

## Asymptomatic hyperparathyroidism: Is the pendulum swinging back?

Kerry Siminoski

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In this issue (page 184) Aliya Kahn and John Bilezikian nicely summarize the progress that has been made in our understanding of the pathophysiological processes underlying calcium homeostasis and the development of primary hyperparathyroidism.<sup>1</sup> They also touch on the approach to patients with so-called asymptomatic hyperparathyroidism, which has been the main clinical issue to be debated in the parathyroid field over the last decade. Until the 1960s hyperparathyroidism was typically diagnosed at an advanced stage and was regarded as a surgical condition. During the 1970s and 1980s hypercalcemia was increasingly being detected by means of multiphasic blood panels, which resulted in a growing proportion of patients who had few severe symptoms.<sup>2</sup> In consequence a contrarian approach

gradually evolved whereby surgery was not recommended for this subset of patients.<sup>3-5</sup> Only those whose condition progressed would undergo neck exploration. Bilezikian has been one of the prominent proponents of this school of thought, which has come to dominate the clinical management of hyperparathyroidism in both Canada and the United States.<sup>3-7</sup> Recent US figures show that only 25% of people found to have hyperparathyroidism undergo parathyroid surgery,<sup>2</sup> and the situation in Canada is probably similar. However, not everyone has accepted this approach. Many surgeons have continued to advise operating, even in milder cases, and they point to a growing body of data that support the advantages of surgery.

Putting aside for a moment the debate over the role of

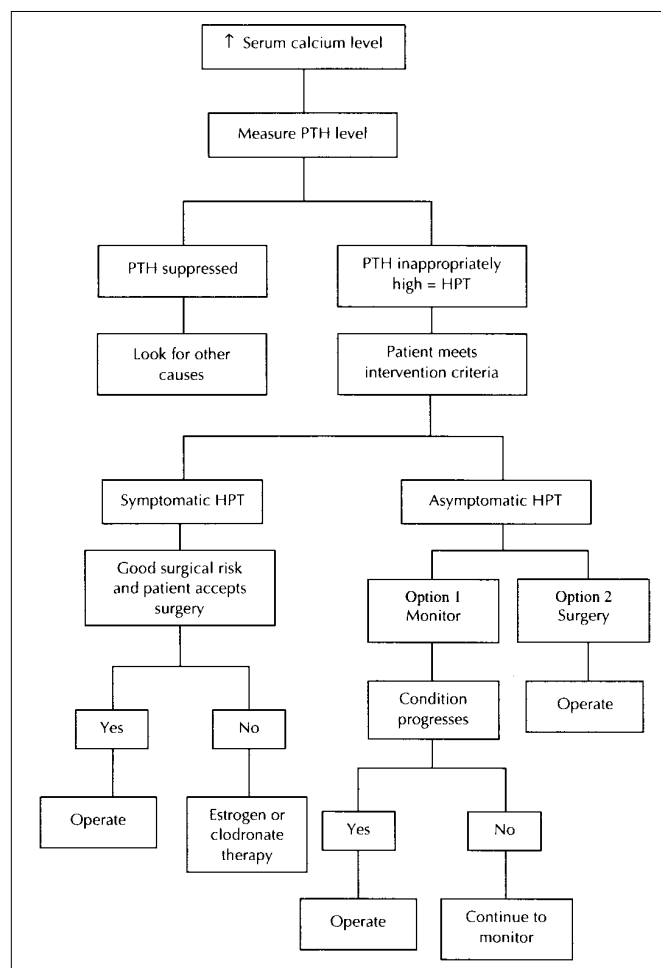
surgery, one of the most important messages arising from the timely presentation of this topic is that physicians need to once again incorporate hyperparathyroidism into their differential diagnoses. Because once-routine chemistry is no longer performed, in order to cut costs, the frequency of diagnosis of this condition has declined.<sup>2</sup> We may anticipate that this state of affairs will regress further so that many patients with hyperparathyroidism will once again evade detection until they have advanced manifestations such as fractures and kidney stones. To counter this trend, physicians need to consider hyperparathyroidism when patients present with any undiagnosed symptoms or findings that could be a result of this condition, such as kidney stones, reduced bone mineral density, gastrointestinal symptoms, mood disturbance, fatigue, or nonspecific neurological or musculoskeletal complaints.<sup>8</sup> Measurement of the total serum calcium level serves as a reasonable screening test, and the presence of serum parathyroid hormone will usually confirm the diagnosis (Fig. 1).<sup>8</sup> The hormone level is not always above the normal range; it may simply be inappropriately high for the calcium concentration. Kahn and Bilezikian

discuss recent information on familial hypocalciuric hypercalcemia, a benign condition that can also produce inappropriately high parathyroid hormone levels in relation to calcium values.<sup>9</sup> Assessment of calcium excretion in a 24-hour urine collection will usually distinguish one condition from the other. Calcium excretion will fall toward the lower end of the normal range in familial hypocalciuric hypercalcemia, whereas hyperparathyroidism leads to a value that is increased or in the upper portion of the normal range.<sup>9</sup>

Once hyperparathyroidism is diagnosed biochemically, the dominant approach in Canada is to assign patients to either high-risk or low-risk groups, the high-risk group undergoing surgery and the others being monitored.<sup>3-7</sup> Let me sketch out this paradigm before presenting the arguments for considering surgery in all patients. Under this protocol, tests are performed to look for evidence of pathophysiological changes resulting from excess parathyroid hormone levels, including renal ultrasonography, creatinine clearance and bone densitometry. Recommendations from a 1990 US consensus conference have served as a guide as to which patients should be sent for surgery, although most metabolic bone specialists apply their own modifications.<sup>3-7</sup> Box 1 in the review by Kahn and Bilezikian presents one variation on these criteria.<sup>1</sup> A serum calcium level greater than 3.0 mmol/L, reduced renal function, moderate hypercalciuria and reduced bone mineral density are widely accepted indications for surgery. Other commonly used criteria include the presence of nephrolithiasis or nephrocalcinosis, a serum calcium level greater than 2.8 mmol/L if associated with symptoms, and a history of serious hypercalcemia. In addition, I also regard reduced bone mineral density at any site, not just areas rich in cortical bone, to be an indication for surgical intervention. Hyperparathyroidism increases the risk of fractures at sites rich in trabecular bone, such as the vertebrae, distal forearm and ribs,<sup>10</sup> and it has been clearly shown that at least some patients have reduced trabecular bone mass that responds to treatment.<sup>5,11</sup>

On average, people with asymptomatic hyperparathyroidism who do not undergo surgery remain stable, with little progression to the more serious manifestations of hyperparathyroidism over 10 years.<sup>2,5</sup> A certain proportion of cases do progress, however, so surveillance is necessary. Serum calcium levels should be measured 3 or 4 times in the first year to detect the rare instance of rapid progression. Calcium levels should then be monitored several times per year for the next 2-3 years, then every 1-2 years after that if they have been stable. Bone densitometry and renal ultrasonography are repeated at 1 year and every 2-3 years. For patients with borderline hypercalciuria, 24-hour urine collections should be checked every few years, or if serum calcium levels are rising. If serum calcium levels increase, bone mineral density falls, hypercalciuria progresses, or kidney stones or nephrocalcinosis appears, treatment should be undertaken.

Those who dissent from this paradigm continue to pro-



**Fig. 1: Algorithm for diagnosis and management of hyperparathyroidism.** PTH = parathyroid hormone, HPT = hyperparathyroidism.

mote surgery for almost all patients with hyperparathyroidism, including the majority of those who do not meet the previously outlined thresholds for intervention. They offer the following points in favour of this approach. First, surgery is safe and effective: surgical risks are low, a single adenoma is usually found and resected, and a cure is typically achieved.<sup>5,12-14</sup> At some research centres surgical methodology has progressed remarkably. For example, a combination of preoperative sestamibi scanning and intraoperative rapid parathyroid hormone assay can make neck exploration a 1-hour outpatient procedure.<sup>13</sup> A second argument for surgical intervention is that asymptomatic hyperparathyroidism is not really asymptomatic: these patients often have real symptoms that cause morbidity. More important, quality of life improves following the surgical cure of mild cases.<sup>15</sup> Third, bone mineral density improves dramatically following removal of an adenoma, even in mild cases.<sup>5</sup> Finally, the cost of monitoring these patients is substantial: it exceeds the expense of surgery after only a few years.<sup>15</sup>

So, how does one reconcile these 2 views in clinical practice? I use the criteria outlined here to identify patients at greatest risk of complications and strongly advise surgery for them. For patients who fall below these thresholds, I review the pros and cons of surgery versus monitoring and allow the patient's preferences to be an important determinant of the approach we take. If the data supporting the benefits of surgical cure continue to grow, and if recent technological advances in parathyroid surgery become established in Canada, then the pendulum will probably swing back and surgery will once again become the primary approach to hyperparathyroidism. Having said this, I continue to keep my fingers crossed in the hope that calcimimetic agents will prove to be effective and render this whole debate obsolete.<sup>1</sup>

*Dr. Siminoski is Director of the Endocrine Centre of Edmonton and an Associate of Medical Imaging Consultants, Edmonton, Alta.*

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**Correspondence to:** Dr. Kerry Siminoski, Endocrine Centre of Edmonton, 608 College Plaza, 8215 112 St., Edmonton AB T6G 2C8; fax 780 438-0200

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