

The Diagnosis and Management of Asymptomatic Primary Hyperparathyroidism Revisited

Aliya A. Khan, John P. Bilezikian, and John T. Potts, Jr., Guest Editors for the Third International Workshop on Asymptomatic Primary Hyperparathyroidism

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Primarily hyperparathyroidism (PHPT) is a common endocrine disease, especially in countries where multichannel biochemical screening, including the serum calcium measurement, is routinely used. As a result of the introduction of the automated serum screening chemistry panel in the United States in the early 1970s, the prevalence and incidence of the disease was shown to be much higher than previous estimates (1). In addition, the clinical profile had shifted from a symptomatic disorder, with hypercalcemic symptoms, kidney stones, overt bone disease, or a specific syndrome of neuromuscular dysfunction, toward a less symptomatic or even asymptomatic state. The modern clinical profile of asymptomatic PHPT, at least in North America and in many other parts of the world, is best characterized as a disorder in which there are neither signs nor symptoms traditionally associated with hypercalcemia or PTH excess. However, there are clearly different presentations of the disease in different countries. In parts of Europe and in developing nations, disease presentation is more typically reported with overt signs and/or symptoms (2).

In light of the shift in the clinical profile of PHPT, it was no longer clear in 1990 whether parathyroid surgery should be recommended for all patients with this disease. Other issues related to medical management, surveillance, and criteria for diagnosis and/or recommendations for surgery all led to the convening of a Consensus Development Conference on the Management of Asymptomatic Primary Hyperparathyroidism (3). This conference, held at the National Institutes of Health (NIH) in October 1990, was sponsored by the Office of Medical Applications of Research and the National Institute of Diabetes and Digestive and Kidney Diseases. The conference was a watershed moment in the history of this disorder because it identified the new asymptomatic profile, raised questions as to who could be monitored safely without surgery, issued guidelines to surgical and nonsurgical management, and described a blueprint for further research. It was clear then, and has become even clearer since, that

greater understanding of this disease was going to require thoughtful observation, prospective studies, and greater insight into its pathogenesis as part of the overall quest for new knowledge. The next 10 yr experienced a resurgence of research along these lines and led to the recognition in the early 2000s that another conference was needed to update the field and to reconsider those previous guidelines for surgical or medical management.

The second international workshop on the management of asymptomatic primary hyperparathyroidism was subsequently held at the NIH in April 2002. Following a format that included formal presentations, discussions, and the convening of an expert panel, this conference led to a revised set of principles and guidelines for diagnosis as well as for surgical *vs.* nonoperative medical management of patients with asymptomatic PHPT (4). At both the first and second conferences, parathyroid surgery was recognized as the only definitive therapy for PHPT and was acknowledged to be always an option, even among those who did not meet guidelines for surgery. This point deserves emphasis. On the other hand, it was also recognized that individuals who met guidelines for surgery might not be candidates for parathyroid surgery if they or their physicians declined or if medical issues were contravening. It is also worth emphasizing that these two conferences were focused upon management decisions for asymptomatic PHPT. There was never any debate, nor should there be now, about those who already demonstrate clear target organ complications of PHPT such as kidney stones, fractures, or overt neuromuscular disease. Serum calcium concentrations that are associated with symptoms and signs of hypercalcemia also invariably should lead to a recommendation for parathyroid surgery. These symptomatic patients with symptomatic PHPT should have parathyroid surgery.

Over the past 6 yr, still further changes have emerged in the presentation and other aspects of PHPT, culminating in the most recent workshop that forms the basis of the supplement to this

issue of *JCEM*. The objectives of this workshop were to review advances made in the diagnosis and management of PHPT since the last workshop in 2002, provide updated recommendations for clinical practice, and identify areas for further research. The Third International Workshop on Primary Hyperparathyroidism was held on May 13, 2008, in Orlando, Florida, with the support of the following national and international organizations: The Endocrine Society, The American Association of Clinical Endocrinologists, the American Society for Bone and Mineral Research, the Canadian Society of Endocrinology and Metabolism, Canadian Endocrine Update, the European Calcified Tissue Society, the Italian Foundation for Bone and Mineral Research, the International Bone and Mineral Society, the International Association of Endocrine Surgeons, the American Association of Endocrine Surgeons, and McMaster University. The objectives of the workshop were to review advances in the diagnosis and management of asymptomatic PHPT since the second workshop held in 2002, to revise guidelines, and to identify areas for further research. The PHPT Steering Committee was responsible for the development and oversight of the workshop, as well as the publication of the proceedings and consensus statements. The members of the Steering Committee were Aliya Khan (Chair), John Bilezikian, Maria Luisa Brandi, Richard Eastell, Ian Reid, and John Potts.

The sponsoring societies nominated representatives recognized for their knowledge and expertise in this field to serve on the PHPT Task Force. These individuals included the Chairs of the Meeting (John Bilezikian, Aliya Khan, and John T. Potts) and the following individuals: Roger Bouillon, Maria Luisa Brandi, Pauline Camacho, Orlo Clark, Richard Eastell, David Hanley, Janice Pasieka, Ian Reid, and Shonni Silverberg.

Members of the Task Force, in addition to the individuals listed above were: Andrew Arnold, Edward Brown, Pierre D'Amour, Andrew Gray, David Goltzman, D. Sudhaker Rao, Mishaela Rubin, Steven Marx, Munro Peacock, Leif Mosekilde, E. Michael Lewiecki, Dolores Shoback, Cord Sturgeon, Robert Udelsman, and J. E. M. Young.

Members were assigned to subgroups addressing the following topics: diagnosis of asymptomatic PHPT, presentation of asymptomatic PHPT, surgery, and medical management. Task Force members identified key questions to be addressed by the comprehensive literature review emphasizing studies that have been conducted since 2002. The published literature was critically appraised and graded based on the quality of evidence. At the workshop, presentations covered the key questions that had been raised and reviewed by this comprehensive survey of the

literature. After the full day of presentations and discussion, a consensus panel was convened. Each question was discussed in detail. A formal consensus process was undertaken with voting on the key consensus statements by the consensus panel members. Based upon the panel's deliberations, manuscripts were prepared by members of each of the four Task Forces. The Co-Chairs then summarized the conclusions of the Task Forces into a summary statement and a set of revised guidelines on the management of asymptomatic PHPT. The summary statement is the second manuscript in this series (5). All manuscripts were circulated to all Task Force Members, and appropriate revisions were made. The manuscripts then underwent peer review by experts in the field who were not part of the workshop. Funding for this workshop was received by unrestricted grants from the sponsoring societies. All conflicts of interest were fully disclosed.

We trust that this process and the results of it will lead to useful recommendations on the management of asymptomatic PHPT. It is apparent that more research will be needed in this field to keep abreast of the changing profiles of this disease and to remain current with regard to management guidelines.

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