Diseases of the Parathyroid Glands

Angelo A. Licata • Edgar V. Lerma
Editors

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To my mentors, colleagues, and friends, at the University of Santo Tomas Faculty of Medicine and Surgery in Manila, Philippines, and Northwestern University Feinberg School of Medicine, who have guided me to where I am right now …

To all the medical students, interns, and residents at Advocate Christ Medical Center whom I have taught or learned from,

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– Edgar V. Lerma

To Cookie,

For her smiles, laughter, happiness, and patience

– Angelo A. Licata

Preface

Parathyroid disease is one of the most common endocrine disorders in general medical practice. It is generally manifested by hyperparathyroidism and less often by hypoparathyroidism. Hyperparathyroid disease is seen more often than previously. It is usually present as solitary disease but can rarely be associated with multiple endocrine neoplastic disorders. It is generally sporadic in nature but a genetic component is now appreciated in many families. Due to automated chemical testing procedures run in general medical practice, hypercalcemia, the telltale sign of the disorder, is found very frequently in the early stage of the disease when it is generally asymptomatic in most patients. Although kidney stones, osteoporosis, fractures, gastrointestinal disease, and psychological problems are the classic textbook findings once considered pathognomonic of the disorder, these problems are now relatively rare. The presence of hypercalcemia and increased parathyroid hormone levels is generally considered diagnostic for the disease. Nowadays, however, normal levels of calcium in the blood along with elevated, or inappropriate levels of parathyroid hormone with respect to the ambient serum calcium, may be characteristic of the entity called eucalcemic or normocalcemic hyperparathyroidism. This is an especially challenging entity to diagnose because of the sporadic fluctuations in serum calcium levels seen in patients from day-to-day. Coupling this with the commonly seen Vitamin D deficiency wherein a high serum PTH level and normal serum calcium is very frequently seen, makes this eucalcemic entity harder to diagnose.

Another entity that involves hyperfunctioning of the parathyroid gland is secondary hyperparathyroidism (also traditionally referred to as renal osteodystrophy), and its relation to chronic kidney disease. It has been recognized that as kidney function deteriorates, there is a progressive alteration in normal mineral homeostasis, with a disruption of serum and tissue concentrations of phosphorus and calcium, and changes in circulating levels of hormones which include parathyroid hormone (PTH), 25-hydroxyvitamin D (25(OH)D), 1,25-dihydroxyvitamin D (1,25$(OH)_2$D), and other Vitamin D metabolites, fibroblast growth factor-23 (FGF-23), and growth hormone. Even in moderately advanced kidney disease (Stage 3 CKD), the ability of the kidneys to appropriately excrete a phosphate load is compromised, thereby leading to hyperphosphatemia, elevated PTH, and decreased 1,25$(OH)_2$D with associated elevations in the levels of FGF-23. The conversion of 25(OH)D to

$1,25(OH)_2D$ is also impaired, leading to decreased intestinal calcium absorption and increased PTH. The kidney fails to respond (resistance) adequately to PTH, which normally promotes phosphaturia and calcium reabsorption, or to FGF-23, which also enhances phosphate excretion. At the tissue level, there is also downregulation of Vitamin D receptor and of resistance to the actions of PTH. In fact, therapy is generally centered on correcting these biochemical and hormonal abnormalities in an effort to limit the complications that arise there from.

The mineral and endocrine functions disrupted in CKD are critically important in the regulation of both initial bone formation during growth (bone modeling) and bone structure and function during adulthood (bone remodeling). As a result, bone abnormalities are found almost universally in patients with advanced stages of CKD (stage 5 CKD; or those requiring dialysis), and in the majority of patients with CKD stages 3–5. More recently, there has been an increasing concern of extraskeletal calcification, i.e. calciphylaxis, that may result from the deranged mineral and bone metabolism of CKD and from the therapies used to correct these abnormalities.

Hypoparathyroidism, on the other hand, tends to be a more symptomatic problem in most cases because it is associated with hypocalcemia and its resulting muscular and neurological problems. Most of these cases follow from postoperative sequellae of neck surgery and resulting parathyroid gland(s) injury; congenital problems are seen, but rarely so. Hypocalcemia, the hallmark of this particular disorder, is not generally missed on routine laboratory testing. Corroboration of its existence by adjusting for serum albumin is well appreciated by all practitioners. Failure to find increased parathyroid hormone levels in this scenario is the hallmark of hypoparathyroidism. Rare problems such as pseudo-hypoparathyroidism can clinically mimic true hypoparathyroidism. Attention to clinical history and symptoms usually aides clinicians in recognizing the distinction. But with the advent of the new assays for parathyroid hormone, these particular problems have become easier to diagnose. The assay for intact parathyroid hormone has made it possible to accurately discern excess of the hormone in the pseudo-state and deficiency of the hormone in real hypoparathyroid state.

For practitioners of all stages of experience, diseases of the parathyroid glands are not as easily deciphered as most textbooks would indicate. There are many subtleties to its pathology and diagnosis. The wealth of new information from molecular medicine makes it very challenging for the individual practitioner to have a total picture of these entities. To help clinicians, this book was developed. It is a small user-friendly text. It provides a present day background on mineral physiology and its regulation and couples this with a variety of clinical topics on parathyroid gland pathology.

Introductory chapters cover calcium regulation and parathyroid gland physiology, drawing upon many of the new aspects of glandular control mechanisms beyond the classical ones associated with calcium alone. The majority of the text covers clinical problems. Although most chapters address problems in adult medicine, three separate chapters are devoted to pediatric problems of hyper- and hypoparathyroidsm and parathormone resistance states. The clinical material for adults is introduced with a general chapter

about the patient with calcium problems. The following chapters cover a broad spectrum of topics, such as diseases of the calcium receptor, new aspects of primary and secondary parathyroid disease, the hypoparathyroid and pseudohypoparathyroid patient, pathophysiology of PTH-related protein and its diseases, multiple endocrine neoplasia, and familial hypocalcuric hypercalcemia. There are several chapters on less common but equally challenging problems, such as parathyroid cancer, calciphylaxis, cystic lesions of the glands, and ectopic glandular disease. The final chapters of the text detail the techniques of parathyroid gland imaging and surgical treatment.

From personal experience, we know that very few people read a textbook from cover to cover. For a variety of reasons, the majority would read only one or a few chapters at any given time. Therefore, we tried to ensure that each chapter would be complete in itself. As a consequence, there is unavoidable overlap among some of the information provided in some chapters; we, however, feel that this was truly necessary, at least from an information-retrieval standpoint, and in this way it will not be necessary for readers to read bits of information between one or more chapters just to get complete information regarding a particular subject.

We trust our readers will refer to this text often in the course of their clinical experiences. As it is with any text of this type, the flow of new material outpaces publishing deadlines. New information accumulates even as the book goes to press. As a result, we welcome useful comments from our audience about what directions future editions should take.

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