition of PTH synthesis and secretion by the parathyroid cell and a decrease in renal tubular calcium reabsorption.
The efficacy of cinacalcet in maintaining serum calcium and PTH concentrations was demonstrated in a 52-week multicenter, randomized, double blind, in which 78 primary hyperparathyroidism (PHPT) with mild to moderate hypercalcemia were randomized to cinacalcet or placebo (2). Serum calcium normalized in the majority (73%) of patients treated with cinacalcet and remained normal for the entire study period. A modest reduction of PTH in the morning sample before the cinacalcet dose was observed; multiple sampling after the dose showed a more marked decrease of plasma PTH. Further data were obtained in a 4.5-yr open-label extension of this study, which included 45 subjects, who were all treated with cinacalcet (3). Mean serum calcium remained in the normal range in all subjects throughout the extension study. No changes in BMD at lumbar spine, hip or wrist were observed during the follow up.
An open-label, single arm multicenter study has evaluated the effectiveness of cinacalcet in patients with intractable PHPT, defined as PHPT unresolved after parathyroidectomy or with contraindications to surgery (4). This trial enrolled 17 patients with serum calcium greater than 12.5 mg/dl. Cinacalcet was titrated to a maximum dose of 90 mg four times daily. Cinacalcet induced a marked decrease in serum calcium, with 15 of 17 patients achieving reductions of ≥1mg/dl. There were no statistically significant changes in the level of PTH during the study.

A multicenter, open-label, single arm dose-titration study has examined the effectiveness of cinacalcet on biochemical and hormonal parameters in patients with inoperable parathyroid carcinoma who failed to improve after PTx (5). This trial enrolled 21 patients with mean serum calcium of 14.1 mg/dl and plasma PTH values of 697 pg/ml. Cinacalcet was titrated up to 90 mg four times daily until serum calcium was less than 10 mg/dl. Serum calcium was reduced by at least 1 mg in about 60% of patients, whereas and PTH levels only slightly declined (-4.6%).
Recently, Peacock et al. in a pooled analysis showed that cinacalcet was effective in reducing serum calcium in PHPT patients across a wide spectrum of disease severity (6).
Cinacalcet has bee effectively used in particular cases, including PHPT in pregnancy and puerperium, lithium-induced hypercalcemia and PHPT, PHPT associated with biliary cirrhosis, and familial hypocalciuric hypercalcemia (7).
A recent randomized, crossover, double blind study has shown that cinacalcet normalized calcium and reduced PTH in patients MEN1-associated PHPT (8). There was no difference in the dose required to normalize serum calcium between patients with MEN1-associated PHPT and those with sporadic PHPT. Cinacalcet can be an alternative treatment option for MEN1 patients who have persistent or recurrent PHPT after PTx. Whether cinacalcet might be considered a first-line treatment in MEN1-associated PHPT remains to be investigated.
Adverse events of cinacalcet therapy (most commonly headache, nausea, arthralgia, and myalgia) are mild to moderate in severity in patients with mild PHPT and often recede within one month (3). In patients with parathyroid carcinoma and intractable PHPT, in whom higher doses of cinacalcet were used to control hypercalcemia, adverse events were more frequent and severe and lead to treatment withdrawal in about one fourth of cases (4, 5). In these cases, the use of the maximum tolerated dose of cinacalcet could be a reasonable choice, provided that a clinically relevant decrease of serum calcium is obtained.
Cinacalcet is approved by the European Medicines Agency (EMA) for the "reduction of hypercalcemia in patients with PHPT, for whom PTx would

be indicated on the basis of serum calcium levels (as defined by relevant treatment guidelines), but in whom PTx is not clinically appropriate or is contraindicated" (9) and by the FDA for "hypercalcemia in patients with parathyroid carcinoma" and treatment of severe hypercalcemia in patients with PHPT who are unable to undergo parathyroidectomy" (10).

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Ideazione grafica e impaginazione: DULCAMARA GRAFICA E COMUNICAZIONE

Stampato da ARTI GRAFICHE TORRI SRL nel settembre 2013

Menarini Foundation Symposia: 237