Hyperparathyroidism: Time to Reconsider Current Clinical Decision Paradigms?

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"*In the final analysis very little is known about anything, and much that seems true today turns out to be only partly true tomorrow. . .* ", Albright and Reifenstein, 1948 (1)

Significant are the changes in our understanding of the evolving clinical profile of primary hyperparathyroidism in general, and substantial are the gained insights into its metabolic bone profile in particular, six decades later.

The epidemiology of primary hyperparathyroidism has fluctuated widely, in large part due to the availability of multichannel chemistry screening. After a marked rise in its incidence from 16 in 100,000 before 1974 to a peak of 82 in 100,000 several years later, the rate has since fallen to 22 in 100,000 (2). Many patients nowadays are thus discovered through work-up of hypercalcemia detected by routine biochemical screening or as part of an osteoporosis evaluation, which may also uncover the normocalcemic variant of hyperparathyroidism. The classical presentation of hyperparathyroidism has shifted from a symptomatic disorder of complaints from "bones, stones, abdominal moans, and groans" to an asymptomatic one in Western countries. Indeed, nephrolithiasis, bone disease, and musculoskeletal complaints are present in only one fifth of patients in developed countries, but symptomatic disease is still the commonest presentation in areas such as India and China, in part due to ascertainment bias and possibly hypovitaminosis D (3).

Because of the shift in the clinical profile of primary hyperparathyroidism, and the fact that it was not a relentlessly progressive disorder in studies extending up to a decade (4, 5), it was unclear whether parathyroidectomy was the most optimal strategy in asymptomatic patients. In 1990, the National Institutes of Health Consensus Development Conference addressed risk factors for the development of complications in such patients and derived a set of guidelines for surgical intervention based on observations pertaining to the natural history of primary hyperparathyroidism (6). These included age less than 50 yr, serum calcium 1–1.6 mg/dl above the upper limit of normal, hypercalciuria (24-h urinary calcium >400 mg), deteriorating kidney function (decrease in creatinine clearance by >30%), and a bone mineral density (BMD) Z-score less than −2 at the forearm. The above criteria were revisited in 2002; the cutoff for serum calcium level changed to 1 mg/dl above the upper limit of normal and that for BMD to a T-score less than or equal to −2.5 at any skeletal site (7).

In 1984, the group at Columbia University initiated a prospective study of 143 subjects with primary hyperparathyroidism to characterize the natural history of the untreated disease, defined by clinical, biochemical, densitometric, and histomorphometric features, and to assess the impact of surgery on these variables. In a 10-yr follow-up of 121 subjects, mostly with asymptomatic disease, serum calcium and PTH levels and BMD were stable, and hypercalciuria did not worsen in 52 patients followed without intervention (5). However, bone loss was noted in 11 of 52 subjects (21%), and disease progression, defined by the development of one or more indications for parathyroidectomy, occurred in 14 of 52 subjects (27%) followed medically (5, 6). Observations on the same cohort of 116 patients with an extended follow-up of 15 yr are now available in this issue of the Journal (8). Fifty-seven patients were followed without intervention, 49 were asymptomatic, and 11 died during the follow-up period. Within that group, 20 patients met surgical criteria for intervention but initially refused, and nearly half ultimately underwent surgery for various reasons. Whereas there were no significant changes in serum PTH levels or urinary calcium excretion, mean serum calcium level increased significantly by 0.6 mg/dl compared with baseline at the 15-yr time point. Lumbar spine BMD was stable throughout the study duration, but significant decrements were noted at the femoral neck and forearm. Overall, 29 of 49 asymptomatic subjects (59%) had more than a 10% decline in BMD at one site within the 15-yr follow-up that became apparent after 8 yr; 19 demonstrated these decrements within 10 yr, and 10 experienced bone loss after 10

Abbreviation: BMD, Bone mineral density.

0021-972X/08/$15.00/0

Printed in U.S.A.

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doi: 10.1210/jc.2008-1305 Received June 16, 2008. Accepted July 2, 2008.

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yr. Meeting surgical criteria (6) at study entry did not predict disease progression. Substantial and sustained increments in BMD were noted at the spine (9–12%), femoral neck (5–10%), and radius (4–7%) in the 59 subjects who underwent parathyroidectomy.

The skeletal profile of the above described cohort at study entry was characterized by reduction in bone mass at cortical sites and relative preservation at trabecular sites, findings consistent with other studies (9, 10). However, a subset of subjects, mostly postmenopausal women, may display an opposite pattern with the most severe decrements noted at the spine, then hip, then forearm (11). Several studies, as well as a previous report from this cohort, had concluded that BMD in patients with hyperparathyroidism is usually stable. Limitations in many studies include relatively short follow-up periods, the heterogeneity of the study groups in terms of age and gender, and importantly, the lack of appropriate controls. Indeed, Guo *et al.* (10) were able to demonstrate substantial decrements in hip and total body bone mass over 2 yr in 33 postmenopausal women with hyperparathyroidism, compared with age-matched controls. Examination of data stemming from the largest modern cohort followed for up to 10 yr (5) and then up to 15 yr (8) leads to differing results and conclusions. Whereas most patients followed without surgery did not experience disease progression or loss of bone mass in the former report, disease progressed in 37% of patients, and cortical BMD decreased in the majority of subjects with longer follow-up. In the former report, a higher baseline serum calcium and onset of menopause predicted loss of bone mass, and younger age predicted disease progression (5). Conversely, although the group that experienced the most loss of bone mass had significant increments in serum calcium, no predictors of BMD loss or disease progression were identified in the current report. Finally, whereas parathyroidectomy resulted in substantial increments in spine and hip but not forearm BMD in the former report, increments were noted at all three skeletal sites in the current update. The investigators explained some of these differences by the more powerful statistical method used and the additional observation points obtained. Although the linear mixed model for repeated measures is more optimal than previous methods used, a shrinking sample size, confounding by intake of antiresorptive drugs in 13 patients (for a median duration of 4 yr), and the switch in densitometers that occurred in over half of subjects followed without surgery are important limitations, and it is unclear whether they could have been appropriately addressed. The small number of patients who reached 10 yr (n = 11) and 15 yr (n = 6) raises questions regarding the comparability of patients in subset analyses and the ability and power of the model to evaluate the impact of study duration and intake of antiresorptive drugs on patterns of loss of BMD over time. Furthermore, onset of menopause during study follow-up was not commented on, although it was identified as a predictor of loss of bone mass in the former report (5). Finally, eight of 11patients followed beyond 10 yr had switched densitometers at a mean period of 4 yr from study entry. This could have, in part, explained the apparently stable BMD in the early years, and it is unclear how this was addressed in the mixed-model analyses.

The relative preservation of trabecular bone mass and the reduction in cortical bone mass at study entry and on follow-up documented by densitometry in this cohort is also reflected by histomorphometric studies. Preservation of cancellous bone mass and structure, despite high bone turnover, is possibly explained by decreased erosion depth, whereas cortical bone loss is due to enhanced endosteal bone resorption with cortical thinning and increased porosity (12). The above observations would imply an increased fracture risk exclusively at cortical sites, but studies have demonstrated an increased risk of fractures both at cortical and trabecular sites (13, 14), and parathyroidectomy seemed to be protective (13). More recently, reduced mineralization density was observed using quantitative backscattered electron imaging, a finding that may reduce the stiffness of bone and, thus, in part explain the observed increased fracture risk (15).

Several observations challenge the notion that modern primary hyperparathyroidism is truly an asymptomatic disorder. Patients with hyperparathyroidism are more likely to suffer from cognitive and psychiatric abnormalities and may be at increased risk for metabolic abnormalities such as obesity, hyperlipidemia, and glucose intolerance. Epidemiological studies suggest a greater risk of cardiovascular abnormalities and cancer (3, 16–19). An increased mortality was reported in Europe, an observation that was validated only in the subgroup with severe hypercalcemia in the United States. The possible improvements in subjective symptoms (19) and in nonclassical outcomes, including mortality, reported in Europe (16) render surgery an attractive alternative. However, the impact of parathyroidectomy on many of these outcomes has not been adequately studied.

It had been suggested that although BMD is decreased in patients with asymptomatic hyperparathyroidism, the lack of evidence for progressive loss of bone mass by densitometry in many but not all studies (5, 9, 17, 19) may justify close observation without surgical intervention in most asymptomatic patients (3, 7). Antiresorptive therapies, mostly bisphosphonates, stabilized BMD in patients with primary hyperparathyroidism in short-term trials (3). They, however, do not cure hypercalcemia and would not be anticipated to impact renal outcomes. Calcimimetics decrease serum calcium, lower serum PTH, and raise serum phosphorous levels but do not increase BMD. Conversely, the substantial increments in bone mass after parathyroidectomy coupled with a substantial decrease in stone risk has led to consideration of surgical intervention as the preferred option for most, if not all patients (20). The data presented here, including the inability of surgical criteria, originally developed in 1990, to identify patients at risk for disease progression, have led to a reexamination of the original guidelines in a recent workshop on hyperparathyroidism (21). The proceedings from that meeting should be published soon. In addition, an evaluation of the ability of any newly revised criteria and better predictors to identify disease progression in that same cohort is needed (7). Receptor activator of nuclear factor-κB ligand (RANKL), a mediator of the effects of PTH on bone, was recently shown to be a good predictor of bone loss in a group of 33 patients, mostly women, with hyperparathyroidism (22).

Substantial are the changes in our understanding of hyper-

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parathyroidism over the last few decades, necessitating periodic adjustments in management decisions for this disease. Many uncertainties still remain and can be addressed only in large multicenter randomized controlled trials. The perseverance of the Columbia group, meeting the challenging task of extending observations in their cohort for up to 15 yr, has allowed valuable observations on the manifestations of modern hyperparathyroidism. These observations invite a reconsideration of the current clinical decision paradigm. Whereas surgery was the gold standard approach before the 1970s and 1980s, observation without intervention was an accepted option for many asymptomatic subjects over the last one to two decades. The substantial proportion of subjects who experience loss of bone mass and disease progression, the lack of consistent predictors for such adverse outcomes, and the unknown impact of chronic hypercalcemia on health outcomes, contrasted with the high cure rate and definite improvement in skeletal and renal outcomes after parathyroidectomy, render surgery a very attractive first option in many patients today.

Acknowledgments

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