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## Disturbances of bone and mineral metabolism in chronic kidney disease: an international initiative to improve diagnosis and treatment

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**Keywords:** diagnostic tools; mineral metabolism; renal osteodystrophy; treatment modalities

Among the numerous complications associated with chronic kidney disease (CKD), disturbances of bone and mineral metabolism have long been recognized. Abnormal plasma calcium and phosphorus concentrations are detected easily by routine biochemistry. Most of the different types of renal osteodystrophy have been reported >50 years ago, others have been described subsequently, and they are all well characterized at present. The problem is that the diagnosis of the precise type of renal osteopathy still requires a bone biopsy, in particular the distinction between low and normal bone turnover. At present, the majority of CKD patients, whether treated by renal replacement therapy or not, refuse to undergo such an invasive diagnostic procedure. The question then arises of how we can do without a bone biopsy, yet provide the patient with a treatment which allows the maintenance or achievement of an optimal bone structure and function in the long term.

### New diagnostic tools

In the last decades, numerous new circulating markers of bone turnover have been proposed [1,2]. They include markers of bone formation such as bone-specific alkaline phosphatase (bAP), osteocalcin, procollagen type I C-terminal propeptide (PICP)

and insulin-like growth factor-1 (IGF-1), and markers of bone resorption such as pyridinoline, deoxypyridinoline, tartrate-resistant acid phosphatase (TRAP), pyridinoline, deoxypyridinoline and procollagen type I C-terminal telopeptide (ICTP). Although some of them they have added valuable information for the distinction between high and normal bone turnover, none of them allows a clear-cut differentiation between adynamic bone disease (ABD) and normal bone.

New assays to measure the entire parathyroid hormone (PTH) molecule have also been developed, after the discovery that the so-called ‘intact’ PTH assays actually measure not only the whole peptide but also large fragments. The diagnostic position of these new measurement methods is uncertain to date and needs to be clarified [3,4].

The increasing use of imaging methods allowing the assessment of bone mineral density (BMD) not only in the general population but also in CKD patients has projected yet another diagnostic tool into the field of renal osteodystrophy. The interpretation of BMD findings and the relative usefulness of the different imaging techniques at hand for renal patients and their potential therapeutic consequences are not established.

### New treatment options

In recent years, promising new therapeutic directions have been taken with the development of calcium-free, aluminium-free phosphate binders and original compounds for a better control of secondary hyperparathyroidism [5–8]. The increasing awareness of extraskeletal manifestations linked to abnormal bone and mineral metabolism, in particular soft tissue calcification, has led to more stringent requests

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concerning the control of plasma calcium and phosphorus levels, as reflected by the recently published Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines [9]. The interrelationship between the pathological extraskeletal calcification process and normal or abnormal bone turnover is probably complex, and not much is known about this and other pathogenetic mechanisms involved in the special case of the CKD patient with a particularly high propensity to calcify blood vessels and other soft tissues [10]. The relative roles of high bone turnover such as osteitis fibrosa, and low bone turnover disease entities such as osteomalacia, ADB and osteoporosis need to be known. Since the presence and type of vascular calcifications are predictive of mortality [11], it is important to recognize them as early as possible and to prevent or treat them, if possible.

The clinical nephrologist has major difficulty in integrating recent advances in this field into clinical practice. Due to a lack of current consensus on therapeutic approaches, the clinical management of mineral metabolism disorders in CKD patients is fragmented and inconsistent among practitioners. Existing recommendations and guidelines on the management of complications associated with bone and mineral metabolism in CKD are very helpful for many aspects of the management and prevention of renal osteodystrophy. However, other aspects are still to be addressed, including abnormal BMD and soft tissue calcification.

### **Recent European algorithms and Australian and American guidelines**

The European Algorithms on Renal Osteodystrophy [12] were probably the first attempt to find an international consensus on how to approach and manage disturbances of bone and mineral metabolism in CKD. These were closely followed by recommendations set up in Australia, by the CARI (Caring for Australians with Renal Impairment) guidelines, in March 2000 ([http://www.kidney.org.au/cari/drafts/new/bone\\_preservation.html](http://www.kidney.org.au/cari/drafts/new/bone_preservation.html)) which also recommended target goals for the management of renal osteodystrophy. More recently, the National Kidney Foundation, as part of its K/DOQI, formed a bone metabolism and disease work group that proposed a comprehensive set of 16 clinical practice guidelines for the management of bone metabolism disorders in CKD patients. It is of interest that the target laboratory values proposed by these three groups closely parallel each other, supporting an international consensus for intensive regulation of bone-related mineral abnormalities in CKD patients.

### **NKF conference in Washington, DC**

The National Kidney Foundation hosted an international conference on March 14–16, 2003 entitled

‘Controversies in Mineral Metabolism and Bone Disease in CKD’, as an initial step in the implementation of the K/DOQI guidelines. Clinical and basic scientists from all over the world came together with the intention to define consensus and controversies among experts in this area, and to identify therapeutic approaches to achieving the target goals defined by these guidelines. Additional tasks were to adapt current views on osteoporosis assessment and management to the condition of CKD patients and to find appropriate means for an early diagnosis of extraskeletal calcifications in CKD and adequate therapeutic and preventive measures. A particular focus was on the identification of pathogenetic links between skeletal and extraskeletal manifestations and their significance for CKD patients.

Furthermore, the recent increased emphasis on extraskeletal manifestations of bone and mineral metabolism indicates that research is needed to address certain key questions that create integrated pathways for the management of mineral metabolism, balancing both the skeletal and extraskeletal manifestations of the disease. Therefore, the conference sought to examine the field of mineral metabolism by re-evaluating traditional views of renal osteodystrophy, and to examine the interrelationship between bone turnover, osteoporosis and vascular calcification.

A final objective of the conference was to identify key questions in bone and mineral metabolism in CKD where controversy remained despite available data and guidelines. These questions could then be used to generate hypotheses to be tested, to discuss methods for testing these hypotheses, and to prioritize research initiatives.

The fruit of the discussions of three distinct working groups formed for the purpose of this meeting, with consensus achieved on several issues and persistent discrepancies on others, will be reported in the March 2004 issue of the *American Journal of Kidney Diseases*, in the form of four companion articles. They are devoted to (i) an introduction and overview, (ii) the epidemiology, diagnosis and assessment of renal osteodystrophy, with particular focus on bone turnover, circulating markers and PTH assays; (iii) osteoporosis, with the suggestion to discontinue this term in CKD and to recognize that the term ‘renal osteodystrophy’ encompasses abnormalities of bone turnover and bone mineral density/content; and (iv) vascular calcification, recognizing the need to assess clinically the two main types of calcification and to develop widely available evaluation methods.

### **Conclusion and perspectives**

After the initial intention to report the three summary papers elaborated by the working groups of ‘The Controversies in Mineral Metabolism and Bone Disease in CKD’ conference in both the *American Journal of Kidney Diseases* and *Nephrology Dialysis Transplantation*, the decision was finally taken to

publish them in only the *American Journal of Kidney Diseases*, together with a short overview article. These manuscripts are readily available for free by visiting the following web site: <http://www2.ajkd.org>, and clicking on 'NKF Special Report'. In turn, we herewith draw the attention of our readership to this common international effort as a starting point for worldwide acceptance within the nephrology community of a more uniform approach to establishing a correct diagnosis of renal osteopathy and associated disturbances, and achieving adequate biochemical and clinical targets.

Subsequent steps will consist of moving the issues of consensus, and controversy, forward. This will be accomplished by standardizing diagnostic tests, and then translating these tests and available therapies into educational initiatives and new research for a better understanding of unclear or unknown matters. The ultimate goal is to treat or even prevent renal bone disease and associated extraskeletal complications such as vascular calcifications.

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## From curing to caring: one character change makes a world of difference. Issues related to withholding/withdrawing renal replacement therapy (RRT) from patients with important co-morbidities

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**Keywords:** co-morbidity; ethics; renal replacement therapy; withdrawal

## Introduction

The widespread availability of renal replacement therapy (RRT), the technical improvements in RRT techniques and the improved survival of patients with associated important co-morbidities, such as diabetes and cardiovascular disease, have led to a situation where, technically speaking, virtually every patient can

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