

## Invited Speaker Abstract

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### **Primary hyperparathyroidism: new concepts, new insights, new guidelines**

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Primary hyperparathyroidism (PHPT) became a common endocrine disorder with the advent of the multichannel autoanalyzer in the early 1970s. Prior to that, PHPT was considered to be a rather rare disorder of calcium metabolism, identified only when signs and symptoms were present. From the earlier era, these individuals presented with a phenotype that was virtually always accompanied by involvement of the major target organs of PTH, namely the kidney (with stones), and the skeleton (with radiologically overt bone disease). After the 1970s, when the serum calcium became part of the multichannel biochemical screening test, hypercalcemia became much more common and was seen in individuals who had neither signs nor symptoms that are classically associated with hypercalcemia or excess parathyroid hormone. The phenotype of asymptomatic PHPT became the overwhelmingly predominant form of PHPT in countries where biochemical screening became routine. In countries where biochemical screening was and still is not routine, PHPT continues to be an uncommon disease.

The incidence of asymptomatic PHPT, as diagnosed by hypercalcemia and elevated PTH levels, continues to make it one of the most common endocrine disorders.

We are now entering yet another era of discovery by recognizing subjects whose serum calcium is consistently normal but in whom the PTH is consistently elevated. How these individuals are coming to attention may influence their presentation, in that they are usually being seen for a disturbance in mineral metabolism (e.g. reduced bone density/fractures) or kidney stones. Whether there is yet another presentation of normocalcemic PHPT, characterized similarly to those who present with asymptomatic disease remains to be seen. A recent NHANES database suggests that normocalcemic PHPT may be even more common than the hypercalcemic variant.

In most series, about 50-60% of individuals with asymptomatic PHPT will meet one or more guidelines for surgery, as recommended by the last international workshop on asymptomatic PHPT in 2002. These guidelines include: a) serum calcium >1 mg/dl above the upper limits of normal; b) marked hypercalciuria, >400 mg/day; c) bone mineral density determination by dual energy X-ray densitometry (DXA) <-2.5 at lumbar spine, hip, or distal radius (1/3 site); d) creatinine clearance reduced by >30% in comparison to age and sex-matched norms, e) age <50.

A limited number of studies have been published since the last workshop on PHPT in which the natural history of patients with asymptomatic PHPT has been described. Some of these studies have included randomization of matched subjects into surgical or non surgical groups. In other natural history studies, subjects are not matched but have favored surgery among those who meet guidelines for surgery and a conservative, non-surgical approach in subjects who do not meet criteria for surgery. However the results of the studies by Silverberg et al. have shown that the natural history of these subjects, with or without surgery, appears to be independent of whether or not they initially met criteria for surgery.

In subjects who underwent parathyroid surgery, the results are, as expected, highlighted by invariable cure of the disorder with rapid correction of the hypercalcemia and elevated levels of PTH. In addition, urinary calcium excretion falls and bone mineral density rises. Bone turnover markers return to normal. Bone mineral density uniformly increases at all three skeletal sites: lumbar spine, hip and distal (1/3) radius. This is an interesting observation in view of the classical pattern of bone loss in PHPT in which there is selective reduction in cortical bone in many subjects. The increase in bone density persists at all three sites over 15 years of follow-up. Microarchitectural features of bone are also improved after parathyroid surgery. In recent

studies, some neurocognitive features have been shown to improve after successful parathyroid surgery. The improvement following parathyroid surgery was similar whether or not patients met guidelines for surgery preoperatively.

A cohort of subjects with PHPT who did not have parathyroid surgery has also been followed for as long as 15 years. For the first 8-10 years, these subjects appear to do well, in general, without significant changes in the serum calcium, PTH, urinary calcium, vitamin D levels or in 3-site bone mineral density determinations. As these patients were followed for the next 5 years, a decline in bone mineral density at the hip and the distal (1/3) radius, but not at the spine, became apparent. The numbers of subjects who met one or more guidelines for surgery after 15 years was 37%. Again, the natural history of these subjects, followed without surgery, was not different among those who did or did not meet guidelines for surgery.

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