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Introduction

RENAL OSTEODYSTROPHY generally is referred to as disorders of bone and mineral metabolism that affect patients with chronic kidney disease (CKD). The past 10 to 15 years has seen an unprecedented explosion in our basic understanding of disorders of mineral metabolism, although these advances are only beginning to translate to improvements in patient care. On a cellular level, we now realize that programmed cell death or apoptosis is critical for normal bone remodeling. The intricacies of cell signaling within the various bone cells, and the interaction of various transcription factors to control gene expression, remains an area of intense research. Understanding of cell-to-cell communication also has accelerated our understanding of normal bone physiology, particularly with the identification of the long sought after coupling factor, osteoprotegerin/receptor activator nuclear factor kappa B-ligand (RANK-L), which appears to be a common pathway by which osteoblasts and osteoclasts communicate with each other. The critical mechanisms that control cell differentiation including bone morphogenic proteins, core binding factor α 1 (Cbfa1), Indian hedgehog, and Wnt factors help us to understand that in some cases it is not how the cell behaves, but abnormal signaling as the cell differentiates, that can induce pathologic changes. The ability of this complex machinery to control cell differentiation and phenotype has led to an appreciation that pathologic changes observed in patients may at times be owing to phenotypic expression in the wrong places. This may be particularly critical in the spectrum of abnormalities observed in renal osteodystrophy.

The activation, or repression, of many of these newfound pathways often are determined by various cell receptors and the intricacies of the conformational changes the receptors can undergo. This has led to an appreciation that systemic hormones such as parathyroid hormone may have different effects, depending on the frequency, concentration, and to which receptor the hormone binds. Understanding how these hormones are stimulated differentially (and in the case of CKD perhaps abnormally stimulated) to interact with different receptors and induce the conformational changes resulting in cell signaling remains an area in which our knowledge is only just beginning. The cloning of the calcium-sensing receptor has led to the development of new pharmacologic agents that only could have been imagined years ago. Clearly the diverse actions of parathyroid hormone and vitamin D are at least in part related to these receptor ligand complexities.

Our further understanding of the systemic effects of these pathways has been expanded further through the use of transgenic animal models. The knock-in and knock-out animal models have led us to a greater appreciation of the interrelationship between bone and mineral metabolism, and systemic processes such as vascular calcification. Clearly, an understanding of the cellular complexities never would have been possible without these techniques. In addition, these animal models can provide important information on the potential systemic effects of therapies aimed at a specific cellular target. Furthermore, these studies have led to an appreciation that the kidney itself has an important regulatory role in normal skeletal homeostasis, and that abnormal mineral metabolism can lead to many extraskeletal manifestations.

Although nature has provided us with a human gene knock-out or knock-in model to help us understand the human phenotype of abnormal genes, these remain limited at the present time. With the final mapping of the human genome it is hopeful that many human diseases will become better un-

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derstood. However, genetic polymorphisms and variable penetrance make this search complex.

Unfortunately, despite these advances, we have not yet optimized the care of our patients with renal osteodystrophy and the diverse set of pathologic problems that occur as a result of the osteodystrophy. Epidemiologic studies have shown that abnormal mineral metabolism, in particular hyperphosphatemia (at levels that once commonly were accepted and unfortunately observed), can lead to increased mortality in addition to morbidity. Clearly our complacency with abnormal serum levels of the various minerals no longer can be tolerated. Epidemiologic data also have shown a very high incidence of hip fracture. There is an interaction between the traditional concept of osteoporosis as assessed by bone mineral density, and abnormal bone remodeling as assessed by bone turnover, and these 2 abnormalities most certainly interact to produce increased fractures as well as other systemic repercussions. The complexities of renal osteodystrophy also are problematic in patients after renal transplant. This is worsened further by the myriad of medications given posttransplant. Although the kidney and patient survival rate posttransplant has improved, we are now seeing many long-term survivors suffer from the morbidity of abnormal skeletal homeostasis.

This great understanding of the basic science and its application to human disease have led to a paradigm shift in our thought process in the management of bone and mineral metabolism in patients with chronic kidney disease. An increased emphasis on controlling serum phosphorus, normalizing (as opposed to increasing) serum calcium, and not oversuppressing parathyroid hormone, and a greater appreciation of the potential toxicities of calcium overload in the development of vascular calcification form the basis of the newly released National Kidney Foundation Kidney/Dialysis Outcomes Quality Initiative (K/DOQI) Guidelines. In keeping with the spirit of the K/DOQI, we use the K/DOQI classification of CKD throughout the journal: CKD-3 (glomerular filtration rate of 60 to 30 mL/min); CKD-4 (glomerular filtration rate of 30 to 15 mL/min), and CKD-5 (glomerular filtration rate of $<$ 15 mL/min or on dialysis). As detailed in these guidelines, there is an expanding appreciation that much of our clinical approach to patients 10 years ago may not have been optimal, and that the abnormalities of the skeleton and mineral metabolism in CKD patients is responsible for significant extraskeletal morbidity and mortality. Although disappointing to many of us, this realization has led to renewed interest in various aspects of bone and mineral metabolism and how the improved understanding can change the clinical approach to our patients.

In this issue of *Seminars in Nephrology* we present articles describing new physiologic understanding of vitamin D, parathyroid hormone, and calcium-sensing receptors. Articles describing our enhanced understanding of the kidney/bone connection, vascular calcification, hypercalcemia of malignancy, and osteoporosis. The genetic and physiologic basis for rickets and urinary mineral wasting syndromes also are presented. Lastly, articles describing the application of this knowledge expansion to the care of patients with CKD and after successful renal transplant are presented. We hope you enjoy this issue of *Seminars in Nephrology*. We feel it is but a glimpse of the substantial increase in understanding of the cellular mechanisms and resulting systemic implications of optimizing mineral metabolism in our CKD patients.

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Guest Editors